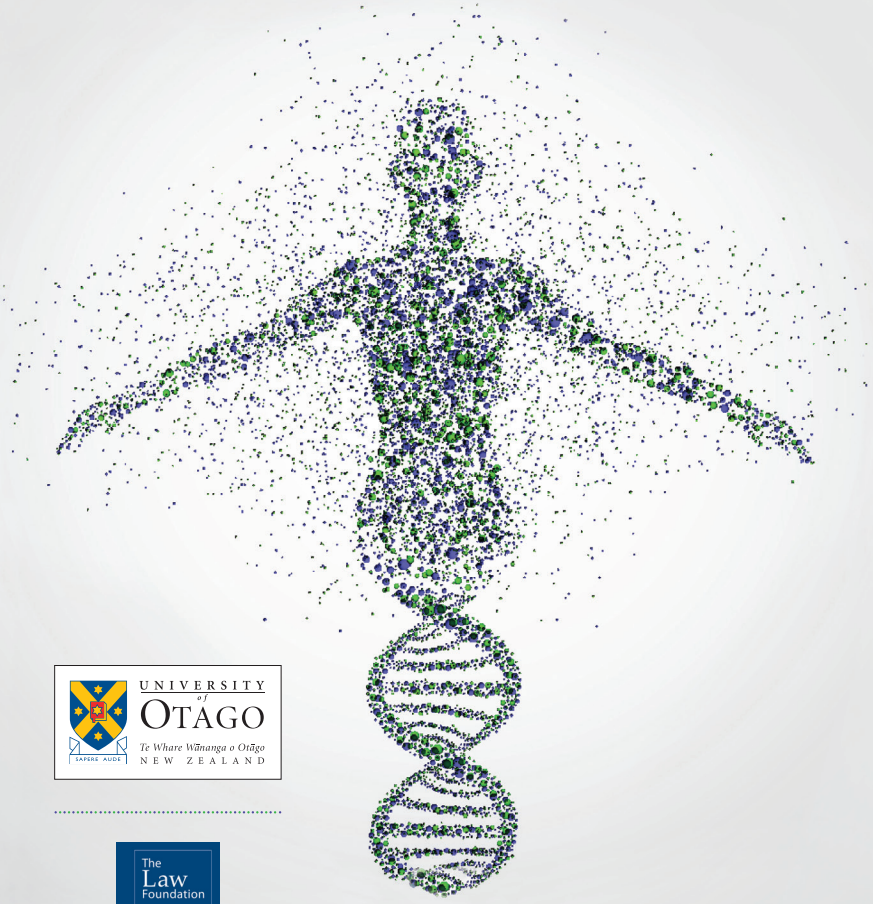
JUDGING GENES & CHOOSING CHILDREN:

revisiting law, ethics & policy in the genomic era



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Preface

This report is the result of a generous funding grant from the New Zealand Law Foundation. It is also a legacy of a previous three-year multidisciplinary research project that the Law Foundation sponsored over a decade ago, which sought to consider the implications of new genetic technologies for society: *Human Genome Research Project, Te Kaupapa Rangahau Ira Tangata: Law, Ethics and Policy for the Future*.

Given the rapid pace of genomics since then, this funding has allowed us to revisit some of the new and/or evolving issues that the new genomics era raises for individuals across the lifespan, particularly in the area of reproduction, and to examine the clinical, ethical and legal implications of these developments.

We would like to thank the Law Foundation, and in particular, Executive Director Lynda Hagan, for its support and patience while this report grew and took longer to complete than expected.

We would also like to acknowledge the support of our colleagues from the University of Otago Faculty of Law and the Bioethics Centre while researching and writing this report. In particular, we would like to acknowledge Professor John McMillan (Bioethics), Professor Mark Henaghan (Law), and Professor Stephen Robertson (Clinical Geneticist). We would also like to acknowledge Josephine Johnston, Research Director of the Hasting Centre New York, who visited and discussed some of these issues with us in the early stages of the project. While we are grateful for their interest and engagement in aspects of this report, the analysis and conclusions contained in it (including any errors) are those of the authors.

The rationale and scope of the project

The initial purpose of this project was to review genomic advances, and to consider what the future of "selective reproduction" might look like as a result of those developments. However, it became clear in the early stages of our research that, given the increasing incidence of genomic testing across the lifespan and the myriad issues it raises, this would require a much broader analysis of the genomics literature.

The transformation of the field of genetics and genomics is largely driven by the prospect, or at least promise, of precision medicine with the approach to investigating the genetic basis of disease evolving significantly in recent times:[1]

> The genetics field has changed perhaps more than any other scientific discipline over the past two decades. This transformation has been focused not only on methodology, but also on a more fundamental shift in the way gene hunting is executed. Traditionally a highly competitive field, gene hunting has evolved into a collaborative endeavor in which consortia and open data sharing are central tenets.

Over the past decade and a half, traditional "genetic" research has transitioned to "genomic" research. While the former is concerned with scrutinising single genes, the latter scrutinises all of the genes in a human genome. Genomics in turn has undergone transformations in terms of the methods used to identify disease-associated gene variants. It has progressed from utilising linkage studies;[2] to positional sequencing;[3] to genome-wide association studies;[4] to family-based next-generation sequencing; and finally, to exome sequencing in large case-control cohorts.[5] This most recent method involves comparing the genomes of large groups of people affected by a particular condition with the genomes of healthy individuals, to identify the specific gene variants involved in the development of disease.[6]

Significant resources have also been deployed internationally. The Human Variome Project is an international non-governmental organisation linked with the United Nations Educational, Scientific and Cultural Organisation (UNESCO), which was founded in 2010. Its mission is to "ensure that all information on genetic variation and its effect on human health can be collected, curated, interpreted and shared freely and openly".[7] In 2012 the United Kingdom announced its "10,000 genomes" project (UK10K) with funding from the Wellcome Trust. The aim of UK10K is to sequence the genomes of 10,000 NHS patients over 3-5 years. This research is focused on patients (and their families) who are undergoing treatment for rare disorders, cancer, and infectious diseases.[8] Genomics England (a Department of Health-owned company) was established in 2013. It aims to sequence 100,000 whole genomes of patients and their families with rare diseases or common cancers by 2017.[9] Other international projects are providing access to control and population sequence data that is necessary to conduct disease research. The United States National Institute of Health (NIH)-funded Clinical

Genome Resource (ClinGen) consortium has also been launched to "systematically sift the genetic evidence and create reliable databases of the genes and genetic variants underlying disease".[10] At the heart of all of these initiatives is identifying the genetic contributors to disease, so that diagnosis and treatments may be developed in the future.

Consequently, the primary question addressed in this research project is what does this new landscape mean for genetic testing and research in general, but particularly in the context of reproduction. Specifically, it questions what issues patients, clinicians, and policy makers are currently navigating, or likely to navigate, in the near future. To answer this question this report reviews the international literature regarding issues raised by clinical and genomic research in general, as well as genomic testing in the paediatric and reproductive context.

The report is set out in two parts. Part I considers genomic testing in the general population, and considers the paediatric population separately, while Part II specifically focuses on the reproductive realm. Chapter 1 provides a brief outline of the relevant science and various genetic/genomic tests, before examining a significant issue associated with the introduction of whole genome sequencing, which is the discovery of incidental findings. Chapter 2 outlines the development of genetic and genomic testing in the paediatric context and reviews the social science literature regarding the clinical and ethical implications of genetic testing for children and parents. Chapter 3 canvasses the clinical, ethical and legal implications of the rapidly developing technology of non-invasive prenatal testing (NIPT), while Chapters 4 and 5 consider developing genomic tests in invasive prenatal diagnosis, and in the preimplantation, context respectively.

Executive summary

CHAPTER 1

Whole Genome Sequencing (WGS) involves sequencing an individual's entire genetic code. The associated ethical and legal challenges arise from the sheer enormity and variability of the information that it provides. A particular issue concerns how to manage incidental findings (IF) that are generated by WGS. IF are findings that may, or may not, be potentially clinically significant, but are not pertinent to the primary diagnostic or research goal. This triggers significant issues such as determining the necessary scope of informed consent prior to undergoing testing or research; how to classify some IF; whether IF should be returned to individuals, and if so what kinds of IF should be returned; whether individuals undergoing genomic testing are obliged to receive the results of certain IF; whether there is a duty to follow-up individuals who have undergone testing as new gene-disease associations are subsequently made; as well as generic issues associated with managing large-scale genomic information. While clinical testing is governed by the general medico-legal framework in New Zealand, there is no explicit policy regarding the management of IF discovered in the course of clinical genomics or research. Further, research may often be conducted in a clinical context, which blurs traditional lines between treatment and research.

Internationally, there is a lack of agreement regarding the management and return of clinically relevant IF following genomic testing, including genomic and biobank research.[11] The various ways in which professional and national bodies have addressed these challenges are illustrated in tables provided in the Appendices to this report. This chapter concludes that physicians have a duty of care to inform patients in the context of clinical genomics regarding the potential for IF. This requires establishing criteria to categorize results, explaining the implications of the various categories in advance, and acting in accordance with the patient's preferences regarding disclosure in the case of clinically significant IF. This duty is grounded in the *Code of Rights* in the clinical context, or when a study involves a clinician-researcher, and could also apply in the case of some pure research.

While there is no clear legal requirement to return clinically significant IF to genomics research participants, there are strong ethical arguments in favour of doing so. These arguments support a presumption that investigators routinely consider instituting a process for managing incidental findings if they have the capacity and it does not impose an unreasonable burden on the researcher or the research project. This presumptive obligation is also subject to certain additional requirements to protect the interests of the individual participant. This includes validation of a test result before it is returned if the original test was conducted in a research laboratory, that consent to disclosure of IF has been obtained from the participant when they consented to the research, and that there is a mechanism to ensure the disclosure of genetic results is by a suitably qualified person.

This conclusion means that clinicians and researchers have a duty to consider how IF will be managed prior to undertaking clinical testing, or when formulating a research protocol. It requires clinicians and researchers to inform participants in advance of the potential for IF, the implications of receiving an IF including the familial nature of the information and that other family members may share the same gene variant, the implications of a definitive result for insurance,[12] and to ascertain the participant's preferences regarding return of information. In the context of research where IF are to be returned, investigators need to clearly determine and communicate the criteria governing what results will, and will not, be reported. A process for validating test results generated in a research laboratory is necessary, as well as determining who has responsibility for disclosing information to participants.

This approach is generally supported by the current research governance framework in New Zealand. These policies clearly endorse the concept of researchers assuming significant obligations in regard to research subjects, which may be directly extrapolated to the genomic research context. However, the boundaries of this obligation are not explicit, and obligations may need to be tailored to specific research studies.

Given the emerging ethical consensus that IF should be returned not only in the clinical but also in the research context, there is a need to determine when, how and what to return to patients and participants. Achieving this requires "anticipatory governance and interoperable policies, as well as sound management to ensure that the resources, both financial and professional, are in place to undertake such a task."[13] Ultimately formulating clear and transparent guidelines governing the management of IF that reflect New Zealand's unique cultural and medico-legal context is warranted.[14]

CHAPTER 2

Chapter 2 considers the implications of new genomic technologies in the paediatric context. Although genetic diseases are individually rare, in aggregate they are common in paediatrics. More than 10% of paediatric hospitalisations involve a child with a genetic condition, and genetic disease represents a major cause of morbidity and mortality in childhood.[15] Guidelines and policies generally support diagnostic testing in children with clinical features suggestive of a genetic disorder, and predictive testing for conditions with childhood onset. However, an enduring concern of traditional genetic testing, or even newborn screening, has been safeguarding children's interests, particularly when it involves predictive testing for later-onset conditions (predictive testing) and/or when it can result in uncertainty regarding future health.

Despite a paucity of psychosocial data, concerns regarding the potential for psychosocial harm have driven the generally precautionary approach adopted to paediatric genetic testing outside the traditional diagnostic realm.[16] However, over the years empirical work in this context has demonstrated that receiving genetic test results in childhood rarely leads to a significant adverse impact on children's psychosocial wellbeing, and in some cases can be beneficial.[17] Although this evidence base remains relatively small, and is

complicated by methodological inconsistencies, it paves the way for further research aimed at improving our understanding of how children and their families respond to newer approaches to molecular genetic testing.[18]

There has been a rapid diffusion of advanced genetic technologies in paediatrics. Chromosomal microarray analysis (CMA) has been widely used to diagnose developmental conditions and other disorders such as autism. Next generation sequencing (NGS) is currently being developed, and implemented, as a diagnostic tool.[19] As technology has evolved, many novel genes associated with disease have been identified and many children and their families have benefitted. Increasingly sophisticated tests are now capable of providing a comprehensive analysis of an individual's genome, providing a far greater range of information.[20] Although there is no question that new genomic tests provide a powerful way to determine the causes of rare conditions and syndromes in the paediatric population, these technologies differ significantly from the older types of genetic testing.

New genomic technologies create tensions between generating a comprehensive analysis of a child's genome to enable the diagnosis of often rare conditions, while limiting the potential problems that may be created by the wealth of data generated.[21] Again, key policy issues include what genetic variants are tested for in a particular context, how to approach informed consent, and how any IF and unclassified variants should be managed post testing. Some professional guidelines recommend targeted gene panels for diagnostic tests where possible to limit the likelihood of detecting additional incidental information, or in the case of genome-scale sequencing recommend restricting subsequent analysis to a limited set of genes.[22] In contrast, whole genome or exome sequencing has the advantage of casting a much wider net, and provides greater information that may assist in a difficult diagnosis.

There is a lack of data concerning the psychosocial implications for a child who undergoes genomic testing in this new era. However, it is possible to extrapolate from past experiences in Newborn Screening (NBS) and paediatric CMA. This literature suggests that in the short term, parents' emotional and psychological reactions to uncertain or ambiguous results vary considerably and can range between relief, a change in self-concept, and/or empowerment.[23] In the context of more advanced tests, some preliminary research suggests that professional concerns regarding information inducing anxiety outweighed the concerns of parents, with indications that some parents prefer to determine what results are reported themselves.[24] Overall, it is likely that the psychosocial impacts will vary depending on the individual's character or socio-economic situation. That is, harms may be greater for individuals who are predisposed to anxiety or worry, or for those who lack access to certain resources such as money, insurance coverage, access to counselling or other services. Ultimately formulating ethically defensible policy in the new genomic era requires clarity regarding the principles that should inform it, particularly in regard to the welfare of the child.

In recent times, there has been a shift in the way that traditional principles have been interpreted, as well as an evolution of paediatric bioethical concepts more generally. Traditionally, the concept underpinning childhood genetic testing and population screening of newborns has been the best interests of the child. Initially these interests were construed in narrow medical terms, such that the focus of NBS was preventing the devastating harm related to late diagnosis of conditions such as phenylketonuria. Similarly, in traditional genetic testing the pervasive view of the child's "best interests" was that testing was only justifiable if it was likely to confer direct medical benefit during childhood. Over the years a much broader conception of benefit has now evolved in NBS with developmental, social and psychological benefits, as well as indirect benefits to families and society widely considered to be relevant. These include not only medical benefits that accrue directly to the infant, but also developmental, social and psychological benefits that may arise from early disease detection, and indirect benefits to families and society.[25] Although still debated, some of the more recent guidelines governing paediatric genetic testing reflect broader considerations that may legitimately inform testing decisions, such as the potential for better psychosocial adjustment to disease risk, and avoidance of the so-called "diagnostic odyssey".

These conceptual shifts are mirrored by the evolution of ethical concepts within paediatric bioethics more generally, where there has been a move away from an individualistic "best interests" standard in paediatric bioethics, towards models that place greater emphasis on parental/familial autonomy. This autonomy is typically constrained only if a child is likely to be harmed as a result of the parents' decision. These evolving ethical concepts have far reaching implications that continue to be debated, but provide an important conceptual backdrop to inform robust and responsive policy and practice as genomics advances. Specifically, this may mean actively considering a greater focus on shared decision-making with parents, an enhanced role and recognition of parental autonomy, and a broader account of children's interests.

This chapter concludes that implementing new molecular approaches requires consideration of how the more "evolved" ethical concepts operate within the current environment of clinical paediatrics. Further, that families' perspectives on all aspects of genetic testing of children will be critically important, but it is likely to necessitate a system that can be tailored to the needs of many different families in different contexts. Ultimately advances in genomic technology may have made consensus on a single preferable course of action regarding genetic testing of children more elusive.[26] As genetics professionals attempt to tailor approaches to supporting families in comprehending and processing increasingly complex genomic results, their efforts will need to be informed not only by consideration of the key ethical concepts, but also by data detailing the lived experiences of parents and children with regard to genomic technology.[27]

CHAPTER 3

This chapter outlines the technical, ethical and legal issues associated with the rapidly evolving technology, Non-invasive Prenatal Testing (NIPT). NIPT is considered by many to be a "disruptive" technology, not only because it radically alters established methods of prenatal screening, but also because it has not followed the usual path to clinical introduction, instead it has been commercially developed and aggressively marketed to pregnant women.

NIPT involves analyzing a maternal blood sample to screen for fetal chromosomal abnormalities by isolating and analyzing cell-free foetal DNA. NIPT may be performed at 10 weeks' gestation, or potentially even earlier.[28] At present, NIPT is mostly restricted to analysing specific chromosomes for several common trisomies (specifically trisomies 21, 18 and 13), rather than facilitating generalised or untargeted screening.[29] Compared with traditional screening performed in the first and/or second semester of pregnancy, NIPT has greater capacity to detect these common trisomies if they are present (sensitivity), and to exclude them if not (specificity).[30] While false positive results still occur, the incidence of these compares extremely favourably with conventional screening (1% cf 5%). As a direct result, NIPT is capable of reducing the number of unnecessary invasive procedures such as amniocentesis following false positive screening results, and also reduces the associated risk of miscarriage.

However, commercial companies are steadily expanding the range of tests that are available on NIPT panels, some of which include screening for additional trisomies, sex chromosome abnormalities, and microdeletion/duplication syndromes associated with rare disorders. This expansion has often preceded scientific and clinical validation of such tests, and the predictive value of a test may vary greatly. A positive result for a less common condition is likely to have lower predictive value, i.e. a higher chance of being erroneous. As more tests are validated, the range of conditions for which NIPT may be used will expand exponentially, but not all of the tests will have well established, or significant, predictive value.

While prenatal screening is not a new phenomenon, NIPT clearly has novel aspects: it is non-invasive and does not pose any physical risk to an established pregnancy; it may be performed earlier in the first trimester than invasive testing such as amniocentesis; it potentially provides expanded screening options for women; and it is available privately in NZ with tests provided by off-shore companies.

Given its potential scope, NIPT has reignited debates involving prenatal testing in general, as well as concerns such as: eugenics; the appropriate scope of parental information and choice regarding future offspring; the implications of new technology for women and the experience of pregnancy; the potential for routinization of expanded screening, the implications for fetal life and termination of pregnancy; as well as disability rights arguments, all of which are discussed in this chapter.[31] This analysis cautiously concludes that, given the concept of screening is to facilitate reproductive choice and/or enable early post-natal intervention once a child is born, and provided a screening test has been proven to be reliable and accurate, there would need to be

good reason to limit private access to expanded NIPT. However, this is subject to acknowledging the technical limitations of NIPT, as well as concern regarding the validity and predictive value of some tests currently available commercially. It also requires an adequate infrastructure and provider knowledge to ensure a sufficient standard of care for women accessing NIPT, and to reduce the risk of harm associated with misunderstanding test results.

Significantly, NIPTs rapid integration into clinical care preceded the formulation of robust clinical guidelines for maternity providers or education. Evidence internationally suggests that many health care providers who refer patients for NIPT do not have sufficient understanding of genetics or the limits of NIPT, which may result in providers and women misunderstanding test results, with harmful consequences. This chapter outlines policy and oversight recommendations for the current provision of NIPT in NZ.

As evidence mounts regarding NIPT's superior capacity to detect common trisomies, particularly but not solely in higher risk obstetric groups, this chapter concludes that maternity care providers have a duty of care to inform women about the availability of NIPT. However, this also requires that patients are adequately informed of the risks, benefits and limitations of NIPT, in particular that it is a screening rather than a diagnostic test, it does not detect all fetal anomalies, and ultrasonography is still indicated for comprehensive screening. This duty of care extends to ensuring that test results are appropriately interpreted and communicated to women. Given that many of the test requisition forms permit a provider/patient to "opt in" or "opt out" of expanded screening it is imperative that providers have sufficient genetic literacy to provide adequate patient counselling regarding these additional screening tests. A related concern is that NIPT essentially outsources testing from genetics services. However, the importance of having access to skilled genetic counsellors if a "high chance" result is received is reinforced in research that indicates the quality of post-test counseling has a significant impact on a woman's subsequent reproductive decision making.

Nevertheless, there is a considerable distinction between operationalising a population-based screening service, and individuals accessing the technology privately.[32] An issue yet to be determined is how NIPT might be incorporated into NZ's public screening service, which attracts different considerations from private NIPT. While publicly funded population screening is subject to specific screening criteria and resource constraints, the same is not the case with individuals who access tests privately, and who may weigh the associated trade-offs differently. Of the possible models reviewed in this chapter, it is concluded that a 3-tiered model has the greatest merit in a public system.

Ultimately the underlying question in this new era is determining what information women want from prenatal screening, and how they balance the risks and benefits of expanded screening, a question that will not be answered universally given that women (and their partners) are not a homogenous group. Hence a specific issue for NIPT is whether the information derived from testing is considered by a woman to be subjectively useful or valuable, given the continually expanding scope of commercial NIPT.

NIPT has an enormous trajectory. It could theoretically, in the future, be used to analyse an entire foetal genome. However, it is likely that an intermediate phase of NIPT will see it become the equivalent of current chromosomal microarray testing that has been introduced in the context of invasive prenatal diagnosis. Consequently this provides an indicator of the types of challenges that may arise if similar testing becomes possible using NIPT, and is considered in detail in chapter 4.

CHAPTER 4

This chapter examines the introduction of chromosomal microarray (CMA) technology into prenatal medicine. CMA, which is a diagnostic test performed following invasive testing such as amniocentesis or chorionic villus testing, enables more extensive chromosomal testing at much higher resolution than traditional tests. CMA may be used to perform targeted or untargeted testing, and is capable of detecting missing or additional whole chromosomes, as well as variation in chromosomal segments, called Copy Number Variants (CNV), which may alter gene function.

CMA identifies a range of conditions, including conditions that may be of variable severity, may be early- or late-onset, and some conditions that may only have a statistical likelihood of actually occurring, rather than a certainty. Some findings may be associated with physical, cognitive, or psychiatric conditions.

A review of the international literature suggests that a particularly challenging aspect of prenatal CMA is the identification of CNVs that are associated with neurodevelopmental disorders. Neurodevelopmental or neurocognitive disorders encompass conditions such as mild intellectual disability, developmental delay, autism spectrum disorders, speech and learning problems, epilepsy, and schizophrenia.[33]

Although the use of CMA was initially limited to cases where there were specific concerns regarding fetal health, its integration into prenatal medicine is increasing. The international literature reflects a distinct shift from the traditional paradigm, where invasive testing was generally only indicated after an anomalous screening result, or in the case of advanced maternal age toward broader testing in the absence of specific indicators of risk. This literature suggests that, when given the opportunity, many prospective parents elect to undertake more expansive invasive prenatal testing, particularly if there are elevated risks associated with a particular pregnancy or fetal abnormalities identified on ultrasound.[34] However, there is also evidence that some information may be overwhelming and challenging for some prospective parents.

Historically, research indicates that prospective parents can experience a range of emotions following prenatal diagnosis of a fetal anomaly, such as anxiety, grief, hopelessness, guilt and anger.[35] The distress experienced may be influenced by the gestational age when the finding is made, the severity of the anomaly (actual or potential), and uncertainty regarding the diagnosis and/or prognosis.[36] Prospective parents may face decisional conflict, between continuing a wanted pregnancy and concerns regarding the potential quality of life of a child with additional and potentially

complex needs.[37] In the CMA era, this may be further complicated by the uncertainty associated with some findings.

Some evidence suggests that prospective parents may value information not only when it would be determinative of a decision to carry a pregnancy, but also when it may have implications for a future child's health or well-being. Several studies have reported that prospective parents prefer to be able to choose to receive information regarding a potential genetic anomaly or susceptibility identified in a fetus, which may reflect greater general acceptance of the ubiquity of genetic vulnerability, and a willingness to know more, rather than less, for multiple reasons. Others caution that 'unfiltered' prenatal information may create intense parental anxiety and potentially alter the parent-child dynamic.[38] Ultimately, a common claim in the clinical reports of CMA is that the factors having greatest influence on a woman's decision whether to continue a pregnancy are not CMA results, but a combination of the gestational age when a diagnosis is made, the severity of the anomaly (actual or potential) and the presence of ultrasound abnormalities.

There are several themes apparent in the international literature on CMA. The first is the assumption often made by prospective parents and clinicians that more information is better than less. Some women may elect additional testing on the assumption that it provides greater control over a pregnancy, or that 'knowledge is power'. While this assumption may be true of testing that provides definitive diagnoses, the severity of some conditions may differ significantly amongst individuals, and clinicians may not be able to predict where the future child may fall on that spectrum. Further, the potential genomic variants detected can include predispositions to complex disorders—when there is no certainty that a condition will develop in the future individual. The reality is that prenatal genomic testing may not provide certainty and, contrary to assumptions, may be anathema to any sense of "control" given potentially ambiguous results. Although prospective parents will engage with, and experience risk and uncertainty differently, it is likely that it will be challenging for many.

Although there is no consensus regarding how, or when, prenatal CMA should be implemented or the kinds of arrays used, two broad approaches are apparent in the international literature. One approach adopts a parental choice model, where women can choose the extent of information that is reported following CMA. Consequently, consent may be limited to disclosure of findings in specified categories that are discussed during the informed consent process: e.g. disclosure may be restricted to findings that are relevant to the abnormality under investigation; or may include findings that may lead to health effects in childhood; or may include findings that may lead to health effects later in life; and lastly prospective parents may choose to receive findings that may be relevant for their own health or reproductive interests.

An alternative approach that is squarely based on the concept of clinical "actionability" involves a mandatory return model, where clinicians predetermine a test platform and return all clinically significant pathogenic results, including both early- and late-onset conditions, with no option for parental choice. On this account, a condition is actionable if it may be improved by preventive measures or early treatment. This essentially constitutes mandatory screening for actionable conditions, directly importing a public health screening model into prenatal medicine.

This analysis suggests that one of the major risks in this context is to make unjustified assumptions about what women want to know regarding a pregnancy, and the danger of adopting a one-size-fits all approach. It suggests that there are good ethical and policy reasons why women should have a choice regarding the categories of results returned to them following expanded screening and diagnosis. This could be facilitated by a negotiated agreement that moderates the return of results, but enables revisiting tests at a later stage if there are subsequent concerns regarding a child's health or development. This approach presupposes an account of pre-parental autonomy that aids the exercise of genuine choice by being provided with good, understandable information, and the opportunity to discuss issues as needed with an adequately trained practitioner.[39] Developing adequate clinical capacity to address these kinds of issues is likely to become a priority for maternal and fetal health services, given the likely trajectory of technology. It is possible that, in the future, the current capacity of prenatal CMA will be replicated in NIPT, transforming it from a screening to a diagnostic test. This could significantly increase the number of women receiving additional genetic information, should they choose to access expanded non-invasive prenatal diagnosis.

CHAPTER 5

Preimplantation Genetic Diagnosis (PGD), which identifies deleterious mutations in an embryo created using in vitro fertilisation (IVF), was developed so that couples with a known risk of transmitting a serious genetic disorder to their offspring could avoid doing so. While PGD identifies a single gene mutation in an embryo, its lesser known counterpart, Preimplantation Genetic Screening (PGS), may be used to identify chromosomal abnormalities (aneuploidy) in an embryo. Because chromosomal aneuploidy is established to be associated with implantation failure or spontaneous miscarriage, and is also known to increase with advanced maternal age, PGS was developed on the theory that in these circumstances, selecting chromosomally normal (euploid) embryos would increase the likelihood of successfully conceiving and carrying a pregnancy to term. PGS, which was introduced clinically before rigorous studies established its efficacy, has been controversial, with scant evidence that it actually increases the 'take home baby rate', and evidence that it may actually reduce it. However, developments in testing techniques, as well as advances in IVF and embryology, promise to alter the nature of PGD and PGS in the future.

The convergence of several technological advances has steadily expanded the scope of PGD, and has also seen the emergence of "PGS-version 2". These advances include changes in embryo biopsy techniques, developments in embryology, as well as ever-increasing sensitivity and capacity of tests.

PGD is performed in the case of known risk and is targeted to a particular gene. Newer testing techniques involving a range of Next Generation Sequencing (NGS) methods enable simultaneous testing for a number of different gene sequences, with less risk of misdiagnosis. While traditional PGS is limited and only examines around half of the full complement of chromosomes, newer methods enable broad testing across all 24

chromosomes (22 pairs and two sex chromosomes). The international literature indicates that it is now possible to perform comprehensive embryo screening, either in conjunction with PGD to diagnose a known genetic condition, or as a stand-alone procedure in an attempt to improve IVF success.

Depending on the method used, it is now theoretically possible to obtain a complex set of genetic diagnoses following PGD and/or PGS. In particular, some new methods of PGS will provide not only information regarding aneuploidy that may be relevant to the success or failure of implantation or the risk of miscarriage, it may also provide a range of health-related information. As in other contexts, the type of health information derived from these high resolution NGS methods will vary significantly, and may include information regarding susceptibility to early- and late-onset conditions, as well as variants of uncertain significance.

Although still not definitive, some recent international studies involving the latest testing methodologies suggest that PGS-version 2 is associated with better pregnancy outcomes than ordinary IVF. If current international clinical trials confirm that PGS-version 2 increases implantation rates compared to standard approaches to assessing embryo quality, it is foreseeable that there will be a professional incentive to provide it, and a public demand to access PGS as an adjunct to PGD, but also in routine IVF. This would signal a move away from recommending PGS based on a predetermined risk threshold, to providing it as an option for all women undergoing IVF, if they are prepared to accept invasive embryo biopsy and the associated cost.

However, it remains unclear whether PGS-version 2 improves IVF outcomes, and debate whether it is good practice to provide it to good prognosis IVF patients. Further, some of the most recent high resolution NGS tests implemented overseas have brought to light the complex features of early embryo development, which makes a binary transfer decision in some instances more difficult.

Indeed, the latest technology has resulted in the emergence of a new category of embryo, the "mosaic" embryo. Mosaic embryos contain a mix of cells, some of which are chromosomally normal, and some that are not. Newer tests indicate that mosaicism occurs at higher rates than previously thought. Because they have an uncertain prognostic outcome, ranging from no effect on a future fetus who will likely be born healthy, to causing fetal demise if the embryo is implanted or, if successfully carried to term may cause illness or impairment in a future child, mosaic embryos currently occupy a "middle ground" in terms of transferability. Consequently, proponents of what is referred to as "high resolution" PGS version 2 now characterise it as a tool for "ranking" embryos on the premise that it will expedite the IVF process and reduce the chance of miscarriage, rather than selecting chromosomally normal embryos.

Early reports from overseas clinics that have introduced this technology report that some women who undergo such higher resolution NGS testing and find that all of their embryos are mosaic face difficult and complex decisions regarding embryo transfer, and may experience ongoing anxiety regarding fetal health when such embryos are transferred. The psychological and emotional toll on prospective parents who receive

ambiguous mosaic results cannot be underestimated, and it is likely to significantly impact the experience of pregnancy and childbirth. The emerging literature suggests that, when informed of the possibilities of mosaic results, some patients elect not to pursue PGS. The invasiveness and expense, in conjunction with the possibility of uncertain results and the burdens of decision-making may reduce the appeal of PGS. Ultimately, whether newer PGS technology improves IVF outcomes by enabling better selection or ranking of embryos is yet to be confirmed in clinical trials, and the effect on women's experiences of conception, pregnancy and birth are yet to be explored.

Ultimately, broad scope preimplantation testing combining PGD and PGS is not a panacea. Recent evidence suggests that some healthy individuals may carry single gene mutations that are annotated as disease-causing, which militates against opportunistically screening for single gene disorders. Further, some of the information derived from expanding PGS will be difficult to interpret clinically, particularly at the embryonic stage where there is no fetal ultrasound to assist in identifying potential physical effects of certain mutations and chromosomal variations. As discussed in chapter 4, the clinical significance of susceptibility loci (CNVs) associated with neurodevelopmental and neuropsychiatric conditions is also both highly variable and uncertain. Another significant factor is that although there is emerging evidence that PGS-version 2 using high resolution microarrays and NGS for aneuploidy *may* improve IVF success rates, randomized clinical trials are yet to provide definitive evidence that it improves outcomes. If it does improve outcomes, this must be balanced against the invasiveness of biopsy, the associated cost, and the implications of additional information derived by the different combinations of possible technologies.

Ultimately the main themes to emerge from this literature review involve issues of the accuracy and reliability of tests, how the increasing information that expanded testing will provide may be experienced by women and their partners, and how it is best managed by professionals and policymakers, as well as conceptions of reproductive responsibility and the appropriate scope of parental liberty.

There is some irony regarding the two broad themes associated with expanded genomics. On one hand, there is concern that, in some instances, parents may want to know too little about a future child's health, and that genetic/parental responsibility presupposes obtaining health-related information. However, much of the additional information that may be derived at the embryonic stage is shrouded in uncertainty, is likely to cause anxiety regarding future fetal health, and may make pregnancies even more tentative than in the past. On the other hand, there is concern that prospective parents might want to know too much about a future child, particularly when it concerns non-health-related traits which is generally thought to be contrary to acting "parentally". Ultimately, the literature reviewed indicates that most prospective parents who elect such testing are generally seeking assurance that their baby will be 'healthy enough', rather than seeking a perfect, made-to-order, baby.

Ultimately, the new reproductive future creates additional, and complex challenges for women who choose to access them, clinicians who provide them, and policy makers responsible for their oversight.

There is as yet no established international policy governing preimplantation NGS testing methods, which trigger a complex range of clinical, ethical and legal issues. However, the United Kingdom Human Fertilisation and Embryology Authority (HFEA) has recently reviewed its policy given these developments. The HFEA, drawing on guidelines for genomic testing in the wider context, have established a constrained parental choice model. Prospective parents who undertake counselling can receive a range of information, but may also opt for non-disclosure of certain results. In this case, clinics may withhold test results if the patient has been given the opportunity to receive genetic counseling regarding the implications and clinics establish protocols to limit, as far as possible, the risk of unwanted disclosure to the patients. However, the UK statutory framework also imposes restrictions on transferring an embryo known to carry an abnormality that poses a significant risk of a serious physical or mental disability or illness. When making transfer decisions, current policy provides that clinicians must have regard to the welfare of the resulting child, and should normally obtain clinical ethics committee approval. In this way, the statutory framework and associated Human Fertilisation and Embryology Authority Code of Practice imposes a "gatekeeper" role on third parties, who have ultimate control over a woman's possible conception.

Ultimately the increasing technologisation and medicalisation of assisted reproduction as a result of expanded testing is likely to not only affect reproductive outcomes, but will directly impact future women's experience of conception and pregnancy. The major issue triggered by all of these technologies is how, and if, they should be integrated into clinical practice in New Zealand. It is hoped that the research and findings in this report provide a starting point to consider the way forward.

PART 1

Chapter One

Whole genome sequencing: managing incidental findings

1.1 Introduction

Although the human genome was first sequenced in 2003, understanding its entire complexity in order to harness its potential to transform the way we understand, prevent and treat disease has not yet been fully realised. However, developments in the last decade and a half, primarily advances in testing technology and the transition from genetics to large-scale genomics research, herald a new era in the history of genetics.

Some genomics enthusiasts consider that Whole Genome Sequencing (WGS), which involves sequencing an individual's entire genetic code, promises to radically change our approach to human health and medicine—while others are much more cautious in their predictions.[40] Nevertheless the last few years has seen the emergence of a plethora of multinational genetics consortia that are all seeking to identify new, or confirm existing, gene-disease associations. This flurry of activity on the genomics frontier has fuelled on-going ethical and legal debate regarding the performance of genomics research in general, as well as its translation into the clinical context.

While issues in genetics are certainly not new, the more novel ethical and legal challenges associated with WGS arise from the sheer enormity and variability of the information it provides. The challenges surrounding genomic tests raise important issues regarding the appropriate scope of informed consent prior to participation in genomic research or when undergoing clinical testing; the necessary scope of disclosure of results post-testing (if any); whether or not there is a duty to follow-up individuals who have undergone testing as new gene-disease associations are subsequently made; as well as issues associated with managing large-scale genomic information.

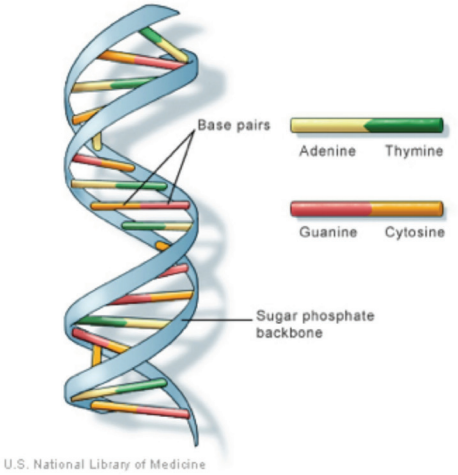
As much of the controversy associated with WGS relates to the types of findings that may be discovered, this section provides an overview of the basic genetics, which is also relevant to the subsequent chapters on paediatric and prenatal testing. The various types of human genetic variation that contribute to human differences and disease are outlined, as well as the kinds of information genetic testing may reveal regarding an individual's genetic status. In particular, it focuses on the nature of information that may be gleaned from the most recent developments in genetic testing, WGS. It also considers an important aspect of the debate regarding WGS—which is the relevance (if any) of the distinction usually made between testing that is performed in the clinical realm versus the research context. It concludes by examining the range of arguments that have been made regarding clinicians and researchers obligations in relation to obtaining consent and subsequent disclosure of findings to patients and research participants.

This analysis highlights the lack of consensus across jurisdictions regarding the management of incidental findings in clinical testing and research, and identifies the potential legal and ethical obligations that may arise in this context.

1.2 Introduction to the science of human genetic variation

The "human genome" is made up of 23 chromosome pairs, consisting of more than 3 billion DNA base pairs. It contains all the information needed to build and maintain our bodies. A copy of the entire genome (including all of our genes) is contained within all cells that have a nucleus.[41]

Figure 1: the human genome



A gene mutation is a permanent alteration in the DNA sequence that makes up a gene, meaning the sequence differs from the norm. Mutations range in size; they can affect anywhere from a single DNA building block (base pair) to a large segment of a chromosome that includes multiple genes.[42]

Events contributing to genomic variation can broadly be divided into three main categories: single-base-pair changes (or point mutations) that disturb the "normal" DNA nucleotide sequence; insertions and deletions of larger numbers of nucleotides in the DNA; and structural rearrangements that reshuffle the DNA sequence, thus changing the order of nucleotides.[43]

Categories of human genetic variation

Single base pair variations

The smallest variations in DNA sequence occur at the level of single nucleotides. Put simply, such variation consists of single letter spelling differences in DNA, referred to as "alleles." If the frequency of the minor (less common) allele is greater than 1% in the population, such variants are called "polymorphisms". However, it is also apparent that rare variants (with population frequencies of approximately 0.1-1.0) can also make a substantial contribution to the multifactorial inheritance of common chronic diseases.[44]

Single-nucleotide polymorphisms (SNPs – pronounced "snips"), which have attracted the greatest interest from researchers, are the most common type of genetic variation among people. On average, a SNP occurs once in every 1000 nucleotides, and each of us have between 3-5 million SNPs. Most SNPs have no effect on health or development, but over the past 5-10 years' genome wide association studies (GWAS) in large patient cohorts have made it possible to measure the associations between mapped SNPs and the presence of common complex conditions. The number of well-validated associations is now in the hundreds, and the list continues to grow. Examples include diabetes, obesity, cardiovascular disease, Alzheimer's disease, age-related macular degeneration and asthma. SNPs also contribute to biological variation such as height and metabolism.[45]

However, most SNPs associated with common diseases explain only a small proportion of the observed contribution of heredity to the risk of disease, in many cases less than 5-10%, but typically 30-50%.[46] This, and the sheer number of genes and environmental factors that may interact in a complex fashion to result in common disorders, substantially limits the use of these markers as predictors of disease risk. While understanding the relationship between SNPs and common diseases has significantly advanced our understanding of disease pathogenesis, as yet there are no evidence-based guidelines that recommend the use of SNP markers in assessing the risk of common diseases in clinical care, although considerable efforts continue to be made in this regard.[47]

In contrast to SNPs, the word "mutation" is generally reserved for changes in DNA that are believed, or known, to be *directly* pathologic. In the case of single base pairs such changes may also be referred to as "point" mutations. An example is the substitution of a thymidine base for an adenine base in the human β-hemoglobin gene that leads to sickle cell disease. Other diseases may be caused by slightly larger (although still tiny) mutations spanning a few base pairs, such as the delta F508 mutation on chromosome 7 that leads to deletion of one amino acid in the cystic fibrosis trans membrane regulator (CFTR) protein channel.[48] These types of mutations were among the first to be described when genes associated with diseases, such as cystic fibrosis (CF), were mapped and cloned some 20 to 25 years ago.[49] Most of these disease-causing gene mutations are uncommon in the general population.[50]

Larger insertions and deletions: copy number variants (CNV)

Larger segments of genetic material may also vary. These larger-scale changes were originally thought to be as uncommon as the point mutations discussed above, and to occur in single genes. Such mutations were typically described in relation to classical Mendelian dominant or recessive diseases such as Duchenne Muscular Dystrophy (DMD), neurofibromatosis (NF) and tuberous sclerosis (TS).

However, in the last 10 years it has become apparent that changes of this magnitude are also very common[51] and occur in many locations throughout the genome. In fact, more than 10% of human DNA appears to contain these differences in gene copy number. Copy number variations (CNVs) can consist of insertions, deletions, inversions, and duplications that result in changes in the physical arrangement of single or multiple genes. Variation in gene copy number can influence the activity of genes and ultimately affect many bodily functions. CNVs can:

- be benign, i.e. have no effect on the phenotype;
- contribute to non-pathologic differences between individuals;
- be disease/condition-causing (through variation confined to single genes e.g. DMD, TS; or spanning multiple genes such as microdeletion syndromes e.g. 22q11.2);
- confer increased risk for certain conditions (such as Crohns disease, autism, or schizophrenia);
- be of uncertain significance (although as more CNVs are recorded in large databases it is likely that our understanding of the significance of these variations will improve).

Future research will focus on the consequences of copy number variation in different parts of the genome to study the contribution of these variations to many types of disease.

Penetrance and expressivity

Penetrance and expressivity vary considerably for CNVs that have been associated with underlying diseases or conditions.

Penetrance refers to the proportion of people with a particular genetic change (such as a CNV) who exhibit signs and symptoms of a genetic disorder. If some people with the mutation do not develop features of the disorder, the condition is said to have reduced (or incomplete) penetrance. Reduced penetrance often occurs in familial cancer syndromes. For example, many people with a mutation in the *BRCA1* or *BRCA2* gene will develop cancer during their lifetime, but some people will not. It is not possible to predict which people with these mutations will develop cancer, or when the tumours will develop. It is thought that reduced penetrance results from a combination of genetic, environmental, and lifestyle factors, many of which are unknown. This phenomenon can make it challenging to counsel patients with some genetic variations.[52]

Expressivity refers to the range of signs and symptoms that can occur in different people with the same genetic condition. Although some genetic disorders exhibit little variation, most have signs and symptoms that differ among affected individuals; which is termed variable expressivity. For example, the features of Marfan syndrome vary widely: some people have only mild symptoms (such as being tall and thin with long, slender fingers), while others also experience life-threatening complications involving the heart and blood vessels. Although the features are highly variable, most people with this disorder have a mutation in the same gene (FBN1). Another example of variable expressivity is the most common human microdeletion syndrome, 22q11.21, which is highly penetrant but has a range of phenotypic expression broad enough to encompass symptoms so mild they remain undiagnosed, as well as disorders that were previously designated as different clinical syndromes (eg DiGeorge syndrome, velocardiofacial syndrome). As with reduced penetrance, variable expressivity is probably caused by a combination of genetic, environmental, and lifestyle factors, most of which are not fully understood.[53]

Structural re-arrangements

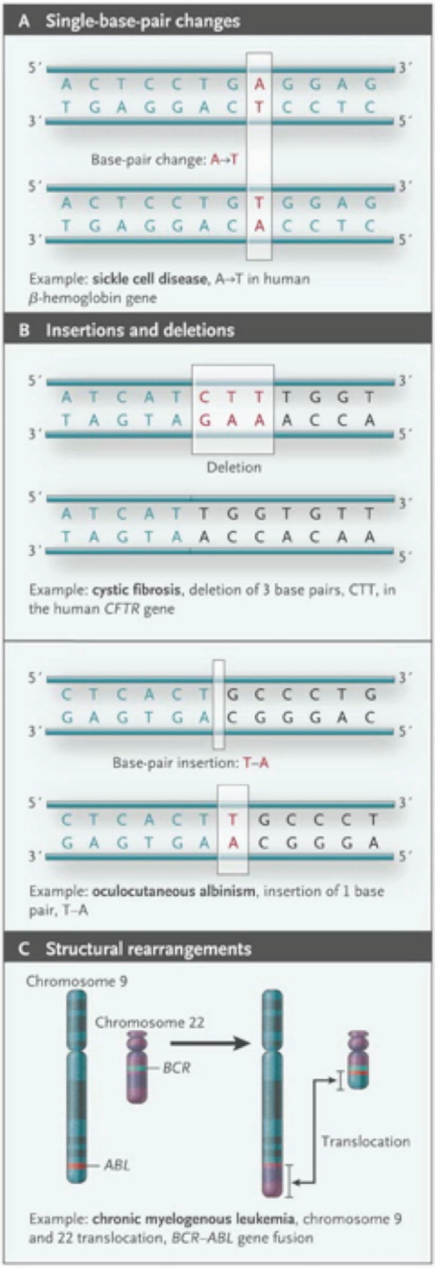
Finally, whole chromosomes may also be duplicated or deleted (e.g. trisomy 21 Down syndrome; 45X Turners syndrome)[54] or there may be structural re-arrangements of large parts of chromosomes, such as translocations which may be balanced or un-balanced.[55]

The scale and consequences of these three groups of changes (summarised in the figure below) vary dramatically depending on where and when such a variation occurs. For example, the change of a single base pair can have profound health consequences (e.g., the substitution of a thymidine base for an adenine base in the human β-haemoglobin gene), whereas a large, balanced translocation event (in which the genetic information on an entire arm of a chromosome may switch places with the arm of another chromosome) may have no direct consequences for the affected person.

Epigenetic variation

Although not discussed in detail here it should be noted that genetic variation may also occur outside of the DNA sequence. Epigenetic variation involves "chemical tags" that act as switches that control genes' activity. Conditions including cancers, metabolic disorders, and degenerative disorders, as well as some syndromes usually diagnosed in childhood such as Prader-Willi, Angelman, and Beckwith-Wiedemann syndromes, have all been found to be related to epigenetic changes.[56]

Figure 2: Human Genetic Variation[57]



1.3 An introduction to genetic testing

Genetic testing is the process by which a person's DNA or chromosomes are analyzed for the presence of particular DNA sequences that encode for traits of interest. Historically, genetic testing involved the analysis of targeted genes or particular chromosomes for evidence of a gene-based or chromosomal abnormality that caused, or contributed to, the development of a particular disease or disorder in an individual. Traditionally such testing was focused either at the molecular DNA level (Sanger sequencing) to determine single gene disorders, or at the cytogenetic level to identify structural or numerical chromosome abnormalities.

More recently new approaches such as WGS and whole exome sequencing (WES) have begun to replace these techniques, but considerable overlap remains concerning the types of information that can be derived. The table below summarises these types of test information and introduces the newer testing modalities.

Table 1: Types of test information[58]

Diagnostic testing	Testing to determine whether symptoms are caused by a genetic disorder and potentially to guide treatment
Predictive testing	Testing to predict the future onset of a health condition with reasonable certainty
Susceptibility testing	Testing for variants that somewhat increase risk for a disease, but where many people who test positive will not actually develop the condition
Carrier testing	Testing for variants that will not influence the health of the person tested but may cause a genetic disease in his or her children
Pharmacogenomic testing	Testing for variants known to influence how pharmaceuticals are processed, leading to personalized use or dosage recommendations
Testing technologies	
Single-gene testing	Testing for variants in a single gene that are typically predictive of a disease
Chromosomal microarray testing	Testing that detects significant chromosomal rearrangements
Whole-exome sequencing	Sequencing of all DNA elements that encode proteins, representing about 1% of the genome
Whole-genome sequencing	Sequencing that aims to obtain an organism's complete genetic code

Table 1 highlights the different types of information that may be gleaned from analysis of a patient's genome, which is examined in greater detail with the aid of key examples.

Diagnostic testing

Examples in this category include single gene disorders such as cystic fibrosis and thalassaemia.

Predictive testing

These may also involve single gene disorders, but the symptoms do not manifest until later in life, eg Huntington disease.

Susceptibility testing

"Susceptibility" mutations fall short of indicating a *certainty* of future disease, but rather indicate a specific risk of developing a condition at some stage over one's life. These susceptibility conditions similarly occur primarily as a result of a single gene mutation, but manifestation of the disease is also dependent on other factors such as the interaction of other genes or the environment. An example is the predisposition to developing breast, bowel or ovarian cancer as a result of a mutation in the *BRCA1* or *BRCA2* genes.

Carrier testing

Genetic testing can also determine if an individual is a "carrier" of a recessive mutation. While being a carrier of a recessive mutation does not generally pose any direct threat to that individual's health, it poses a risk to a future child if the individual conceives a child with a reproductive partner who carries the same recessive mutation within their genetic code.

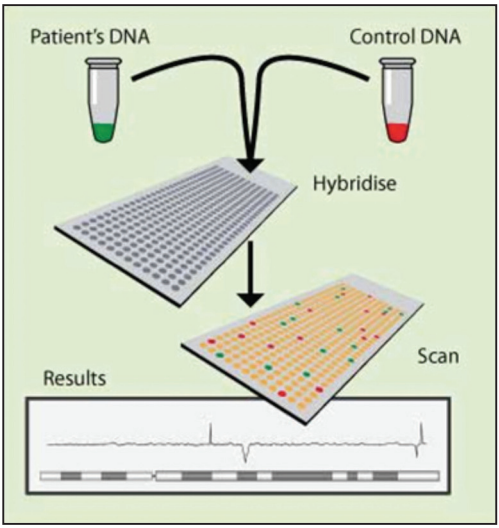
Testing technologies: new approaches to molecular diagnosis

The table above highlights the different types of new testing technologies available. These are described further below.

Chromosomal microarray tests

This term refers to technologies that assess the presence of CNVs at locations throughout the genome. "Chromosomal microarray" (CMA) refers to a microchip-based testing platform that allows high-volume, automated analysis of many pieces of DNA at once. CMA chips use labels or probes that bond to specific chromosome regions. Computer analysis is used to compare a patient's genetic material to that of a reference sample. A difference between a patient's DNA and the reference sample is called a variant.

Figure 3: Chromosomal microarray analysis[59]



Microarray-based genomic copy-number analysis is now a commonly ordered clinical genetic test.

It is offered under various names, including CMA; "molecular karyotyping"; "array based comparative genomic hybridization" (aCGH); and SNP arrays.[60]

Testing is broad (i.e. across the genome) but CMA is currently performed in many different laboratories with different technology platforms and different array design and content. Determining the clinical significance of CNVs can be challenging.

Whole exome and genome sequencing

WES and WGS may also be termed "next-generation/high-throughput sequencing" as these technologies permit rapid sequencing of large portions of the genome, vastly increasing the throughput over classic Sanger sequencing.

WGS and WES are broad genetic tests (approx. 20000 genes) but do not evaluate 100% of the genes (only 85-92%). The tests can have false positives and are not 100% sensitive. Although testing can be successful in identifying a genetic cause for a condition, in the majority of cases a cause will not be identified.[61]

WGS is rapidly becoming part of clinical practice in a variety of contexts, particularly in paediatric practice where it has been used to diagnose the cause of rare genetic disorders in children.[62] There are several reasons why paediatrics has been one of the first cabs off the rank to utilise WES, primarily because many paediatric diseases are genetic, with 85% of mutations exomic. In such clinical situations, the objective is to make a diagnosis to facilitate treatment and enable family-centred care.[63] Issues related to paediatric testing are discussed further in Chapter 2.

While testing remains a simple procedure itself, the process of whole genome/exome sequencing is complex. WGS involves sequencing all six billion base pairs of DNA in an individual. Hallowell et al neatly capture the complexity involved in the following:[64]

> Genome sequencing comprises a set of interrelated activities that follow on from the generation of the sequence of the base pairs across the entire genome/exome. These activities include (a) the identification of defined variants in the sequence as compared with some reference sequence, (b) the selection of those areas of the genome that contain variants that are pertinent to the clinical or research question and (c) the interpretation and analysis of the data within those selected areas.[65] It is at the final stage when the sequence variations are interpreted that judgements are made about the meaning of the variants that exist in the analysed sequence.[66]

Two important points may be extrapolated from this. First is that a diverse range of information may be derived from such testing. The second is that a significant aspect of WGS involves the analysis and interpretation of sequence data and results.

The analytic validity of many of these new approaches to molecular diagnosis remains somewhat unclear. Several recent studies have suggested there are significant differences in what is defined as a variant between different platforms[67] and analytic "pipelines", although this can be improved by having multigenerational family samples to assist in interpretation.[68]

1.4 Genomics: challenging traditional ethical and legal terrain

Conventional genetic testing is governed by traditional medico-legal principles such as informed consent; patient autonomy; the professional duty of care; and maintaining privacy and confidentiality. However due to the inherent complexity of genomic technology, determining the scope of professional obligations is not a straightforward endeavour. Indeed, WGS/WES has presented largely uncharted ethical and legal terrain for scientists, clinicians and policy-makers across the world.

This chapter considers one particularly challenging aspect of genomic technology that has significant relevance to testing in childhood and, in particular, reproductive genomic testing. This concerns the vast range of information that genomic testing may provide and, in particular, the issue of "incidental findings" discovered in the course of clinical testing or research.

As already indicated WGS/WES conducted either in the context of research or as part of a clinical diagnostic process provides a potentially wide spectrum of results. While some of these results will be 'pertinent' to the primary diagnostic or research goal, other less directly relevant but nevertheless clinically significant findings may also be generated. These kinds of findings have variously been described as "incidental", "unsolicited", "coincidental", "secondary", "unanticipated", "off target",[69] "opportunistic" or "discovery findings". For the purposes of this report these findings[70] will be referred to by their most frequent descriptor: incidental findings (IF).

Incidental findings

The concept of IF is not new. IF have a long history in various areas of medical practice such as unexpected anomalies discovered during a surgical or diagnostic imaging procedure.[71] However the potential for IF in clinical and research genomics is significantly greater. In addition to the comparative frequency of discovering genomic IF, the implications of such findings extend beyond the single individual who has undergone testing as a result of the familial nature of genomic information.[72] Further, the clinical relevance of some IF may not always be scientifically established.

Clinically significant variants versus variants of unknown significance

While some types of IF may be considered scientifically or clinically "significant", others are of "unknown" significance. Hallowell et al explain these distinctions:[73]

> "Scientifically significant" findings are those findings for which there is statistical evidence of a relationship between the genotype (genetic variation) and a particular phenotype (eg, disease symptoms/risk factors). If there is insufficient evidence to support this relationship, then the finding is often designated a "variant of uncertain significance" (VUS). Labelling a particular genetic variant as a VOUS does not necessarily mean that the genotype–phenotype relationship does not exist, but rather that it has not been confirmed statistically at this time in this population. WGS generates a large amount of data, and many observed variants will be of uncertain significance. Further clinical investigation may be required to determine their significance, and this may necessitate disclosure to patients or feedback to research participants for the purpose of gathering more data (eg, biospecimens and phenotypic data from other family members).

Even when a gene-phenotype relationship is scientifically established, there may still be considerable uncertainty regarding its effect on the individual. The implications of a clinically or scientifically significant incidental finding may range from posing a major threat to an individual's health in the short or long-term, to relatively minor repercussions that may or may not eventuate in the future and that may or may not be preventable or treatable.

The potential for false positives

The range of findings discovered in the course of WGS/WES is further complicated by the fact that, given the large range of potential candidates for causal mutations in any human genome, whole genome data sets are likely to generate erroneous results (false-positives/false negatives).[74]

Summary

Given the complexity of information, there has been considerable debate about what "incidental" information should be reported back to patients, and whether such obligations should extend beyond clinical relationships into research scenarios. The following section considers the nature of this on-going debate amongst scientists, ethicists, policy makers and lawyers.

1.5 Medico-legal obligations

CMA or WGS/WES may be conducted in the context of research, or in the course of providing clinical care. To establish the necessary background to the discussion regarding IF in genomics, this section considers the legal rules (largely derived from common law) and the normative ethical principles that govern the ordinary provision of clinical care and research, before returning to the specific issue of genomics.

In the ordinary clinical relationship, it is uncontroversial that a health care provider has ethical and legal obligations to act in the interests, and for the benefit, of the patient. In legal terms these duties primarily arise in: (a) criminal law (treatment without consent in the absence of a lawful justification constitutes an assault/battery);[75] (b) tort law (a duty to provide non-negligent care);[76] and (c) equity (fiduciary duty). These duties impose extensive obligations and underpin the range of ethical, professional and legal duties imposed on providers.

Extensive obligations are also imposed in the research context. However, the nature of the relationship between a researcher and research participant may vary significantly. The research may be therapeutic (likely to benefit the participant) or non-therapeutic (unlikely to directly benefit the participant), undertaken locally or at a distance, it may be short-term or longitudinal. The type of research being conducted can impact the nature and extent of the duties owed to a research participant.

The following outlines the legal duties that arise in the clinical realm, before considering the scope of legal duties in the context of research.

Ordinary medical care

Clinicians have a legal obligation to provide services with "reasonable care and skill".[77] A necessary pre-requisite to any medical procedure performed on an individual, whether therapeutic or not, is the individual's voluntary and informed consent. This encompasses a legal duty to provide adequate information regarding the associated risks and benefits of a treatment or procedure to facilitate a sufficiently informed decision.

In New Zealand this common law position is reflected in the *Code of Health and Disability Services Consumers Code of Rights* promulgated under the Health and Disability Commissioner Act 1994 (HDC Act). Together these create a distinct category of civil or *"Code"* liability.[78]

The *Code of Rights* states that a consumer has the right to have services provided with "reasonable care and skill" and "that comply with legal, professional, ethical, and other relevant standards".[79] The standard of care expected of any practitioner is a legal matter. It is determined by reference to the level of skill expected of a reasonably competent practitioner practicing in that particular field, and is also informed by standards that are applicable to that particular profession.[80] Providers must also observe patient confidentiality.[81]

There is an established consensus in the common-law world that, when it comes to disclosing the possible risks and benefits of a procedure, the requisite standard of disclosure is ascertained by reference to the information that a reasonable patient, in *that*

patient's circumstances, would expect to receive.[82] This common-law position is reflected in the *Code of Rights*.[83]

All of these medico-legal obligations apply when genomic testing is performed in the context of clinical care to diagnose an unknown condition. However, distinctions are sometimes made regarding researchers' obligations when pure research is conducted (as opposed to research that is part of clinical care), with less onerous obligations arising in the context of pure research. The following considers to what extent this is assumption is accurate.

Health research and the duty to inform

Policy governing research is generally informed by widely accepted norms that are enshrined in several international instruments.[84] These include the Nuremberg Code of 1949; the World Medical Association's Declaration of Helsinki 1964; and the Council for International Organizations of Medical Sciences (CIOMS) *International Ethical Guidelines for Biomedical Research Involving Human Subjects*.[85] These instruments all reiterate the need for consent in research, as well as the general duty to inform a prospective participant of the aims of a proposed study, the anticipated benefits and potential risks of participation, as well as disclosing any conflicts of interests to participants.[86] The extent of the duty to inform participants may be implicated by the nature of the research, particularly if it is non-therapeutic and has associated risks.

Non-therapeutic research norms: implications for genomics

International case law, such as the Canadian case of *Halushka v University of Saskatchewan*[87] suggests that the duty to inform in the context of non-therapeutic research is no less, and potentially more extensive, than in the general therapeutic context.[88] *Halushka* involved a student who was a paid participant in a trial that involved inserting a cardiac catheter and administering an experimental anaesthetic drug.[89] Despite being told that the test was safe, the participant suffered a cardiac arrest after the drug was administered. After he recovered, the participant brought a claim against the clinician-researchers. The trial court held that the negligent failure to sufficiently inform the participant meant that no "effectual consent" had been obtained to participation in the trial.

On appeal, the Saskatchewan Court of Appeal suggested that the duty to inform may be more onerous in the context of non-therapeutic research compared with the requirement when providing ordinary medical care. It stated "the duty imposed upon those engaged in medical research … to those who offer themselves as subjects for experimentation … is at least as great if not greater" than that owed in the ordinary patient-physician context.[90]

The rationale given by the court for such "heightened" disclosure obligations was because there could be no exception to the duty to inform, as might (rarely) arise in the context of ordinary medical practice on the basis of "therapeutic privilege".[91] The principle in *Halushka* was reaffirmed in the Superior Court of Quebec in the case of *Weiss v Solomon*.[92]

Although the reasoning of the courts is somewhat outdated in terms of the concept of therapeutic privilege, the expectation of extensive information disclosure for invasive non-therapeutic research is clearly justifiable. There are different trade-offs when

participating in therapeutic versus non-therapeutic research. Any risks involved will arguably assume greater significance if they are not off-set by potential direct health benefits. In this case requiring extensive disclosure requirements is a legitimate means of discouraging inappropriate inducement or exploitation of research subjects, particularly when subjects are paid for their participation as in *Halushka*. In ethical terms, it is based on the concept of respect for persons and the ethical duty not to treat another person as a mere means. In *Halushka* the research participant was particularly vulnerable due to the invasiveness of the procedure, his lack of knowledge regarding the risks associated with the procedure, and the concomitant trust placed in the individual(s) performing the procedure. The decision in *Halushka* is manifestly defensible.

However, genomics research is qualitatively different from other kinds of research. Although genomic research may identify gene variants that are highly relevant to an individual's current or future health, it is only minimally invasive. Further genomics research may be conducted by international or national groups. As Zawati notes, genomics research is progressively becoming [93] more "international, collaborative, longitudinal", and "less individually oriented". This raises a significant normative question for the law, which is the extent to which, if any, obligations of disclosure arise in regard to clinically significant incidental findings discovered during the course of genomic research. He states:[94]

> … although *Halushka* and *Weiss* provide guidance on the duty to inform in the context of consent, they fail to address the issue of return of results in the context of research. *Does the return of findings fall within the scope of the duty to inform?* Given the increasingly blurred lines between research and clinical care, this issue has become all the more important.

At first blush, it may seem unusual that Zawati draws on cases such as *Halushka* and *Weiss*. The duty to inform regarding the risks and benefits of research participation is, at least plausibly, a distinct and separate issue from determining whether there is a duty to return information regarding incidental findings discovered in the context of genomics research. However, the ethical and legal obligations of clinicians exist on a continuum that extends beyond obtaining initial consent to performing testing and could, at least theoretically, extend to researchers. In addition, any analysis in the New Zealand context must take into account the *Code*.

The *Code* explicitly states that all of the rights contained in the *Code* apply when a consumer "is participating in, or it is proposed that a consumer participate in, teaching or *research*."[95] A "health consumer" is further defined as "any person on or in respect of whom any health care procedure is carried out";[96] and a "health care procedure" includes any "health treatment, health examination, health teaching, or *health research* administered to or carried out on or in respect of any person by any health care provider".[97] Consequently participants in any genomic research will constitute "health consumers" for the purposes of the *Code*. But do all researchers, in particular non-healthcare researchers, constitute "health care providers" for the purposes of the Act

and the *Code*? To determine this requires a consideration of the statutory definition of a "health care provider".

Significantly, the HDC Act extends the definition of a "health care provider" beyond a registered health practitioner to include "any other person who provides, or holds himself or herself or itself out as providing, health services to the public or to any section of the public, whether or not any charge is made for those services".[98] Consequently the question as to whether the non-clinician researcher is a "health care provider" turns on the definition of "health services".

The HDC Act defines "health services" as services to promote or protect health or to prevent disease or ill health, and includes both "treatment services" and "diagnostic services".[99] The Act specifically states "that 'health treatment'" includes *treatment* that involves (or is related to) taking human tissue from that person "for all or any of the following purposes …", one of which specifically includes *"research purposes"*.[100]

Consequently, the *Code* applies to genomics research involving clinical researchers *and* it potentially extends also to non-clinical researchers who conduct research on human tissue. What can be concluded is that the *Code* makes no distinction between the duties and obligations of clinician researchers and non-clinical researchers if the person(s) conducting the research falls within the definition of a "health care provider". However, an academic who recruits students for a genomic research project is unlikely to constitute a "health care provider", given that they are not holding themselves out as providing services to "promote or protect health", or to "prevent disease or ill health".[101]

The *Code* imposes significant obligations on providers and confers rights on consumers, including the right to be 'fully informed'.[102] This includes the "right to the information that a reasonable consumer, in that consumer's circumstances, would expect to receive". The right to be fully informed specifically includes being informed of the "results of tests" and the "results of procedures".[103]

Hence for the purposes of *Code* liability, the issues in any research situation will be what information a reasonable consumer/research participant in that consumer/participant's situation would expect to receive, and whether incidental findings discovered in the course of research, particularly non-clinical research, constitute "test" results.

In the case of population biobanks, it is possible that a "reasonable" participant would not expect to receive results when the research is conducted in a non-therapeutic setting by non-clinical personnel. Although empirical research may suggest that some research participants may *prefer* to be informed of significant results, this is not the same as having a reasonable expectation of disclosure. Clause 3 of the *Code* is also relevant when determining the scope of any duty to disclose findings discovered during genomics research.

Clause 3 states that a provider will not be found in breach of the *Code* if it can be demonstrated that they took "reasonable actions" in the circumstance [which includes *all* the relevant circumstances] to give effect to the rights, and comply with the duties specified in the *Code*". "Circumstances" extends to the consumer's clinical circumstances as well as the provider's resource constraints. In some circumstances, it may not be reasonable to expect a researcher to return individual research results (a possibility

that is considered further below). In some instances, researchers may clearly adopt and communicate a standard policy of non-disclosure.

While the *Code* clearly applies to the general context of clinical care, and having explored the applicability of the *Code* to pure/non-clinical health research, the following considers whether there is a basis for imposing a normative duty to disclose clinically significant incidental findings discovered in the course of clinical genomic testing and, if so whether it extends to non-clinical/non-therapeutic research.

1.6 Genomics and the challenge of incidental findings

As noted above, general medical law principles apply to clinicians who conduct genomic tests. It is also established that in the context of research, clinicians/investigators who recruit donors for DNA biobanks must inform participants regarding the proposed use of their samples,[104] including who will have access to their samples, as well as the approach taken to anonymisation and information regarding storage.[105]

However, a significant issue is whether, and if so to what extent, there is a duty to return clinically significant incidental findings where results may potentially impact upon that participant's immediate or future health.

This issue moves from a duty to inform prior to undergoing a procedure into the altogether different terrain of whether a clinician/researcher owes a *duty of care* to the research participant that mandates disclosure of *clinically significant* IF. The following considers first whether there are grounds for finding that a duty of care exists and, if the answer is yes, what the scope of that duty might be.

Clinical testing

The duty of care owed by clinicians to patients is well established. In common law countries, a clinician may be (tortiously) liable for any harm caused as a result of negligent patient care or management. However, in New Zealand compensation for personal injury/treatment injury is provided under the statutory Accident Compensation scheme and a clinician will not be personally liable (although claims for exemplary damages are not precluded under the scheme).[106] Despite this local idiosyncrasy, determining the existence and scope of any clinical duty of care remains relevant in the interests of establishing the requisite standard of care or "best practice" for clinical genomic testing and clinical obligations under the *Code*.

Is there a legal duty of care to report incidental findings in clinical testing?

In the case of clinical genomic testing, a genomic test is performed to diagnose a condition that the patient presents with, and any IF identified are unrelated to the presenting complaint. As noted above, the *Code* requires providers to inform patients of the "results of tests".[107] While this duty could be argued to be limited to information relevant to the presenting complaint, it is highly likely that a clinician who performs genomic tests will have a duty under the *Code* to disclose any clinically significant IF discovered in the course of clinical genomic testing to a patient.[108]

Although a clinician's duty to recognise and disclose an IF discovered in the course of genetic testing has not been tested judicially, a recent survey of US legal databases identified eight cases where plaintiffs alleged medical negligence on the basis that an IF had either not been identified, or not appropriately acted upon, following medical imaging.[109] The outcomes of these cases were largely dependent upon expert evidence regarding the applicable standard of care and establishing a causal link (proof of causation) between the omission and the harm suffered.

In one case a radiologist reporting a CT scan that had been ordered to investigate a suspected liver tumor failed to note a 3cm pancreatic cyst, reporting that the pancreas was normal.[110] The patient was subsequently diagnosed with pancreatic cancer and died. The executor of the plaintiff's estate claimed damages for wrongful death on the basis that, had the cyst been reported, it could have been removed before it became cancerous and the death averted.

At trial the radiologist accepted that failure to identify the cyst was negligent, but claimed that there was no causal link between the negligence and the patient's subsequent death. The single expert witness to give evidence (a general surgeon) testified that the pancreatic cancer originated from the original cyst, which he deduced must have initially been benign as the patient would not have survived the ensuing three years with "a cancer of that magnitude". The expert's opinion, which he posited with a "reasonable degree of medical certainty", was that the patient would still be alive *if* the original cyst had been reported and removed *before* it became cancerous. Consequently, the court held that the radiologist's negligence was a proximate cause of the plaintiff's subsequent death. The case was appealed to the Supreme Court of Virginia, which upheld the trial court's finding.

In four other cases where plaintiffs brought proceedings alleging negligence related to IF, the defendant's application to have the proceedings dismissed (i.e. summary judgment) was refused, leaving open the possibility that the plaintiffs claim might succeed at trial.[111] In such cases where the courts have declined to find that negligence cannot be sustained on the facts and refuse an application to dismiss the proceedings, the parties may elect to negotiate a settlement rather than go to trial. None of the four cases proceeded to trial. In two other cases summary judgment was awarded to the defendant on the grounds that the plaintiff did not provide pertinent expert evidence to the court to establish a breach of the applicable standard of care in the circumstances.[112]

In another US case a radiologist was found not to have breached the necessary duty of care when he failed to note a rare congenital arteriovenous malformation in a patient's CT scan, which subsequently caused an intracranial haemorrhage.[113] Expert witnesses testified that due to the rarity of the defect and the patient's presentation at the time, it was unlikely that a general radiologist would have recognised the significance of the defect. Consequently, the defendant's failure did not fall below the standard expected of a reasonably competent general radiologist. The experts also attested that the malformation had likely worsened after the initial scan.

In a recent Australian case (although of limited authority as it was only a district court case) the plaintiff was awarded $609,939.50 in damages after a radiologist failed to identify and report an IF (a lesion) on a woman's CT scan.[114] The patient had a prior history of Non-Hodgkins lymphoma and presented acutely with severe abdominal pain.

After a CT scan was performed the patient was diagnosed with acute pancreatitis. However, the CT scan also revealed a lesion on one kidney, which was not identified or reported at the time. Four years later the same lesion was diagnosed as a malignant tumor (Wilm's tumor). The plaintiff experienced significant complications following an invasive diagnostic procedure. She claimed personal injury and consequential psychiatric injury due to the delayed diagnosis.

The trial court accepted expert evidence that the lesion was a visible and uncommon finding in a person of the plaintiff's age, and could easily have been investigated further. The majority of the expert medical testimony considered the lesion should have been identified and reported, and not doing so constituted "a significant miss".[115] The court accepted that it was inconsistent with widely accepted peer professional opinion regarding competent professional practice, despite one contrary expert witness testimony.

Once it was established that failing to spot the lesion constituted a breach of the requisite duty of care, the legal question was whether the negligence was causative of the damage suffered. This required determining whether the plaintiff's treatment would have differed had she been diagnosed earlier, and the extent to which the delay "caused or contributed" to the physical injuries and psychiatric injury that she subsequently suffered. The court reiterated the relevant principles of causation in medical negligence originally articulated by the High Court of Australia in *Chappel v Hart*:[116]

> In principle, therefore, if the act or omission of the defendant has done no more than expose the plaintiff to a class of risk to which the plaintiff would have been exposed irrespective of the defendant's act or omission, the law of torts should not require the defendant to pay damages. Similarly, if the defendant has done no more than expose the plaintiff to a risk for which the defendant has not undertaken responsibility and to which the plaintiff was always exposed, the law of contract should not require the defendant to pay damages for injury arising from that risk even if it follows upon a breach of contract. No principle of the law of contract or tort or of risk allocation requires the defendant to be liable for those risks of an activity or course of conduct that cannot be avoided or reduced by the exercise of reasonable care unless statute, contract or a duty otherwise imposed by law has made the defendant responsible for those risks.

Ultimately the plaintiff was partially successful in her claim for damages. Although the court held that the treatment she received would not have differed had her condition been diagnosed earlier, it also found that the delay in diagnosis caused her to suffer a period of ill health that would have been avoided had she undergone investigations and treatment earlier. The court also held that the delay "in all probability affected the prospect of recovery,"[117] and held that the delay in treatment and the diagnostic complications were a major contributing cause of the plaintiff's subsequent mental illness.

In all of these cases, the starting point for establishing the applicable standard of care was determined by reference to the skills and expertise expected of a person in that particular clinical specialty. If it was found that a duty of care exists, additional issues included to whom the IF should be communicated, and how it should have been subsequently acted upon, (e.g. a duty to refer the patient for appropriate follow-up investigations). Finally, the claimant had to establish causation, i.e. that on the balance of probabilities, the omission was causative of the harm experienced.

Although case law involving incidental findings is relatively slim, some courts are willing to find that a clinician's duty of care extends to ensuring that a patient is informed when a clinically significant IF is discovered in the course of providing medical care for an unrelated condition. Arguably there is no good reason why this duty would not extend to the case of a clinically significant IF discovered in the course of clinical genomic testing, when a patient is informed that incidental information has been discovered, and consents to its disclosure. In addition, it should be noted that liability under the *Code* for any failure to disclose is not dependent on a finding of harm.

While there is an established duty of care between a patient and clinician, the extent of the duty is unclear in the context of genomics. The extensive range of information that may be derived from testing means that there is uncertainty as to what clinically significant findings should, as a rule, be communicated to patients and how consent processes should be modified to account for potential IF. In this context, developing practice will have a role to play in determining the required standard of care. Institutional and professional guidelines are likely to play a role in informing any legal determination of the scope of professional obligations in this context.

Given the relevance of professional practice and guidelines to determining the standard of care, the following section considers guidelines that were released by a major US body in 2013.

The ACMG guidelines: an aberration or new policy paradigm?

Guidelines released by the American College of Medical Genetics and Genomics (ACMG) triggered extensive debate regarding the obligations of clinicians and the rights of patients when clinical genomic testing is performed. Given that the ACMG is highly influential internationally, the following considers some of the problematic aspects of these recommendations.

As some commentators note, there is little difference between a focused diagnostic investigation and a nonspecific-screening test in the context of WGS. When WGS is used to provide a clinical diagnosis, it is axiomatic that it will potentially reveal a range of additional susceptibilities or conditions.[118] This possibility is compounded as the number of genes tested increase with respect to the disease for which testing is performed.[119] Consequently the traditional boundary between a focused diagnostic genetic test to identify the root cause of ill-health, and performing asymptomatic screening, two activities that have historically been guided by distinct normative frameworks, are blurred.[120] However at least one professional group, the ACMG, has encouraged, indeed requires, the performance of opportunistic screening whenever clinical testing is indicated.

The ACMG is described on its website as a selective and influential society of genetic and genomic specialists aiming to promote the integration of genetics and genomics in all health fields.[121] This objective is achieved by issuing evidence-based guidelines generated by expert opinion and consensus in the form of Working Groups.[122]

The ACMG issued a policy statement in 2012 in which it recognised the value of genomic sequencing in the clinical evaluation of individuals with suspected germ-line genetic disorders.[123] It acknowledged that such testing would generate both diagnostic results and secondary findings. The statement stressed the need for guidelines on the interpretation of secondary findings (as well as results generated in the course of screening asymptomatic individuals) limiting reportable findings to those of clear clinical relevance. This was necessary in order to "avoid burdening the health-care system and consumers with what could be very large numbers of false-positive results".[124] To this end a Working Group was established to make recommendations on the management of IF in clinical exome or genome sequencing.[125] The following year the College released its guidelines for the return of IF, which it defined as:[126]

> the results of a deliberate search for pathogenic or likely pathogenic alterations in genes that are not apparently relevant to a diagnostic indication for which the sequencing test was ordered.

Arguably the ACMG definition of an "incidental" finding is problematic. In contrast to a genuine "IF" as the term is ordinarily understood, the ACMG testing guideline advocates testing for a predetermined list of genetic anomalies. These findings are more accurately termed "secondary findings" rather than incidental because they are deliberately sought in addition to the primary/pertinent findings. Although the ACMG acknowledged that "there was insufficient evidence about benefits, risks, and costs of disclosing incidental finding to make evidence-based recommendations"[127], it recommended that laboratories performing clinical diagnostics actively search for 56 listed mutations.

A list of 56 Genes: mandatory screening for 30 conditions

The ACMG list was generated by a consensus-driven process that examined the clinical validity and utility of 56 genes associated with 30 conditions (see appendix 1). It includes early onset conditions such as retinoblastoma and *WT1*-related Wilms tumour; other conditions that can present at any age, such as Marfan syndrome and familial medullary thyroid cancer; and, more controversially, adult onset conditions such as hereditary breast and ovarian cancer or colorectal adenomatous polyposis. These were prioritised as disorders "for which preventative measures and/or treatments were available and disorders in which individuals with pathogenic mutations might be asymptomatic for long periods".[128]

Although the Working Group considered the issue of patient autonomy and the individual's right to choose which genetic tests would be undertaken, it concluded that in the context of WGS, the amount of genetic counselling and information required to obtain informed consent would be overwhelming and impracticable.[129] The ACMG recommended that testing all 56 genes should be *mandatory* for all patients undergoing clinical testing.[130] Significantly, it does not differentiate its policy of reporting results based on the age of the person being sequenced.

The ACMGs deviation from the principle of self-determination appears to be based on pragmatic reasons, rather than ethical principles. Ultimately, the working group considered that if an individual considered the risk of discovering incidental findings outweighed the benefits of testing, he/she could refuse to undergo clinical sequencing. However, they could not undergo testing and refuse disclosure of some results.[131] Curiously it was suggested that this take-it-or-leave-it approach preserved patient autonomy.

The ACMG recommendations extended to children, and in contrast to widely accepted policies, it advocated predictive testing for some adult-onset conditions.[132] The Working Group considered that as genomic testing is still in transition, and access to inexpensive and easily interpretable WGS sequencing is relatively limited, "an incidental finding relevant to adult disease that is discovered and reported to the clinician through clinical sequencing of a child may be the only way in which that variant will come to light for the parent".[133] The American Society for Human Society of Human Genetics (ASHG) position statement issued in 2015[134] recommends that predictive or pre-dispositional testing for adult-onset conditions should be deferred until adulthood or adolescence unless there is a clinical intervention appropriate in childhood.

However, the ACMG recommendations were not extended to preimplantation genetic diagnosis (PGD); nor to prenatal diagnosis and newborn screening; nor did it recommend sequencing "healthy" adults and children. The ACMG stopped short of recommending population screening given the "complex questions of potential benefits and downstream risks".[135]

The ACMG guidelines were controversial, triggering a swift backlash. The two most contentious aspects were the inclusion of minors in predictive testing for adult-onset conditions,[136] and the initial proposal that results would be returned regardless of the patient's preferences. This was described by one prominent policy group as a paternalistic throwback to the "physician as gatekeeper" model.[137]

The ACMG policy was subsequently modified to allow for an opt-out scheme.[138] However, it recommends that patients undergoing genomic testing cannot exercise a choice to receive results for some of the conditions and not others; i.e. it is an all or nothing scenario. Thorogood and Knoppers observe somewhat skeptically that the "ACMG's justification to require testing and reporting of a curated list of variants is rooted … in the logic of the duty to inform and *fear of subsequent liability*".[139]

Any relevant incidental findings are reported to the ordering clinician. The clinician is then responsible for contextualising such information based on the patient's personal and family history, physical examination and any other relevant findings.[140]

The ACMG regime presents a radical departure from the long-standing principles of patient autonomy and informed consent. It justified this on the basis that "clinicians and laboratory personnel have a *fiduciary duty* to prevent harm by warning patients and their families about certain incidental findings and that this principle supersedes concerns about autonomy".[141] However it is arguable that the ACMG misapprehended the nature of fiduciary duty.

Critiquing the ACMGs 'fiduciary duty' justification

Fiduciary duty is a legal concept. It is premised on the existence of a special relationship that, by its nature, gives rise to obligations of loyalty, trust, a duty to act within the scope of authority, and an overriding duty not to exploit a position of power to the beneficiaries' disadvantage.[142] While it is plausible that fiduciary duties extend to the research context, it is less plausible that the ACMG approach may be justified on the basis of fiduciary duty. As one critic cogently argues "the principles of fiduciary law establish that a clinician has a duty to respect a patient's self-determination in a way that precludes the unconsented [or coerced] analysis, report, and disclosure of secondary target genomic analysis".[143]

It is certainly arguable that mandatory disclosure of information is contrary to autonomy. Although contested in some quarters, it is generally accepted that individuals have a "right not to know" certain information about themselves, unless not knowing would compromise the rights of others.[144]

> The interest an individual has in not knowing, or the alleged right not to know, one's genetic future has, at least in the past, been generally perceived as a contestable moral claim, rather than as a legal right.[145] The right not to know genetic information is widely accepted in genetics literature, subject to the qualification that the right not to know 'presumes people understand what it is that they have chosen not to know about'.[146] It is apparent in international human rights instruments and in guidelines on genetics.[147]

However, some claim that a right not to know is incongruous with conceptions of autonomy that presuppose agency and rational choice. Indeed, some commentators argue that "where genetic information is pertinent to one's future autonomy" premising a right not to know' on autonomy is untenable.[148] These kinds of arguments are premised

on the view that without knowledge of pertinent information, subsequent decisions are not fully informed and autonomous. However, it is plausible that a broader liberty-based understanding of autonomy, which permits a person choice with respect to the information that they receive, may be construed as the "right to informational self-determination".[149]

Because some genetic information may have implications for the health of other family members, some commentators argue that there is an obligation to know genetic information. Genetic information may have benefits for the wider family, and disclosure could be justified based on communitarian interests. In addition, endorsing the right not to know may compromise clinicians. Harris and Keywood state:[150]

> The claim of an entitlement to be shielded from information relevant to one's health status and to future decisions the individual will face places health professionals in a dilemma. The patient is in effect declining to face and take responsibility for decisions about the management of their condition and indeed about their lives which are not properly theirs to take. While the desire to abjure responsibility is understandable, and even attractive in some circumstances, it is less clear that others can be placed under an obligation not only to respect the claim to irresponsibility but to shoulder some of the responsibilities refused by others.

Arguably, the authors elide a preference not to know with genetic irresponsibility, effectively asserting a *duty* to know certain information. However, a person who decides to forego knowing their genetic status is simply maintaining the status quo. Morally requiring the acquisition of knowledge, when it is contrary to that individual's perception of what is in their best interests, seems irreconcilable with autonomy and suggests moral paternalism.[151]

Mandatory disclosure in some instances may even cause harm in the form of worry or emotional stress. Some commentators note that screening and disclosure of secondary findings indicating a predisposition to disease could "lead to a diagnostic odyssey, long-term medical surveillance, involvement of family members in testing, iatrogenic harm and psychosocial consequences".[152] Further, refusing the option of not receiving some genomic results may cause some individuals to refuse diagnostic testing and forego the benefits it may provide.

The process used to generate the ACMGs list of mandatory genetic mutations has also been criticised. Holtzman argues that the ACMG recommendations are "based on the beliefs that the presence of these incidental findings indicates that the patient or his/her relatives will suffer future harm and that interventions are available to reduce or prevent harm,"[153] a claim that is not scientifically valid. The potential for false positives militates against any mandatory reporting regime. As Holtzman argues, the reliability of sequencing and quality control in clinical laboratories should be improved before the ACMG focusses on mandatory testing.[154] This is highly pertinent given recent findings regarding the accuracy of some gene-disease associations. A recent review of submissions to the ClinVar variant database in the United States illustrated the lack of coordination amongst clinical laboratories which lead to multiple interpretations of the same variant.[155]

In the New Zealand context, any such mandatory reporting regimes would be in direct contravention to the Bill of Rights Act 1990, which enshrines the right not to be subjected to medical or scientific experimentation without informed consent,[156] as well as the right to refuse medical treatment.[157] A further concern raised by the ACMG guidelines is the failure to consider the fiscal implications of such a policy, such as who pays for the additional testing and genetic counselling; the patient, insurance companies, or researchers. Mandatory testing is likely to strain laboratory resources particularly in a publicly funded health system, although this may be less of a concern for some commercial genomic laboratories in the United States. The implications that mandatory testing has on health or life insurance for individuals who test positive is also a valid concern.

The United States federal government introduced the Genetic Information Nondiscrimination Act (GINA) in 2008. GINA prohibits health insurers from using genetic test results to discriminate in rates or coverage. However, GINA only applies when genetically at-risk individuals are asymptomatic. Once a disease manifests—GINA does not apply.[158] Further GINA does not extend to life insurance or disability insurance. In New Zealand there is no similar legislation, and insurers generally require clients to disclose genetic test results.[159]

The legal and ethical status of guidelines and professional practice

Although the ACMG guidelines are not legally binding, it is commonly acknowledged that guidelines formulated by professional bodies may be used as evidence of the standard of care for practitioners.[160] In the UK, for example, guidelines issued by the National Institute for Health and Clinical Excellence (NICE) are perceived as necessary to achieve the government's aim of uniformity in healthcare quality.[161] In New Zealand, right 4(2) of the *Code of Rights* provides that consumers have the right to have "services provided that comply with legal, professional, ethical, and other relevant standards". However, the source and quality of the standards may affect the degree of reliance placed on them when determining the appropriate standard of care.

Interestingly a US survey has shown that the majority of genetics professionals surveyed agreed that the ACMG recommended minimum list of genes should be reported, regardless of the indication for which the screening was initiated.[162] However just over half indicated they would honour patients'/families' wishes not to receive results. This requires policies to manage the undisclosed information, as well as establishing guidelines for clinical laboratories governing testing and reporting of IF and "variants of uncertain significance" VOUS.[163]

Contrasting the Presidential Commission Bioethics Committee's Report

Nine months after the ACMG recommendations were published, the US Presidential Commission for the Study of Bioethical Issues (Presidential Commission) issued its report: *Anticipate and Communicate: Ethical Management of Incidental and Secondary Findings in the Clinical, Research, and Direct-to-Consumer Contexts*.[164] The Commission divided IF into two categories, those that are "anticipatable" (findings known to be associated with a test or procedure, e.g. misattributed paternity) and those that are "unanticipatable" (findings that could not have been anticipated given the state of current scientific knowledge).[165] It suggested that in both clinical and research contexts, there is a duty to inform subjects/patients

about the likelihood of such findings arising as part of the informed consent process.[166] However with regard to reporting IF, the consensus was that clinicians should respect patient's autonomy in returning results, including the right not to know.[167] Additionally, it considered the ethical obligation of non-maleficence supports the use of "therapeutic parsimony" meaning that clinicians should only actively look for IF if the risk of harm of pursuing an IF is less than the risk that the finding is present in the first place.[168]

Genomic research: incidental findings and researchers obligations

The expanding field of genomics has triggered a flood of debate by policy makers, academics and researchers regarding the informational obligations of researchers to research participants. There has been a steady stream of empirical research reporting subjects' preferences regarding the return of clinically significant results.

When considering this issue, it is important to distinguish the current legal obligations on clinicians and researchers, and ethical or moral arguments that challenge the current normative framework. Accordingly, the following section aims to identify the current legal standard of care owed by genomics researchers to research participants, before considering the arguments that challenge this default position. The strength of these arguments are assessed in terms of their normative credentials and their effect, if adopted, on public policy. In doing this the nature of the physician-patient relationship is first considered to determine if, and how, such duties might translate in the genomic research context.

There are several distinct contexts in which genomic testing occurs, which arguably have different implications for those undertaking testing and the legal obligations of clinicians and researchers. These possible scenarios include:

1. Genomic testing that occurs *solely* for research purposes such as DNA contributed to a public biobank (i.e. "pure" research).
2. Genomic testing that occurs in the course of providing/receiving patient care i.e. clinical investigation to find a definitive diagnosis for a complaint.
3. Genomic testing performed in the context of medical therapeutic research e.g. clinical trials involving a therapeutic doctor-patient relationship or when the researcher is simultaneously the patient's treating clinician.

Of these three categories, only the first constitutes "pure" research. In the following, Hallowell et al outline the conventional distinction made between pure research and clinical research:[169]

> Traditionally research and clinical investigations have been understood as different types of activity, stemming from very different motivations. In theory, the former is carried out independently of individual patient's interests, is hypothesis-driven and primarily aimed at answering a research question. The latter is motivated by individual patient's needs, and its prime purpose is to benefit individuals not the wider patient population.

For example, in the genomics context the research objective may seek to determine links between a gene variant and certain disorders, and is aimed at groups of people, rather than targeting a specific individual. In such instances the principles of justice, beneficence and respect for persons requires that general research results are made public, including the participant population.[170] However when testing occurs in a therapeutic context (i.e. category 2 and possibly category 3) "ethical, deontological, and legal rules arguably impose different, more extensive duties" on researchers to individuals in relation to information provision prior to, and following, genetic testing.[171] This is because the patient-doctor relationship imposes an obligation to act in the interests of the individual patient.

Although different considerations traditionally arise when conducting "pure" research versus providing clinical care, the ordinarily bright line often becomes blurred in genomic medicine. Health providers are increasingly becoming aware of the implications of genetics on health and disease development. Often, health providers assume a dual role of clinician and researcher. This poses some challenges:[172]

> Distinguishing research from clinical activities is seen as critical from an ethical standpoint[173] as the actors involved in these different activities are seen as having different rights and duties; but in reality the boundary between these activities is becoming increasingly indistinct particularly in genetics and genomics.[174] The result is that patients and research participants may find it difficult to distinguish between research and clinical activities, particularly when their clinician is also a researcher interested in investigating their condition[175] or the research participant is also a patient.[176] Moreover, clinical activities are increasingly regarded as having a research element.[177] This confusion may lead to research participants and researchers viewing research interventions in genomics, as well as in other areas of medicine as being motivated primarily by clinical intent.[178]

Nevertheless, Hallowell and colleagues conclude that:[179]

> … notwithstanding this ambiguity, in every clinical encounter there is always a primary problem brought by the patient to the clinician that needs to be solved, and although the context in which research and clinical care takes place is now increasingly indistinct, it is important, and it should be easy, to be clear and transparent about the primary purpose of any encounter.

It is axiomatic that the doctor-patient relationship imposes a professional duty on the clinician to provide a reasonable standard of care, determined by reference to the standard provided by a reasonably competent practitioner practising the same skill. In the case of clinical care which generally involves therapeutic goals[180] clinicians have also been held to owe a fiduciary duty to their patient.[181]

While the duty of care and the doctrine of fiduciary duty are central features of clinical practice and would likely extend to the conduct of clinical research,[182] the nature of the relationship between a "pure" researcher and research participant and the existence and extent of professional duties is less clear. With the development of national and international genomic biobanks, the issue of managing clinically relevant test results discovered incidentally in the course of research is a pressing issue. Susan Wolf noted recently:[183]

> The debate over return of individual research results and incidental findings to study participants is a key frontier in research ethics and practice. This is fundamentally a problem of translational science—a question of when information about an individual that is generated in research should be communicated for clinical attention, particularly as technologies such as whole-genome sequencing and whole-exome sequencing are increasingly used in clinical care. There is growing consensus that investigators should offer participants at least those individual findings of high clinical importance and actionability. Increasing attention to what information biobanks and secondary researchers owe people who provide data and specimens offers an opportunity to treat these source individuals as research partners. Cutting-edge issues include return of results in pediatric populations and return to kin and family, both before and after the death of the proband, as well as how to manage incidental findings in clinical sequencing.

Given the debate regarding the extent of researchers' obligations to research participants when genomic testing identifies clinically significant health information, the following considers arguments against, and in favour, of recognizing a duty of disclosure for clinically significant results in the case of research.

Arguments against the return of individual research results

There are several arguments that militate against returning significant results obtained in the context of *pure* research, such as biobank research. A primary argument is that it may act as a form of "inducement" to participate in research. An expectation of receiving significant results could change the nature of altruistically donating DNA or tissue for research purposes to providing an opportunity for a genomic health "warrant of fitness". This may reinforce a belief that the participant will directly benefit from participating in research (the so-called "therapeutic misconception") when the traditional goal of research is not to confer individual health benefits, but rather to produce generalisable data.[184]

Other concerns regarding obligations of disclosure are more pragmatic, such as the burden that returning clinically significant results may impose on researchers in terms of interpreting results and the use of scarce resources in following up participants. Although WGS research generates significant amounts of data that are not amenable to manual oversight, some research groups have established automated systems that can facilitate the return of results to researchers.[185] However actual disclosure to participants can be resource-intensive, may diminish research budgets and negatively impact on work-force requirements.

Another concern is that some results that have uncertain significance may generate health anxiety for recipients of the information, or trigger a cascade of further investigations.[186] Significantly any results that are generated in a research laboratory would need to be validated in a clinical laboratory, which poses additional research costs.

While these considerations are not insignificant, the following considers the arguments for a presumption in favour of disclosure.

A legal duty or an ethical obligation to return genomic research results?

In a short but seminal article regarding researchers' obligations to participants, legal academic Michelle Meyer reinforces the US *Belmont Report's* concept of a research subject as essentially a "volunteer".[187] The Belmont Report, commissioned by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research following the infamous Tuskegee Study, is based on three fundamental principles: respect for persons, beneficence, and justice.[188]

Meyer argues that while physicians have fiduciary duties to their patients, the fiduciary relationship does not extend to research/biobank participants stating:

> Physicians have such a duty to their patients, but by definition research seeks not to serve the interests of participants but to create generalizable knowledge designed to benefit society and future patients. Thus, if biobank research is properly entered into, the volunteer will understand that she has donated her time and tissue to, and undertaken certain privacy risks in service of, an essentially altruistic end (better understanding and treatment of complex diseases) from which she may well never directly benefit. While subjects serve as means to this end, they are not mere means, because in making an informed decision to volunteer, they adopt this end as their own.[189]

In the context of biobanks, Meyer posits that the researcher-subject relationship is better conceptualised as a type of "arms-length donative contract—an agreement under which the donor-subject agrees to make a gift to the donee-researcher, who arguably holds the gift in trust for society".[190] However she also concedes that the donee/researcher has duties to disclose "material information" to prospective donors regarding the study, and to allow the participant to withdraw at any time.[191]

Significantly, Meyer argues that this donative contract does not provide any moral or legal obligation to return research results to participants, dismissing claims that participants are essentially owed their results as compensation for their participation. However, again using the analogy of contract law, Meyer argues that there may be instances where researchers may have a *moral* obligation to return some results to participants.

She states:[192]

> A contract's terms, however, must not sink to the level of unconscionability. Researchers are not fiduciaries for subjects, but they do not have lesser obligations to subjects than they do to third parties, and we all have moral (if not legal) duties to rescue or warn others, especially when we are uniquely positioned to do so, with minimal risk to ourselves. Agreements that purport to contract around this duty—such as those providing that researchers will not return results indicating that a subject might have a serious but treatable or preventable disease—are presumptively unconscionable.

Meyer goes so far as to state that a duty to warn may possibly exist even when a subject has expressed a preference not to be warned:[193]

> It is worth noting that even here, where researchers might be thought to have the strongest obligation to honor preferences about returning results, it is not clear that the subject's preferences alone determine whether the researcher must disclose … The familial nature of genetic information arguably extends a researcher's duty to warn to subject's relatives, whose preference may have independent weight.

While some stakeholders may sympathise with this non-individualist view, it is arguably problematic to subordinate research participant's own wishes regarding the return of results. This fails to respect the autonomy of research participants, based on an assumption that reporting of results will benefit third parties.

While Meyer concludes that there is no *legal* obligation on researchers to return results to research participants—it is clear that she is not claiming that researchers *ought* not to offer results to participants. Rather she considers that given empirical data that participants often wish to receive results, "researchers ought to move cautiously in the direction of returning most results". [194] However the implications of returning results should be made known when eliciting the preferences of participants because, she posits, fewer participants may wish to be offered the option of receiving results if they know the opportunity-cost of returning results is that less research may be conducted.

This potential for participants to re-think their preference for the return of results is supported by a recent study. It involved 4961 members of the general public, 533 genetic health professionals, 843 non-genetic health professionals and 607 genomic researchers.

The authors state:[195]

> Although the empirical data from this research show that all four stakeholder groups are in favour of returning genomic results of *perceived utility* to research participants, we also show that when pushed, no stakeholder group actually expects these to be provided in a research setting if doing so would compromise the ability of researchers to answer their research question. Hence, policy does not need to obligate researchers to return IFs from research sequencing studies. Policy development in this area should take into account not only the empirical data from stakeholders, as well as the ethical debate, but also other compelling practical considerations – most notably, the confidence (or lack thereof) with which such variant data can be accurately interpreted and the implications for successful and financially viable research.

Ultimately Meyer emphasises the distinction between arguments that support the return of results, versus equating this with normative rules of return. Normative arguments for return of results that are based on participants' preferences or that researchers "*ought* to offer results out of supererogation [going beyond which is strictly required by way of duty] or prudence are not the same as arguments that they *must* do so, and the distinction is worth preserving".[196]

While Meyer may be correct that, in the particular context of research biobanks it is unlikely that fiduciary obligations exist that *require* the return of clinically significant results, it is not the case that other types of research (therapeutic or non-therapeutic) will not create fiduciary obligations.[197] For example the fact that the student in *Halushka* was a willing volunteer did not preclude the finding that the nature of the research relationship triggered fiduciary obligations that, in the particular case, were badly breached.[198]

In summary, although there is an arguable moral obligation to return individual research results that indicate an unequivocal health or welfare risk to the subject in the context of pure research, it is based on the moral duty to rescue, rather than a duty based on legal obligations.[199]

This approach has been adopted in some current guidelines in Europe and North America,[200] where a general consensus has emerged that researchers should *consider* returning IF to participants that reveal a significant risk of a serious health condition *and* the participant's willingness to receive such results has been previously established during the informed consent process.

There are several reasons to support a presumption in favour of broad disclosure of genetic research findings to participants.[201] The first of these is the interest an individual has in knowing personal information that may have a positive health outcome or benefit—which is grounded in the principle of beneficence. Another is that information sharing may encourage greater acceptance of genetic testing, and will lead to greater participation in genomic research. Some commentators claim that the concept of reciprocity suggests that volunteers should receive access to the knowledge that their participation in research

engenders, which extends to individual research results.[202] Ultimately it is often claimed that return of results demonstrates respect for the research participant.

In contrast the arguments against return of genomic information to research subjects (as opposed to patients in a clinical setting) are generally based on non-maleficence.[203] Most research subjects have a limited understanding of genetics. As already discussed, not all gene-disease associations recorded in human mutation databases are accurate or reliable. Return of clinically significant but not clearly actionable IF could induce anxiety or stress. In addition, there is a risk that such information could lead to an increase in potentially harmful and unnecessary follow-up testing in an attempt to determine the relevance of information.[204] Yet the fact that these challenges exist is not a definitive claim against the presumption in favour of returning results. Rather it suggests mechanisms are required to prevent, minimise, or mitigate the potential risks associated with disclosure.[205]

While the preceding analysis considers the arguments for and against a presumption in favour of disclosing clinically significant IF, the following considers normative arguments for establishing a legal framework governing IF.

Ancillary care obligations and genomic research: a normative claim?

Prominent legal academic Roger Brownsword has examined the putative obligations on researchers regarding genomics research participants through the lens of emerging "ancillary care" literature.[206] Brownsword's approach is normative—that is he considers how we *ought* to deal with the question of what obligations, if any, researchers may owe participants in genomic research biobanks.

Brownsword's long and distinguished career studying the interface between law and technology is premised on a particular idea of what he calls a "moral community". His analysis is framed on the basis of what he calls a hypothetical "community of rights", rather than being guided by predominantly utilitarian or duty-based principles. He explains the rationale for this normative approach:[207]

> Given that a community of rights is a particular kind of moral community, it must systematically embed a moral standpoint (in the formal sense), and because it is a community of *rights*, the substantive moral approach embedded is rights-led. The significance of this latter point is that, by taking a rights-led approach, such a community distinguishes itself from its two principal rivals, namely those communities in which the governing ethic is, in the one case, utility maximizing and, in the other, duty driven.

Brownsword's approach is synonymous with a Rawlsian or Dworkinian approach of "taking rights seriously".[208] This approach privileges notions of individual rights over conceptions of the common good and is antithetical to utilitarianism. Another feature of Brownsword's community of rights is that it is a "reflective and interpretive society".[209] This means that although its commitments and standards are "binding and universalisable", it also "constantly keeps under review the question of whether the current interpretation" of its standards "is the best interpretation".[210] The

challenge for such a community is determining what rights ought to be recognised, their appropriate scope, and how conflicts between rights-holders are managed. A particularly important question is whether positive rights should be recognised in a community, and the extent of the corresponding responsibilities that should be imposed on other(s) (ie *not* freely assumed).

In determining the moral contours of a community of rights, Brownsword uses the hypothetical example of experienced swimmer (A) who witnesses another swimmer getting into difficulties (B). He asks whether a community of rights would, because of its baseline moral standards, fix A with a positive obligation to rescue in the circumstances? Although a community of rights would recognise such a background obligation, the vital issue is under what conditions the duty arises. Brownsword posits three considerations that assist in determining whether there is a prima facie responsibility to assist:

1. first B must be in a position and have the capacity to provide assistance;
2. it is reasonable to require assistance in the circumstances-because taking into account A's own interest is not a case of supererogation[211] or imposing an unfair burden on A; and
3. requiring assistance would not involve the rescuee taking unfair advantage of the rescuer.

Using this as a theoretical platform, Brownsword uses the example of the UK Biobank to consider how a community of rights might respond to the proposition that biobank contributors have a reasonable expectation that researchers will respond to their need for ancillary care.

The UK Biobank is solely a research resource, but it is plausible that researchers may become aware of a serious health problem about which the participant is completely unaware. Applying Brownsword's test, the preliminary question is whether it is in a position to assist a participant, and whether it has the capacity to do so. Given that the researchers have information that is material to the health and wellbeing of the participant—the simple answer to the preliminary question is yes. The more difficult issue is whether it is *required* to disclose the information.

In determining this issue Brownsword's test requires an assessment of whether the demand made of the Biobank is reasonable "relative to its own essential interests".[212] It is here that there is room for debate. The Biobank's essential interest is the conduct of research, and the *reasonableness* of a requirement to disclose clinical information must be judged relative to this fundamental endeavor.

While the burden involved in contacting individual participants and facilitating disclosure is not insignificant, it is not apparent that it would be an unreasonable expectation, even if inconvenient. This is particularly so if the information concerned a serious medical condition directly implicating the participant's interests, and the participant cannot plausibly be construed as taking unfair advantage of the Biobank research institution.

Brownsword concludes:[213]

> Seemingly, then, the Biobank has a prima facie background obligation to feed back to participants important personal medical information where it happens to have it. This is not to suggest that the Biobank should actively seek out such information for all participants or offer treatment to them; nor does this discount the possibility that the Biobank might face competing or conflicting rights claims advanced by the potential beneficiaries of its research activities. Nevertheless, relative to the four-stage test, a participant's claimed right to be informed where the Biobank knowingly holds (and withholds) relevant medical information surely gets to first base.

While it is likely that this analysis would be replicated in a legal system that is underpinned by the same ethic of Brownsword's hypothetical 'community of rights', the question is how it might translate into our extant legal system. That is how would the courts respond to a claim of a reasonable expectation of ancillary care, in the form of informational disclosure, in contract or in tort?

Although the landmark case of *Donoghue v Stevenson*[214] established the rule that "one should take reasonable care to avoid acts or omissions that one can reasonably foresee as having an injurious effect on other agents" (i.e. the "neighbor" principle), subsequent decisions have been cautious about extending the circumstances in which a legal duty of care will be recognised.[215] The "default ethic" that implicitly informs such legal regimes is arguably one of self-reliance and individualism; i.e. the law has been more willing to recognise and enforce negative rights (right not to be harmed by another) than to impose positive rights and duties to rescue. Brownsword cites Lord Hoffman's justification for this policy approach:[216]

> It is one thing for the law to say that a person who undertakes some activity shall take reasonable care not to cause damage to others. It is another thing for the law to require that a person who is doing nothing in particular shall take steps to prevent another from suffering harm … One can put the matter in political, moral or economic terms. In political terms it is less of an invasion of an individual's freedom for the law to require him to consider the safety of others in his actions than to impose upon him a duty to rescue or protect.

Consequently in the absence of an express or even implicit assumption of responsibility or the existence of a special relationship between researcher and research participant, it is not likely that the law would be overly sympathetic to a claim based on a reasonable expectation of a positive act of assistance in the form of disclosure.[217] While theoretically a reasonable expectation of informational disclosure could be argued on the basis that the relationship between the Biobank and the participants is analogous to a patient-doctor relationship and thus a duty to provide any "material" information to a participant arises, this analogy does not seem tenable in the case of a research-only Biobank.

Brownsword concludes that traditional common law regimes are not likely to find a claim of a positive duty of informational disclosure on the basis of ancillary care. But importantly, he also observes that national courts may not be the best institutions to develop policy in this area. He concludes that:[218]

> … once ancillary-care responsibilities are taken seriously, it should be possible for research ethics committees to translate the relevant background requirements into the foreground commitments of research protocols and, moreover, to do so in such a way that improves the prospect of the reasonable expectations of all stakeholders being satisfied.

Somewhat ironically, if such a policy is established at the national level it may eventually assume a quasi-legal effect. That is, in the absence of a specific undertaking to provide such assistance a participant could claim a *reasonable* expectation of receiving ancillary care from researchers based on it being common practice; or alternatively it could be claimed on the basis of an external standard such as international or professional guidelines.[219] As researchers from the Baylor-Hopkins Center for Mendelian Genomics recently noted, consensus is "building" that primary and incidental findings from exomic and genomic research should be offered to participants under some circumstances.[220]

Summary

It is likely that as sequencing becomes more reliable and more links between genes and diseases are confirmed, the interpretation of variants will become more precise.[221] Nevertheless, the nature of genetic variability means that there will always be some uncertainty regarding gene-disease associations as well as the impact of IF and VOUS. It is more likely that a degree of consensus may be found regarding the management of IF in the clinical context than in the research context, particularly in regard to known gene-disease associations.[222]

In the course of clinical research, the ordinary duty of care owed to a patient by a clinician remains. Consequently, the disclosure of incidental genomic findings within the clinical setting is not contentious and is legally required subject to clinical judgement regarding the clinical significance of the finding, the information a reasonable patient in that patient's circumstances would expect to receive, as well as the patient's right not to know. However, the extent of the duty owed by a researcher to a research participant is less straight-forward.

Although this analysis rejects construing research subjects as mere "volunteers", the extent of the duties that are putatively owed to research participants is context-specific. In the context of research, any duty to disclose information is likely to be derived from ethical principles, rather than from a legal obligation to inform a participant of a material result discovered in the course of research. Determining whether there is an ethical duty to provide information disclosure in any case requires consideration of the institutional capacity to return results and its implications on the research endeavor in general, such as the effect on detracting resources from the research effort itself, and the reasonableness of the requirement taking into account the relative burden imposed.

It is also pertinent that clinical investigations may reveal findings that extend beyond those relevant to the primary clinical issue. Consequently, the implication of integrating genomic research into clinical care has significant implications for clinicians. Knoppers notes:[223]

> The possibility of incidental findings from WGS testing means not only that the clinician's duty to inform the patient will expand but also that there will be the need to offer choices to the patient as to whether they want to be so informed. The duty to follow will also be affected as the significance of such results becomes clear over time. Although there is no *duty to hunt*, the delimitation of the duty to follow one's patient over time is a topic for urgent discussion. Professional guidance is also needed, as reflected by the 2013 Report of the Presidential Commission for the Study of Bioethical Issues and the subsequent 2014 discussion of the ACMG guidance. The German National Ethics Council has also called for standards, as has the UK PHG Foundation and the Canadian College of Medical Geneticists. In short, professional guidance on the return of incidental findings should be obtained before ordering WGS, even in the clinical context (emphasis added).

As noted, determining whether or not to disclose incidental findings discovered in the course of a clinical relationship is less contentious than decisions regarding the return of research results. In the context of pure research this analysis suggests that there is an ethical duty to return clinically significant results to an individual, unless doing so would impose an unreasonable burden on the researchers or unless there is a compelling/good reason for non-disclosure. This presumption in favour of returning clinically significant results to adults is subject to obtaining the participant's consent to return.

1.7 Options for managing return of genomic incidental findings

Genomic research may differ in significant ways. Currently there is no consensus as to how information generated in the course of clinical testing and research should be managed.[224]

Given the challenges associated with WGS/WES (specifically consent to testing, return of results, counselling and confidentiality) there has been a proliferation of guidance formulated by professional organisations, think tanks and, to a lesser extent, legislatures. However, no global consensus has emerged. Internationally there are varying clinical approaches to the identification and return of genomic results, each placing different emphasis on patient autonomy and the clinician/researcher obligations. A recent survey undertaken by Knoppers et al identified four different approaches to the return of genomic results that reflect different professional attitudes, cultures and legal frameworks.[225]

1. No results are returned (research only).

This default research option of not returning any results is premised on the traditional view that providing individual results to research participants creates a therapeutic misconception,[226] which conflicts with the primary goal of research which is to discover generalisable findings.[227] Ostensibly providing information as a *quid-pro-quo* for taking part in research risks giving "mixed messages". However as the discussion above suggests, there are good reasons to question whether this traditional view should always apply in the genomic context.

2. Results are returned on an ad hoc case-by-case basis

Some policies facilitate flexible arrangements, whereby a laboratory will report results, but it is left to the individual clinician or researcher to determine the appropriate action in the circumstances. Consequently, a researcher may consult an ethics committee for advice when an unforeseen IF occurs, or a clinician may consult a colleague. However, there are disadvantages associated with this approach. It presupposes that physicians can interpret genetic results, and or that researchers can determine with constitutes a "clinically significant" finding.

3. Targeting sequences or panels of specific genes to reduce IF in clinical testing and research

Many of the challenges associated with generating large amounts of genomic information may be avoided by limiting sequencing so that it is targeted as narrowly as possible. Some commentators suggest that in the context of *clinical* WGS, the sole focus should be on providing diagnoses and avoiding opportunistic screening. This may be achieved, to some extent, by the use of filters.[228]

Similarly, in the research context some researchers may selectively filter data in an attempt to reduce the likelihood of identifying incidental findings.[229] Despite such attempts it is unlikely that the potential for discovery of IF will be eradicated, some of which will be of unknown effect. Further by their nature some investigations may require examining large segments of the genome.

4. "Binning": return of results based on ACA criteria: analytical validity, clinical significance and actionability

A fourth option is to essentially triage results and return those results that are scientifically reliable and clinically useful. In a seminal 2011 paper, Berg and colleagues set out a comprehensive means of categorising unexpected findings that are generated in genomic sequencing.[230] This approach groups genomic results into various "bins" depending on the known effect of a particular gene or variation.

Determining a result's appropriate bin involves a tripartite assessment of: analytic validity (the test accurately identifies a specific genotype), clinical validity (it consistently predicts a genetic condition), and clinical utility (actionability: i.e. preventive or treatment options are available).

A broader tool created by the US Centers for Disease Control and Prevention (CDC 2013) to evaluate genetic tests and assist in genomic policy development contains an additional evaluative limb (ACCE). This requires considering the ethical, legal and social implications of a genetic test when determining the advisability of returning results. This would require consideration of issues such as the potential for a test to generate participant distress such as stigma or discrimination, as well as the implications of a test result for others.[231]

Figure 4: Proposed System for 'Binning' of incidental WGS results[232]

	Criteria:	*Clinical Utility*	*Clinical Validity*			*Unknown Clinical Implications*
Genes	Bins:	**Bin 1 Medically actionable incidental information**	**Bin 2A Low risk incidental information**	**Bin 2B Medium risk incidental information**	**Bin 2C High risk incidental information**	**Bin 3 All other loci**
	Examples:	*BRCA1/2 MLH1, MSH2 FBN1 NF1*	PGx variants and common risk SNPs	*APOE* Carrier status for recessive Mendelian disorders	Huntington Prion diseases ALS (SOD1)	
	Estimated number of genes/loci:	10s	10s (eventually 100s – 1000s)	1000s	10s	~20,000
Alleles that would be reportable (YES) or not reportable (NO) in a clinical context						
Variants	Known deleterious	YES	YES/NO [1]	YES/NO [1]	YES/NO [1]	N/A [2]
	Presumed deleterious	YES	N/A [3]	YES/NO [1]	YES/NO [1]	NO [4]
	VUS	NO	N/A [3]	NO	NO	NO [4]
	Presumed benign	NO	N/A [3]	NO	NO	NO
	Known benign	NO	NO	NO	NO	NO

N/A: not applicable; VUS: Variant of uncertain significance
[1] Reporting through decision making with an appropriate provider if elected by the patient.
[2] By definition, variants in genes with unknown implications could not be considered deleterious.
[3] By definition, SNPs or PGx variants will either be present or absent.
[4] Variants in genes with unknown clinical implications would not be reported; however, they may serve as an important substrate for research, potentially uncovering new disease genes.

Fig. 1. Proposed system for "binning" of incidental WGS results

As Berg and colleagues explain, Bin 1 houses incidental/unexpected genes or variants that are known to be serious and are clinically actionable, which are *categorically* reported. Bin 2 contains clinically valid, but not directly actionable findings that are subcategorised according to low, medium and high risk incidental findings. These findings are not routinely returned but may be returned depending on individual patient preference. Bin 3 encompasses findings of unknown clinical significance, which are not returned.

Some research studies, such as the UK10K project, have adopted similar processes for feeding back clinically significant findings to research participants as part of its governance framework.[233]

Most international guidelines permit participants to opt-out of receiving findings that are not directly relevant to the research being undertaken, or which are outside of the primary indication for the clinical test.[234] The capacity to "opt-out" of receiving information is premised on protecting an individual's interest in not knowing unsolicited genetic information, which is reinforced by the Universal Declaration on the Human Genome and Human rights (UNESCO) and in the Convention on Human Rights and Biomedicine of the Council of Europe that declares a right not to know genomic information.

In Australia recent guidelines developed by the National Health and Medical Research Council conclude that, in the clinical context, the return of IF is dependent upon whether a patient has consented to their return.[235] In the case of research, return of incidental findings will be dependent on the particular research protocol but, when return "is feasible, and the results are adequately validated, informed individuals participating in research should have autonomy to decide whether or not to request return of incidental findings".[236] However, it also cautions that IF should only be returned following testing in an accredited laboratory (to confirm a result that originated in a research/non-clinical laboratory) and with appropriate genetic counseling.[237]

5. A new approach: personalising testing and results disclosure in clinical and research genomics?

While it is apparent that determining which category a finding falls into is a matter for experts, research participants and patients are likely to have different views regarding disclosure of what results should be returned to participants. Some studies indicate that research protocols may be crafted in such a way that the return of results is effectively "personalised". Hallowell et al describe several studies that have adopted this approach:[238]

> Shahmirzadi et al[239] informed the patients in their study that their diagnostic exome sequencing might generate a number of 'secondary' findings and asked them to choose what type of additional findings they received. Even though the clinical team in this instance made the initial judgement about which categories of additional findings could be disclosed (ie, carrier status for recessive diseases, cancer predisposition mutations, early-onset disease and late-onset disease) and which specific

findings fell into these categories in any particular case, this study demonstrated that it is possible to incorporate some form of shared decision making in the disclosure of WGS and WES findings in a clinical situation despite the ACMG recommendations on clinical sequencing, which advised against offering patients such choices.[240] It is also interesting to note that 16% of adult patients in this study opted out of receiving additional findings in one or more categories. This observation suggests that non disclosure of some findings that are unrelated to the original diagnostic question is valued by some patients.[241]

Hallowell et al also note that personalising feedback has major implications for the informed consent process:[242]

… allowing research participants to have a greater role in choosing the type of information they receive has recently been supported by Anastova et al, who have called for research participant input into the use of filtering algorithms used in WGS research.[243] Arguably, enabling individual research participants to determine which WGS or WES findings are to be returned, if any, opens the door to the personalisation of feedback, which in turn would require personalising consent processes. However, as Kaye et al point out,[244] despite the scale of some research projects, this could easily be achieved by the use of information technologies and web-based platforms, which could also be used to provide access to different types of research findings. In this scenario, participants would be responsible for determining what level of research participation they consent to, and thus, which results they would access. For example, individuals could opt to receive feedback about the generic results of the research study (we found gene X in our study population), the family's results (we found gene X in members of your kinship) or their personal results (we found gene X in you).[245]

One biobank research group at Boston's Children's Hospital (BCH) has gone to considerable lengths to determine participant preferences regarding results, while also acknowledging a duty to prevent harm to its paediatric participants. The study, called the Gene Partnership (GP), involves a longitudinal paediatric repository for the study of the genetic and environmental contributions to childhood health and disease at BCH. The research links biospecimens and genetic data to phenotypic data abstracted from a participant's electronic medical record.

The researchers have instituted mechanisms to balance respect for participant preferences regarding information with concerns regarding the ability of recipients to understand the information elicited; the risk of medical and psychosocial harm from disclosure of results; and increased demands on the research enterprise. The group utilises ethical review and oversight by an oversight body, the Informed Cohort

Oversight Board (ICOB). Over a three-year period the ICOB formulated guidelines that focus on providing accurate and understandable results according to participant preferences in a manner that minimises harm. The researchers explain:[246]

> The preference-based approach that we have taken is also grounded on the view that participants have a moral claim for results but goes a step further by allowing them to modulate that claim according to their own assessments of their interests. This approach places a high value on participant autonomy and the right to know, or not to know, information that may affect their health.[247] This approach acknowledges the personal meaning of genomic information to participants[248] and is sometimes designated as "personal utility,"[249] in contrast to actionability, which, although important to consider, may not completely encompass the range of findings that many participants desire.

The GP has identified and operationalised several strategies to minimise or mitigate the risk of harm when returning results under what they call the "Informed Cohort Model":[250]

> A key feature of the Informed Cohort is the ability of participants to set their preferences for return of individual research results and to change them over time. This model evolved into the three-dimensional "Multidimensional Results Reporting" model,[251] which incorporates participant preferences, communicability of the result (i.e., how likely it is that the information contained in the result will be understood by the participant), and the significance of the result (analytic validity, clinical validity, and possibility for medical intervention) into the decision-making process for return of individual genomic information. The Informed Cohort model hypothesizes that respecting participant autonomy by taking into account personal preferences for results provides the most benefit and least harm to participants. At the same time, oversight by the ICOB is essential to establish a protective framework so that the Informed Cohort can safely return research results to participants while ensuring maximal respect for participant preferences.[252]

The GP imposes some limits on the return of results, such as results that lack analytic or clinical validity. In addition, results for a minor child (< 18) are generally not returned if they implicate reproductive risk or intrude on the child's "sphere of privacy".[253] This encompasses late onset diseases for which there is no treatment (e.g. Huntington Disease), carrier status and nonmedical traits (e.g. athletic ability). However some late-onset disorders that may have implications for other family members (eg *BRCA* genes, female carrier of an X-linked mutation) may be disclosed in accordance with parental preferences. In rare instances where parents have declined disclosure of a

result that predicts a risk of serious preventable harm (eg juvenile leukaemia) the ICOB will consider disclosing the result to a treating physician.

What is notable about the BCH approach to personalisation is the research infrastructure they have established. Further, the ICOB implemented several novel strategies to mitigate the risk of harm, including the requirement that any researchers seeking access to GP data for proposed studies should be able to support individual results, and tests are performed in a CLIA-certified laboratory.

A duty to follow / recontact?

Establishing an "incidental pipeline" to manage data derived from research-based sequencing or untargeted clinical sequencing depends upon algorithms that provide efficient and evidence-based analysis of variants. It also requires access to genomic expertise to advise on issues regarding the generation, interpretation, and use of genomic information.[254]

Even when an incidental pipeline is established, it is possible that new or revised information may subsequently emerge. Consequently, while a genomic test may constitute a single test, it may nevertheless be subject to long-term analysis and revision. In such a context, does the clinician or researcher have a duty to re-contact sequenced individuals?

In legal terms this requires consideration of three broad questions. The first is whether there is a duty of care between the patient/subject and the clinician/researcher in the circumstances. This will require consideration as to whether there has been an assumption of responsibility between the patient/subject and the clinician/researcher and whether it is on-going. Second is whether it is foreseeable that, if information regarding a gene-disease association is not disclosed to the individual, the individual will suffer harm. Even if the first two questions are answered affirmatively, it is then necessary to consider if it is reasonable, as an issue of public policy, to impose a duty on the clinician or researcher to recontact in this situation. This would require consideration of the burdens associated with imposing such a duty and its down-stream effects, and where the public interest lays overall.

Research Governance in New Zealand

Health and Disability Ethics Committees (HDECs) are responsible for considering whether proposed health and disability research is consistent with the ethical standards established by the National Ethics Advisory Committee (NEAC).[255] These standards are the *Ethical Guidelines for Observational Studies* and the *Ethical Guidelines for Intervention studies*.[256] However it was emphasised in recent changes to the framework for ethical review that the role of HDECs is to "check ethical issues, rather than scientific or governance issues".[257]

Health and disability research studies require HDEC review if participants are recruited in their capacity as consumers of health or disability support services.[258] Studies funded by the Health Research Council of New Zealand (HRC) also require HDEC review, unless they are able to be reviewed by an institutional ethics committee approved by the HRC's Ethics Committee (HRCEC).[259] Establishing a tissue bank also requires HDEC review.[260] HDECs are required to consider governance arrangements, the circumstances in which stored tissue may be provided to researchers, and "where relevant, details of

whether and how donors and their relatives will be provided with clinically significant information obtained as a result of research on their tissue."[261]

In addition, a study that involves the use, collection or storage of human tissue requires HDEC review unless "informed consent (which may include informed consent to future unspecified research) has been obtained for such use, and tissue will not be made available to researchers in a form that could reasonably be expected to identify the individual(s) concerned".[262]

The Ministry of Health *Guidelines on the Use of Human Tissue for Future Unspecified Research Purposes*[263] permits researchers to obtain consent for the use of tissue in future unspecified research, subject to certain requirements. It specifies the information that must be provided to donors when obtaining consent. Amongst other things, researchers are required to inform the donor whether they "may be contacted in the future regarding their tissue sample" and "whether or not, and under what circumstances, information about the future unspecified research will be made available to the donor and/or (where relevant) their clinician".[264] Before granting ethical approval for a researcher to obtain consent to use of human tissue for future unspecified use, the HDEC must be "satisfied" that:[265]

> there are appropriate procedures and processes in place to recontact the donor or their clinician where researchers have agreed to provide clinically relevant information that arises from the research.

Although HDEC review may not be required for every case involving the use, collection or storage of human tissue if informed consent had been obtained to such use and the information de-identified, it seems that HDEC review would still be necessary if research participants are recruited when acting as consumers of health or disability support services.

1.8 Conclusion

Genomic research has considerable implications for individuals, it also raises specific additional concerns for indigenous peoples in New Zealand.[266] While clinical genomic testing is governed by the general medico-legal framework in New Zealand, there is no clear policy regarding the management of IF discovered in the course of genomic research. Internationally there is a lack of agreement regarding the management of such genomic information and returning clinically relevant findings following genomic testing, including biobank research.[267] The various ways in which professional and national bodies have addressed these challenges in their respective policy documents are illustrated in tables provided in the Appendices to this report.[268]

This analysis has argued that physicians have a duty to inform patients in the context of clinical genomics regarding the potential for IF, and to act in accordance with the patient's preferences regarding disclosure in the case of clinically significant IF. The *Code of Rights* supports recognising such a duty in the clinical context, and may also apply in the case of pure research.

While there is no clear legal requirement to return clinically significant IFs to genomics research participants, there are strong ethical arguments in favour of doing so. These arguments support a presumption that investigators always consider instituting a process for managing IF when they have capacity to do so, and when it does not impose an unreasonable burden on the researcher or the research project. This presumptive obligation to ensure participants are informed of clinically significant findings in the context of genomic research is also subject to certain additional requirements, including clinical validation of a test result (if the original study was conducted in a research laboratory), that consent to disclosure of IF has been obtained from the participant when they consented to the research, and there is a mechanism to ensure the disclosure of genetic results by a suitably qualified person.

This conclusion requires that clinicians and researchers consider how IF will be managed when undertaking clinical testing or when formulating a research protocol. It requires clinicians and researchers to inform participants in advance of the potential for IF, the implications of receiving an IF, including the familial nature of the information and implications for insurance,[269] and to ascertain the participant's preferences regarding return of information. In the context of research, investigators need to consider the boundaries of the "incidental pipeline" i.e. what kinds of results will, and will not be reported, a process for validating any test result generated in a research laboratory, and determining who will have responsibility for disclosing the information to participants.

The approach advocated here is supported by the current policy approach to health research in New Zealand. The NEAC has established ethical standards to guide researchers and the HDEC reviewing such research proposals,[270] which are currently contained in the *Ethical Guidelines for Intervention Studies*[271] and the *Ethical Guidelines for Observational Studies*.[272] These policies are applicable to all health and disability research, regardless of whether the research comes within the HDEC review remit.[273]

The *Ethical Guidelines for Intervention Studies* states that investigators must provide information to participants,[274] which should include foreseeable risks and side effects of participation, including risks to family members.[275] It also provides that participants (and their main care provider) "must be informed" if in the course of an intervention study, any clinically significant abnormal laboratory result or clinical observation is detected.[276] Specifically, the guidelines provide that if a study identifies a previously undetected health care need in a participant that is unrelated to the study, arrangements "should" be made for the participant to receive the necessary care.[277] This research governance framework clearly endorses the concept of researchers assuming significant obligations in regard to research subjects, which may be extrapolated to the genomic research context. In addition, the most recent iteration of the Council for International Organizations of Medical Sciences (CIOMS) *International Ethical Guidelines for Health-related Research Involving Humans* noted that there is an "emerging consensus" that some findings must be returned to participants.[278]

Given this analysis it seems necessary to formulate clear, transparent and consistent guidelines governing the management of incidental findings in both the clinical and research context in New Zealand.[279] As Knoppers et al state:[280]

> While we are moving forward in our understanding of interpreting the clinical relevance of results from WGS-based genetic testing, the question of whether to return is becoming how to return, who should return and when to return. This requires anticipatory governance and interoperable policies, as well as sound management to ensure that the resources, both financial and professional, are in place to undertake such a task.

While this chapter has been concerned with outlining the nature of genomic testing and its implications for patients, participants, clinicians and researchers, the remainder of this report specifically examines issues arising from genomics in two particularly challenging areas: the paediatric context and in the reproductive realm.

Endnotes

1. A Singleton and B Traynor "For complex disease genetics, collaboration drives progress: Exome sequencing identifies a gene that causes amyotrophic lateral sclerosis" (2015) 347(6229) Science 1422 at 1423.
2. Linkage analysis is a gene-hunting technique that attempts to establish linkage between segments of the genome that are associated with given traits/diseases.
3. Positional sequencing involves sequencing specific candidate genes (ie genes thought to be related to a particular condition) based on their chromosomal location.
4. Often referred to as "GWAS", these studies compare DNA markers across the genome in people with a disease or trait to people without the disease/trait.
5. This involves sequencing the protein-coding region of the genome.
6. Complex diseases are conditions that are caused by a multitude of contributing factors such as the interaction of various genes and environmental influences.
7. http://www.humanvariomeproject.org/about/about-the-human-variome-project.html.
8. CF Wright, A Middleton, H Burton et al "Policy Challenges of Clinical Genome Sequencing" (2013) 347 BMJ f6845.
9. https://www.genomicsengland.co.uk/about-genomics-england/
10. E Lander "Cutting the Gordian Helix—Regulating Genomic Testing in the Era of Precision Medicine" (2015) 372 (13) New England Journal of Medicine 1185; See also HL Rehm, JS Berg, LD Brooks et al "ClinGen—The Clinical Genome Resource" (2015) 372 (23) N Engl J Med 2235.
11. Elcke J Kranendonk, Corrette Ploem and Raoul CM Hennekam "Regulating biobanking with children's tissue: a legal analysis and the experts' view" (2016) 24 European Journal of Human Genetics 30.
12. When applying for insurance, individuals are required to disclose relevant information, which extends to the results of genetic tests.
13. B Knoppers, MH Zawati and K Senecal "Return of Genetic Testing Results in the Era of Whole-Genome Sequencing" (2015) Nature Rev Genet 553 at 558.
14. For a discussion of the implications of such an approach, see Isabelle Budin-Ljøsne, Deborah Mascalzoni, Sirpa Soini, Helena Machado, Jane Kaye and others "Feedback of Individual Genetic Results to Research Participants: Is it Feasible in Europe?" (2016) 14 Preservation and Biobanking 241. See also Matthijs Gert and others "Guidelines for diagnostic next-generation sequencing" (2015) 24 European Journal of Human Genetics 2.
15. LG Biesecker and BB Biesecker "An approach to pediatric exome and genome sequencing" (2014) 26(6) Curr Opin Pediatr 639 at 639.
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17. CH Wade, BS Wilfond, CM McBride "Effects of genetic risk information on children's psychosocial wellbeing: a systematic review of the literature" (2010) 12 Gen Med 317.
18. Id, at 318.
19. SC Hillman, D Willams, KJ Carss, et al "Prenatal exome sequencing for fetuses with structural abnormalities: the next step" (2015) 45 Ultras Obs Gyn 4 at 6.
20. BR Korf and HL Rehm "New approaches to molecular diagnosis" (2013) 309(14) JAMA 1511 at 1513 at 1513.
21. JR Botkin, JW Belmont, JS Berg et al (ASHG) "Points to Consider: Ethical, Legal, and Psychosocial Implications of Genetic Testing in Children and Adolescents" (2015) 97 Am J Hum Genet 6 at 7.
22. JR Botkin, JW Belmont, JS Berg et al "Points to Consider: Ethical, Legal and Psychosocial Implications of Genetic Testing in Children and Adolescents" (2015) 97 Amer J Hum Genet 6; JR Botkin, JW Belmont, JS Berg et al "Points to Consider: Ethical, Legal and Psychosocial Implications of Genetic Testing in Children and Adolescents" (2015) 97 Amer J Hum Genet 6.
23. M Reiff, BA Bernhardt and S Mulchandani et al "'What does it mean?': uncertainties in understanding results of chromosomal microarray testing" (2012) 14 Genet Med 250 at 254.
24. A Townsend, S Adam, PH Birch et al "'I want to know what's in Pandora's Box': comparing stakeholder perspectives on incidental findings in clinical whole genomic sequencing" (2012) 158A Am J Med Genet A 2519 at 2524.
25. D Alexander and PC van Dyck "A vision of the future of newborn screening" (2006) 117 Pediatrics S350.
26. KD Lakes, E Vaughan, M Jones et al "Diverse perceptions of the informed consent process: implications for the recruitment and participation in the National Children's Study" (2012) 49 Am J Commun Psychol 215.
27. JC Sapp, D Dong, C Stark et al "Parental attitudes, values, and beliefs toward the return of results from exome sequencing in children" (2014) 85 Clin Genet 120 at 123.
28. While NIPT may theoretically be done at seven weeks, it may result in a lower fetal fraction when it is conducted before 10 weeks.
29. A Mauron "Choosing among possible persons: The ethics of prenatal selection in the postgenomic age" (2015) 338 C. R. Biologies 566 at 569.

30. This is in relation to: trisomy 21, trisomy 18, trisomy 13, monosomy X. See P Devers, A Cronister, K Ormond et al "Noninvasive prenatal Testing/Noninvasive Prenatal Diagnosis: the Position of the National Society of Genetic Counselors" (2013) 22 J Genet Counsel 291 at 293.
31. H Farrimond and S Kelly "Public viewpoints on new non-invasive prenatal genetic tests" (2011) 22 Public Understanding of Science 730.' This study identified "four distinct "viewpoints" amongst 71 UK men and women: 1. NIPD as a new tool in the ongoing societal discrimination against the disabled; 2. NIPD as a positive clinical application offering peace of mind in pregnancy; 3. NIPD as a medical option justified for severe disorders only; and 4. NIPD as a valid expansion of personal choice. Concerns included the "trivialisation of testing" and the implications of commercial/ direct-to-consumer tests."
32. C Munthe "Permissibility or Priority? Testing or Screening? Essential distinctions in the Ethics of Prenatal Testing" (2017) 17 American Journal of Bioethics 30.
33. L. Govaerts, M. Srebniak, K. Diderich, M. Joosten, S. Riedijk, M. Knapen, A. Go, D. Papatsonis, K. de Graaf, T. Toolenaar, S. van der Steen, G. Huijbregts, J. Knijnenburg, F. de Vries, D. Van Opstal and R.-J. Galjaard "Prenatal diagnosis of susceptibility loci for neurodevelopmental disorders – genetic counseling and pregnancy outcome in 57 cases"
(2017) 37 Prenatal Diagnosis 73.
34. B Oneda and A Rauch "Microarrays in Prenatal Diagnosis" (2017) Best Practice & Research Clinical Obstetrics and Gynecology (available online).
35. JJ Detraux, F Gillot-de Vries, S Vanden Eynde and others "Psychological impact of the announcement of a fetal abnormality on pregnant women and on professionals" (1998) 18 Ann N Y Acad Sci 210–19; SR Leuthner, M Bolger, M Frommelt and R Nelson "The impact of abnormal fetal echocardiography on expectant parents' experience of pregnancy: a pilot study" (2003) 24 J Psychosom Obstet Gynecol 121–9; LM Mitchell "Women experiences of unexpected ultrasound findings" (2004) 49 J Midwifery Women's Health 228–34; A Kersting, M Dorsch, C Kreulich and others "Trauma and grief 2–7 years after termination of pregnancy because of fetal anomalies – a pilot study" (2005) 26 J Psychosom Obstet Gynecol 9–14.
36. A Kaasen and others "Acute maternal social dysfunction, health perception and psychological distress after ultrasonographic detection of a fetal structural anomaly" (2010) 117 BJOG 1127.
37. DW Britt, ST Risinger, MK Mans, MI Evans "Devastation and relief: conflicting meanings of detected fetal anomalies" (2002) 20 Ultrasound Obstet Gynecol 1–5; GR Benute, RM Nomura, AW Liao and others "Feelings of women regarding end-of-life decision making after ultrasound diagnosis of a lethal fetal malformation" (2012) 28 Midwifery 472–75.
38. G Donley, S Hull and B Berkman "Prenatal Whole Genome Sequencing: Just Because We Can, Should We? (2012) Hastings Center Report 28 at 33.
39. For a discussion of a two-stage informed consent process see S Chen, D Wasserman "A Framework for Unrestricted Prenatal Whole-Genome Sequencing: Respecting and Enhancing the Autonomy of Prospective Parents" (2017) 17 AJOB 3 at 7.
40. T Caulfield, J Evans, A McGuire and others "Reflections on the Cost of "Low-Cost" Whole Genome Sequencing: Framing the Health Policy Debate" (2014) 11 PLOS Biology.
41. http://ghr.nlm.nih.gov/handbook/basics/dna.
42. http://ghr.nlm.nih.gov/info=mutations_and_disorders/show/alltopics.
43. WG Feero, AE Guttmacher, FS Collins "Genomic Medicine-an Updated Primer" (2010) 362 N Engl J Med 2001 at 2003.
44. W Bodmer and C Bonilla "Common and Rare Variants in Multifactorial Susceptibility to Common Diseases" (2008) 40(6) Nat Genet 695.
45. Human Genome Project Information Website SNP Factsheet, http://www.ornl.gov/sci/techresources/Human_Genome/faq/snps.shtml.
46. Personal Communication, Professor Stephen Robertson, Clinical Geneticist, University of Otago.
47. WG Feero, AE Guttmacher, FS Collins "Genomic medicine-an updated primer" (2010) 362 N Engl J Med 2001 at 2010. See also: http://ghr.nlm.nih.gov/handbook/genomicresearch/snp
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49. http://www.ncbi.nlm.nih.gov/books/NBK20363/.
50. http://ghr.nlm.nih.gov/info=mutations_and_disorders/show/alltopics.
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53. http://ghr.nlm.nih.gov/handbook/inheritance/penetranceexpressivity. See also: http://ghr.nlm.nih.gov/condition/22q112-deletion-syndrome.
54. BR Korf and HL Rehm "New approaches to molecular diagnosis" (2013) 309(14) JAMA 1511 at 1513.
55. WG Feero, AE Guttmacher, FS Collins "Genomic medicine-an updated primer" (2010) 362 N Engl J Med 2001 at 2008.
56. Sciences NIoGM. Human Genetic Variation Fact Sheet, http://www.nigms.nih.gov/Publications/

Factsheet_GeneticVariation.htm.

57. WG Feero, AE Guttmacher, FS Collins "Genomic medicine-an updated primer" (2010) 362 N Engl J Med 2001 at 2008.
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61. LG Biesecker and BB Biesecker "An approach to pediatric exome and genome sequencing" (2014) 26(6) Curr Opin Pediatr 639 at 641 Figure 2.
62. A Thorogood and B Knoppers "The Ethical and Legal Duties of Physicians in Clinical Genetics and Genomics" in Y Joly and B Knoppers (eds) *Routledge Handbook of Medical Law and Ethics*, (Routledge, Abingdon, 2015) 319 at 325. CH Wade, BA Tarini, BS Wilfond "Growing Up in the Genomic Era: Implications of Whole-Genome Sequencing for Children, Families, and Pediatric Practice" (2013) 14 Annu. Rev. Genomics Hum. Genet. 535 at 537.
63. S Robertson, Genetics Symposium (Bioethics Centre, University of Otago) 25 September 2013.
64. N Hallowell, A Hall, C Alberg et al "Revealing the results of whole-genome sequencing and whole-exome sequencing in research and clinical investigations: some ethical issues" (2015) 41 J Med Ethics 317.
65. S Moorthie, A Hall, C Wright "Informatics and clinical genome sequencing: opening the black box" (2013) 15 Genet Med 165.
66. RL Zimmern, M Kroese "The evaluation of genetic tests" (2007) 29 J Pub Health 246.
67. BA Tarini, DA Christakis, HG Welch "State newborn screening in the tandem mass spectrometry era: more tests, more false-positive results" (2006) 118(2) Pediatrics 448 at 452.
68. American College of Medical Genetics Newborn Screening Expert Group (ACMGNSE Group) "Newborn screening: toward a uniform screening panel and system" (2006) 117 Pediatrics 296.
69. N Hallowell, A Hall, C Alberg et al "Revealing the results of whole-genome sequencing and whole-exome sequencing in research and clinical investigations: some ethical issues" (2015) 41 J Med Ethics 317.
70. RC Green, JS Berg, WW Grody et al "ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing" (2013) 15 Genet Med 565.
71. For a recent case involving an incidental finding and the clinician's duty of care in the context of imaging, see *Freestone v Murrumbridgee Local Health District* [2016] NSWDC 53.
72. Presidential Commission for the Study of Bioethical Issues *Anticipate and Communicate: Ethical Management of Incidental and Secondary Findings in the Clinical, Research, and Direct-to-Consumer Contexts* (Bioethics Commission, Washington DC, 2013).
73. N Hallowell, A Hall, C Alberg et al "Revealing the results of whole-genome sequencing and whole-exome sequencing in research and clinical investigations: some ethical issues" (2015) 41 J Med Ethics 317.
74. DG MacArthur, TA Manolio, DP Dimmock et al "Guidelines for investigating causality of sequence variants in human disease" (2014) 508 Nature 467 at 470.
75. PDG Skegg "Consent to Treatment: Introduction" in PDG Skegg R Paterson (eds) *Medical Law in New Zealand* (Thomson Brookers, Wellington, 2006) at 147.
76. While tort may also include a claim for battery, the general approach, for reasons of public policy, is that claims in tortious battery should be restricted to instances where no consent has been provided at all (legal exceptions to the requirement for consent aside) or when a procedure is performed that goes beyond the scope of a patient's consent. However, claims that involve a failure to disclose relevant risks of a procedure when obtaining consent, which results in harm, should fall within the scope of negligence. See *Reible v Hughes* [1980] 2 SCR 880, 890.
77. This is known in common law jurisdictions as the Bolam standard of care after the UK case *Bolam v Friern Hospital Management Committee* [1957] 2 All ER 118. In addition, section 155 of the Crimes Act 1961 states that persons delivering surgical or medical treatment which is, or may be, "dangerous to life" are under a duty "to have and use reasonable knowledge, skill, and care". Section 150A further provides however that a person will only be criminally responsible if, in the circumstances, the omission or neglect of a legal duty is a 'major departure from the standard of care expected of a reasonable person to whom that legal duty applies in those circumstances'.
78. See the *Code of Health and Disability Services Consumers' Rights* (Code of Rights) promulgated under the Health and Disability Commissioner Act 1994. The Code of Rights explicitly states that all of the rights contained in the Code apply to research: right 9.
79. The Code of Rights, rights 4(1) and (2). However, the Code also goes considerably further, stating that a consumer has a right to have services "provided in a manner consistent with his or her needs"; and "to have services provided in a manner that minimises the potential harm to, and optimises the quality of life of, that consumer". Rights 4(3) and (4).

80. The Code of Rights, right 4(2).
81. This is mostly enforced via the Privacy Act 1993 and the Health Information Privacy Code 1994.
82. This is endorsed in seminal case law from major common law jurisdictions and includes: in the United States: *Canterbury v Spence* 464 F.2d 772 (D.C. Cir. 1972) (adopts a "prudent patient" approach); in Canada: *Reibl v Hughes* (1980) 114 D.L.R. (3d) 1, 13 (S.C.C.); in Australia: *Rogers v Whitaker* (1992) 175 C.L/R. 479, 489 (HCA) (material risks must be disclosed and "a risk is *material* if, in the circumstances of the particular case, *a reasonable person in the patient's position*, if warned of the risk, would be likely to *attach significance* to it") and most recently in the United Kingdom: *Montgomery (Appellant) v Lanarkshire Health Board* [2015] UKSC 11.
83. See the Code of Rights, right 6.
84. MH Zawati "Liability and the Legal Duty to Inform in Research" in Y Joly and B Knoppers (eds) *Routledge Handbook of Medical Law and Ethics* (Routledge, Abingdon, 2015) at 201.
85. The CIOMS Guidelines were revised in 2016. See CIOMS *International Ethical Guidelines for Health-related Research Involving Humans* (Fourth Ed, Geneva, 2016).
86. For a discussion of an infamous incidence of failure in this regard, see R Fretwell Wilson "The Death of Jesse Gelsinger: New Evidence of the Influence of Money and Prestige in Human Research" (2010) 36 Am Law Med 295 at 322.
87. [1965] 53 DLR (2d) 436.
88. MH Zawati "Liability and the Legal Duty to Inform in Research" in Y Joly and B Knoppers (eds) *Routledge Handbook of Medical Law and Ethics* (Routledge, Abingdon, 2015) at 200.
89. In NZ, ACC cover may be available for a research participant who suffers injury as a result of participating in an intervention study—but only in limited circumstances. Cover is theoretically available only if a participant suffers injury as a result of treatment provided as part of an intervention study for which ethics committee approval has been given *and* the ethics committee considers the trial was not to be conducted principally for the benefit of the manufacturer or distributor of the medicine or item being trialled (which puts the onus of compensation on the entity conducting/benefiting from the trial). Accident Compensation Act 2001, s 32.
90. *Halushka v University of Saskatchewan* [1965] 53 DLR (2d) 436 at [29].
91. The so-called doctrine of therapeutic privilege provides that in rare circumstances, information may be withheld from a patient if disclosure would be harmful. However, in contemporary times Skegg observes that 'if the doctrine of therapeutic privilege has any continuing role, it is an extremely limited one': PDG Skegg "The Duty to Inform" in PDG Skegg, R Paterson (eds) *Health Law in New Zealand* (2nd ed, Thomson Reuters, Wellington, 2015) at 275.
92. [1989] 48 CCLT 280.
93. M Zawati "Liability and the Legal Duty to Inform in Research" in Y Joly and B Knoppers (eds) *Routledge Handbook of Medical Law and Ethics* (Routledge, Abingdon, 2015) at 211.
94. Ibid.
95. The *Code of Rights*, right 9 (emphasis added).
96. Health and Disability Commissioner Act 1994, s 2(1).
97. Health and Disability Commissioner Act 1994, s 2(1).
98. Health and Disability Commissioner Act 1994, s 3.
99. Health and Disability Commissioner Act 1994, s 2.
100. Health and Disability Commissioner Act 1994, s 2 (emphasis added).
101. Health and Disability Commissioner Act 1994 s 2 in turn defines "health services" as including: "services to promote health"; "services to protect health"; "services to prevent disease or ill health" and "diagnostic services".
102. The Code of Rights, right 6.
103. The Code of Rights, right 6(1)(f). Right 7(10) further provides that substances removed in the course of a health care procedure may only be used with the informed consent of the consumer or 'for the purposes of research that has received the approval of an ethics committee' or for specified activities undertaken for quality assurance purposes.
104. Tissue donors may also consent to "future unspecified use of samples", which is distinct from consent to collection and use the sample in specified research. The Ministry of Health *Guidelines on the Use of Human Tissue for Future Unspecified Research Purposes* (Wellington, 2007) specifies the information that must be provided before informed consent to future unspecified use of tissue can be obtained. The *Guidelines* were developed to assist Health and Disability Ethics Committees (HDECs) assess applications involving human tissue research. HDECs are established by the Ministry of Health and are responsible for considering applications to conduct research, subject to the *Standard Operating Procedures for Health and Disability Ethics Committees* (version 2, 2014). Recent changes mean that HDEC review is no longer required if informed consent for "future use" was obtained at the time of collection, and the samples are anonymised.
105. A Beaton, B Smith, V Toki et al "Engaging Maori in Biobanking and Genetic Research: Legal, Ethical and Policy Challenges" (2015) 6 Intl Indigen Policy J; M Hudson, K Southey, L Uerata et al "Key Informant Views on Biobanking and Genomic Research with Maori" (2016) 129 NZMJ 1447.

106. Accident Compensation Act 2001.
107. *The Code of Rights*, right 6(1)(f).
108. *The Code of Rights*, right 4(4) also provides the right 'to have services provided in a manner that minimises the potential harm to, and optimises the quality of life of, that consumer'.
109. EW Clayton, S Haga, P Kuszler et al "Managing Incidental Genomic Findings: Legal Obligations of Clinicians" (2013) 15 Genet Med 624.
110. *Lo v Burke* 455 S.E. 2d 9 (Va. 1995).
111. *Davy v Shiffer* 6/6/2008 NYLJ 30 (col 1) (CT suggestive of lung cancer), 2008 NY Misc.; *Durham v County of Maui* 2010 WL 2943358 (D. Haw. 2010) (echocardiogram showing an enlarged aorta); *Cooper v Cicarelli* 2009 WL 539911 (D. Kan. 2009) (failure to notify a nodule seen on an X-ray); *Workman v O'Brien* 001 WL 663819 (Ind. App. 2001) (enlarged bladder).
112. *Riley v Stone* 900 A.2d 1087, 1095 (RI 2006); *Cifaretto v Dalton* 23 A.3d 414 (2011), 207 NJ 188.
113. *Stallworth v Boren* 54 P.3d 923 (Haw. App. 2002).
114. *Freestone v Murrumbidgee Local Health District* [2016] NSWDC 53.
115. Civil Liability Act 2002, ss 5B, 5O provide that: "1) A person practising a profession … does not incur a liability in negligence … if it is established that the professional acted in a manner that (at the time the service was provided) was widely accepted in Australia by peer professional opinion as competent professional practice. (2) However, peer professional opinion cannot be relied on for the purposes of this section if the court considers that the opinion is irrational. (3) The fact that there are differing peer professional opinions widely accepted in Australia concerning a matter does not prevent any one or more (or all) of those opinions being relied on for the purposes of this section. (4) Peer professional opinion does not have to be universally accepted to be considered widely accepted."
116. *Chappel v Hart* [1998] HCA 55; 195 CLR 232 at [28].
117. Id at [131].
118. AG Clarke "Managing the ethical challenges of next-generation sequencing in genomic medicine" (2014) 111 *Brit Med Bull* 17-30 at 18.
119. M Hegde, S Bale, P Bayrak-Toydemir et al "Reporting Incidental Findings in Genomic Scale Clinical Sequencing – A Clinical Laboratory Perspective" (2015) 17 J Molec Diagnostics 107 at 109.
120. A Thorogood and B Knoppers "The Ethical and Legal Duties of Physicians in Clinical Genetics and Genomics" in Y Joly and B Knoppers (eds) *Routledge Handbook of Medical Law and Ethics*, (Routledge, Abingdon, 2015) 319 at 327. The World Health Organization's screening criteria developed by Wilson and Jungner in 1968 remain instructive: in addition to screening tests having analytic and clinical validity, acceptable treatment should be publicly available. In addition screening should be economically justifiable.
121. www.acmg.net/ACMG/About_ACMG/Mission_Statement/ACMG/About_ACMG/Mission_Statement.aspx?hkey=473005e6-49fb-4604-84fc-31db71a6a368
122. RC Green, JS Berg, WW Grody et al "ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing" (2013) 15 Genet Med 565 at 566.
123. ACMG Board of Directors "ACMG Policy Statement: Points to consider in the clinical application of genomic sequencing" (2012) 14 *Genet Med* 759-61.
124. Id at 760.
125. RC Green, JS Berg, WW Grody et al "ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing" (2013) 15 Genet Med 565 at 565.
126. Id at 566.
127. Id at 567.
128. Ibid.
129. RC Green, JS Berg, WW Grody et al "ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing" (2013) 15 Genet Med 565 at 568.
130. This includes competent adults and parents of minor children or guardians of decisionally impaired adults.
131. Id, at 568.
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147. See Article 10(2) of the *Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine*, Council of Europe, Oviedo, April 1997, 'Everyone is entitled to know any information collected about his or her health. However, the wishes of individuals not to be so informed shall be observed'. See also Article 5c of the *Universal Declaration on the Human Genome and Human Rights*, UNESCO, Adopted 11 November 1997, 29th General Conference, Paris which states that 'the right of every individual to decide whether or not to be informed of the results of genetic examination and the resulting consequences should be respected'. See also table 7 of the ethical guidelines of the World Health Association, *Guidelines on Ethical Issues in Medical Genetics and the Provision of Genetic Services* (1997) which provides that 'the wish of individuals and families not to know genetic information, including test results, should be respected, except in testing of newborn babies or children for treatable conditions'. See also Article 7d of the World Medical Association *Declaration on the Rights of the Patient* (1981 as amended in 1995) which states that "the patient has the right not to be informed on his/her explicit request, unless required for the protection of another person's life'.
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152. LF Ross, MA Rothstein, EW Clayton "Premature guidance about whole-genome sequencing" (2013) 10 Personalized Med 523-526.
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180. It could be that there may be some procedures that are not necessarily "therapeutic" in the ordinary sense of the word—such as cosmetic surgery. However, this is still medical treatment provided for the direct benefit of the patient (whether or not strictly "therapeutic") and so is still provided in the context of a fiduciary relationship.

Chapter Two

Genomic testing in the paediatric context

2.1 Introduction: why consider childhood genetic testing?

The field of selective reproduction is poised to expand dramatically due to advances in technology, declining costs, and less invasive testing methods such as non-invasive prenatal testing. However, paediatric genetic testing, which uses similar technologies and generates similar issues, is considerably further advanced in terms of its clinical implementation than is the case of prenatal testing or preimplantation genetic diagnosis (PGD). Some commentators predict dramatic and imminent changes to the paediatric genetic testing landscape that may, in the future, facilitate personalised medicine:[1]

> Over the course of the next few decades, the availability of cheap, efficient DNA sequencing technology will lead to a medical landscape in which each baby's genome is sequenced, and that information is used to shape a lifetime of personalized strategies for disease prevention, detection, and treatment.

Given that paediatric genetic testing is arguably further along the genomic spectrum relative to testing in other clinical contexts, this chapter considers the evolution of paediatric genetic testing, its current landscape, and its potential future. It examines empirical findings from childhood genetic testing, outlining some key areas where knowledge and experience could be highly informative for the reproductive project.

The following analysis considers two important clinical contexts involving childhood testing: newborn screening and paediatric genetic testing. In each of these areas the standard (i.e. "pre-Next Generation Sequencing") guidelines are reviewed, focusing on the key concepts that underpin them, as well as the evidence regarding the psychosocial implications of testing. After establishing this background, the analysis shifts to considering how new approaches to molecular diagnosis challenge these established guidelines, blurring the lines between testing and screening, and in some instances run counter to established ethical norms of paediatric genetics.

2.2 Newborn screening (NBS)

General description

History and development

Before considering the ethics of NBS and the empirical evidence underlying it, it is necessary to briefly describe the nature of NBS. NBS is a comprehensive system that includes testing, diagnosis, follow-up, treatment, education, and evaluation. It was recently named one of the Top 10 Great Public Health Achievements by the Centres for Disease Control and Prevention (CDC).[2]

NBS is one of (if not the) most efficient and effective of all screening programmes internationally, with most countries reporting coverage of between 95 and 100% of the population.[3] Screening is accomplished through the collection and analysis of heel prick blood samples from babies between 2 and 5 days of age. Confirmatory tests are necessary for positive results, but treatment can usually be instituted within 10-14 days of birth. Early identification of the conditions on the screening panel (mostly genetic metabolic disorders) facilitates timely intervention that results in significant decreases in morbidity, mortality, and disability.

NBS began in the 1960's when Dr Robert Guthrie developed both a novel method of blood collection onto filter paper, and a simple test to detect the genetic metabolic disorder phenylketonuria (PKU).[4] The devastating neurological consequences of untreated PKU, and the availability of a relatively straightforward dietary intervention that prevents these effects, coupled with the existence of this inexpensive assay ultimately made wide scale population screening both feasible and acceptable.[5]

Over the years NBS for PKU has been lauded as the "epitome of the application of human biochemical genetics", and a model for genetic medicine and public health.[6] NBS in New Zealand was established in the mid-late 1960s when Guthrie took sabbatical leave to Dunedin, with Professor Arthur Veale initiating the programme from the Otago School of Medicine. Dr Dianne Webster now leads the service which is based at LabPLUS at Auckland City Hospital. The National Screening Unit (within the National Health Board of the Ministry of Health) has responsibility for the funding, monitoring and strategic direction of the programme.[7]

Selection criteria for NBS

It has long been recognised that public health initiatives such as the NBS programme should be guided by an underlying set of principles. These principles incorporate important scientific, ethical, legal and other perspectives into decisions about which disorders should be screened for. In 1968 the World Health Organisation commissioned a study by Wilson and Jungner, who enumerated 10 criteria "to guide the selection of conditions that would be suitable for screening." (Table 2). These principles covered aspects of the disease, its treatment, the scientific validity of the test, and the organisational infrastructure associated with the screening programme. Although not written specifically with either genetic tests or children in mind, the criteria have served as a policy standard for NBS over the past four decades.

Table 2: Wilson and Jungner classic screening criteria[8]

1.	The condition sought should be an important health problem.
2.	There should be an accepted treatment for patients with recognized disease.
3.	Facilities for diagnosis and treatment should be available.
4.	There should be a recognizable latent or early symptomatic stage.
5.	There should be a suitable test or examination.
6.	The test should be acceptable to the population.
7.	The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8.	There should be an agreed policy on whom to treat as patients.
9.	The cost of case finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10.	Case finding should be a continuing process and not a "once and for all" project.

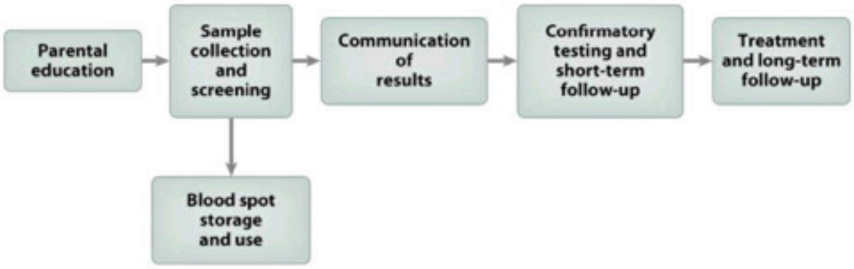
Data from ref. 22.

Policy and guidelines

Over the years, considerable efforts have been invested in addressing governance and policy issues for NBS, largely in response to the way the NBS has evolved. Although this expansion has not (as yet) been related to next generation sequencing, important lessons can be learned and potentially inform other clinical contexts. It has been predicted that NBS will be the next clinical focus for implementation of WGS, with considerable research efforts already underway in this regard. NBS may represent an important ongoing resource when considering clinical applications of WGS.

In most jurisdictions NBS is governed through a comprehensive framework covering all aspects of the screening pathway.[9]

Figure 5: Screening Pathway[10]



In 2011, the New Zealand Ministry of Health, in conjunction with clinical and scientific experts, community organisations and other Government agencies, developed new policy and governance arrangements for NBS.[11] This framework formalised policy for all aspects of the programme including:

- overall programme policies and governance
- programme provider responsibilities
- lead maternity carer responsibilities
- laboratory responsibilities
- processes for the return, storage and uses of residual blood spot samples
- requirements for changes to the programme.

Australia has also recently conducted a similarly broad, consultative, multidisciplinary review of NBS services and produced a new Australian policy framework.[12]

The following section highlights some of the key challenges that NBS programmes have faced over the last few years, as these experiences may inform other clinical contexts.

The evolution of NBS and its challenges

NBS programmes have expanded significantly over the past two decades. Until 2006 New Zealand screened for 7 conditions, but now screens for 28.[13] Similar expansions have occurred across the developed world.[14] It is however, much more difficult to unpack what has driven these changes. Some of the key, inter-connected, factors are:

- technological advances;
- changes to the selection processes for conditions; and
- evolution of the underlying aims and ethical concepts.

Technological advances

Much of this expansion has been attributed to the application of a technology called tandem mass spectrometry (MS/MS).[15] In the past, adding a new condition to a programme meant adding new laboratory equipment and/or processes to an already complex system. MS/MS, however, allows simultaneous screening for dozens of different metabolic conditions through analysis of blood spots for characteristic changes in their biochemical profile.[16] While MS/MS works by detecting biochemical abnormalities rather than directly interrogating DNA sequences, the majority of the conditions it can detect are autosomal recessively inherited disorders.[17]

Expanded screening using MS/MS has been implemented in many parts of the world, including European countries,[18] as well as come countries in the Middle East and North Africa,[19] the US, Canada, Australia and New Zealand.[20] There is extensive literature concerning MS/MS, but perhaps the most pertinent issue for this report is reflected in the following quote from a biochemist who was instrumental in developing the technology:[21]

> The original paradigm for newborn screening was fairly clear cut. The disorder had to be treatable; it had to have dire consequences if not detected early. There had to be a simple and available test—the PKU paradigm we used to call it. And tandem mass spectrometry interceded on top of that and created a different paradigm. It shifted into a technological paradigm and away from a considered disease-by-disease paradigm.

Changes to the selection process for conditions

While the Wilson and Jungner principles remain at the core of NBS policy, some commentators have noted difficulties in applying them.[22] These difficulties arise from issues such as the inter-relatedness of the principles, the subjective nature of the principles, and difficulties in their quantification and comparison. For example, many of the principles are couched in qualitative terms such as: "the natural history of a condition should be *adequately* understood", "there should be a *suitable* test or examination", with no clear indication as to when these requirements are met.[23] This creates problems translating the principles into criteria, or conditions that must be fulfilled, before a candidate disorder can be accepted onto a screening panel. These difficulties have perhaps become more apparent as support for evidence-based medicine has increased, and more clarity is called for in the decision-making process.[24]

These issues have led some centres to advocate for modifications to the criteria to incorporate contemporary values such as quality assurance, equity, and scientific evidence of effectiveness.[25] For example the Human Genetics Society of Australasia (HGSA) has defined a set of criteria by which conditions can be recommended for NBS panels. These include:[26]

- There is benefit for the baby from early diagnosis (benefit to the family may also benefit the baby);
- The benefit is reasonably balanced against financial and other costs;
- There is a reliable test suitable for newborn screening;
- There is a satisfactory system in operation to deal with diagnostic testing, counselling, treatment, and follow up of patients identified by the test.

Other countries have attempted to develop more proscriptive guidelines for selecting disorders to be included in NBS panels. The UK National Screening Committee (UK NSC) has developed 19 screening criteria and specifies 87 items of information under 35 general headings needed for their evaluation.[27]

Similarly, in 2002, the American College of Medical Genetics (ACMG), under contract to the Federal Health Resources and Services Administration, also derived 19 criteria based on the original Wilson and Jungner principles.[28] In an attempt to standardise application of these criteria, the ACMG developed a questionnaire allocating numerical scores to 84 candidate disorders, depending on the degree to which they met the criteria. After evaluating the empirical evidence for these conditions opinions were also gathered from experts and advocacy constituents.[29]

Despite similarities in process, the final results were dichotomous. The UK NSC recommending screening for a total of 5 disorders (increased to 9 in 2014). In comparison, the ACMG identified 29 primary target conditions and an additional 25 secondary targets (defined as conditions that would be identified because they are part of the differential diagnosis of a condition in the core panel, are clinically significant and revealed with screening technology but lack an efficacious treatment, or represent incidental findings for which there is potential clinical significance).[30]

These reports represent major efforts to provide objective means of assessing disorders for NBS, but have nevertheless stimulated further debate and controversy.[31] Concerns have been raised regarding limitations of the ACMG process, including:[32]

- the survey used to collect opinions was poorly designed;
- there was lack of justification for weights used in aggregating the survey responses to rank conditions;
- the sample population was poorly defined, for example respondents were biased toward individuals actively involved in NBS services and lay advocacy groups;
- the accompanying literature review did not follow the standard framework for comprehensive literature views;
- its scope was limited, particularly with respect to ethical, legal and psychosocial issues.

Similarly concerns have been raised that, even when disorders fulfil specific criteria, the infrastructure to deliver adequate services and monitor harms and benefits will not be in place if programs expand too rapidly.[33]

In response to these criticisms the US Advisory Committee on Heritable Disorders in Newborns and Children developed more stringent criteria for adding conditions to the recommended uniform panel. Only one additional condition has since been added to the "Guthrie test" panel (severe combined immunodeficiency in 2010).[34]

Similarly in Australia one of the key drivers of the recent project to develop a comprehensive policy framework was the need to "assess the benefits and harms of screening for new conditions to enable governments to make nationally consistent decisions on which conditions should be included in the programs."[35] It specifically recognized that "science and technology related to the testing and treatment of conditions included in the NBS programmes, as well as other conditions for which NBS could be offered, is rapidly changing."[36]

Changes in the underlying aims of NBS

Perhaps surprisingly, the fundamental normative question of what the underlying aims of NBS programmes should be has been relatively neglected in comparison to advances in relevant scientific knowledge and techniques. It is helpful to pause, and consider these overall goals.

Ethical concepts: the nature of benefits

As discussed in relation to PKU, the historical rationale for NBS was the prevention of devastating harm to affected infants by the provision of immediate treatment.[37] This rationale has been described as "an urgent response to avert a potential emergency of public health importance".[38] Thus in a similar way to the childhood genetic testing paradigm (discussed in the next section) the medical best interests of the child have traditionally been the key focus of decisions about NBS.

However, various factors, including the success of established NBS programmes and the development of new technologies such as MS/MS, have caused some to question whether these traditional justifications are too narrow. Certainly, since the advent of MS/MS the rationale seems to be evolving, as although screening for most disorders may still prevent mortality and morbidity, for some conditions the benefits are less dramatic, less immediate or may not directly accrue to the child. In other words, whereas traditionally the only relevant benefit has been benefit directly to the infant of a timely and effective treatment for a serious condition,[39] it now seems that the notion of benefit may have become broader, encompassing not only benefit to the child but also benefits to families and society.[40]

For example, the ACMG evaluation also considered the benefits of screening that might accrue to the family even if none accrued directly to the child being screened. Since then other benefits that appear to fall into four broad categories have been suggested:

- Elimination of the "diagnostic odyssey". This phrase refers to the experience of families of children with rare disorders who often face multiple investigations, significant frustrations and time delays before being correctly diagnosed. A recent report found that it takes patients on average six years and trips to eight doctors, from noticing symptoms to being correctly diagnosed.[41]
- Provision of reproductive risk information to parents.[42]
- Enabling research with children affected by rare disorders.[43]
- Developmental, social and psychological benefits that may arise from early disease detection even in the absence of availability of specific treatment.[44]

There is no consensus as to whether this broadened conception of benefit is ethically appropriate, and if it is, how such benefits should be weighed and judged when making policy decisions. For example, although "family benefit" as a justification for screening has been supported by one professional group statement,[45] it has been rejected by others.[46] Despite this lack of agreement NBS already appears to operate not solely as a response to a "public health emergency"[47] but rather as a public health service with greater emphasis on more moderate and parent-centred benefits.[48]

Ethical concepts: the nature of harms

Although many health professionals and parent advocacy groups press for further expansion to NBS panels on the grounds that knowledge is beneficial to families, expanded screening also carries potential harms. Because the overall frequency of disorders in the apparently healthy newborn population is relatively low (i.e. those who will benefit from NBS), there is reason to be concerned about false positive results and other psychosocial impacts (harms of NBS).

Empirical data: Psychosocial evidence concerning harm

The majority of research in the field of NBS is designed to determine whether testing produces tangible clinical benefits for the child. While this is undoubtedly important, it is also relevant to examine the unintended effects of screening that are often psychosocial in nature. The following section reviews the existing evidence concerning these effects.

The focus of research relating to psychosocial aspects of NBS has primarily been the effects of false positive results and, to a lesser degree, true positive results upon parents. The most commonly measured variables have been knowledge, anxiety and other affects and attitudes, with the majority of early studies focusing on a single disorder.[49] There is less information available regarding effects of NBS on parent-child interaction, although some studies have investigated effects on parental perceptions of child health, parent-child bonding and parental behaviour.[50]

As screening practices have evolved, interest has grown in other areas. For example, in relation to cystic fibrosis (CF) studies have examined issues such as: the effects of carrier identification; effects upon parental reproductive decision making; and comparisons between infants diagnosed through screening and those diagnosed symptomatically at a later stage. Even more recently the issue of ambiguous results has been addressed, particularly in relation to Medium-Chain Acyl-Co A Dehydrogenase Deficiency (MCAD), CF and Krabbe disease.

Although it is possible to criticise the existing body of research, it is apparent that there have been robust attempts to investigate psychosocial issues related to NBS. The findings of this somewhat diverse group of studies are summarised below. For each element of the NBS pathway, evidence relating to short and long term parental emotional reactions and effects on parent-child interaction, including perceptions of child health, are documented.

Table 3: Summary of empirical evidence regarding psychosocial effects of newborn screening

Immediate reaction to abnormal NBS result	There is consistent evidence of significant parental distress e.g. anxiety, depression.[51] The degree of distress may be less if parents are well informed.[52] Limited evidence demonstrates that parents report willingness to tolerate this distress to achieve potential gains.[53] There is also limited evidence of altered parent-child interaction.[54]
Reaction while awaiting results of diagnostic tests	There is consistent evidence of significant parental distress e.g. worry, depression.[55] State of uncertainty is described as a major source of distress.[56] It is possible to reduce this through attention to protocols e.g. minimising waiting periods.[57] There is evidence of altered parent – child interaction such as monitoring child's health and "medicalisation".[58]
Reaction to true positive results	Consistent evidence shows that parental distress is considerable but no more than that created by clinical diagnosis.[59] Most quantitative studies suggest the mother-child interaction is not adversely affected,[60] but qualitative data suggests subtle difficulties.[61] Parents value the ability to access information, support and services for their child.[62] Studies show that parental attitudes and uptake of prenatal services are very variable.[63]
Reaction to false positive results (i.e. initial NBS positive, subsequent testing clearly negative)	Short-term emotional reaction is consistent with "immediate reaction to abnormal NBS result" (as the eventual nature of the result is unknown initially). For long-term emotional reactions, the evidence is conflicting. Some studies demonstrate an absence of persistent anxiety,[64] others report anxiety up to four years later.[65] There is some evidence of long-term anxiety associated with carrier status,[66] or unrelated medical issues of the child.[67] The evidence is conflicting concerning parent-child interaction: some studies show an absence of parenting stress,[68] while others demonstrate evidence of continued parenting stress and ongoing concerns about the child's health.[69] Conflicting evidence is found regarding healthcare utilisation from no increase,[70] to increased hospitalisation rates.[71] There is no evidence of altered perception of child's health at 11-14 years.[72] It should be noted that since the advent of MS/MS, there are larger numbers of false positive results.[73]

Reaction to carrier status (CF studies only)	In the short-term anxiety, knowledge deficits, and misconceptions about health status are common.[74] Although anxiety and concern about the carrier infant's health is not the norm,[75] it has been demonstrated consistently to occur in a significant minority.[76]
Reaction to ambiguous results (ie initial NBS positive, subsequent testing ambiguous, may be impossible to determine conclusively whether the disease is present or absent) (CF, Medium-Chain Acyl-Co Dehydrogenase Deficiency (MCAD), Krabbe)	Evidence indicates short-term distress is common.[77] Long-term distress is lower, but an underlying worry remains.[78] Difficulty in coping with uncertainty is noted.[79] The issue of living between sickness and health, i.e. being "patients in waiting" is a concern.[80] Families require counselling about the many uncertainties regarding diagnosis, treatment, and prognosis.[81] There is some evidence of an altered parent child interaction and increased parental monitoring of child health.[82]
NBS in a research context: reaction to susceptibility to later onset disorder (*a*1-Antitrypsin Deficiency, (AATD) hypercholesterolaemia, Type 1 Diabetes (TID)	Studies have shown significant short-term parental distress for AATD.[83] For T1D, there was generally no distress on rating scales, but in subgroups e.g. ethnic minority, at very high risk, it was observed.[84] In some cases, there were parental reports of distress.[85] In addition, there was evidence of impaired mother child interaction[86] and increased risk-related behaviour among parents (smoking) for AATD.[87] Parental distress in diagnoses of AATD was long-term.[88] There was no evidence of long-term distress with T1D.[89] There was no evidence of adverse effects on mother-child interaction for T1D, although some health-related behavioural change was reported.[90]

Summary: Key psychosocial issues related to expansion of NBS

There are many ways in which this research can inform future expansions of NBS, as well as potentially contributing to decision-making about PGD. Key points include:

More false positives

As discussed above, as more conditions are added to screening panels, particularly if these disorders are rare, more false positive results will eventuate.

There is clear evidence that when the initial NBS result is positive, parents experience considerable distress, regardless of whether the initial result eventually turns out to be a false positive, true positive, ambiguous or reflect carrier status, regardless of the particular disorder. There is some evidence that this distress may persist for some time, and be associated with altered parental perceptions of child health even when this is later shown to represent a false positive result. Overall, studies suggest that false positive expanded NBS results may create expectations of illness in an otherwise healthy child, in a similar manner to antecedent health problems, such as innocent heart murmurs or jaundice, that have been implicated in the Vulnerable Child Syndrome.[91]

Less well defined diseases and/or ambiguous results

For some disorders, such as CF and MCAD, it can be difficult to know what screening and subsequent testing results actually mean. For example, while newborns are screened for CF with a view to providing early treatment and avoiding complications, some infants with a mutation in the relevant gene are unlikely ever to have symptoms. It is unclear whether or not they have the disease. As Dr Frank J Accurso, Professor of Paediatrics at the University of Colorado states: "We don't know what to call these infants. We don't even have a good language for it yet."[92]

There is some evidence that such ambiguous or uncertain NBS results contribute to parental monitoring of child health and increased healthcare utilisation. There is increasing evidence that uncertainty (eg waiting for sweat test results, unclear prognosis etc) appears to be difficult for parents to cope with and is likely to result in parents pursuing a range of strategies to attempt to reduce uncertainty, including searching for information and monitoring their child's health (see the example of MCAD below). When surveyed about the appropriate scope of NBS, parents have cited the prognostic reliability of the test as an important consideration.[93]

Challenges to informed consent

There have been longstanding debates concerning the ideal nature of "informed consent" for NBS. Approaches to this issue vary geographically. In the US, NBS is said to be mandatory (prioritising the concept of the best interest of the child), although parents are able to opt out for religious reasons. In many other countries, including the UK and NZ, NBS is a matter of parental choice (prioritising the concept of parental autonomy). There is a clear ethos that screening should only proceed once parents have been provided with information and made an informed decision.

In practice, parents may not experience screening as optional. Instead screening may occur on the basis of "informed compliance" with a routine procedure.[94] In reality, these different approaches probably operate in a broadly similar, proceduralised way.

Notwithstanding this debate about the appropriate way to proceed regarding parental consent, there are clear challenges in adequately informing parents, particularly as the number of conditions screened expands. However, surveys reveal that both practitioners and parents believe such information to be vitally important.[95] Screening programmes around the world have responded to these challenges by incorporating education material into routine prenatal care, making it available in a range of languages and many modalities including web-based, DVD and written material.[96] In NZ a range of excellent resources are available through the National Screening Unit website and in hard copy through lead maternity carers.[97]

These resources include important information and messages such as: a strong recommendation to test, parental choice, storage of bloodspot cards, advice that most babies will test negative, the occurrence of false positives, and discussion of disorders in "groups" with advice on how to obtain further information on specific conditions.

An example of the on-going challenges faced by NBS: the case of MCAD

The most common disorder currently screened for using MS/MS is Medium-Chain Acyl-Co A Dehydrogenase Deficiency (MCAD), with a birth prevalence of 1 in 10 – 20,000 in populations derived from Europe.[98] Most of the other conditions, while broadly similar to PKU and MCAD in that they are autosomal recessive metabolic disorders, are much rarer with frequencies generally less than 1 per 100,000 births.[99]

MCAD is a disorder of fatty acid metabolism caused by the lack of an enzyme required to metabolise fat to produce energy. Affected children may have life–threatening or neurologically damaging episodes of hypoketotic hypoglycaemia (a type of low blood sugar) during periods of catabolic stress (such as fasting or intercurrent illness). In between episodes children are healthy and may indeed never become sick.[100] It has been clearly shown that early diagnosis through screening, plus the adoption of management plans involving the avoidance of catabolic stress, has resulted in a much lower incidence of serious episodes or death.[101] Strategies for avoiding catabolic stress include frequent feeding, which in infancy may involve waking the child at night and later may necessitate the provision of cornstarch at bedtime to provide sufficient glucose overnight. Treatment of catabolic stress (for example if the child has diarrhoea and vomiting) may mean admission to hospital for intravenous fluids.

In some respects, MCAD shares salient features discussed in relation to PKU, in that it is relatively common, difficult to diagnose clinically, and has an effective intervention. It also shares another more problematic feature of testing for PKU in that benign or mild variants of the disorder may also be detected by screening. This issue appears to be more significant for MCAD in that the number of cases of benign hyperphenylalaninaemia detected through screening for PKU is small, but screening for MCAD has detected almost twice as many cases as had been expected from clinical presentations.[102] It is thought that some forms of MCAD detected by screening may present in adulthood or be entirely asymptomatic,[103] but these mild variants cannot presently be distinguished prospectively from those that are more severe.

The adoption of new screening technologies has therefore generated diagnostic uncertainty not only about whether a newborn will develop a disease, but also what the condition actually is. For some newborns, this "space" between normal health and pathology may be prolonged and the term "patients-in-waiting" has been used as an umbrella concept for those under medical surveillance. Many of these children will derive no benefit from early diagnosis, and some may even be harmed through unnecessary interventions.[104]

For parents, it may be very difficult to pick the appropriate path between awareness of potential illness and maintenance of "normality" in childhood. These issues are due to "poor genotype phenotype correlation", meaning that individuals with the same mutations may not have the same traits and symptoms. This issue is also relevant to several other conditions recently added to NBS panels, and clearly has major implications for potential future screening programmes.

Summary

The rapid expansion that has occurred recently in NBS is related both to technological advances and to changes in approaches to NBS criteria and aims. The fact that such a shift has occurred, and may well still be occurring, has important implications for the future of NBS. It seems likely that there will be pressure to further expand NBS, for example to include WGS. Lessons learned from these programmes to date may inform not only expansion of NBS but also changes occurring in other clinical contexts such as PGD.

2.3 Childhood genetic testing

Although genetic diseases are individually rare, in aggregate they are common in paediatrics. More than 10% of paediatric hospitalisations involve a child with a genetic condition and genetic disease represents a major cause of morbidity and mortality in childhood.[105] The diagnosis of such conditions is therefore of considerable importance.

Testing prior to the introduction of new approaches to molecular diagnosis

General description

In the older era of childhood genetic testing, tests were primarily offered for two reasons:[106]

- Diagnostic purposes in a child with medical or developmental features suggestive of a specific genetic condition. Examples include well-described conditions including cystic fibrosis and spinal muscular atrophy.
- Predictive purposes in a child at risk of a genetic condition (usually because of a positive family history) and when treatment or surveillance started during childhood is likely to prevent or ameliorate later symptoms. Examples include familial adenomatous polyposis (FAP).

Both of these situations typically required that there be a clear medical indication for genetic testing. Typically, a specific genetic test was performed after rigorous genetic counselling, discussing both the medical and psychological implications of obtaining such genetic information, as part of informed consent.[107]

Policy/guidelines

There has been a long-standing consensus on the indications for testing as reflected in the policy and position statements of all major societies including the:

- American Society of Human Genetics Board of Directors and American College of Medical Genetics Board of Directors[108]
- European Society of Human Genetics[109]
- Human Genetics Association of Australasia[110]

However, more recently (although pre-dating the advent of Next Generation Sequencing (NGS)),[111] there had been a slight shift in practice (and in guidelines) towards acknowledging that in some families, it may be beneficial to confirm or exclude a genetic condition even without the availability of treatment or prevention strategy in childhood.[112]

> The AAP and the ACMG continue to support the traditional professional recommendation to defer genetic testing for late-onset conditions until adulthood. However, predictive genetic testing may be appropriate in limited circumstances. In deciding whether a child should undergo predictive genetic testing for late-onset conditions, the focus must be on the child's medical best interest; however, parents and guardians may also consider the potential psychosocial benefits and harms to the child and the extended family.

This shift in guidelines concerning predictive testing in minors acknowledges some of the issues discussed below in relation to psychosocial evidence and evolving ideas about paediatric ethical concepts. What are these guidelines based on?

Best interests

In a general sense these policy statements and guidelines are underpinned by an acknowledgement that the focus should be on the child's medical best interests. This concept is discussed again below in the section on psychosocial effects, as there have been recent calls to widen its scope.

The rationale for restricting predictive genetic testing of minors unless the results are likely to lead to altered medical management during childhood is similarly underpinned by ethical and psychosocial concerns, namely:

- Testing may infringe upon the child's future autonomy
- Testing may cause psychosocial harm to the child

Autonomy

These policies draw upon the need to respect the "future autonomy" of the child. Experts argue that the parent's decision to proceed with testing could violate the child's "right to an open future" by making available genetic information that the child, as an adult, might have chosen not to know.[113] Empirical support for protecting the right of individuals "not to know" their genetic status is most often derived from psychological research with adults who have a family history of Huntington's Disease (HD), as the majority of these individuals choose not to be tested. Although at-risk adults are more likely to refuse predisposition genetic testing when no therapeutic or preventive interventions for the condition in question exist (as with HD), some decline testing even when such interventions are available.[114]

However, others have suggested that such arguments oversimplify the concept of autonomy and in fact not testing children may also constrain autonomy as they lose the opportunity of growing up with genetic knowledge and adapting to it gradually over time.[115] It is further argued that such self-knowledge may in fact promote more autonomous decision making about one's life.[116] These arguments have been gaining traction over the years, and may have contributed to some variation in practice by individual geneticists.[117]

Psychosocial harm: empirical data

Perhaps the most extensive set of arguments against predictive genetic testing in childhood has been based on the potential for psychosocial harm.[118] The suggested psychosocial consequences of parents knowing their child's genetic test result which may be harmful for a child include:

- altered family dynamics;
- an altered parent child bond such that the parent's expectations of the child change or a "vulnerable child syndrome" develops;[119]
- direct consequences of children knowing their own genetic status (eg feelings of unworthiness or loss of self-esteem, as well as anxiety and depression);[120]
- stigmatisation or discrimination.[121]

These concerns have driven the generally precautionary approach traditionally adopted in paediatric genetic testing. However, for many years there was a distinct paucity of psychosocial data to support these arguments,[122] or indeed the counter argument that *not* testing may also cause harm if, for example, parents remain anxious, finding uncertainty difficult to cope with.[123] However, psychosocial evidence has gradually emerged and to date there is virtually no data suggesting that receiving genetic test results leads to a significant impact on children's psychosocial wellbeing.[124]

While it is true this evidence base remains relatively small and is complicated by methodological inconsistencies, small samples, and reliance on assessments most appropriate for psychopathology, it is nevertheless important. In order to gain a more nuanced understanding of how children respond to genetic testing further research will be required, using rigorous approaches to address children's emotional states, self-perception, and social wellbeing.[125]

Incorporating psychosocial issues into best interests

The possible benefits of early testing, including the potential that it results in better psychosocial adjustment than later testing when lifestyle and life choices are already firmly established, are also under-researched.[126] Although these issues are by no means resolved, the group revising European guidelines on childhood genetic testing has recently suggested that the concept of best interests should be widened to incorporate not only medical benefit, but also potential psychological or social benefits.[127] These ideas have gained traction over the last 5 years or so. Extending consideration beyond the child's medical best interests recognises that the interests of a child are embedded in, and dependent on, the interests of the family unit. In some families, the psychosocial burden of ambiguity may be so great as to justify testing during childhood, particularly when parents and mature adolescents jointly express interest in proceeding.

Consent for testing, parental autonomy and decision-making

There is general agreement that education and counselling for parents and the child (depending on maturity), should precede genetic testing, and should also be readily available after disclosure of results. Similarly, it is acknowledged that the permission of parents and, as appropriate, the assent of the child or consent of the adolescent, must be obtained prior to testing.[128]

There is an inherent tension between the role of healthcare professionals as advocate for children's best interests regarding a genetic test, and the general practice of respecting parental decision-making about their children's health care. While it is assumed that both parents and providers should proceed cautiously with regard to genetic testing in children, given the lack of evidence of psychosocial harms discussed above, it has been argued that parental requests to obtain genetic testing in their children should be respected.[129] This may explain why, despite generally restrictive guidelines and policy statements, surveys suggest[130] that testing children for adult onset disorders and carrier status is not uncommon.[131]

Summary

Prior to the new approaches to molecular diagnosis discussed below, most paediatric genetic testing involved the use of specific tests designed to diagnose or rule out a single condition. The most frequently diagnosed conditions included Down syndrome (trisomy 21), Turners Syndrome, Fragile X, and CF, and predictive tests might be considered for disorders such as familial adenomatous polyposis (FAP).

Guidelines concerning such genetic testing of children were (and for the most part still are) highly consistent and relatively restrictive, with testing advised only for conditions amenable to treatment in childhood. These policies reflect a focus on:

- The medical best interests of the child;
- Concern about breaches of the child's future autonomy;
- The potential for psychosocial harm.

However, arguments supporting a wider conception of best interests, for example including psychological and social benefits, have gradually been gaining traction and in practice some clinicians may accede to parental requests for genetic testing even if they arguably fall outside of practice guidelines.

2.4 How are new approaches to molecular diagnosis challenging existing paradigms?

The preceding part of this chapter can be nicely summarised using the words of Jeffrey R Botkin:[132]

> Twenty years ago, genetic tests were first being introduced into clinical medicine, and they focused on single-gene disorders in the context of family history and population screening. At that time, we had limited data on how genetic testing affected children and their families, and generally suggested that unless obtaining this data could provide timely medical benefits to the child, testing should be deferred to adulthood.

The previous part of this section addressed policy, empirical data and ethical concepts in relation to conventional genetic testing in childhood. In recent years approaches to genetic testing have changed significantly from this clinically based evaluation that focused on single genes, to a much broader "genomic" approach. These changes and their policy and practice implications are discussed below.

New approaches to molecular genetic diagnosis in childhood

Knowledge of the human genome sequence and the declining cost of genomic analysis are driving substantial advances in genetic and genomic testing. As a result, a greater variety of rare genetic and chromosomal disorders can be diagnosed, and risk of common disorders such as diabetes, can be estimated.[133] However, these new approaches create a tension between the need to generate a comprehensive analysis of an individual's genome to address a clinical challenge, and the need to limit problems created by a wealth of data, including secondary findings and findings of uncertain clinical significance.[134] The earlier section of this report outlines a fairly straightforward system of genetic testing with the following main features:

- children were tested on the basis of clinical features or family history of a relatively small number of specific disorders;
- the decision to test was based on likelihood of medical benefit to the child;
- the test result was either positive or negative, with established counselling practices related to both outcomes.

With new approaches to molecular diagnosis the situation is significantly more complex, with some of the key differences noted below:

Making a diagnosis

The range of clinical features considered to be suggestive of a genetic aetiology is now much broader (see discussion below on genetic testing for autism and cerebral palsy) and a greater proportion of children tested will receive a genetic diagnosis (up to 30%).[135]

While this is generally a positive feature of NGS techniques some of these "diagnostic" results will involve various types of uncertainty related to difficulties interpreting pathogenicity of rare mutations, and incomplete information concerning penetrance and future health risks of rare or novel disorders.[136] In addition false negative results may still occur, as even "WGS" actually evaluates only 85-92% of known genes.[137]

Incidental findings

One of the most significant differences between earlier approaches to genetic testing and NGS is the potential to detect genetic susceptibility to conditions unrelated to the indication for the test. Such unexpected health information may be clinically relevant for the child at the time of testing or in the future, or clinically or socially relevant for family members.

Variants of unknown significance

NGS may identify genetic variations that are ambiguous or of uncertain significance (VOUS). A VOUS is a DNA sequence alteration or copy number variation (deletion/duplication), which is not common in the general population, but for which a definite link to human disease cannot be made on current data. Some VOUS will be redefined as pathogenic mutations in the near future as more cases are ascertained; others will be classified as non-pathogenic with time. For this reason, post-test interpretation can be challenging, highly complex, non-definitive and potentially confusing for parents.[138]

These features of NGS testing significantly complicate all aspects of the analysis of new molecular approaches to genetic diagnosis of children as evidenced in the following sections on policy, ethical concepts and psychosocial implications.

New approaches to molecular diagnosis in paediatric practice

In order to consider some of the issues related to these new approaches in more detail, the following describes some of the ways in which such tests are currently used in clinical paediatric practice:

Table 4: Current paediatric genetic tests

1)	**Testing at single genes**	For some disorders, such as Achondroplasia (dwarfism) and Sickle Cell Anaemia, a specific mutation in a specific gene is found in all affected individuals. In children with clinical features of these disorders new sequencing technologies can therefore be used in a highly focused or specific way reminiscent of older methods.[139]
2)	**Sequencing at single genes and single gene panels**	A range of different mutations within a single gene may cause other disorders, such as CF and Neurofibromatosis. In children with clinical features of these disorders the entire gene may therefore require sequencing or alternatively a panel of common mutations may be interrogated.[140]
3)	**Sequencing of multiple genes and multiple gene panels**	For other disorders, such as hereditary deafness or cardiomyopathy, a diagnostic panel across multiple genes may be required, or several genes may be sequenced.
4)	**Micro-Array (CMA) or SNP-based comparative genome hybridization (CGH)**	These "gene chips" (also described in the previous chapter under the heading "new approaches to molecular diagnosis") can detect CNVs (additions or deletions of genetic material) at locations throughout the genome.[141] This process has diffused rapidly into clinical practice (see below).
5)	**Whole exome or genome sequencing**	Genome-wide sequencing is becoming part of clinical practice. It may be considered in the investigation of a child when his/her phenotype or family history suggests a monogenic aetiology with unknown causal mutation(s), and one or more of the following additional conditions apply: • the phenotype is associated with a high degree of genetic heterogeneity; • specific genetic tests have failed to arrive at a diagnosis and testing of other clinically relevant genes is appropriate; • genome-wide sequencing is a more cost-effective approach than available individual gene or gene panel testing.[142]

As the cost of such genetic testing decreases, it has become cost effective to utilise some of these broader approaches as first steps in diagnostic testing. There are several key examples where NGS technologies are significantly changing paediatric practice. Specific examples include:

Developmental delay and autism

Although there are established criteria and methods for diagnosing children with developmental delay/intellectual disability (DD/ID) and autism (ASD), the underlying cause for a specific child is frequently elusive. Over the last few years, CMA has been increasingly utilised for genetic testing of individuals with unexplained DD/ID, ASD, or multiple congenital anomalies (MCA). Indeed, a recent consensus statement supports its use as a first-tier clinical diagnostic test for children presenting with these features.[143]

CMA offers a much higher diagnostic yield (15%-20%) than earlier types of genetic tests such as G-banded karyotype (approximately 3%, excluding Down syndrome and other recognisable chromosomal syndromes) primarily because of its higher sensitivity for submicroscopic deletions and duplications. Occasionally this genetic information may point to a specific management strategy, but more frequently its main use is in explaining the child's condition to parents, prognostication and to inform reproductive decision-making. Variants of unknown significance do occur; international collaborative efforts to catalogue phenotypically significant variants are underway in an attempt to minimise the uncertainty associated with cytogenomic findings.[144] However, as discussed further below, these issues have not been completely resolved and may still present problems for both health professionals and parents/patients.[145]

Cerebral palsy

A similar approach has been proposed for Cerebral Palsy (CP) even more recently. CP represents a group of non-progressive clinically heterogeneous disorders that are characterised by motor impairment and early age of onset, frequently accompanied by co-morbidities. The cause of CP has historically been attributed to environmental stressors resulting in hypoxic damage to cerebral tissue, and while genetic risk factors have also been implicated, guidelines for diagnostic assessment of CP do not generally recommend routine genetic testing. However, a recent study utilising CMA to genotype a population-based prospective cohort of children with CP and their parents identified *de novo* CNVs in 8/115 (7.0%) of CP patients (~1% rate in controls). Overall, the authors concluded that CMA results would have impacted diagnosis or classification of CP in 11/115 (9.6%) families.[146] Such testing is already in use in some specialised centres, and it seems likely that testing for CP will rapidly follow the same path as DD/ID and ASD.

Newborn intensive care units (NICUs)

In NICUs, the science and art of prognostication is a complex endeavour that often has life and death implications.[147] Approximately 5% of infants admitted to NICU die, with genetic diseases and congenital abnormalities the leading cause of death both in NICUs, and among infants in general (children aged <1 year).[148] The majority of deaths are preceded by decisions to withdraw or withhold life-sustaining treatment[149] following discussions between the family and clinical team. These decisions are generally based on assessments of the infant's chance of survival and on the predicted duration and nature of the infant's survival if treatment is provided.[150]

A variety of clinical, biochemical, genetic and radiological tests have traditionally been employed to estimate prognosis in the NICU. CMA is already used for critically ill neonates with congenital malformations,[151] but until the advent of WGS and WES, timely molecular diagnosis of suspected genetic disorders had been largely precluded in acutely ill infants by virtue of clinical and genetic heterogeneity, and the time delays associated with standard genetic tests. However, it is now possible to decode an ill infant's genome in 24 hours (STATseq) and to use clinicopathologic correlation software to evaluate the likelihood that their symptoms are the result of any of the 3,500 known monogenic disorders.[152]

Proponents of these rapid sequencing approaches (that currently remain in a research rather than routine clinical context) cite benefits including: the potential for tailored management; avoidance of unnecessary tests and unhelpful treatments, and assistance for parents making decisions about care when the child is diagnosed as having a fatal disease.[153] Such test results may aid critical care decision-making by predicting functional outcome, important comorbidities or poor prognosis despite treatment.[154]

Opponents suggest that the information derived from such testing will rarely be actionable, may be confusing or psychologically harmful, and resources would be better directed elsewhere.[155] However this type of testing is the subject of significant ongoing research investment with four newborn-sequencing studies that each received multimillion-dollar grants from the US National Institutes of Health (NIH) beginning in September 2013.[156]

Potential future uses

There are many other potential uses of NGS in clinical paediatric practice. Commercial companies are already offering WGS direct to consumers.[157] In the future, these tests could be used to screen healthy newborns, which has become technically feasible from dried blood spots[158] and which appears to be of moderate-to-high hypothetical interest to parents.[159]

These developments in the clinical implementation of NGS have occurred very rapidly and in tandem with discussions concerning ethical issues. The two key aspects of these debates, common to all the above examples, have been:

- Which genetic variants to test for, including how to approach informed consent;
- How the reporting of incidental findings and unclassified variants should be managed.

Emerging policy and guidelines about paediatric usage of new molecular diagnostic tests

General Policy

Guidelines and policies continue to support diagnostic testing in children with clinical features suggestive of a genetic disorder, and predictive testing for conditions with childhood onset. Similarly, although the updated set of general guidelines concerning childhood genetic testing published by the ACMG in conjunction with the AAP[160] continue to support the recommendation not to test minors for adult-onset conditions, there is an implied expansion of "clinical indication" to include consideration of parental interests and their potential effect on the child.[161] This has resulted from the lack

of evidence supporting actualisation of potential harms, along with broader appreciation of psychosocial benefits that testing can provide.[162]

This slightly "less restrictive" position is shared by other significant groups, such as the ESHG[163] and HGSA:[164]

> The interests of the young person, the parents and the family need to be considered in relation to pre-symptomatic and predictive testing of a young person. The benefits and harms should be categorised into short and long-term medical, psychosocial and reproductive issues. Ultimately, the best interests of the young person must prevail, and it is important that the health professional be an advocate for the young person during the genetic counselling process.

All relevant guidelines also stress the need for adequate pre-and post-test counselling, with the HGSA including reference to psychological assessment and support if predictive testing for adult onset disorders is considered in an adolescent.[165]

> It is strongly recommended that testing be arranged through a clinical genetics service, in conjunction with an adolescent psychologist or psychiatrist who ideally has experience in pre-symptomatic or predictive testing.

Practice guidelines: the example of CMA

Against this backdrop of clinical caution regarding predictive genetic testing for specific disorders in childhood, new forms of molecular genetic diagnosis have diffused rapidly into practice. There is now a wide consensus, including in Australia and NZ, that CMA is an appropriate first tier clinical diagnostic test for children with developmental disabilities and multiple congenital abnormalities.[166] This potentially creates tensions with the general guidelines as it is acknowledged that variants associated with late onset conditions will be identified routinely as IF when performing WGS or WES, and to a lesser extent CMA. The use of CMA has also raised some concern among paediatricians in NZ and elsewhere about the difficulties of utilising such tests in practice, for example in relation to the management of VOUS and how to approach informed consent.[167] These, and other concerns are also reflected in the recent ASHG statement:[168]

> Use of these arrays has increased the utility of cytogenetic testing by increasing the rate of positive diagnoses (allowing the identification of much smaller deletions and duplications than cytogenetics alone), and with increasingly precise definition of breakpoints and gene content for deletions and duplications, it has allowed the identification of many new syndromes. However, these tests also allow the identification of copy-number alteration of disease-associated genes unrelated to the initial reason for study, allow the identification of excessive homozygosity indicating potential consanguinity or incest, and have a significant likelihood of identifying a variant of uncertain significance. CMA also has the potential to identify secondary findings.

The ASHG statement further suggests that:[169]

> Clinicians and parents should be adequately informed about the complexities of CMA testing before CMA testing is ordered and results are provided to patients. Clinicians should understand the concepts of variants of uncertain significance, variable expressivity, and reduced penetrance and the potential need to consider testing of other family members.

As NZ paediatricians note, this can be difficult to achieve in general paediatric practice due to time constraints in clinics and difficulties for generalists keeping pace with new developments in genetics.[170]

Incidental Findings

Adding to these tensions, the ACMG issued guidelines concerning the reporting of IF in clinical exome and genome sequencing.[171] It recommends that laboratories seek pathogenic mutations in 56 genes and return those results to the referring clinician to incorporate this information into the patient's health care, *regardless of the patient's wishes or age*.[172] (See appendix 1 for a list of the 56 conditions.) These recommendations have generated significant discussion, especially over questions of whether they undermine patient autonomy to choose whether to receive IFs[173] and return of results for children, given that many of the conditions are adult-onset.[174] The choice of which genes to include in such return of results is also the subject of ongoing controversy, as the ACMG itself recognises that there are insufficient data on clinical utility to fully support the recommendations for all of the genes.[175] Many authors have been critical both of the way this policy was developed, as well as its content.[176]

While the ACMG initially recommended all clinical exome and genome sequencing should seek and report the 56 specified conditions *"without seeking preferences from the patient and family and without limitation due to the patient's age"* (emphasis added),[177] it has subsequently revised its position:[178]

> The ACMG has 'listened carefully' to views and 'appreciates the many forums in which divergent and valuable opinions have been expressed' before concluding that among their own membership there 'appears to be a consensus' that patients should have an opportunity to opt-out of the analysis of medically actionable genes as an adjunct to whole exome or genome sequencing.

This is more consistent with the ASHG position statement that advises that if "secondary findings" (defined as clinically relevant information unrelated to the condition for which the sequencing was originally ordered) do arise:[179]

> ASHG recommends that clinicians offer to disclose secondary findings for a child to the child's parents or guardians only when the information has clear clinical utility for the child and/or his or her family members. In any clinical genomic endeavor that has a substantial likelihood of generating clinically relevant secondary findings, ASHG recommends that there should be a robust informed-consent process. ASHG recommends that, in general, parents should be able to decline to receive secondary findings in advance of genetic testing. However, when there is strong evidence that a secondary finding has urgent and serious implications for a child's health or welfare, and effective action can be taken to mitigate that threat, ASHG recommends that the clinician communicate those findings to parents or guardians regardless of the general preferences stated by the parents regarding secondary findings.

The issue of what should be on a list of "clinically relevant secondary findings" also remains a complex and contestable issue, which has certain parallels with the choice of conditions for NBS panels. In this regards the ASHG recommends that:[180]

> work be conducted for assembling a list of genes in which duplications or deletions are clearly associated with clinically important diseases. This list could function as a secondary-findings list with implications for what should and should not be reported back to families.

The issue of managing IF therefore remains very much a "live debate": while there are ongoing attempts to achieve consensus, there remains considerable divergence in practice in different jurisdictions.[181] These debates are covered in greater detail in chapter 1.

Targeted or limited results

It is likely that there will be further clinical indications for CMA as time goes on and other forms of testing (such as WES/WGS) will also rapidly diffuse in to practice. Anticipating the rapid developments in this field and the likely exacerbation of tensions between underlying guidelines and practice (that is generated by IF and VOUS) the ASHG recommends limiting sequencing as far as possible:[182]

> When clinically indicated, the scope of genetic testing should be limited to single-gene analysis or targeted gene panels based on the clinical presentation of the patient. Targeted testing using genome-scale sequencing, but restricting analysis to a limited set of genes relevant to the clinical indication, is an acceptable alternative to a single-gene analysis or targeted gene panel in certain circumstances. When genome-scale sequencing is performed but the analysis is restricted to a limited set of targeted genes, ASHG finds it ethically acceptable for the laboratory to limit the analysis to the genes of clinical interest.

The latest ESHG guidelines also recommend targeted diagnostic testing should occur wherever possible to limit the likelihood of detecting IF.[183] There is significant interest in the development of more targeted approaches. Although sequencing the exome has the advantage of casting the net wide, targeted gene panel sequencing provides finer detail in specific regions and can be designed to avoid IF including those associated with adult-onset conditions.[184]

2.5 Key issues contributing to debates about childhood NGS

In the previous sections of this chapter, a *de facto* consensus was identified, with national and international clinical guidelines generally recommending against targeted predictive clinical testing of asymptomatic children for adult-onset disorders for which childhood intervention was unnecessary or unavailable.[185] This analysis also encompassed the role of both ethical concepts and empirical research concerning psychosocial effects that underpinned the relevant policy and guidelines.

However NGS has reignited the debate about what is appropriate to test for in childhood, and disrupted the previous consensus. Given this the following discusses the role of ethical concepts and empirical research into psychosocial effects of testing in these debates.

Ethical concepts

There is little controversy about which key ethical concepts are relevant to these discussions. They are broadly similar to the key ethical considerations related to earlier forms of genetic testing, namely:[186]

- The "best interests of the child", including consideration of psychosocial harms and benefits and the child's future autonomy
- Parental autonomy (given that the permission of parents must generally be obtained prior to testing).

However, the meaning of these concepts has become significantly less clear, as noted in the recent ASHG statement:[187]

> The notion of "best interest" is intended to place the child's welfare foremost in medical decision making.

But as the statement continues:

> Given the subjective nature of the interests of those who cannot speak for themselves, defining an individual child's "best interest" is often complex and controversial, particularly in medical circumstances involving burdensome treatments and profound disabilities.

Evolution of "paediatric ethical concepts"

It is not surprising that the meaning of these concepts is disputed in relation to NGS as they have been debated extensively in paediatric bioethics more generally, and have evolved significantly over recent years. Most notably, current discourse questions the primary role of best interests in paediatric healthcare decision-making, and a number of alternative ethical models have been proposed:

Expanded Conceptions of Children's Interests

These debates are related to an increasingly nuanced appreciation of what is actually meant by "children's interests". In general terms this is easy to understand: "interests" are aspects of wellbeing. For example, Wilkinson states that:[188]

> an individual's interests together contribute to their wellbeing – how well or badly their life overall is going.

What is more difficult to capture is how we might determine what the individual components of this general state of wellbeing may be – or put very simply, what items might feature on a list of children's interests.

In a recent review, Salter characterised and distinguished six different existing versions of the "best interests standard", differentiating them according to a taxonomy scheme based on the types of interests considered, and the priority assigned to them.[189] Using this scheme, it becomes clear how variable different concepts of "best interests" can be. Some are highly individualistic (they do not admit of other-regarding interests), whereas others may be "restricted relational" (they admit of other-regarding interests to a limited extent). Some prioritise cognitive-developmental interests (such as interests 'related to developing certain cognitive capacities, knowledge, and skills'),[190] whereas others prioritise relational interests (such as those that concern interpersonal connections, or relationships').[191] Finally, some of them focus on future-oriented interests (such as interests in developing the capacity for autonomy), whereas others focus on present-oriented interests (like interests in avoiding pain).[192]

While this debate concerning the nature of children's interests is by no means settled in children's healthcare in general, there has been a gradual shift in focus from acute physical or physiological interests towards a greater appreciation of the importance of psychological and relational interests. For example, the treatment of children with disorders of sex development (DSDs) now focuses more on overall wellbeing, than on the early surgical creation of unambiguous external genitalia.[193] Similarly, the predominant model of patient care in contemporary paediatrics, known as "Family Centered Care"[194] explicitly acknowledges the critical role of parents and the relevance of their own interests in decision-making for the child.

Finally, the importance of "future interests" is increasingly acknowledged, although it remains difficult to know how to weight such interests in childhood. For example when adults make medical decisions for themselves, they might tolerate short term discomfort in order to maintain certain key functions related to autonomy, but exactly

how this preference relates to healthcare decisions for children has received little explicit attention.[195] It may be useful to reflect upon the ways in which what is done to the child now might limit or promote their future autonomy, or protect their right to an open future;[196] but if interests themselves are viewed in a more nuanced way these issues become more complex.

Challenges to the best interest standard

Given that it is difficult to adequately define "children's interests" it seems even more problematic to try and determine what is "best" in individual cases. It may ultimately not be possible to completely resolve disagreements concerning which types of interests matter most.

More recently a second problem with the best interests standard has been articulated. Starting with a child's best interests can obscure the ethical claim of the parents to be the decision-makers for the child. It is well recognised in paediatric bioethics literature that parents are the default decision-makers for their child, albeit usually with advice and guidance from doctors. There are good reasons why this is so, including:[197]

- Most parents care about their children and will therefore desire what is best for them, and make decisions that are beneficial to them.
- The interests of family members may conflict or compete and parents are usually better suited than people outside the family unit to weigh and balance such interests and make a final decision.
- Parents should be able to raise their children how they see fit, according to their own values and philosophies.
- Parents are generally in the best position to be knowledgeable about their child's interests.
- Parents themselves are the ones who bear much of the primary burden and consequences of medical decisions that are made for their child.

In everyday life it is also widely acknowledged that parents can and do make decisions on behalf of their children that are not absolutely optimal. Diekema suggests that:[198]

> few would argue that a college education would not be in the best interest of most children. Yet we do not require parents to provide their children with a college education. Nor do we require parents to send their children to the best elementary schools.

It would be holding parents to a very high standard if "best interests" was to be understood as defined by Brock and Buchanan as, "acting so as to promote maximally the good of the individual".[199] This does not suggest parents can make any decision they wish, but in practice parents are only over-ruled as decision-makers when there is good reason to do so.

Responses to the challenge to "best interests"

These objections to the best interests standard form the basis of contemporary ethical tools for dealing with paediatric healthcare decisions when parents and doctors disagree. The Harm Principle proposed by Diekema suggests that the feature of parental decision-making that justifies interference is not that it does not align with the child's *best* interest, but rather that the decision poses some harm to the child.[200] The Zone of Parental Discretion (ZPD) has been proposed as a means of operationalising the Harm Principle, in a clear, step-by-step process. The ZPD refers to the ethically and legally protected space where parents may legitimately make decisions for their children, even if the decisions may be sub-optimal for those children (that is, not absolutely the *best* for them).

Parental autonomy

Tools such as "the harm threshold" and the "ZPD" prioritise parental autonomy (or the parents' rights to make decisions on behalf of their children) and only limit this discretion if their decision is likely to cause significant harm to their child. While the terminology of the best interests standard remains widespread, these tools now feature strongly in paediatric practice as well as in the academic literature on Paediatric Bioethics.

Relevance to arguments concerning genetic testing of children

The relevance of these evolving ideas about paediatric ethical concepts to genetic testing has been relatively neglected in relation to genetic testing, with the notable exception of Wilfond and Ross:[201]

> Ethical evaluation of genetic testing in children is traditionally based on balancing clinical benefits and risks. However, this focus can be inconsistent with the general practice of respecting parental decision-making about their children's health care. We argue that respect for parental decision-making should play a larger role in shaping pediatric genetic testing practices, and play a similar role regarding decisions to use emerging genomic technologies.

Closer analysis of debates concerning NGS in childhood suggests that implicit differences in understanding and implementation of key ethical concepts are indeed major contributors to differences of opinion. For example, why is it that critics of the ACMG guidelines argue that the new recommendations are inconsistent with the historical consensus against predictive clinical testing of minors for adult-onset disorders, but supporters disagree?[202]

Individualistic versus family centered approaches

Understanding these opposing arguments is complicated by the fact that both supporters and critics tend not to explicitly define what they mean by "best interests".[203] Critics of broader genomic testing approaches (such as for the 56 conditions noted in the ACMG report) appeal to highly individualistic accounts of children's interests, ruling out the relevance of relational interests. The ACMG, in turn, strongly emphasises the importance of these relational interests. In this way, both parties can consistently maintain their position as being in the best interests of the child because they mean different things by "best interests".[204]

Child's future interests

Similarly, different conceptions of "the child's right to an open future" seem to complicate the current debate. Individualistic versions of this principle (such as Feinberg's account which dominated the early genetic literature) indicate that physicians should not test for adult onset disorders and carrier status, in order to preserve the child's future right to make his or her own decisions about genetic testing. The focus is very much on parents and physicians not constraining children's abilities to make a wide variety of life choices when they are adults.[205] However more family oriented versions (such as Ruddick's Life Prospect principle) suggest that children's interests are always inter-twined with those of their parents. In these accounts parents are seen as more active participants in their children's path towards autonomy.[206] This latter account gives parents greater discretion to act on their personal views concerning what is best for their child and arguably fits better with the more contemporary approaches to paediatric healthcare decision-making described above.

Summary

These debates concerning ethical concepts remain at the core of many of the current tensions concerning genetic testing of children. To begin to remedy this situation, commentators should be encouraged to explicitly recognise, acknowledge, and defend their interpretations of the relevant underlying concepts. However, it ultimately seems likely that more family centred approaches should have greater priority in the context of genetic testing, just as they do in paediatric ethics more broadly. Intuitively it also seems difficult to maintain a highly individualistic approach to genetic testing for children. For example, as Bush notes:[207]

> It is manifestly in the child's best interest to have the parents alive and healthy enough to raise them. If the family does not have prior knowledge of a mutation (for example *BRCA1*), its provision through the ACMG recommendations has the potential to be lifesaving, and I believe most children would chose to foreclose their opportunity for self decision making at age of majority for the opportunity of having their parent be able to take care of them. The benefit to the child of preserving the health and life of their parent(s) would seem to clearly outweigh the far less probable risk of an attachment disturbance or a "vulnerable child" syndrome.

Others have made similar arguments that overly individualistic approaches to good practice in genetic testing may not be appropriate in situations where the results (including IF and VOUS) often have relevance to other family members.[208]

Empirical data concerning psychosocial effects of paediatric NGS

Although these debates concerning ethical concepts are by no means resolved, what is clear is that empirical research about the impacts of broader genomic approaches on children and families is urgently required to inform them.[209] We have previously discussed the empirical evidence base related to NBS and pre NGS paediatric genetic testing. In both of these contexts such data has gradually helped to inform the approach to both screening and testing. Given that the new molecular genetic diagnostic techniques discussed in this section have only very recently become available, the lack of evidence concerning their purported risks and benefits poses a considerable challenge. Similarly the multitude of different types of findings that families may receive adds additional complexity to any empirical study. However, such evidence is critically important to any overall analysis.

The following reviews currently available data, which largely consists of the opinions, attitudes and experiences of health professionals and parents who have already had direct clinical involvement with genomics enabled approaches.

To aid analysis of this data the testing process is compartmentalised chronologically, addressing:

- Pre-test counselling, including the informed consent process;
- Disclosure of results;
- Post-test sequelae.

Pre-test counselling/informed consent

There are several aspects of genomics enabled approaches (GEA) that create new or amplified challenges for informed consent. These include their complexity, the variety and uncertainty of potential results, the broad implications of those results, and the elevated expectations of personal benefit from testing.[210]

Complexity

Data from studies involving both health professionals and parents suggests that a key challenge to informed consent will be the inherent complexity of GEA. Because tests such as CMA are often performed when a child's diagnosis is uncertain, it is likely to be impossible to counsel parents regarding potential implications of the hundreds of possible diagnoses that might follow, or the potential future health impacts of variants not associated with child's underlying disorder. Parents have already reported concerns that this type of complexity is unlike any other type of medical testing they have encountered.[211] This perspective is not unrealistic given that informed consent for genomic sequencing may involve many decision points, such as whether to participate, selection of any optional findings offered as part of sequencing, and decisions about future use and storage of data. Consequently, there are many opportunities for disagreement among parties who may participate in the decision-making process.[212]

Uncertainty

GEA are not only complex, they may also be uncertain. Uncertainty in this context can take many guises. Studies of health professionals' attitudes towards these new approaches tend to indicate concerns regarding the technical and interpretative limitations of the tests, and how to convey this level of uncertainty to families.[213] Despite the recent emergence of large databases or catalogues of human genetic variation it can still be difficult, even for experienced clinicians, to fully understand the meaning of copy number variants (CNV) for an individual patient. Even determining whether or not a variant is likely to cause a disease can be problematic.

It is acknowledged that as routine care moves from the use of CMA to WES/WGS, providers and patients are likely to confront these complexities more often, and hence are more likely to need to canvas them in pre-test counselling sessions.[214] This issue is particularly pertinent for non-genetic professionals. Study data supports the view that educational resources need to be developed for non-genetics providers to facilitate their counselling of families and interpretation of CMA results.[215]

Time constraints

The literature also acknowledges that although full disclosure of all potential implications of genetic variants may not be feasible, pre-test discussions still require significant time and frequent assessments of understanding.[216] In one study of health providers in paediatric practice, tensions were revealed between the need for comprehensive informed consent for all families and the challenges of communicating time-consuming and potentially anxiety-provoking information regarding uncertain and incidental findings that may be relevant only in rare cases.[217]

Automatic acceptance

Another potential barrier to informed consent identified in the empirical literature is that parents, driven by their desire to know the cause of their child's condition and likely prognosis, will automatically accept GEA. This issue has been acknowledged by both parents and professionals and is likely to contribute to difficulties in ensuring that incidental findings or other potential risks are carefully considered in pre-test counselling.[218]

High expectations

Interviewees in a study of health professionals with clinical experience of GEA highlighted the challenges of working with participants with extremely high expectations for diagnostic results from sequencing, which may be out of alignment with published estimates of sequencing diagnostic yield.[219]

Importance of context and longitudinal perspective

While test related factors such as clinical utility and analytical validity will be important in determining which results are relayed to parents, it is also likely parental preference will play a role. Studies suggest that such preferences will vary considerably based upon factors such as: pre-existing beliefs about family disease history; perceptions of family or personal vulnerability to particular diseases; anticipation of negative emotions associated with receiving certain results; and life circumstances. In these studies preferences were

not viewed as immutable and participants anticipated that circumstances would change previous choices and decisions about receiving genetic results for a child. This data is consistent with recent observations that life circumstances can change preferences for genetic or genomic information. It supports suggestions for a tiered re-consent or flexible consent process for the return of individual results.[220]

Summary of informed consent section

Several aspects of GEA create new, or amplify, challenges for informed consent. Empirical data suggests that there is general agreement amongst parents and health professionals that pre-test discussions are crucial to facilitate informed decision-making and to order to avoid "surprises" related to IF. There is also agreement that this is immensely difficult to achieve in practice because of the inherent complexity and uncertainty with these approaches.[221] There continues to be a lack of consensus concerning what the critical elements of pre-test counselling and informed consent process might be. In some aspects of clinical practice areas of agreement concerning informed consent have emerged,[222] but paediatrics continues to pose considerable challenges. It is noteworthy that a recent study highlights that as experience with GEA accumulates, genetic health professionals tend to place less emphasis on standard elements in the consent form and technological aspects of sequencing. Instead they focus on addressing misperceptions and helping patients/parents develop realistic expectations about the types and implications of possible results, including secondary findings.[223] Future research should address the extent to which various stakeholders agree on key elements of informed consent with the aim of working towards consensus.

Disclosure of results

What to disclose

With GEA it is no longer a potential outcome that one will receive results beyond the specific clinical indication for testing, but rather a certainty. It is estimated that an average exome yields 30,000–40,000 variants, with 3–8 of these being clearly medically actionable.[224] Most of these secondary variants represent heterozygous status for recessive diseases.

One notable model for returning results from GEA has been outlined by Berg and colleagues and includes three categories (or "bins") of IF: medically actionable variants (e.g., Lynch syndrome, *BRCA1/2*), clinically valid findings (e.g. pharmacogenetic variants, carrier status), and variants of uncertain significance.[225]

However while this model may provide a basis for categorising IF and may provide some guidance concerning the informed consent process,[226] different stakeholders have very different opinions concerning which categories should be disclosed. This has led to considerable debate in the literature concerning who should make these decisions and under what guidelines.[227] The following presents data from studies canvassing relevant opinions (for example from parents, the general public and health professionals) concerning this issue in paediatric clinical practice.

Parents views

Study data to date highlight that many parents of children with genetic conditions would want to receive all results from WES, including those relating to the cause of the child's current condition, cancer pre-disposition, carrier status, and adult-onset, untreatable disease. Reasons for wanting such results include the opportunity to prepare for the future, the possibility of further developments in medical treatment and prevention, and the belief that they were entitled to all sequencing data. They also noted that their experience in caring for a child with a genetic condition, including negotiating the health care system, would prepare them for dealing with complex health information.[228]

Similarly parents whose children with developmental delay were participating in a genomic research repository reported that they would like to receive all individual findings, including those with uncertain implications or no clinical utility, citing personal utility and adeptness at dealing with uncertainty.[229] Interviews conducted with parents tested for *BRCA1/2* mutations found that almost 50% supported testing of minors for this adult-onset hereditary cancer predisposition syndrome. Reasons for support of testing minors included the opportunity to foster preventative behaviours, a claimed individual right to test, and absence of harm in testing.[230]

However, it is interesting to note that when parents who have already experienced WGS for one affected child are asked to consider testing for another child, they are much less enthusiastic, citing concerns about "labelling", worry and the potential for unwarranted medical intervention.[231] Similarly parents whose children were tested for genetic risk of T1D at birth do not regret the decision 12 years later, but significantly they would not test a subsequent child or recommend testing to other parents.[232]

Lay groups from the general population also recognised challenges in handling complex datasets. However, they highlighted that scientific uncertainty and IF should be discussed pre-test to support patients to make informed decision about options. These groups emphasised their desire to have the choice to learn about the probability of conditions that may develop, so they could choose whether to live with uncertainty. They felt it important that they were able to undertake a "risk analysis" themselves rather than have the professionals make decisions on their behalf.[233]

No parent or lay group appears to believe that that disclosure should be based on clinical relevance alone. They maintained that because individuals interpret "relevance" and "seriousness" differently, patients should not be presented with pre-categorised packages filtered by professionals, because professionals should not decide about relevance on patients' behalf. The majority think that the return of incidental results should be guided by individual preferences.[234] However this finding should be balanced alongside genetic counselling experience that has shown that patients often become saturated after 20–40 minutes discussion of return of results.[235]

Professionals' views

In contrast to parental preferences, clinical relevance dominates health professional opinions and attitudes about return of results from GEAs. In one Australian study health professionals valued the availability of prevention and treatment for the condition above all other characteristics when evaluating IF for disclosure.[236] Similarly another health professional group expressed concern over allowing parents to choose to receive results that would not lead to immediate changes in medical management, and maintained that only particular test data be analysed to avoid problems of handling extensive data and to limit IF.[237]

Summary of what to disclose

In general health professionals agreed that WGS should involve limiting the data for analysis and discussion with patients by "focusing the focus" of the test. They considered it was unrealistic to include all data in pre-test discussions, would not benefit patients, and could be burdensome. Lay groups acknowledged practical challenges of handling extensive, uncertain data, but emphasised patients' rights to be informed to facilitate choice. These contrasting perspectives reflect the challenges that NGS poses to shared decision-making in the clinic. Given these practical challenges, further investigation will be required to determine how such sharing of information and decision-making can be achieved.[238]

How to disclose

One study addressed how results from CMA and NGS should be delivered. Parents and professionals agreed that return of results should be administered in a two-step process with variants relating to the child's current condition taking precedence over findings not relevant to the child's condition such as carrier status. Both professional and parent groups focused on the responsibility of the healthcare provider to make these results available, and to re-interpret results, over time.[239]

Meaning of results

Understanding of uncertain results

The aim of undertaking NGS in a child is to diagnose a genetic cause for the child's condition, but in the majority of cases sequencing will not yield this information, and might yield results of unclear significance.[240] In this regard Reiff et al have identified incomplete comprehension of test results and scientific uncertainty as prominent themes for families receiving results in both the pathogenic and uncertain variant categories.[241] However other studies addressing parental perceptions of the meaning of their child's results have produced somewhat conflicting results.

Some parents have reported that CMA was important for understanding their child's diagnosis and they were satisfied with the information even if it included VOUS.[242] Other participants struggled with meaning and future implications of the VOUS.[243] In a different study, participants maintained contradictory interpretations themselves, describing results as answers while also maintaining that little clarification of their child's condition had been provided.[244]

Genetic counselling regarding VOUS results has been found to contribute positively to both parental understanding and support.[245] However, uncertainty remains a key theme in this emerging research with another study reporting that parents experienced uncertainty regardless of the type of microarray result received. Pathogenic and benign variants as well as VOUS also appeared to be associated with lack of clarity in meaning for diagnosis, prognosis, management and implications for future pregnancies.[246] These authors comment that as "genomic uncertainty" manifests more often, given the increasing use of genome scanning technologies, parents' emotional reactions to it, regardless of the type of variant identified, will likely warrant a comprehensive and sustained counselling response.[247] Parents' strategies for managing this uncertainty have also been found to vary considerably from philosophical acceptance (i.e. "live with it"), to spiritual beliefs as a source of strength, trust in experts and hope for the future (e.g. that science may ultimately provide concrete answers).[248]

Post test sequelae – early and late psychosocial outcomes

As yet there is very little data concerning later psychosocial effects, and none that assesses impact on the child themselves. In the short-term, parents emotional and psychological reactions to CMA results, both of uncertain and pathogenic significance, vary considerably and can include relief, changes in self-concept, and empowerment.[249]

Anxiety has also been found to be a key consideration, although professional concerns about patient anxiety outweighed parent and public concerns. Lay groups maintain that parents should assess the impact for themselves and that it is their right to choose what to know and whether this outweighs any personal risk of anxiety.[250]

Overall it is considered likely that psychosocial impacts will vary: harms may be greater for individuals who are predisposed to anxiety or worry, individuals who lack certain resources (money, insurance coverage, access to counselling or other services) or individuals who have particular pre-existing beliefs about family health or medical history and vulnerabilities. Harm may also be greater for individuals who interpret findings as more significant or influential to their personal health or the health of their child, while having fewer options to pursue alternative means of obtaining clarity about the findings, or beneficial genetic and medical information.[251] Alternatively, decreased potential for harm regarding the return of results may be present for those who have greater social support, when results are more communicable, and when participants' expectations for the information are not violated.[252]

Overall summary of empirical section

The emerging evidence in this field paints an extremely complex picture. There is considerable variation between individuals concerning how the informed consent process should be managed and what types of results should be disclosed to parents. Psychosocial reactions to the uncertainty that is frequently a major component of test results also varies considerably such that balance of harms and benefits may ultimately be dependent on the characteristics of the individual (or family) undergoing testing. To complicate this further, there are suggestions of intra-individual variation in reactions over time and a lack of data concerning impact on children.

Case example

The following case highlights some of the issues discussed in this chapter. Rather than attempting to argue for one particular approach the following presents some of the arguments for and against providing comprehensive results. In a similar way to the body of this chapter, these arguments are underpinned by policy, ethical concepts and physical and psychosocial implications of testing.

Testing for ASD/Developmental delay

A 5-year-old girl, Emily, undergoes CMA testing to try to identify an underlying cause for her autism and mild developmental delay. Results indicate a deletion on chromosome 17 that is associated with development delay. However, it also included the *BRCA1* gene, which indicates a significantly increased lifetime risk for breast and ovarian cancer.

Providing Emily' parents with information about the IF of *BRCA1* mutation would:

- Contravene the general presumption against predictive genetic testing in childhood.
- Be consistent with other guidelines including those of the ACMG.
- Remove Emily's right to choose for herself whether to undergo *BRCA1* testing in the future.
- Potentially cause parental anxiety about future problems (for Emily and themselves) when they are already concerned about Emily's current difficulties.
- Provide potential benefits to Emily given that there are steps that can be taken to reduce her cancer risks and that screening is available for early detection.
- Potentially benefit Emily's parents if they elect to be tested themselves, test positive, and then undergo surveillance.

Not providing this information to the parents would:

- Be consistent with the general presumption against predictive genetic testing in childhood.
- Be inconsistent with other guidelines such as those of the ACMG.
- Maintain Emily's right to choose testing for herself, although in reality this may not be readily available if there is no family history of breast cancer.
- Restrict Emily's ability to choose early surveillance and/ or prevention for breast cancer risk if she remained unaware of her *BRCA1* status.
- Avoid worrying Emily parents with information they may or may not have understood they could receive (depending on the consent process).
- Potentially result in harm to Emily if she were to develop breast cancer.
- Potentially result in harm to Emily's parents if one of them also possessed the *BRCA1* mutation.

Summary

NGS is already being used in pediatrics. There is no question that in the paediatric population, sequencing provides a powerful way to elucidate the molecular causes of rare conditions and multiple congenital anomaly syndromes.[253] However these technologies differ significantly from the older types of genetic testing and place tension on the previous consensus against predictive testing in childhood.

Continuing the clinical implementation of new molecular approaches to diagnosis will require explicit consideration of how the more "evolved" ethical concepts discussed earlier in this chapter operate with regard to genetic testing within the current environment of clinical paediatrics, with its emphasis on family centred care and shared decision making. Ultimately it seems clear that families' perspectives on all aspects of genetic testing of children will be critically important, but this is likely to necessitate a system that can be tailored to the wants and needs of many different families in different contexts. Advances in genomic technology may have made consensus on a single preferable course of action regarding the genetic testing of children more elusive.[254] As genetics professionals attempt to tailor approaches to supporting families in comprehending and processing increasingly complex genomic results, their efforts will need to be informed not only by consideration of the key ethical concepts, but also by data detailing the lived experiences of parents and children with regard to genomic technology.[255]

2.6 Can what we know about childhood genetic testing inform the future of selective reproduction?

Considering the experience of genetic testing in childhood arguably informs, and enhances, discussions regarding reproductive genetic testing. A central aim of both pre-implantation genetic diagnosis (PGD) and prenatal testing (including NIPT) is to enable prospective parents to achieve a successful pregnancy and ultimately a "healthy" child. Arguably the impact of parental knowledge regarding the embryo, foetus and future child's genetic information upon parents and the future child should inform any future guidelines or policy around selective reproduction. As both NIPT and "expanded" PGD currently share features of screening and diagnostic tests, experiences with newborn screening and childhood diagnostic testing are relevant to this analysis.

Why consider childhood genetic testing?

Genetic testing in childhood is considerably further advanced in terms of its clinical implementation than for either PGD or prenatal testing. Chromosomal microarray analysis (CMA) has been widely used for several years, and next generation sequencing (NGS) has been adopted in some centres with large research studies aiming to catalyse its use as a diagnostic tool.[256] Consequently, although the issues are by no means resolved, the ethical concepts and psychosocial implications of testing have already been the subject of much debate. Given the similarities between these technologies there should be some consistency in the extent to which liberty interests are weighed against putative harms. However, this does not suggest that current experience of childhood genetic testing can, or should, provide all the answers to questions concerning the future of selective reproduction. The ethical and legal frameworks guiding reproductive decision-

making in the case of a child-not-yet-born clearly differ. Despite this, there are several areas where knowledge and experience arising from genetic testing in childhood could be informative.

Rapid diffusion into clinical practice

This review clearly demonstrates the impact that technological advances have had on genetic testing in childhood. The development of tandem mass spectrometry (MS/MS), was a substantial contributor to the dramatic expansion of NBS programmes in the 2000s. Similarly, NGS is having a significant impact on paediatric practice, including in acute settings such as neonatal intensive care units (NICUs). It is now possible to decode an ill infant's genome in 24 hours (STATseq) and employ software to evaluate the likelihood that their symptoms are the result of any of the 3,500 known monogenic disorders.[257] While both these initiatives have the capacity to improve outcomes for children and/or their families, it has become increasingly clear that they may also have adverse effects, and may even subtly shift the entire focus of such programmes:[258]

> The original paradigm for newborn screening was fairly clear cut. The disorder had to be treatable; it had to have dire consequences if not detected early. There had to be a simple and available test--the PKU paradigm we used to call it. And tandem mass spectrometry interceded on top of that and created a different paradigm. It shifted into a technological paradigm and away from a considered disease-by-disease paradigm.

The so called "technological" imperative to expand screening has already begun to impact upon the field of selective reproduction. However reservations about expanding the scope of NBS and paediatric testing do not necessarily imply that expansion within the field of selective reproduction should only occur in a highly precautionary manner. (In Ben Wilfond's words it may not be appropriate to adopt an "Eeyore phenotype", characterised by woe about the perils of genomics).[259] But neither should the field of selective reproduction simply embrace all advances without considering their wider consequences (the "Tigger phenotype", characterised by confidence that our future will be enhanced through genomics).[260] Rather, the implications of using next generation sequencing (NGS) in selective reproduction should be urgently but carefully considered (the Christopher Robin phenotype),[261] taking note of both short and long term consequences, and including those that are more subtle and difficult to measure, as well as those amenable to standard empirical investigation.[262] The existence of "technological imperatives", that have clearly played a major role in childhood genetic testing, highlight the pressing need for a comprehensive and nuanced analysis of the likely ethical, legal and social impacts (ELSI) of expansions of selective reproduction services. Again some of the ELSI analyses within paediatrics genetic testing that are discussed below may provide pointers for such research.

The expanded scope of childhood genetic testing

The appeal of approaches such as MS/MS in NBS, as well as CMA and NGS in paediatric testing, is their capacity to more quickly and thoroughly interrogate the sample or genome at a fraction of the cost of previous technologies. However, this means that such approaches are not only more likely to determine a pathologic variation that can account for the patients phenotype, but also to detect other variations.

NBS psychosocial implications

The psychosocial implications of NBS and childhood genetic testing have been the subject of considerable interest over time. As with all screening programmes NBS involves complex trade-offs between medical benefits and the burden associated with false positive or uncertain findings. Although NBS remains, on balance, a highly beneficial programme, the volume and nature of psychosocial harms have arguably been amplified as it has expanded. As more disorders, some of which are very rare, have been added to NBS panels, the volume of false positive results has increased. As discussed previously in this chapter, these may result in both short and long-term parental distress, and can impact parent-child interaction. In addition, there is emerging evidence that issues with genotype-phenotype correlation (such as may occur in screening for cystic fibrosis (CF) and medium chain acetyl dehydrogenase deficiency (MCAD)) can create ambiguity for parents whose children sit somewhere in a "space" between normal health and pathology.[263]

Arguably, such psychosocial issues are of even greater import for selective reproduction. The implications of uncertainty regarding the genetic status of an embryo, or fetus, for parents and reproductive decision making requires particularly careful consideration. Emerging evidence specific to these areas (as well as that from NBS) should be carefully analysed and used to inform the development of communication strategies and selective reproduction policy more generally.[264]

Paediatric genetic testing: Next Generation Sequencing (NGS)

Findings from NGS may fall within one or more of the following categories:[265]

- Clinically relevant to the diagnostic question;
- Clinically relevant for the individual, but not relevant to the diagnostic question (incidental findings (IFs));
- Clinically or socially relevant for family members, for example, reproductive relevance to other members, but not relevant to the diagnostic question (IFs);
- Not clinically relevant, ('neutral' variants, which are not reported); or
- Variants of uncertain clinical significance (VOUS), but potentially pathogenic and/or related to the primary clinical question.

This wide variety of potential outcomes has created significant issues both pre and post analytically.

Pre-test counseling/informed consent

There are several aspects of NGS that create new or amplified challenges for informed consent. These include the complexity, variety and uncertainty of potential results; the broad implications of those results; and the elevated expectations of benefit from testing.[266] While there is general agreement amongst parents and health professionals that pre-test discussions are crucial to facilitate informed decision-making and to order to avoid "surprises" related to IF, it is also acknowledged that this is immensely difficult to achieve in practice.[267]

There is, therefore, a lack of consensus in paediatric genetics practice regarding what should constitute the critical elements of pre-test counselling and informed consent process. Two points are particularly relevant when considering these issues in relation to selective reproduction. Firstly, general paediatricians in NZ have raised some concerns about the use of CMA: time constraints in clinics and difficulties for generalists keeping pace with new developments in genetics make it problematic to undertake the necessary discussions with families.[268] Secondly, a recent study has highlighted that as experience with NGS accumulates, genetic health professionals tend to place less emphasis on standard elements in the consent form and technological aspects of sequencing. Instead they focus on addressing misperceptions and assisting patients/parents to develop realistic expectations about the types and implications of possible results, including secondary findings.[269]

Given the current emphasis on parental choice within selective reproduction all health care professionals involved in its clinical implementation should receive adequate training and resources, including time, to enable them to properly discuss testing and deliver results to their patients. Future research in relation to pre-test counselling should aim to address the extent to which various stakeholders can agree on the key elements of informed consent in the pre-implantation and prenatal context. The goal should be establishing a consensus consistent with the underlying aims of such services.

Requirement of an adequate infrastructure

Challenges to established norms in pre-test counselling in paediatric genetic testing suggest a need to reconsider the design of clinical services, or the infrastructure that surrounds testing. Similar arguments can be made in relation to NBS. As NBS has evolved over the last few decades it has become increasingly evident that it operates not simply as a test but rather a comprehensive system that includes testing, education, follow up, treatment, management and evaluation. Hence the policy issues are also considered broadly, including everything from test parameters, to which conditions should appear on testing panels, to informed consent processes, to long term follow up of both true and false positives. Such policy is now generally developed in a transparent and highly consultative, multidisciplinary manner. For example Australia has recently undertaken a major project to develop a comprehensive NBS policy framework. One of the key drivers of this was recognition of the need to:[270]

> assess the benefits and harms of screening for new conditions to enable governments to make nationally consistent decisions on which conditions should be included in the programs.

There is clear acknowledgement that the:[271]

> science and technology related to the testing and treatment of conditions included in the NBS programmes, as well as other conditions for which NBS could be offered, is rapidly changing.

It is possible, even likely that selective reproduction will undergo a similar dramatic expansion. Much could be learned from these processes that have been adopted within NBS and paediatric genetic testing. Failure to ensure that the infrastructure and associated policy are adequate to address issues, such as what to test for, and how to discuss testing with parents, is likely to seriously challenge some of the underlying premises of reproductive services (such as reproductive choice).

What to test for: NBS as an example

As NBS has expanded, the criteria (initially developed by Wilson and Jungner) used to guide the addition of disorders to NBS panels has been revised. Given the pace of technological advances, this has become a highly complex endeavor. While several countries have made major efforts to provide objective means of assessing disorders for NBS, there is not complete agreement.[272] Hence the number of disorders on testing panels varies considerably by country, with the UK testing for 9 conditions,[273] NZ for 28,[274] and the US uniform screening panel including 30. While it has not been possible to achieve complete consensus, the processes underlying selection of conditions are now much more transparent and arguably the screening panels are gradually becoming less divergent across jurisdictions.

The appropriate scope of testing is also an issue in paediatric genetic testing. The ACMG guidelines initially recommended that when performing clinical genome or exome sequencing, laboratories seek pathogenic mutations in 56 genes and return those results to the referring clinician, regardless of the patient's wishes or age.[275] These recommendations triggered criticism that it undermined patient autonomy by limiting a choice concerning whether to receive IF,[276] and concerns regarding return of results for children, given that many of the conditions are adult-onset.[277] Many have been critical both of the way the policy was developed as well as its content.[278] The ACMG subsequently revised their position such that patients/parents have an opportunity to opt-out of the analysis of medically actionable genes as an adjunct to whole exome or genome sequencing.[279]

The ASHG position statement advises that if "secondary findings" arise, clinicians should only offer to disclose findings to the child's parents or guardians when the information has clear clinical utility for the child and/or his or her family members. ASHG also recommends that parents be given an opportunity to decline to receive secondary findings in advance of genetic testing. However, when there is strong evidence that a secondary finding has urgent and serious implications for a child's health or welfare and effective action can be taken to mitigate that threat, it recommends the clinician communicate those findings to parents or guardians regardless of their stated preferences.[280]

The content of a list of "clinically relevant secondary findings" detectable through exome or genome sequencing therefore remains a complex and contestable issue, which has certain parallels with the choice of conditions for NBS panels. In this regard, the ASHG recommends assembling a list of genes in which duplications or deletions are clearly associated with clinically important diseases. This list could function as a secondary-findings list with implications for what should and should not be reported back to families, and may also be of considerable relevance for selective reproduction services.[281]

One response to this controversy has been an increased focus on targeted or limited results. For example the ASHG recommends limiting sequencing as far as possible so that when clinically indicated, the scope of genetic testing should be limited to single-gene analysis or targeted gene panels based on the clinical presentation of the patient.[282] The latest European Society of Human Genetics (ESHG) guidelines also recommend targeted diagnostic testing should occur wherever possible to limit the likelihood of detecting IF.[283]

The question of how to manage IF in paediatric genetics therefore remains very much an issue. While there are ongoing attempts to achieve consensus, practice in different jurisdictions diverges.[284] Given the heightened ethical sensitivities related to the field of selective reproduction, and the predominance of "parental choice" as its governing principle, it should be anticipated that there will be greater challenges in reaching complete consensus on which conditions may be appropriate for screening panels used in PGD or prenatally. The implications and strategies for managing such impending difficulties require early consideration. These might include tailored approaches to return of results, or alternatively, it may be that multidisciplinary input is sought into which conditions might be suitable for reporting, or for screening panels, with the capacity to regularly re-evaluate decisions, in a similar way to the advisory groups that exist in relation to NBS.

Psychosocial impact of paediatric genetic testing

Despite initial concerns regarding the psychological effect of testing children for late onset disorders, there is virtually no evidence in psychosocial studies to suggest that receiving genetic test results leads to a significant impact on children's psychosocial wellbeing.[285] However a new empirical evidence gap has emerged in the NGS era. The major psychosocial issues relate to the post-analytic complexity and uncertainty, such the effects of IF and VOUS. There is a lack of data concerning the psychosocial effects of less certain results, particularly in relation to longer-term effects and direct effects upon children themselves.

However experience from NBS programmes of the difficulties associated with ambiguous information may potentially be helpful to future debates regarding IF and VOUS. Similarly, a small body of evidence regarding experience of CMA suggests that in the short-term, parents' emotional and psychological reactions to CMA results (ie both uncertain and pathogenic results) vary considerably and can include relief, changes in self-concept, and empowerment.[286] Anxiety has been identified as a key factor, although professional concerns about patient anxiety outweighed parent and public concerns. Lay groups maintain that parents should have the right to assess the likely impact for

themselves, and choose what to know and whether this outweighs any personal risk of anxiety.[287] Overall, it is considered likely that psychosocial impacts will vary depending on the individuals character or socio-economic situation: i.e. harms may be greater for individuals who are predisposed to anxiety or worry, or for those who lack certain access to resources (money, insurance coverage, access to counselling or other services).

Such varied psychosocial response to NGS adds additional complexity to decision-making in the context of selective reproduction. Further longitudinal research, including the impact upon children themselves, will be necessary to inform policy. Ultimately a balance must be found between very broad approaches, with their attendant increase in detection of IFs and VOUS that may be difficult for prospective parents to cope with, and more focused approaches that mitigate these risks but do not produce as much information.

If the degree of variability in psychosocial response that has been documented in emerging research is confirmed, an approach to genetic testing (including in selective reproduction) that can be tailored to individual needs may be preferable from a psychosocial perspective, although potentially complex to operate in practice.

Evolution of ethical concepts

The key ethical concept that underpinned both NBS programmes and childhood genetic testing discussed earlier in this chapter was to serve the best interests of the child. However, over the years the focus of NBS has shifted from preventing devastating harm (e.g. untreated PKU[288]) to a much broader conception of benefit. The benefits generally considered relevant in contemporary NBS programmes are not only medical benefits that accrue directly to the infant, but also developmental, social and psychological benefits that may arise from early disease detection, and benefits to families and society.[289]

Similarly, the predominant view concerning "best interests" with regard to "pre-NGS" genetic testing of children was that testing should only occur if it was likely to be of medical benefit during childhood. More recent guidelines reflect broader considerations that may legitimately inform testing decisions, such as the potential for better psychosocial adjustment to disease risk and avoidance of 'diagnostic odysseys'.

These issues remain somewhat contentious. This is highlighted by the fact that although "family benefit" as a justification for screening has been supported by one professional group statement,[290] others reject it.[291] Despite this, NBS now appears to operate not solely as a response to a "public health emergency,"[292] but rather as a public health service with greater emphasis on more moderate and parent-centred benefits.[293]

These shifts in relation to the "best interests" of the child are mirrored by the evolution of paediatric ethical concepts more generally. Within paediatric bioethics there has been a move away from the "best interests" standard, towards models that focus on parental/familial autonomy. This autonomy is typically constrained only if children are likely to be harmed as a result of the parents' decision.[294] These changes in relation to ethical concepts may have far reaching societal implications. Debates and misunderstandings concerning the meaning of ethical concepts underlying paediatric genetic testing remain at the core of many of the current tensions concerning policy and practice in this area.

This raises two key issues for selective reproduction. First as selective reproduction is poised to expand, there should be a detailed and nuanced re-evaluation of what prospective parents and society really want and need from such services, and in turn what is really meant by the ethical concepts that underpin such practices in contemporary society. As in paediatric genetics, lack of clarity concerning the meaning of ethical concepts is likely to hinder further debate and progress. Secondly, the shifts in meaning of ethical concepts underlying paediatric genetic testing require acknowledgement within selective reproduction.

It is plausible that there should be some congruence between approaches to selective reproduction, and genetic testing that may occur later in childhood. Specifically, this may mean actively considering a greater focus on shared decision-making with parents than exists in paediatrics, the enhanced role and recognition of parental autonomy, and a broader account of children's interests.

Conclusion

Expansions to genetic testing services are already having a significant impact on clinical paediatrics. Many novel genes associated with disease have been identified, and many children and their families have benefitted. However, the analysis provided in this chapter highlights the myriad practical, ethical and psychosocial complexities and uncertainties associated with these new technologies.

The theoretical and empirical material canvassed in this chapter provides important background context for the remaining chapters in Part II of this report, which focus on the future of selective reproduction. Chapter 3 briefly outlines the history of prenatal testing, before considering the recent development of non-invasive prenatal testing. Chapter 4 considers genomic advances in invasive prenatal diagnosis, and Chapter 5 concludes with an analysis of the impact of new genomic technologies on preimplantation genetic diagnosis.

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PART 2

Chapter Three

The Future of (Selective) Reproduction

3.1 Introduction

Prenatal screening and its technological counterpart, prenatal diagnosis (PND) have been the subject of extensive debate since their inception, particularly given PND's inextricable links with abortion.[1] Despite this, prenatal screening policy and practice has evolved over the last few decades and is now well established. However, a recent permutation of prenatal testing, Non-invasive Prenatal Testing (NIPT), heralds a distinctly new era in prenatal testing and diagnosis.

NIPT was first performed in 2011 and has been subject to rapid commercialisation. While some commentators suggest that NIPT promises to change "everything" [2] and that the "brave new world of widespread prenatal genetic diagnosis" may finally have arrived,[3] others are more moderate in their views regarding its actual and potential impact.[4] Consequently, this chapter examines what effect NIPT is likely to have in the immediate, as well as the future, reproductive context.

What is NIPT?

Non-invasive Prenatal Testing (NIPT) is premised on a phenomenon known as "cell-free DNA". While most of our DNA is contained within our cells, small amounts of "cell-free" DNA may also circulate freely in the bloodstream.[5] Similarly in pregnancy, a small percentage of cell-free DNA that derives from the placenta and which typically matches the DNA of the fetus is detectable in a pregnant woman's blood.[6]

NIPT involves isolating fragments of placental DNA, which acts as a proxy for cell free fetal DNA (cffDNA), from the maternal blood for chromosomal analysis. At present, NIPT is mostly restricted to analysing specific chromosomes for numerical abnormalities (trisomies 21, 18 and 13) rather than facilitating generalised or "untargeted" genetic testing across the genome.[7] However, commercial companies are incrementally expanding the range of tests that are available on NIPT panels.

NIPT may be performed at 10 weeks' gestation, and potentially even earlier.[8] Compared with traditional serum screening which is performed in the first and second semesters of pregnancy, NIPT has been shown to have higher sensitivity (capacity to detect a disease if it is present) and specificity (to exclude the disease if it is not present) for some common trisomies.[9] While false positive results still occur in NIPT (approximately 1% for the common trisomies) this compares favourably with the incidence of false positives in conventional screening (approximately 5%).

Although initial studies suggest that NIPT has the potential to provide comparatively lower false-positive rates and, as a consequence, reduce the incidence of invasive follow-up diagnostic procedures such as amniocentesis, specialist physicians have urged that these studies be interpreted carefully.[10] There are currently limitations to NIPT of which referring clinicians must be cognisant and which require careful communication to women who are offered, or request, NIPT.

Two distinct narratives have accompanied the rapid introduction of NIPT by private for-profit laboratories. Commercial entities push NIPT as an expansive testing regime with a potentially huge scope. The implicit message is that increased testing capacity is an unqualified good. In contrast, clinicians and professional bodies have construed NIPT as a narrower "second tier" screening option for women who are at elevated risk of conceiving a fetus with particular trisomies (trisomy 21, 18 and 13).[11]

Why is NIPT an issue?

There are several reasons for the attention that NIPT has garnered. First, it is likely that as more tests are validated, the range of conditions for which NIPT may be used will expand exponentially.[12] Given that the objective of prenatal testing is to provide information regarding fetal health, some screening and subsequent positive diagnoses may result in a decision to terminate a pregnancy. While this is not a new issue, it is likely that NIPT will reinvigorate public and political debate regarding the appropriate limits of lawful termination of pregnancy.

In addition, the way that NIPT has been integrated into clinical practice is highly unusual. The technology has been developed and driven by commercial entities, with direct-to-consumer marketing effectively generating awareness and consumer demand. Consequently, clinical uptake preceded the establishment of clinical practice guidelines and standards.

NIPT has become widespread globally since its introduction. The global NIPT market was estimated at US$0.22 billion in 2012, and is projected to be US$3.62 billion in 2019.[13] As of 2014, NIPT was offered in over 60 countries throughout six continents, with the bulk of revenue generated in North America, followed by Europe.[14] Companies have taken advantage of online mediums, such as You Tube, Twitter and Facebook to market NIPT to pregnant women.

There are two distinct fields of critical analysis apparent in the literature on NIPT. For policy makers, the central issue is if, and *if* so *how*, NIPT should be integrated into existing (publicly funded) screening programmes.[15] However, the central issues exercising ethicists and lawyers concern not only the immediate challenges of expanded prenatal screening, but also what the future of NIPT might look like.

In terms of the future direction of NIPT, the evolution of array comparative genomic hybridisation (CGH)-based NIPT[16] and whole genome screening is fairly certain. NIPT could, in the future, be used to analyse an entire fetal genome. Indeed proof-of-principle of fetal whole genome sequencing has already been established, although prohibitively expensive currently.[17] Nevertheless, given the likely expansion of NIPT, the issues include:

- what are the implications of such extended information for expectant parents and the children subsequently born following NIPT;
- should prospective parents be able to access unlimited fetal information;
- should restraints should be placed on the scope of parental choice in this context and, if so, on what basis.[18]

NIPT in New Zealand

Currently, all pregnant women have access to the public screening system in New Zealand.[19] Public prenatal screening policy is determined at the national level under the auspices of the Ministry of Health Manatū Hauora (MoH).[20] Although NIPT is not part of the publicly funded programme, it is available commercially on a user-pays basis via overseas-based laboratories.[21]

Several providers offer NIPT in New Zealand. The tests range from NZD $1,000 to $1,575 and require a referral from a lead maternity provider. Results are available within seven to 14 days on average. While no laboratories manufacture the actual tests in NZ, samples are sent offshore for analysis, primarily to the US, but also to Australia and Hong Kong.

In terms of professional responses to NIPT, the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) has expressly noted the widespread public awareness and interest in NIPT.[22] It recently commissioned a Cochrane Review of NIPT. A subsequent RANZCOG communiqué emphasises that NIPT is a screening, rather than a diagnostic test and that any abnormal result requires an invasive test to confirm the presence of a condition.[23] Although no professional guidelines have yet been released, the Human Genetics Society of Australasia and the Australasian Association of Clinical Geneticists have endorsed the joint European Society of Human Genetics and American Society of Human Genetics position statement on NIPT.[24] This statement emphasises the importance of balanced pretest information and non-directive counselling. It also advocates a "cautious" expansion to NIPT if tests are validated and the implications of such screening tests are fully evaluated.[25]

In 2016, the New Zealand Maternal Fetal Medicine Network (NZMFMN) released a brief *Statement on the use on Non-Invasive Prenatal Testing*, acknowledging that "NIPT has been shown to be a useful screening test in both low and high risk pregnancies".[26] It emphasises pre-test counseling and recommends that screening be limited to testing for the common trisomies (21, 18 and 13) as well as sex chromosomes, provided the implications of testing are understood by the woman undergoing testing.

Chapter outline

This chapter provides an introduction to NIPT and outlines the technical, ethical and legal issues associated with this rapidly evolving technology. A pertinent factor in this new era of prenatal testing is the distinction between operationalising a state-mediated screening programme, and individual prospective parents accessing the technology privately.[27]

In order to put this analysis in context, a brief overview of the current approach to traditional prenatal screening and diagnosis in New Zealand is first provided. The

evolution of NIPT is then mapped, detailing its current scope, before finally considering what its future may hold. The ultimate aim of this chapter is to examine the issues that NIPT raises, primarily for women who might access this technology, and what might constitute an appropriate policy response to this evolving technology.[28]

3.2 Historical evolution of prenatal screening and diagnosis

The ostensible goal in prenatal screening is to identify the presence of fetal anomalies to facilitate informed reproductive decisions. If a fetal anomaly is confirmed, a woman/couple may elect to continue a pregnancy prepared with that knowledge, or alternatively may elect to terminate the pregnancy. The following section considers the way in which prenatal screening has evolved in the last few decades.

Traditional prenatal screening & testing paradigm

As early as the 1920s, scientists conjectured that advanced maternal age is associated with a risk of conceiving a child with fetal anomalies. In 1939, it was claimed that the probability that a woman would have a child with Down syndrome "is more than doubled for every increase of five years after the age of 25".[29] It was not until 1959 that the cause of Down syndrome, an extra 21st chromosome, was discovered.[30] Conditions involving an extra copy of a particular chromosome are primarily the result of meiotic nondisjunction,[31] a phenomenon that statistically increases with maternal age.

In the 1970s, prenatal screening for chromosomal abnormalities, technically termed "aneuploidy" screening, was offered to women over the age of 35. This age threshold was based on evidence of a risk-benefit ratio that at 35, the risk of pregnancy loss from amniocentesis equals the increased chance of delivering a child with aneuploidy.[32]

A relatively recent study analysing the prevalence of trisomies in Europe over 20 years showed that a rise in maternal age led to an increase in the number of trisomy-affected pregnancies.[33] Despite this, prenatal screening and elective termination of pregnancy have meant that the prevalence of infants born with Down syndrome remained relatively stable over the period. However there is significant variation in prenatal screening uptake by women across different countries. In 2010, the screening uptake was 61% in England, compared with 84% in France and 26% in the Netherlands in the previous year.[34] Denmark has the highest screening uptake at 90%.[35] These differences may reflect the different policies and health systems.[36]

Although the risk of a having a child with a trisomy increases with maternal age, age alone is not an accurate screen. By some figures, up to 70% of all children with Down syndrome are born to mothers under the age of 35.[37]

Ultrasound/nuchal translucency

Ultrasound scans constitute a mainstay of prenatal screening. A nuchal translucency (NT) scan is a detailed ultrasound scan carried out between 11.3 and 13.6 weeks of gestation. Nuchal translucency is a measurement of the fluid between the back of the head and neck. Increased NT is considered a non-specific indicator of certain aneuploidies, including Down syndrome and Turner syndrome: [38]

Increased nuchal translucency (greater than 99th centile) is associated with increased risk for a broad spectrum of genetic and developmental disorders, including single-gene mutations, especially Noonan syndrome, chromosome abnormalities, cardiac malformations and pregnancy loss.

Early ultrasound can also detect certain fetal structural anomalies, provide data relevant to the viability of the pregnancy, as well as multiple pregnancy.

Fetal anatomy/anomaly ultrasound scan

The optimal time to survey fetal anatomy is between 18 and 20 weeks' gestation.[39] Fetal ultrasound in the second trimester can detect both structural variants (termed soft markers) and structural defects (e.g. when some or all of the abdominal organs remain outside the abdomen, congenital heart disease, or skeletal dysplasia).

Serum screening

In the 1970s, UK scientists discovered an association between elevated levels of alpha-fetoprotein (AFP) in maternal serum and neural tube defects (NTDs).[40] AFP is a protein produced by a fetus that is detectable in amniotic fluid, as well as in the maternal blood stream. Neural tube defects are serious abnormalities of the brain, spine or spinal column that are of variable severity. As the majority of neural tube defects occur in the absence of specific risk factors, this suggested a simple blood test to measure serum AFP could constitute an appropriate population-based screening measure for NTDs.

AFP has proved to be suggestive of a much wider range of fetal conditions than just neural tube defects. In 1983, clinicians reported that maternal AFP levels were significantly lower for women carrying infants with trisomies.[41] This led to a recommendation that combining advanced maternal age and serum AFP would result in a better screening process for Down syndrome.[42] Measuring AFP became quickly routinised as part of prenatal screening. Subsequently, it was discovered that measuring levels of human chorionic gonadotropin (hCG) and unconjugated estriol (uE3) further improved the sensitivity of serum screening for aneuploidy and were used in conjunction with AFP screening.[43]

Invasive diagnostic testing

There are a range of invasive diagnostic procedures that may be performed to investigate fetal health after a positive screen or, in the absence of an identified anomaly, to provide information in the hope that it will allay a woman's anxiety regarding fetal health. These procedures encompass amniocentesis, chorionic villus sampling, placental biopsy, cordocentesis and fetal biopsy. However, these procedures carry a risk of pregnancy loss, estimated at between 0.5% and 1.0%. [44]

Amniocentesis

Amniocentesis is performed between 15 and 20 weeks gestation, and involves the transabdominal needle aspiration of amniotic fluid from the amniotic sac that houses a fetus. Given the risk associated with amniocentesis, which for many women is

extremely significant, decisions to undertake prenatal testing using invasive methods have historically been based primarily on specific risk factors, such as a woman's "advanced" maternal age (AMA), an obstetric history of multiple prior miscarriages or prior pregnancies with trisomy, abnormal ultrasound scan results, or abnormal maternal serum markers. However in some cases invasive diagnostic procedures may also be performed as a result of maternal anxiety regarding fetal health.

Women's engagement with prenatal screening: social science insights

Social science research has provided an important critique of women's engagement with prenatal screening initiatives.

In a small US study undertaken in the early 1990s, Press and Browner examined how low risk women perceived, and responded to, AFP's inclusion in routine prenatal screening.[45] The authors reported that despite variation in participants along both class and ethnic lines, "not only did the overwhelming majority [of women] agree to be tested, but they showed marked similarities" in reasoning.[46]

The authors considered that this largely homogenous response was due to the way the test was framed by clinicians and in the written material women received, as well as the way it was provided. They suggest that the structure and content of the information "increased test acceptability far more than it succeeded in increasing knowledge about the test". The authors coined the euphemistic term "collective fiction" to describe the similarity in responses of the participants regarding screening, observing:[47]

> … we believe it demonstrates that there exist a set of cultural beliefs, understandings, and values, shared by those who offered and those who accepted AFP screening, which enhanced the acceptability of the test. Central among these is a fundamental faith in the power and value of scientific knowledge and the solutions science provides. In pregnancy, this view is expressed in the belief that undergoing routine prenatal care will help lead to a healthy birth. Yet in the arena of prenatal diagnostic testing, this optimistic faith must coexist with the more ominous themes of serious birth anomalies, selective abortion, and eugenic selection that prenatal diagnostic testing by definition entails. These contradictions create a tension which makes health professionals uncomfortable discussing, and women uncomfortable contemplating, the realities of AFP screening. Our data suggest that this tension is reduced through the creation of a collective fiction: the presentation of AFP screening as a simple and routine part of prenatal care ... this fiction is effective because it serves the interests of all parties involved. It serves the state public health program's purpose of trying to reduce the incidence of neural tube defects, health care providers' desire to limit their legal liability, and women's complex needs to be reassured about the outcome of their pregnancy and to leave open but uncontemplated the option of terminating an affected pregnancy.

Clearly an offer of prenatal screening may be framed in various ways. Nevertheless, there is a significant distinction between undergoing a screening test, and a subsequent decision to terminate a pregnancy.

In 1986, Barbara Katz Rothman published the first detailed study of women's experiences of amniocentesis.[48] Rothman concluded that amniocentesis had radically changed women's experience of pregnancy. She found that many women considered they were not "really" pregnant until their decision was made to carry a pregnancy to term—which was highly dependent on the results of amniocentesis. Rothman famously adopted the notion of the "tentative pregnancy" to describe the way that many women conceptualise their pregnancy prior to undergoing amniocentesis.[49]

In a seminal paper published in 1993, social scientists Dorothy Wertz and John Fletcher claimed that most women "accept prenatal screening, if offered at no cost" citing evidence that 60-90% of women in Europe accept prenatal diagnosis and only 7% of pregnant women in Britain declined testing for moral reasons. [50] Significantly they note: [51]

> The history of prenatal diagnosis also points to women's active and personal choices. By contrast with other areas of experimentation in the history of obstetrics, where poor women especially were exploited as research subjects, the history of prenatal diagnosis suggests that women actively encouraged research in this area. Women who participated in the early experiments with amniocentesis tended to be white, middle class, well educated, and vocal, characteristics that encouraged physicians to pursue this line of research with more vigor than they might have otherwise.

Although the ethics of prenatal testing has long been vigorously debated,[52] there has been a steady demand for prenatal screening and diagnosis.[53] However, the purpose, or value, of invasive testing may be two-fold. The information derived may enable the prospective parents to prepare for the birth of a child with particular challenges associated with impairment or illness and for the additional care that may be required.[54] Alternatively, it may inform a decision whether or not to continue the pregnancy. Nevertheless, PNT is inextricably linked with the possible termination of pregnancy.

Evolving best practice: screening and diagnosis

In recent decades, there has been a steady improvement in screening and diagnostic capacity. By 1992, studies indicated that detection rates of Down syndrome could be increased to approximately 70% by second semester screening of three maternal serum markers (AFP, human chorionic gonadotropin (hCG), and estriol) in combination with maternal age, followed by the offer of amniocentesis in the event of an abnormal result.

In 2007, large studies in the UK and the US demonstrated that combining nuchal translucency measurements with levels of hormone free β-hCG and pregnancy-associated plasma protein A (PAPP-A) yielded highly accurate results in assessing the risk of aneuploidy.[55] Consequently, in 2007, the ACOG released a practice bulletin, which stated that ideally *all* women should be offered aneuploidy screening before 20

weeks of gestation, regardless of maternal age.[56] Similarly, the Society of Obstetrics and Gynecology Canada recommend offering noninvasive prenatal screening to all pregnant women, regardless of age, while reserving invasive diagnostic procedures for women at increased risk of fetal aneuploidy (based on multiple marker screening results, abnormal ultrasound findings, or a previous history of a chromosomal abnormality).[57] As a result of these recommendations, combined with results from two US multicentre studies validating the accuracy and detection of both first and second trimester screening, there has been an "explosion" of screening options available to, and uptake by, pregnant women.[58]

Review of screening in New Zealand

Significantly, in 2007, the NZ National Screening Unit (NSU) undertook a review of Down syndrome screening in New Zealand. The report concluded that the existing ad hoc and variable practice of screening using only maternal age and/or NT without biochemical markers had not kept up with international best practice and was inadequate. It stated:[59]

> Studies have shown that screening tests, which involve combinations of first and second trimester markers, can reduce the number of women assessed to have a fetus with an increased chance of Down syndrome (Wald et al 2003; Malone, Canick et al 2005) ...
>
> At the same time, the screening tests that are currently available are not always offered, or provided in a way that meets best practice, particularly in relation to practitioner competence, quality assurance, monitoring and evaluation. There is significant variation in practice across New Zealand, especially in relation to ultrasound screening. The types of tests offered or available to women vary, depending on what is available locally, the knowledge of the practitioner, the knowledge of the woman, and the woman's ability to pay for some tests. As a result, some women are:

- not offered any form of screening or diagnostic test at all;
- offered invasive diagnostic procedures on the basis of their age alone;
- offered an NT ultrasound scan, with the chance that it will be provided by an unaccredited practitioner using unsuitable equipment.

The report identified multiple issues with the provision and practice of antenatal screening and maternal care. The NSU subsequently introduced quality improvements to Antenatal Screening, funded by the Ministry of Health which are detailed in the following section. However, a recent Monitoring Report released by the National Screening Unit suggests that the NZ screening system is, once again, performing below international standards. Specifically, detection rates for Trisomy are only 78%, thought to be primarily due to poor quality NT measurements in first trimester screening.[60]

Current prenatal screening in New Zealand

In New Zealand, there are two screening options available for women who are less than 20 weeks pregnant. First trimester (10-14 weeks) "combined screening" combines an ultrasound to measure NT with serum screening for beta-human chorionic gonadotrophin (β-hCG) and pregnancy-associated plasma protein A (PAPP-A). The results are correlated with maternal age, weight and gestational age to assign a value of "low" or "increased" risk of aneuploidy.[61] Women who are categorised as at "increased" risk on the basis of the combined screening measures are offered further invasive diagnostic testing. Women who are between 14 and 20 weeks pregnant are offered a serum screen (the "quad" test that examines four analytes) as well as a fetal anomaly scan.[62] Women who have a positive screen are offered a diagnostic test, usually amniocentesis.

While the use of step-wise screening has substantially increased the sensitivity of screening for chromosomal abnormalities, screening tests are not conclusive and false positive and false negative results may occur. This uncertainty can have paradoxical implications. While anxiety regarding a prospective child's health may not be allayed for some women despite a negative screening result, other women may be overly reassured by a negative screening result. Conversely, a positive screening result may occur even though the woman is carrying a healthy fetus, and a negative screen does not guarantee a healthy child. Wilson et al capture the issues this raises in the following:[63]

> The primary limitation of screening is that it does not provide a definitive diagnosis, leading to the potential of increased anxiety in women with an unaffected pregnancy and the potential of false reassurance in women who have a pregnancy with a chromosome aneuploidy.

This catch-22 has provided an ongoing incentive for scientists to develop more accurate screening tests to mitigate this uncertainty and to reduce the incidence of unnecessary invasive diagnostic tests such as amniocentesis. The first step in realising the goal of developing a noninvasive prenatal screening test occurred in 1997 after scientists at the Chinese University of Hong Kong discovered fetal DNA circulating in maternal blood.[64] This finding set the scene for research into the clinical potential of NIPT using maternal blood.

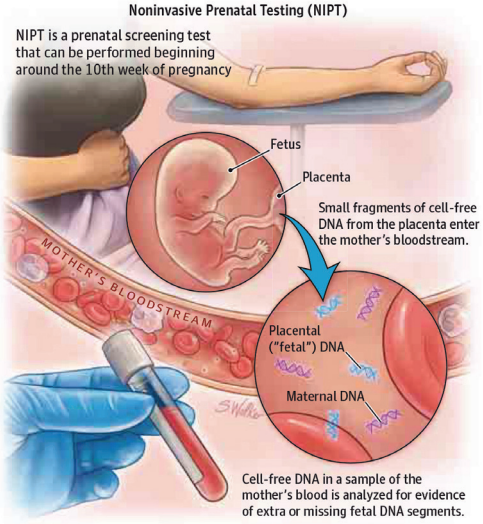
3.3 Non Invasive Prenatal Testing

As noted above, scientists have sought for many years to develop an accurate noninvasive prenatal test that can be performed early in high-risk pregnancies,[65] largely motivated by the desire to reduce the incidence of invasive tests. These procedures are not only physically unpleasant for the woman undertaking it, but are also associated with a 1-2% risk of fetal loss—a significant risk for many women carrying a wanted pregnancy. The first steps in realising noninvasive prenatal screening occurred in the late 1990s.[66]

Development of NIPT[67]

Following the discovery of fetal DNA in maternal blood, the United States National Institutes of Health established a large-scale multicenter study, the National Institute of Child Health and Human Development Fetal Cell Isolation Study (NIFTY).[68] Its aims were twofold: to isolate placental (fetal) cell-free DNA from maternal serum; and to improve detection rates for chromosomal abnormalities without increasing false-positive rates. This public/private research partnership succeeded in isolating fetal cell-free DNA (cffDNA), which could then be analysed using polymerase chain reaction (PCR) for chromosome-specific sequences.

Figure 6: Noninvasive Prenatal Testing (NIPT)[69]



Significantly, the introduction of NIPT coincided with advances in DNA sequencing technology and improved bioinformatics methods for interpreting data.[70] NIPT is currently performed using massively parallel sequencing techniques.[71] This involves mapping and aligning short sequence tags of cell-free DNA to a reference human genome, after which the tags are counted to determine the selected chromosome's status.[72] For example, if an increase on the relative number of tags of a particular chromosome is observed compared with the normal reference chromosome, it suggests trisomy.

NIPT first became available commercially in 2011 in Hong Kong. It is now in widespread use in China with the Chinese Food and Drug Administration (CFDA) requiring premarket validation of safety and accuracy. NIPT is also widely available in the USA, the UK, Europe and Asia.[73] In countries where NIPT is not available locally such as New Zealand, samples are sent offshore for testing.[74]

The original focus of NIPT was on detecting trisomy 21, but has quickly extended to trisomies 13 and 18—the same trisomies that are the focus in traditional serum screening.[75] Beyond screening for the common trisomies. NIPT can also identify Rh antigen status and sex.[76]

Commercialisation and clinical uptake

Against the background of rapid commercialisation, a group of Harvard clinicians and academics expressed concern regarding its unorthodox mode of clinical integration in 2013, stating:[77]

> … the diffusion of cfDNA testing into routine prenatal care may be occurring too quickly. Professional societies do not recommend these tests for normal-risk pregnancies because their clinical utility in the general population is not well established. Yet because the Food and Drug Administration (FDA) is not empowered to require testing companies to produce evidence of clinical utility before receiving marketing approval, companies have been free to build consumer demand for cfDNA testing by aggressively marketing the tests, emphasizing data that do not answer key questions. As a result, cfDNA testing seems to be drifting into routine practice ahead of the evidence.

These concerns were due to the then limited evidence regarding how NIPT performs in the general population, as well as the fact that companies have not, generally, disclosed information regarding the positive predictive value (PPV) of these tests.[78] PPV indicates the likelihood that a "positive result" is a true indicator of fetal aneuploidy. Arguably, PPV is more important than reporting the sensitivity and specificity of a test—as will be explained further in the following section outlining the technical limitations of NIPT.

Expansion of NIPT panels

Initially designed to test for trisomies 21 (Down syndrome), 13 (Patau syndrome) and 18 (Edwards syndrome), NIPT has advanced rapidly. Clinical implementation of NIPT was originally constrained as an advanced screening test for the group of women who are assessed as "high risk" for fetal abnormality based on conventional screening criteria, such as AMA, an abnormal serum screen or ultrasound scan, or a family history.[79] However, studies indicate that it is not only high-risk women accessing NIPT. Two recent studies, both sponsored by Ariosa Diagnostics Inc (HarmonyTM) suggest that NIPT for Trisomy 21[80] and 18 performs well in routine (i.e. average or low risk) populations.[81]

Since it was first developed, NIPT capacity has expanded to include tests for other less common trisomies, as well as sex chromosome abnormalities and microdeletion syndromes. Some companies provide these additional tests either on an "opt-in" or

"opt-out" basis. Several companies have launched new tests that include detection of trisomy 16 and 22 as well as some common microdeletions—such as 22q deletion (including DiGeorge syndrome), 5p deletion (cri-du-chat syndrome), 15q deletion (Prader–Willi and Angelman syndromes), and 1p36 deletion. However, there is concern in some quarters regarding this expansion given that "detailed clinical validation of this additional detection has not been published."[82] Recent research sponsored by Sequenom Laboratories claims that NIPT can be expanded to include detection of subchromosomal copy number variants.[83]

The following chart illustrates the tests that were offered by commercial NIPT providers in 2015. A description of each these conditions are provided in appendix 8.

Figure 7: Commercial noninvasive prenatal genetic testing (NIPT) options[84]

Table 1 Commercial noninvasive prenatal genetic testing (NIPT) options

		Berry Genomics[a,b]	BGI[a]	Igenomix[a]	Illumina (Verinata)	LifeCodexx[a]	Natera	Premaitha[a]	Roche (Ariosa)	Sequenom	
Test name		Bambni	NIFTY	NACE	verifi	PrenaTest	Panorama	IONA[h]	Harmony	MaterniT21 PLUS	VisibiliT
Test price		NA	NA[c]	NA	$1,500	€595–895[f]	$1,495	NA	$795	$2,762	$790
Chromosomal aneuploidies detected	Trisomy 9			✓[d]	✓[e]						
	Trisomy 13	✓	✓	✓	✓	✓[f]	✓	✓	✓	✓	
	Trisomy 16			✓[d]	✓[e]					✓[j]	
	Trisomy 18	✓	✓	✓	✓	✓[f]	✓	✓	✓	✓	✓
	Trisomy 21	✓	✓	✓	✓	✓[f]	✓	✓	✓	✓	✓
	Trisomy 22									✓[j]	
	45,X		✓	✓	✓[e]	✓[f]	✓		✓[i]	✓[j]	
	47,XXY		✓	✓	✓[e]	✓[f]	✓		✓[i]	✓[j]	
	47,XXX		✓	✓	✓[e]	✓[f]	✓		✓[i]	✓[j]	
	47,XYY		✓	✓	✓[e]	✓[f]	✓		✓[i]	✓[j]	
	48,XXYY								✓[i]		
Microdeletions detected	Test option		NA	Opt-in[d]	Opt-in[c]		Opt-in			Opt-out	
	1p36		✓	✓[d]	✓[e]		✓			✓[j]	
	2q33.1		✓								
	4p			✓[d]	✓[e]					✓[j]	
	5p		✓	✓[d]	✓[e]		✓			✓[j]	
	8q									✓[j]	
	11q									✓[j]	
	15q			✓[d]	✓[e]		✓			✓[j]	
	22q11.2			✓[d]	✓[e]		✓			✓[j]	
Other conditions detected	Fetal sex	NA	✓	✓	✓[e]	✓	✓[g]		✓[i]	✓	✓
	Triploidy						✓				
	Vanishing twin						✓				

		Berry Genomics[a,b]	BGI[a]	Igenomix[a]	Illumina (Verinata)	LifeCodexx[a]	Natera	Premaitha[a]	Roche (Ariosa)	Sequenom	
Additional indications	Twin pregnancies		✓	✓	✓	✓			✓	✓	
	IVF/donor egg pregnancy		✓	✓					✓	✓	
Reference(s)		75	28, 29	91	92, 93, 95	115, 116	95, 136, 137	100	11, 95	95, 101, 170	101, 171

Companies currently offering NIPT are shown along with test name, price, genetic conditions included on test panels, and additional indications for testing, such as whether the test can be used with twin or IVF/donor egg pregnancies. Only independent companies are shown; licensed providers of these companies' tests that have rebranded the tests under their own label (e.g., LabCorp's informaSeq test, which was developed using a license for Illumina's verifi test) are not shown. The microdeletions currently included on test panels are 1p36 deletion, 2q33.1 deletion, 4p– (Wolf-Hirschhorn syndrome), 5p– (cri-du-chat syndrome), 8q deletion (Langer-Giedion syndrome), 11q deletion (Jacobsen syndrome), 15q deletion (Angelman and Prader-Willi syndromes), and 22q11.2 deletion (DiGeorge syndrome or velo-cardio-facial syndrome). Abbreviations: IVF, in vitro fertilization; NA, information not available.

[a]These companies are based outside the United States, and their tests are not marketed within the United States.

[b]In March 2014, Berry Genomics suspended testing pending approval from the Chinese FDA; this approval was granted on March 31, 2015 (75).

[c]Test prices vary regionally (28).

[d]NACE examines only trisomies 13, 18, and 21 and sex chromosome aneuploidies; the NACE PLUS test additionally examines trisomies 9 and 16 and six microdeletion syndromes.

[e]The basic verifi test examines trisomies 13, 18, and 21, and a wider option (at no extra charge) examines sex chromosome aneuploidies and fetal sex. An additional option examines trisomies 9 and 16 and six microdeletion syndromes.

[f]There are three PrenaTest options: Option 1 (€595) examines trisomy 21; Option 2 (€745) examines trisomies 13, 18, and 21; and Option 3 (€895) examines trisomies 13, 18, and 21 and sex chromosome aneuploidies (115). In addition, results can be expedited by paying a €100 express charge.

[g]Optional.

[h]IONA will initially screen for trisomies 13, 18, and 21 but will add sex chromosomal aneuploidies later (100).

[i]The Harmony test includes an option to examine sex chromosomes.

[j]These results are reported as an additional finding (170).

Additional trisomies

As indicated above, additional trisomies that have been included on some NIPT panels include trisomy 22, trisomy 16 and trisomy 9. Trisomies 22 and 16 are generally associated with nonviable pregnancies that spontaneously miscarry.[85] Consequently, the clinical utility of including these in NIPT is arguable, given the risk of false positive and false negative results with these rare disorders. [86] In its 2016 position statement, the ACMG Noninvasive Prenatal Screening Work Group recommends that screening should be limited to the three main trisomies because other whole-chromosomal aneuploidies are generally lethal—implying that there are more disadvantages than advantages associated with testing for such conditions.[87]

Sex chromosome abnormalities

Sex chromosome aneuploidies (SCAs) involve a numerical abnormality of an X or Y chromosome (such as an addition or deletion of an entire X or Y chromosome) which cause syndromes that affect sexual development. These include Turner syndrome (monosomy X, 45, X), Klinefelter syndrome (XXY) and triple X-syndrome (XXX).[88] The combined incidence of sex chromosome abnormalities in live births has been estimated at around 0.3%[89] or alternatively 1/350–1/400 live births.[90] Klinefelter syndrome is the most common SCA, with an estimated incidence of 1 in 450-660 live male births.[91] SCAs constitute the most frequent condition diagnosed by amniocentesis after Down syndrome.[92]

SCAs typically have milder phenotypes than other aneuploidies. For example individuals with Triple X syndrome are phenotypically normal. However, (less commonly) some SCA may be associated with very serious anomalies. A fetus with Turner syndrome, one of the most common SCAs, may have serious cardiac abnormalities.[93] Turner syndrome is also a common cause of pregnancy loss in the first trimester.[94] However, a fetus identified with SCA that does not have any physical anomalies detectable on ultrasound generally has a good prognosis with normal mental function.[95]

The extent to which an individual's health may be affected by a SCA is variable, with many individuals either remaining undiagnosed over their lifetime, or only diagnosed after they have undergone investigations following fertility difficulties. Historically, sex chromosome abnormalities have been discovered incidentally in the course of invasive diagnostic testing. Given that most SCAs tend not to be associated with severe phenotypes, the issue of whether or not to routinely screen for SCAs is not new.[96]

A European organisation that collects data on prenatal screening and the prevalence of congenital anomalies (EUROCAT) indicates that the termination rate for SCAs (36%) is much lower than for Down syndrome (80-96%), which indicates greater parental ambivalence regarding SCAs in offspring.[97] A 2012 systematic review identified five factors that were shared in decisions to terminate or to continue a pregnancy in the context of a SCA. These are: the specific type of SCA; the gestational week at time of diagnosis; parental age; the providers' expertise in genetics; and the woman/couples' number of children/desire for (more) children.[98] It found that prospective parents were most likely to terminate a pregnancy if the fetus was diagnosed with Turner syndrome or Klinefelter syndrome than other SCAs.

A 2014 study of decision making following NIPT examined 11 cases where results suggested SCAs.[99] In four cases where the female fetus was suspected to have XXX, all four women continued the pregnancy and declined to have any further investigations. Another four cases suggested monosomy X. On further testing, one of these was found to result from maternal mosaicism. Another of the four suggested the female fetus could have Turner syndrome. After counseling, the woman continued the pregnancy. Amniocenteses indicated that the final two cases involved a chromosomal structural rearrangement that would not affect sexual development, and both couples continued the pregnancy. In three cases, NIPT suggested fetal XXY. Two of these were confirmed on testing either by amniocentesis or at birth, and in the third case the parents declined further testing and continued the pregnancy. Significantly, none of the 11 cases reported resulted in termination of pregnancy.

A more recent study retrospectively reviewed 2,851 women that underwent NIPT and who received a high risk of SCA result.[100] SCA was predicted in 18/2,851 patients (0.63%). Five cases suggested XXX, and two cases suggested Klinefelter syndrome. All NIPT results were confirmed subsequently either by invasive diagnostic testing or at birth (no pregnancies were terminated when an invasive test confirmed the NIPT result). While monosomy X was suggested in 11 cases, 10 were false positives yielding a surprising positive predictive value of only 9%. The authors note the adverse effect this had on couples emotionally and in terms of undergoing (unnecessary) invasive tests. Significantly, the authors reported that several of the couples regretted learning of the SCA risk prenatally, and six (38%) declined invasive testing. The authors caution that any woman who wishes to test for fetal sex should be made aware that SCA may be discovered incidentally and women undergoing NIPT for SCA should be made aware of the high false positive rate for monosomy X.[101]

Some parents may welcome such additional prenatal information, particularly given potential benefits associated with early diagnosis. Some studies indicate that children who are diagnosed with SCAs prenatally benefited from early interventions, including physical and behavioural therapy as well as hormone therapy.[102] While some prospective parents might consider knowledge of a sex chromosome abnormality relevant to reproductive decision-making, it cannot be assumed that all prospective parents would wish to undergo routine screening for such a condition or that those who do will elect to terminate a pregnancy if a SCA is diagnosed. Significantly, research indicates that how and by whom prospective parents are counselled (eg by specialist or general staff) influences parental choice after a SCA is identified.[103]

Several commercial companies have added SCA tests to NIPT panels, either on an opt-in or opt-out basis. However, there is currently limited data on the accuracy and predictive value of SCAs. Validation in large-scale studies is difficult given that the incidence of the conditions is low, which in itself affects the positive predictive value. This poses challenges for counselling, as well as uncertainty regarding the effect of knowing in advance that a child has a SCA for both the parents and the resulting child.[104]

Microdeletion and microduplication syndromes (Copy Number Variations)

A microdeletion is a tiny (typically less than 5 megabase) deletion in a chromosomal segment that is too small to be detected by usual cytogenetic testing.[105] A microduplication is a similarly tiny submicroscopic duplication that creates a chromosomal "segmental trisomy".[106] Both of these forms of genetic variation fall into the larger category known as copy number variations (CNVs). Microdeletion and microduplicaton syndromes (MMSs) usually involve several adjoining genes, and while the exact location and extent may vary, "a specific 'critical region' is consistently involved".[107] Unlike aneuplodies, the most common MMSs are not associated with advanced maternal age.

Prior to 2000, only a few MMSs were known. Since the advent of new technologies for high-resolution analyses of whole genomes, more and more MMSs have been identified.[108] In particular, the use of chromosomal microarray analysis (CMA) in children presenting with developmental delay has led to the description of multiple new MMSs.[109] Researchers recently reported accurate results for detecting deletions of 22q11.2, 1p36, distal 5p, and the Prader-Willi/Angelman region using a targeted single-nucleotide-polymorphism-based approach—although confirmatory invasive diagnosis was still advised.[110] These conditions have been described as having "clinically severe phenotypes".[111]

It is currently difficult to provide accurate data regarding the overall prevalence of microdeletions and duplications in the general population because many of the associated disorders have only recently been described, are likely to be rare, and data comes from specific patient groups such as children with intellectual disability. However, estimates suggest that clinically relevant micro-deletions/duplications occur in 1.7% of pregnancies that appear to have "structurally normal" chromosomes on traditional testing.[112] In the past, invasive prenatal diagnosis for microdeletion/duplications has been performed if clinicians had a reason to suspect such a syndrome due to family history or clinical assessment. However, this testing may now be added to a routine cffDNA screen for aneuploidy.

The most common microdeletion syndrome is 22q11.2, which has a prevalence of approximately 1:4,000.[113] The frequency of other deletion syndromes varies widely from 1:10,000 live births (1p36 deletion syndrome) to 1:50,000 live births (cri-du-chat). As these syndromes constitute "low-prevalence disorders", they are inevitably associated with false-positive results and low positive predictive values.[114] Allyse and Chandrasekharan succinctly state the problems associated with including rare subchromosomal anomalies in routine NIPT:[115]

> With rare conditions, large clinical validation studies become less feasible; the rarity of the conditions has a negative impact on the positive predictive value and negative predictive value of tests. Statistically, NIPS for [subchromosomal abnormalities] and sex chromosome aneuploidies will yield more false positives than tests for more common conditions such as trisomy 21, and anecdotal account from physicians, patients, and genetic counselors concur. This leads to an increase in confirmatory invasive testing, thus eroding the benefits of NIPS in reducing unnecessary invasive procedures needed to confirm common

> trisomies. Without accurate information about the positive predictive value and negative predictive value of… [subchromosomal abnormalities], clinicians may make uninformed decisions about ordering these tests and interpret test results inaccurately. Furthermore, patients and providers may see NIPS as a way to avoid invasive microarray testing despite the fact that invasive testing remains the gold standard for diagnosing … [subchromosomal abnormalities].

However, in the case of a woman who has a fetal structural anomaly identified in early prenatal ultrasound but declines invasive microarray testing to diagnose the condition, NIPT may provide additional information to prepare for the delivery and birth.[116]

A further issue with including MMSs on NIPT panels concerns a concept known as "variable expressivity". This term refers to the fact that microdeletions such as 22q11.2 have a range of phenotypic expression. They may encompass symptoms so mild they remain undiagnosed, as well as disorders that were previously designated as different clinical syndromes (e.g. DiGeorge syndrome, velocardiofacial syndrome) affecting several organ systems such as the heart and immune system. In particular, the degree of intellectual disability associated with 22q11.2 is variable and difficult to predict on the basis of genetic test results. Pathogenic 22q11.2 deletions are also associated with an increased incidence of schizophrenia and other treatable neuropsychiatric conditions including epilepsy and early-onset Parkinson's disease, although there is no way of predicting individual outcomes.[117] Of particular relevance to NIPT is that while many microdeletions detected prenatally occur spontaneously (de novo), some may be inherited from phenotypically "normal" parents, leading to considerable post-test counselling challenges.[118] Parents may assume the child will be similarly unaffected—which may not be an accurate assumption.

Although technologically possible, there are different views as to whether these syndromes should be included in routine prenatal screening if no fetal abnormality has previously been detected by ultrasound, and there is no familial reason to suspect one of these disorders may be present.[119]

It is also debatable whether NIPT for submicroscopic abnormalities should be introduced into routine screening when the accuracy and reliability of testing is not established.[120]

This current knowledge gap triggers medico-legal and ethical considerations—such as the inability to provide adequate information regarding the accuracy and reliability of tests and to predict outcomes in future offspring if a subchromosomal deletion or duplication is discovered. This can make decision-making and counselling problematic, despite the relative ease of testing.[121] However, supporters of NIPT for microdeletion syndromes recently claimed:[122]

> The fact that clinically relevant microdeletions and duplications occur in >1% of pregnancies, regardless of maternal age, challenges the notion of "low-risk pregnancies" and suggests that offering NIPT-based microdeletion screening to the general pregnancy population may be appropriate.

Another group performing subchromosomal NIPT in the case of high-risk pregnant women advocates extending screening to encompass MMS in the following terms:[123]

> Parents of a child with a microdeletion/microduplication syndrome may not receive a specific diagnosis of the condition for several years into development, resulting in the so-called 'diagnostic odyssey'. This time period can be financially draining and physically and emotionally distressing to the child and his or her family. Additionally, enrollment into early intervention programs, combined with improvements in medical techniques to treat certain physical conditions associated with these syndromes may lead to long-term improvements in the health and quality of life of affected individuals.

Several professional position statements indicate that they do not currently support including microdeletions and microduplication on NIPT panels due to the risk that it will increase the incidence of invasive testing because of the uncertainty of results.[124] While this might be a valid consideration for policy makers considering a public screening programme where one of the specific objectives is to reduce the number of unnecessary invasive diagnostic procedures, different considerations may apply in the context of individuals who wish to access these tests on a private basis.[125] Individuals are likely to balance the relative risks and benefits of procuring additional fetal information differently.

Women's perceptions: screening for sex chromosome aneuploidy and MMs

Decisions regarding testing are delegated to the clinicians and counsellors involved with providing tests and the women/couples seeking them. Given expanded NIPT is relatively new, few studies have assessed women's perceptions of such expanded NIPT test panels.

One small US study surveyed 31 women who had recently delivered a child, most of whom (80.6%) had undergone prenatal screening or testing.[126] The women had previously participated in research regarding NIPT as a screening tool for the common aneuploidies (trisomy 21, 18 and 13). Focus groups were used to facilitate discussions regarding use of NIPT for SCAs and microdeletion syndromes.

The authors reported that participants were less familiar with SCAs, although they supported including the conditions provided that women were informed prior to testing and given post-test options. In regard to microdeletions and microduplications the researchers observed that:[127]

> [o]verall, participants perceived the value of NIPT on a continuum based on the conditions the test assesses and their perceptions of the usefulness of test results. Participants generally saw the value of screening for Trisomies 21, 18, and 13 but less for [sex chromosome aneuploidies] and questioned the utility of screening for microdeletion syndromes. This was due, in part, to uncertainties associated with these conditions, given their range of phenotypic expression. Furthermore, in light of the expanding capabilities of NIPT, some participants thought that women should be able to choose the conditions assessed.

It seems reasonable that women who undergo NIPT should be able to determine the scope of the NIPT panel. For example, prior knowledge of a SCA may enable a child's early treatment, while some SCAs or MMS may potentially be serious and trigger doubts about continuing a pregnancy. Other women may not seek this additional information. The authors concluded that[128]

> It is critical that clinicians educate patients about their screening and testing options, test benefits and limitations, as well as results and implications. This includes a discussion of the lower sensitivity and specificity of NIPT for … [sex chromosome aneuploidies] compared with those for autosomal aneuploidies. To make an informed choice about NIPT, pregnant women must have information that addresses all conditions assessed by the selected testing platform. This includes information about the ability of NIPT to provide information about sex chromosome aneuploidies, not only fetal sex. One aspect of counseling that warrants consideration is that the clinical expression of these conditions is highly variable, and these conditions may be undiagnosed at birth and identified later in childhood or adult life. To foster an informed decision, participants suggested that pregnant women understand the capability and accuracy of NIPT for each condition. For now, this includes autosomal and [sex chromosome aneuploidies]; in the near future, this will include microdeletion syndromes. The counseling process should also address how pregnant women would integrate fetal genetic information into their framework of values and preferences ... It is critical that information regarding all conditions being evaluated is disclosed before prenatal testing, as the post-test period is not the time for women to consider an abnormal result and the impact of that information on their pregnancy.

What is highlighted by this research is that providers need to ensure that women understand the implications of expanded NIPT and are made aware of the option to limit the scope of testing performed.

Access to commercial NIPT has resulted in testing for SCA screening and select copy-number variants (CNVs) becoming commonplace "because there are no other screening options to identify these conditions".[129] However a recent systematic review that examined the nature of information provided on websites by companies advertising NIPT revealed that although some websites contained balanced and accurate information, the majority did not provide evidence to support their claims. Specifically, information regarding false positives and negatives and the need for invasive testing to definitively diagnose aneuploidy was considered inadequate.[130]

The Chromosome Abnormality Screening Committee of the International Society for Prenatal Diagnosis states that when cffDNA is extended to MMs or rare trisomies "the testing should be limited to clinically significant disorders with a well-defined severe phenotype".[131] Further, it states that the detection rates should be estimated

and the false-positive rates provided to patients as well as information regarding the clinical significance for each disorder for which screening is performed. A 2016 position statement from the ACMG notes:[132]

> Expanding NIPS to include detection of specific conditions caused by a CNV (e.g. 22q11.2 deletion, 1p36 deletion, 15q11.2–13 deletion) is technically possible (analytical validity). The phenotypes associated with these conditions can be severe; therefore, they may be appropriate conditions for prenatal screening. However, providers and patients must be aware that expanding the use of NIPS to include the detection of CNVs requires in-depth knowledge of the limitations of the technology, return of results, and follow-up.

Although testing for sex chromosome aneuploidies (such as Turner syndrome and Klinefelter syndrome) and microdeletion syndromes is currently provided by commercial companies, some commentators claim that there is a "paucity" of published data regarding false-positive and false-negative rates for microdeletion syndromes.[133] Despite this, US researchers recently reported obtaining highly accurate results for 5 microdeletion syndromes using SNP-based NIPT.[134] The authors concluded that, because these clinically relevant microdeletions and duplications are present in >1% of pregnancies, NIPT should be considered for the general obstetric population.

Technical limitations of NIPT

There are significant limitations to the kind of conditions that can currently be detected by NIPT. While NIPT detects chromosomal abnormalities, it does not detect all chromosomal[135] or structural anomalies. Specifically, NIPT does not identify structural birth defects such as neural tube defects involving the brain, spine, or spinal cord. Hence, NIPT does not negate the indications for ultrasonography as part of prenatal screening.

NIPT is not always accurate. Some tests may be inconclusive or fail to reveal a result for a range of reasons. Alternatively, false positive results may occur where a result is suggestive of a disorder that, on further invasive testing, is not present. Each of these is examined further below.

Fetal fraction

Fetal fraction refers to the amount of placental DNA in the mother's blood. At 10 weeks' gestation, the fraction of cffDNA in the maternal circulation is generally 10-20%, with 4% considered by most laboratories to constitute the minimum amount necessary for testing purposes.[136] Factors influencing fetal fraction include gestational age, maternal weight, the sample collection method as well as the transport conditions.[137] For example, there appears to be a link between low fetal fraction (and a subsequent "no result") and higher maternal body weight. Significantly, a "no result" on cffDNA has been associated with a higher incidence of aneuploidy in pregnancy.[138] This suggests that additional screening, or even invasive diagnostics, should be offered to a woman who receives such a result.

Despite this data, not all laboratories providing commercial NIPT report fetal fraction when returning results. In contrast, testing standards in the context of invasive prenatal *diagnosis* (amniocentesis/chorionic villus testing) require a minimum number of cell colonies to be present before a diagnostic result is reported. Some clinicians consider fetal fraction to be a key factor in ensuring accuracy of NIPT. This conviction motivated two maternal-fetal medicine specialists to recently conduct an ad hoc "sting", which they loosely described as an "experiment".[139] The specialists sent blood samples from two 44 year-old-women to five US laboratories for NIPT. Although neither of the women were pregnant, the requisition forms stated the women were both 12 weeks pregnant. Two of the five laboratories reported that there was insufficient fetal DNA to enable a result. However, three laboratories (one of which measured fetal fraction and two that did not) reported results that were consistent with a normal female fetus—meaning that their report was based on the maternal DNA. The result of this unorthodox experiment supports the clinicians' claim that measurement of fetal cffDNA is necessary as a quality assurance mechanism to ensure reliable interpretation of results.[140] This gap has arguably occurred as a result of NIPT being driven commercially without quality assurance standards being prioritised.

False Positives and False Negatives

False positives and false negatives are not novel events; indeed, they are part of the screening landscape. For example, traditional prenatal sequential screening (ultrasound and serum screening) rates for trisomy 21 utilise algorithms that provide detection rates of between 81-96%, with false positives around 5%.[141] This means that some tests will not detect trisomy 21, and in other cases it will give an erroneous positive result.

Early reports revealed NIPT detection rates for the main trisomies (21, 13, 18) that were significantly better than occurred in traditional screening. However, a vital factor in interpreting NIPT results is what is called the Positive Predictive Value. As the range of conditions included on NIPT screening panels increase, understanding the significance of PPV, or the incidence of "true disease status", is vital.

Positive Predictive Value (PPV) refers to the reliability of a positive test (i.e. true positive). Negative Predictive Value (NPV) refers to the reliability of a negative test (i.e. true negative).[142] Essentially, the PPV is the statistical likelihood that a positive test actually reflects the presence of the disease (i.e. the number of true positives out of all of the positives).[143] This is explained in the figure below.

Figure 8: Positive Predictive value[144]

In the example below 1,115 subjects received a positive screening test, but only 132 actually had the disease according to the gold standard diagnosis. Accordingly, if a subject's screening test was positive, the probability of disease was 132/1,115 = 11.8%.

Table - Illustration of Positive Predicative Value of a Hypothetical Screening Test

Positive predictive value focuses on subjects with a positive screening test in order to ask the probability of disease for those subjects.

	Diseased	Not Diseased	Total
Test Positive	132	983	1,115
Test Negative	45	63,650	63,695
Column Totals	177	64,633	64,810

The positive predictive value is 132/1,115 = 0.118, or 11.8%.

Interpretation: Among those who had a positive screening test, the probablility of disease was 11.8%.

The NPV is the statistical likelihood that a negative test actually reflects the absence of the disease (i.e. the number of true negatives out of all of the negative results).[145]

Figure 9: Negative Predictive value[146]

In the same example, there were 63,895 subjects whose screening test was negative, and 63,650 of these were, in fact, free of disease. Consequently, the negative predictive value of the test was 63,650/63,695 = 99.9%.

Table - Illustration of Negative Predicative Value of a Hypothetical Screening Test

Negative predictive value focuses on subjects with a negative screening test in order to ask the probability that subjects with a negative test are truly not diseased.

	Diseased	Not Diseased	Total
Test Positive	132	983	1,115
Test Negative	45	63,650	63,695
Column Totals	177	64,633	64,810

The negative predictive value is 63,650/63,695=0.999, or 99.9%.

Interpretation: Among those who had a negative screening test, the probability of being disease-free was 99.9%.

PPV depends not only on the sensitivity and specificity of the test used, but is also determined by other factors, including the prevalence of the disease in the population tested. Lutgendorf et al explain:[147]

> The lower the disease prevalence [in a population], the higher the negative predictive value (true negatives) and the lower the positive predictive value (true positives).

For example, when a screening test has a sensitivity of 100% and specificity of 99% (1 false-positive in 100) and the disease prevalence is high (risk of 10 per 100, 10%), screening 1,000 patients would yield 100 true positive results, and 10 false positive results. The PPV would therefore be 100 true positives/110 total positives, or 91%. If, however, there is a lower disease prevalence (risk of 1 per 1,000, 0.1%) but the same sensitivity and specificity of 99% (1 false positive in 100), screening 1,000 patients would result in a much lower positive predictive value of 1 true positive/11 total positives, or 9%. Lutgendorf et al conclude that:[148]

> … the prevalence of the condition being screened for must be taken into account when interpreting test results, particularly the positive predictive value, as with a lower disease prevalence, a positive result is less reliable (more likely to be a false-positive result).

This phenomenon has been highlighted in recent studies of NIPT. For example, one study evaluated the true-positive rate for a range of conditions that gave a positive result following NIPT. The study examined 109 cases reporting positive results for either trisomy 21, trisomy 18 or trisomy 13.[149] These results were then evaluated using standard cytogenetic testing methods.[150] The study confirmed the following: (a) true positives for trisomy 21 in 38 out of 41 NIPT positive cases; (b) true positives for trisomy 18 in 16 out of 25 NIPT positive cases; and (c) true positives for trisomy 13 in 7 out of 16 NIPT positive cases. The PPVs varied significantly and were, respectively, 93% for trisomy 21; 64% for trisomy 18; and 44% for trisomy 13.[151]

Similarly, a recent blinded prospective study comparing the performance of NIPT with standard screening to estimate the risk of trisomy 21 in a large unselected population demonstrated an overall PPV of 80.9%, although a secondary analysis limited to women < 35 years of age indicated a PPV of 50%.[152] The PPV was lower in the second group because of the lower incidence of trisomy 21 in women under 35.

While both of these values are far superior compared to standard first trimester screening (3.4%), they indicate potential limitations of NIPT and a need to evaluate larger numbers of false positive results to establish predictive values for NIPT in the general population.[153] This was emphasised by a group from Stanford University School of Medicine that recently described eight cases where NIPT returned positive results for trisomy 13 and 18, although the fetus was found to be healthy following invasive

testing.[154] They concluded that further study of the causes of false-positives, as well as a formal process for reporting false positives/negatives is critical before NIPT is offered to the general (low risk) obstetric population.[155] This would require some form of "adverse event" monitoring system internationally. This includes the need to identify the potential reasons (biological or technical) contributing to false positive results.[156]

While false negatives are less common, a recent case report from the Netherlands describes two cases, one involving trisomy 13 and the other trisomy 18, which were not detected by NIPT. In one of these cases, the condition was only diagnosed after a 20-week fetal anomaly scan revealed multiple abnormalities.[157] These late diagnoses after a prior negative NIPT result caused significant distress for the women and families involved. The authors note that there was no obvious causal explanation for the discordant results and appealed to all parties involved in NIPT to collaborate to "unravel possible biological causes and to improve the process of patient care from initial counselling to communication of the result".[158] They recommended that "an international registry for systematic recording of all discordant NIPT results and their causes, as was done when CVS was introduced in prenatal diagnosis more than 30 years ago" be established in order to "provide insight into the frequency and causes of false negative and false positive NIPT results".[159] Meanwhile, counselling patients about the PPV of tests before they are performed, as well as including information on PPV in clinical laboratory reports, seems essential.

The implications of "no call" results

Low fetal fraction may result in a "no call" result, with low fetal fraction associated with an increased risk of fetal aneupolidy.[160] This correlation enforces the need for companies to report the reason for such a result—specifically if a low fetal fraction was identified. Failure to obtain a result may be due to problems with the sample collection or as a result of a failure in sequencing or testing methodology.[161]

Additional reasons for discrepant/discordant results

Several additional factors may contribute to erroneous or discrepant or discordant results following NIPT where the result does not match the direct fetal karyotype. Discrepant results may be caused by chromosomal biology in combination with technical features of a test. These include the presence of placental mosaicism; a vanishing twin (also known as co-twin demise); or an undiagnosed maternal tumour.[162]

Mosaicism

While placental DNA is usually the same as fetal DNA, in a subset of cases, aneuploidies detected may be confined to the placenta, and not represent the fetus.[163] Confined placental mosaicism (where two or more chromosomally different cell lines that are confined to the placenta and not present in the fetus) occurs in approximately 1% of chorionic villus samples, although its incidence in NIPT is unknown.

Vanishing Twin

The phenomenon of a vanishing twin occurs when an initial multiple pregnancy is spontaneously reduced after one of the fetuses is miscarried. The fetal tissue is then resorbed and the twin "vanishes". In this context NIPT may result in an erroneous result if the cell free DNA tested belongs to the vanishing twin.[164]

Maternal Malignancy

The number of women who become pregnant not knowing that they have cancer is rare, but not unknown. Bianchi et al explain:[165]

> The diagnosis of cancer during pregnancy is relatively uncommon, with an incidence of about 1 in 1000 gestations. The most common malignancies observed in pregnant women are breast and cervical cancers, Hodgkin and non-Hodgkin lymphomas, malignant melanoma, leukemia, ovarian cancer, and colorectal cancer.

Recently, there have been studies indicating that a subset of false-positive findings in NIPT can be explained by the presence of malignant tumours in the mother.[166] In two case reports from 2013[167] and 2015, two young, asymptomatic pregnant women who had received false-positive NIPT results were both subsequently diagnosed with cancer. The malignant cells showed evidence of multiple aneuploidies that mirrored the findings reported by maternal cffDNA analysed for NIPT.[168]

In order to analyse the relationship between maternal cancer and abnormal NIPT results, Bianchi et al retrospectively examined sequencing data in a group of pregnant women whose NIPT results were reported as positive for aneuploidy who subsequently received cancer diagnoses after prenatal testing. The women were identified from a population of 125,426 women who undertook NIPT for chromosomes 13, 18, 21, X and Y. Of these 3% (3757) returned "aneuploidy-detected" results.[169] However not all of those positive results were true positives and diagnostic fetal testing revealed normal chromosomes (euploidy).

Of those 3,757 "aneuploidy-positive" cases, maternal cancers were subsequently diagnosed in 10 women. Bianchi et al reviewed eight of the ten cases. Seven of the eight cases had discordant NIPT results: although the NIPT indicated aneuploidy, fetal diagnostic testing indicated that the fetus was chromosomally normal. These discordant results were assumed to occur when tumour DNA (malignant cells) was "shed" into the maternal circulation and detected by NIPT.[170] Consequently the authors conclude that in the small subset of cases where there is abnormal discordant NIPT results (particularly in the presence of multiple aneuploidies with a normal fetal karyotype) the possibility of maternal cancer as a reason for the discordant result should be considered. For some women with discordant results, they may be faced with a differential diagnosis of maternal cancer—which may have both negative (anxiety if cancer is not present) and positive outcomes (cancer may be detected earlier).

Regulatory oversight and quality assurance: the US example

New Zealand consumers accessing NIPT must rely on the regulatory oversight and quality assurance mechanisms imposed on test manufacturers in the country in which the test is developed. Consequently, the standards required of offshore companies are highly relevant.

Because a NIPT test is a diagnostic laboratory test performed on human tissue outside of the body, it constitutes an "in vitro" diagnostic or "IVD". In the US, the Food and Drug Administration (FDA) has responsibility for regulating IVD products.[171] IVD are subject to both the FDA's pre-and post-market controls, in addition to the requirements set out by the Clinical Laboratory Improvement Amendments (CLIA) of 1988.[172]

However, in the US, one category of IVDs constitutes "laboratory developed tests" (LDT). These are tests that are intended for clinical use and are designed, manufactured and used in a single laboratory, in contrast to other IVDs that are made by conventional manufacturers and are used by multiple laboratories.[173] Although LDTs fall within FDA authority, the FDA has discretion whether or not to actively regulate LDTs. It may decide whether or not to enforce applicable provisions under the Act and regulations.[174] Currently, non-commercial LDTs developed and performed in-house in hospital settings to diagnose or monitor diseases are not usually subject to FDA approval, but are still subject to the federal CLIA law.

The CLIA is the regulatory authority for LDTs and is administered by the federal agency, the Center for Medicare and Medicaid Services, CMS. The focus of the CLIA is on the operations of laboratories. While CLIA sets standards for clinical laboratory testing of LDTs, the regulations are not intended to specifically regulate IVDs.[175] Compared with the FDA requirements governing IVDs, the CLIA regulation is not as onerous. It does not require a research phase, the requirement for analytic validation is not as robust, and clinical validation of a test is not required.[176]

Currently companies performing NIPT in the US claim that these tests are LDTs developed in CLIA laboratories.[177] As Lutgendorf et al note, LDTs are being developed for NIPT and licensed to a laboratory, but are actually intended for commercial use and are being accompanied by aggressive direct marketing to health professionals and the general public. Essentially, companies are able "to gain rapid market access" for their NIPT tests without FDA oversight.[178] In 2014, Lutgendorf et al stated that:[179]

> In essence, NIPT is now commercially available and is aggressively marketed to health-care providers and patients. The lack of clinical validation is not widely publicized. Patients and providers may be unwittingly participating in a large phase IV clinical trial without formal, centralized tracking of adverse events (including false-positive and false-negative test results). Although the testing is not diagnostic, some patients may choose to act on results without confirmatory invasive diagnostic testing.

Lutgendorf et al's claims have been reinforced by a recent review conducted by the FDA that was reported to the US Congress in November 2015.[180] The FDA Report confirmed Lutgendorf et al's concerns and more, stating:[181]

> At least four companies in the U.S. have recently begun offering these tests, using a technique called cell-free DNA testing (cfDNA). Marketing materials cite very high accuracy rates. One company claims that its test has a "very low false-positive rate,"[182] while another company claims a specificity of 99.9% for trisomy 18 (1 out of every 1000 results expected to be a falsepositive) and 99.95% for trisomy 13 (5 out of every 10,000 results expected to be a falsepositive).[183]
>
> However, trisomy 18 and 13 are so rare (1 in 5,000 for trisomy 18 and 1 in 10,000 for trisomy 13) that even these high specificities should yield more false-positive than true-positive results, requiring followup testing for confirmation[184] … A 2014 investigative report described three families who considered abortions based on what further testing showed to be false-positive results.[185] A study of one test calculated a PPV of 83% for 4 tested genetic conditions, and found that 22 (6%) of women who received positive results obtained abortions without a follow-up invasive diagnostic test.[186] Citing concern that these tests could be used in the general, low-risk population with resulting low PPVs, the American College of Obstetricians and Gynecologists issued a statement in December 2012 that NIPT should not be offered to such women.[187]
>
> Although the main concern is over the test's PPV for the rarer trisomies, in 2012, a patient reported a false-negative result to FDA after she received normal NIPT results and unexpectedly delivered an infant with trisomy 21. Additional cases were documented in an investigative report in the Boston Globe in 2014."[188]

The FDA concluded by outlining the pre-market and post-market measures that the CLIA did not ensure or require. Specifically, the CLIA did not:[189]

- Ensure the safety and effectiveness of LDTs prior to marketing.
- Assess the quality of the design and manufacture of devices.
- Ensure test labeling provides adequate directions for use.
- Require truth in marketing materials and other labeling.
- Require adverse event reporting.
- Permit removal of unsafe devices from the market.
- Require informed consent for patients participating in clinical studies of LDTs.
- Establish procedures for the conduct of such studies.

Ultimately, it concluded that enhanced FDA oversight of LDTs was necessary "to promote access to LDTs that provide benefits to patients and the health care system, while helping to ensure patients are not unduly exposed to harm." The Report highlights the current inadequacies of the regulatory framework governing the safety and quality of NIPT tests developed in the US. These tests, in particular HarmonyTM, currently constitute some of the common NIPT tests accessed by pregnant women in New Zealand.[190]

Standardisation of results

An issue that compounds the challenges for NZ providers is the lack of uniform conduct by companies when reporting NIPT results. Rather than being dictated by professional guidelines or standardised algorithms, analysis of sequencing data and reporting of results varies between companies. For example, when reporting results, Sequenom states that there is either increased chromosome material or not—which may suggest to some providers that it is essentially a diagnostic result. In contrast, Ariosa provides an assessment of risk—which is more consistent with screening terminology. Verinata classifies results as "aneuploidy detected", "aneuploidy suspected" or "no aneuploidy detected".[191] This is clearly a case where international standardisation would be beneficial for clinicians and patients. Some groups have urged using the terminology of "high chance" or "low chance" of fetal aneuploidy to describe NIPT results.

Closing the gap between noninvasive screening and diagnosis?

One of the limitations of cffDNA described above is that current noninvasive tests do not analyse all of the chromosomes, consequently invasive diagnostic testing remains the gold standard for prenatal diagnosis. However, a recent Sequenom-sponsored study compared a new NIPT test (MaterniT®GENOME) with invasive test results of women who were high risk for fetal aneuploidy.[192] It reported that it succeeded in extending NIPT beyond detection of the common trisomies and sex chromosome abnormalities to genome-wide detection of sub-chromosomal and whole chromosomal abnormalities of 7Mb or greater. The authors claimed that examining chromosomes at this resolution is comparable to traditional cytogenetic karyotyping stating:[193]

> … genome-wide non-invasive prenatal testing for fetal chromosomal abnormalities can provide high resolution, sensitive, and specific detection of a wide range of sub-chromosomal and whole chromosomal abnormalities that were previously only detectable by invasive karyotype analysis.

While the study confirmed the capacity to extend cffDNA testing, technical challenges remained. Nevertheless, the authors conclude:[194]

> In pregnancies that can benefit from additional information, this test provides more clinically relevant results than previous NIPT options. However, its role as a follow-up test to abnormal ultrasound findings or as a general population screen will likely be debated for the foreseeable future.

This research suggests that comprehensive testing for sub-chromosomal and whole chromosomal abnormalities previously undetected by non-invasive screening is clinically valid.

3.4 Ethical and legal considerations of selective reproduction: new technology, same debates

Although prenatal testing is not a new technology, NIPT introduces novel aspects: it is non-invasive and does not pose any physical risk to an established pregnancy; it may be performed earlier in the first trimester than invasive testing; it provides expanded screening options for women, and it is commercially available. Given its potential scope, the introduction of NIPT has seen a resurgence of debates involving selective reproduction such as eugenics, the appropriate scope of parental choice regarding future offspring, and disability rights arguments.[195] The following section discusses NIPT against a background of these older, and on-going, controversies.

The history of eugenics

The eugenics movement of the late 19th and early 20th century continues to taint debate regarding prenatal testing and termination of pregnancy for fetal abnormality. Historically this intellectual and social phenomenon was driven by the broad social goal of improving humanity through selective breeding, and spanned the western world".[196] Eugenic policy encompassed a range of initiatives, but broadly "positive" eugenics aimed to increase the incidence of desirable traits in a society. This involved encouraging the genetically well-endowed to reproduce, while "negative" eugenics involved discouraging (or preventing via sterilisation) the "unfit" from reproducing.[197] As a putatively intellectual theory, it drew upon flawed pseudoscience that oversimplified heredity, ultimately designating certain undesirable individuals as genetically unfit.[198] Those labelled unfit included "criminals, illegitimate children, alcoholics, poor people, chronic invalids, epileptics, homosexuals, prostitutes and those loosely called 'idiots', 'lunatics', 'imbeciles' or 'feeble-minded"'.[199] Eugenic philosophy was also often linked to race, with non-white or immigrant races deemed genetically inferior.[200] At its zenith, eugenics reinforced and legitimised class biases, bigotry, moralism and racism.[201] However, the popularity and support of eugenics waned following the Second World War, and its decline continued in the following decades.

Contemporary genetics and prenatal diagnosis

In contrast, contemporary clinical genetics has strived to dissociate itself from the past eugenic movement and is generally based on rigorous science. Genetic counsellors generally adopt the paradigm of non-directiveness, based on the concepts of value-neutrality and respect for reproductive liberty and choice.

Despite the outward commitment to non-directiveness as a core professional value, some commentators challenge the authenticity of aspiring to value neutrality in the context of reproductive screening programmes. For example, geneticist Angus Clarke contends that:[202]

> … an offer of prenatal diagnosis implies a recommendation to accept that offer, which in truth entails a tacit recommendation to terminate a pregnancy if it is found to show any abnormality. I believe that this sequence is present irrespective of the counsellor's wishes, thought, or feelings, because it arises from the social context rather than the personalities involved—although naturally the counsellor may reinforce those factors.

It is axiomatic that reproductive decisions are not made in a vacuum. Although the ostensible objective of providing prenatal screening is to enable reproductive choice, various groups have challenged the extent to which genuine "choice" is possible in this context.[203]

Reproductive decisions are influenced directly and indirectly by an array of factors.[204] These include "individual beliefs and experiences, interpersonal and family relationships, clinician–patient relationships, cultural, societal mores, or both, and, possibly, even evolutionary-influenced decision-making."[205] In the New Zealand context the perspectives of Māori may vary, but are often derived from, or influenced by, a distinct value system.

It has been said that for Māori "reproduction is the physical means of perpetuating the divine genealogy of the gods and ensuring the political and economic survival of the collective".[206] Historically reproductive practices within Māori culture were premised on the tapu (sacredness) of whakapapa (genealogy) and collective observation of kaitiakitanga (guardianship), manifesting in complex cultural practices that aimed to strengthen bloodlines.[207] While this cultural and spiritual world view is at the heart of Māori culture, the way that it translates to modern reproduction may differ for individuals:[208]

> Contemporary reprogenetics may offer an additional means of protecting whakapapa by alleviating the experience of whare ngaro (infertility) and the prevalence of genetic disorders within the Māori population. Whether engaging in pre-birth genetic testing is a sustainable extension of tikanga Māori [customary practice] must be treated cautiously as opinions and interpretations of customary values differ.

The following diagram indicates the range of factors that may implicate reproductive decision-making following genetic counselling.

Figure 10[209]

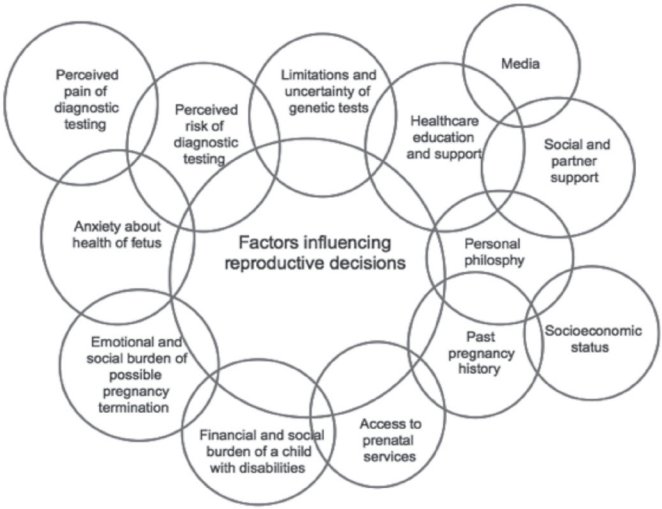


Fig. 1. Factors influencing reproductive decisions after genetic counselling.

A feminist-inspired critique of prenatal testing claims that true "choice" is illusory when prenatal diagnosis is presented as a routine procedure, or is assumed to be required behavior of a responsible citizen.[210] Susan Kelly contends that, collectively, critiques of prenatal testing emphasise:[211]

> … the moral or existential dilemma facing prospective parents through the routine presentation of choice and responsibility for the health and 'quality' of potential children, societal effects of the 'backdoor' (Duster 1990) eugenics of selective termination of 'defective' fetuses, and transformation of the socio-cultural experience and meaning of pregnancy, particularly as testing has become associated with responsible maternal behaviour.[212]

The way in which prenatal testing has been instantiated as a standard part of prenatal care has attracted criticism not only from feminist scholars, but also from bioethics, critical social science and disability rights perspectives.[213] Sonia Suter stated almost two decades ago:[214]

> The routinization of [traditional] prenatal testing has impoverished the informed consent process in many ways; little emphasis is placed on the many emotional and psychological ramifications of undergoing such testing, leaving patients unprepared for certain choices and emotional reactions … patients are often uninformed about the implications of undergoing such testing, which can result in anxiety or decisions inconsistent with their values or preferences.

There is extensive literature regarding the challenges of promoting informed choice in the context of traditional prenatal screening.[215] Indeed, there is evidence that the quality of informed consent for standard serum screening is often poor, with many women indicating that they did not realise they were acceding to testing, or declining it without understanding its purpose.[216] Information provision may be inadequate for a variety of reasons, including lack of knowledge on the part of the provider, or as a result of time constraints. However, the complexity of obtaining informed consent is highlighted by some commentators who note that facilitating what a woman subjectively considers is an adequately informed choice may be difficult when women and clinicians have "different information priorities".[217]

Despite the professional emphasis on non-directiveness, it is not always reflected in women's subjective accounts of prenatal screening.[218] Women have variously reported feeling pressured by professionals, partners or other family members to make certain decisions. Some women and their partners may fear that they will not receive adequate social support should they elect to continue a pregnancy, including financial support for a child with complex needs.[219] Yet making a decision under pressure, particularly if it is ill-informed or not consistent with a person's values or preferences, may cause significant moral distress.

While a multitude of factors influence parental decision-making, certain themes are discernible in the literature:[220]

> Many studies have investigated different aspects of prenatal screening or testing and the impact on parents. It appears that people are more likely to accept prenatal testing if they perceive an abnormality to be more serious and that choices are also based on their perceived ability to cope with a child with a disability. It has also been suggested that health professionals and lay groups sometimes make judgements about women's decisions to continue a pregnancy in the case of a child with a disability. A woman who declines testing or continues a pregnancy where a fetal anomaly has been detected, may be seen as more to blame and less deserving of sympathy compared to a woman who did not have the option of testing.

Pregnancy-related decisions directly implicate a woman's physical, emotional, economic and social life. In the context of fetal ill-health, the decision to either continue or terminate a pregnancy is invariably difficult and emotionally laden, not least because it involves a choice between two outcomes, neither of which was originally desired.[221] While these issues compound the complexity of decision-making, arguably respecting and facilitating genuine reproductive choice should be a fundamental tenet of reproductive clinical care even if, at times, securing such genuine choice may be aspirational given individual circumstances, social realities and wider political factors.

"Routinisation" of NIPT

One of the major issues raised regarding NIPT is its capacity for "routinisation", which is compounded by its ease and simplicity. Because NIPT involves a simple blood test, it may become just another blood test in the battery of existing prenatal healthcare services.[222] Hence, there is concern that some women may be complacent regarding the potential implications of testing,[223] and fail to consider the repercussions of a positive screening test and the difficult decisions it may trigger.

Although NIPT does not pose any physical risk to a woman or her pregnancy, the procedure is not without potentially significant implications. Just like traditional prenatal testing NIPT[224]

> … can initiate a cascade of clinical decisions and ethical consequences for the pregnant woman and her family. This cascade hinges on decisions about whether to obtain genetic information about the fetus, consideration of one's acceptable levels of risk to acquire that information, and what to do with the information generated from the screening test.

Yet it is not clear that all women undertaking NIPT consider it to be risk-free. Empirical research has shown that although NIPT reduces the incidence of false positives, the majority of women undertaking NIPT consider that the same risks and benefits associated with traditional prenatal screening exist, i.e. the possibility of a positive result which requires further decision-making regarding invasive diagnostic testing.[225]

Research suggests that some professionals consider that the extent of information provision required prior to obtaining consent to NIPT is less than that required for invasive testing, which has raised concerns.[226] A prospective study involving British obstetricians and midwives indicated that the providers surveyed anticipated giving significantly less counselling and decision-making time for NIPT than they would for invasive testing.[227] Yet this is perhaps unsurprising, given that invasive testing will usually be considered only when there has been an anomaly detected on routine screening, or against a background of increased risk. Obtaining informed consent to NIPT in general terms could plausibly be less involved than obtaining informed consent to amniocentesis after a risk has been identified, because the relative risks change markedly when amniocentesis is a possibility. Invasive testing involves a trade-off between obtaining/excluding a definitive diagnosis against the risk of suffering a miscarriage. Nevertheless, this distinction between test-related risk does not negate the need to provide adequate information prior to performing NIPT. Although NIPT obviates the need to discuss risk associated with invasive procedures, patients must nevertheless understand the nature of the test, in particular that it is not diagnostic, and the limitations of the test.[228]

Although NIPT for the common trisomies demonstrates greater sensitivity and specificity, NIPT is not 100% accurate. Ultimately anxiety regarding fetal health may continue even after a negative NIPT result. While NIPT may appear novel and attractive, it does not necessarily "simplify women's decision-making processes or reduce the support they need to make choices that align with their needs and preferences".[229]

NIPT as enhancing autonomy and privacy

Because NIPT is a relatively new technology, there is little available evidence of the impact NIPT has had on women's reproductive decision-making. However, some recent studies report positive maternal experience.

A recent study by Farrell et al explored how 53 women, who were either pregnant or had recently delivered a child, experienced NIPT.[230] The study revealed that for some women, the relative ease of NIPT and its capacity to be performed discreetly is beneficial given the decisional implications of prenatal screening. Specifically, they considered that it enabled increased privacy when contemplating the future of a pregnancy. Some women considered this aspect of NIPT to be empowering; a factor not previously alluded to in the literature. The authors observe: [231]

> Participants underscored the need for pregnant women to make autonomous and private decisions regarding prenatal genetic testing, particularly when there was disagreement with their partners. Because prenatal genetic testing touches upon polarizing issues of disability and termination, the ability for women to make intimate decisions about the pregnancy is paramount.[232] The ease and

convenience of NIPT may enhance women's decision-making autonomy and privacy with regards to prenatal genetic testing. Specifically, the procedural single blood draw simplifies the testing process so that woman may have testing without the knowledge of others, including partner and family. Thus, NIPT may present women with the option for a new level of privacy that is not as easily obtained by other forms of testing.

This apparent "advantage" could, however, be seen by some as an undesirable aspect of NIPT, or even a subversive use of technology because it may implicate the extent of involvement of reproductive partners in decision-making. However, if NIPT is to be legitimately associated with the notion of reproductive liberty and a woman's interest in making autonomous decisions regarding prospective parenthood, this should not necessarily be problematic. It is arguable that in this respect NIPT is not extending choice *per se*, but rather altering the environment in which reproductive choices are made.

The fetalist critique: prenatal screening and abortion

A particular critique of NIPT is that by making prenatal screening accessible and safe it may "contribute to trivialising abortion and abortion decisions".[233] However this concern fails to take into account that some women who consider NIPT as a screening test may do so in the hope that it will enable them to *avoid* invasive diagnostic testing and the associated risk of miscarriage—which suggests that a termination would not be undertaken lightly.

However, given that prenatal screening is already widely available, the concern that NIPT may trivialise abortion seems to be a slightly anomalous argument. If NIPT is limited to the same conditions as are currently identified in routine screening there will be less false positives, and more true negatives which means there will be less fetal loss overall due to fewer invasive tests. On this account, the fetalist critique of NIPT is rendered obsolete. However, there are several discrete issues that may legitimately contribute to anxieties regarding increased abortions as a result of NIPT.

NIPT and its implications for abortion in general

Widening the scope of conditions that are screened for using NIPT may directly increase the number of NIPT positive screening results. This may increase the number of individuals/couples who might subsequently contemplate terminating a pregnancy. However, even if expanded screening identifies a serious or lethal condition in a fetus that would not normally have been found on routine screening, this is not inconsistent with existing ethical and legal frameworks that permit abortion for fetal abnormality. Indeed, it seems paradoxical to suggest that NIPT is objectionable on this basis.

It is also questionable whether it is accurate to assume that all NIPT positive screens will ultimately result in a decision to terminate a pregnancy. While some prospective parents may elect to terminate a pregnancy in the case of a fetal anomaly, it is not always the case.[234] A recent US study of 332 parents involving 272 pregnancies that were prenatally diagnosed with trisomy 13 or 18 (described as serious life-limiting conditions) found that over a third (128) of the parents that underwent invasive PND elected to continue

the pregnancy. The reasons described included: "moral beliefs (68%), child-centered reasons (64%), religious beliefs (48%), parent-centered reasons (28%), and practical reasons (6%)".[235] Significantly there is some evidence that not all positive NIPT tests have resulted in a maternal decision to terminate.[236]

Another consideration, again speculative, is that if a positive NIPT result for trisomy is obtained earlier in the pregnancy when the fetus is less developed, there may be greater likelihood that a woman will elect to terminate a pregnancy.[237] An early medical abortion (EMA), whereby miscarriage is induced by oral medication, can be performed up to nine weeks, but NIPT is generally recommended at 10 weeks. Further if there is a positive result, invasive testing will still need to be undertaken, either by chorionic villus testing at 10-11 weeks or amniocentesis between 15-16 weeks. A first trimester surgical abortion is performed up to 12 weeks and six days. Less commonly second trimester abortions may be performed for fetal abnormality, either by induction of labour or surgery.

Recent research confirms that in the case of women who elected termination following a positive NIPT result for trisomy 13, 18 or 21, termination occurred up to three weeks earlier in the context of NIPT compared with traditional testing. [238] Significantly, women were much less likely to have a termination after 18 weeks (four times) or 20 weeks (three times). Assuming that NIPT provides earlier results that enable earlier diagnostic investigation, this also provides more time to process information and obtain information about the anomaly. If termination is elected, the fact that it occurs earlier in a pregnancy may mean it is (if only marginally) less physically, emotionally, and morally difficult for the woman/couple involved.

Clearly, some commentators have expressed concern that a "no-risk" prenatal test will encourage women who may have previously chosen not to undertake an invasive diagnostic test to undertake NIPT. While NIPT alters the risk-benefit ratio, it is debatable that a woman who wished to avoid invasive procedures out of a desire to protect her fetus would terminate a pregnancy for trivial reasons. Undergoing NIPT may also be motivated by the desire to optimise the management/outcome of her pregnancy and birth.

There is evidence that in some countries, more women are interested in undertaking NIPT than traditional screening. A survey of 381 pregnant women conducted in the Netherlands (where the uptake of first trimester combined screening is only around 27%)[239] reported that half of the women surveyed would be interested in NIPT if it was available, including 33% women who had declined first trimester screening.[240]

As well as providing earlier, non-invasive and more accurate screening for the common trisomy's than conventional screening, NIPT has the capacity to screen for a range of additional conditions. As NIPT becomes more powerful, it is likely that more detailed fetal and genomic information–or even a fully diagnostic test will become available. [241]

If it is accepted that the goal of reproductive screening/testing is to provide information that may inform reproductive choices, then NIPT is prima facie consistent with that goal. If NIPT is problematic, it cannot be on the basis that it may increase the number of serious conditions detected, potentially increasing the number of terminations subsequently be performed. Rather, the major issue with NIPT is determining the

scope of information that may be potentially obtained by NIPT, including less serious conditions, and what information prospective parents may access. While expanding the number of conditions screened for by NIPT *may* trigger an increase in abortion rates, it seems that the inherent concern for some is that some conditions may constitute "less serious" disorders or non-medical conditions such as sex selection.

Extent of information: fetal sex

The major concern of critics of NIPT is not solely termination for serious fetal anomalies, but rather non-medical selection, primarily sex-selective abortion. Given such concerns, some organisations such as the UK Nuffield Council recommend that NIPT should not be permitted to diagnose sex, *unless* there is a risk of a child transmitting a sex-linked disorder to offspring.[242] In contrast, a recent survey of 122 European laboratories indicated that only a minority of laboratories do not disclose fetal sex.[243]

There are several issues to consider in regard to disclosing fetal sex. It is not uncommon for women to want to know the sex of the foetus during the course of prenatal investigations such as ultrasound. There is no specific law or policy governing disclosure of fetal sex in New Zealand.[244] Prospective parents may value knowing fetal sex in advance for various reasons. Some women may consider it enhances the capacity to bond with a fetus and future child, and it may contribute to preparing themselves and their family for the child's birth. Consequently, preventing access to information regarding fetal sex requires good reasons to justify such a prohibition, such as the avoidance of harm.

The main grounds for opposing sex selective abortion is that it is discriminatory, a claim which is generally based on an unsupported assertion that the preferred sex will be male and, if unregulated, sex selection may result in skewed sex ratios which creates negative effects for society. The preliminary question therefore is whether there would be in interest in, or demand for, sex selective abortion in New Zealand and, if so, whether it is likely to be to the extent that it would skew sex ratios.

Countries such as China and India have seriously skewed sex ratios as a result of socio-political systems that create widespread son-preference. These societies experience significant problems that are compounded by the predominance of males (such as higher crime, particularly crimes against women).[245] While social sex selection may pose a societal threat by skewing sex ratios, son-preference in these cultural contexts is based on the ideology of male superiority and socio-political systems that confer/instantiate male privilege.[246] However, at least in Western countries, concerns regarding skewed sex ratios are overstated. As Dworkin notes:[247]

> It is true that in certain communities-in northern India, for example—male children are apparently preferred to female ones. But that preference seems so sensitive to economic circumstances, as well as to shifting cultural prejudices, that it offers no reason for thinking that the world will suddenly be swamped with a generation dominated by males.

In the absence of such a patriarchal socio-political system, the risk of individuals engaging in sex selection to the extent that it would, in the aggregate, impact population sex ratios in society is extremely low. Nevertheless, some Western countries such as the United States harbour concerns that ethnic minorities may seek sex selection. Some US states have introduced laws banning sex selective abortion, largely justified on the grounds that they are necessary to combat sex-based discrimination, particularly amongst Asian Americans. However, a group of US academics that recently undertook a rigorous study of sex selection found that:[248]

> … the few empirical studies in this field have been used improperly to support the contentions that: (1) all Asian Americans are sex selecting; (2) all Asian Americans sex select because of a preference for sons and an aversion to daughters; and (3) abortion is the method by which sex selection is achieved ... In fact, recent polling data refutes the existence of son preference among Asian Americans
> in the United States. The 2012 National Asian American Survey on opinions among Asians and Pacific Islanders posed the following question: "In some countries, people are allowed to have only one child. If, for whatever reason, you could only have one child, would you want it to be a boy, a girl, or does it not matter?" Chinese, Korean, and Indian respondents showed very slight and equal preference for sons and daughters. Overall, 92% of Chinese, 92% of Indians and 89% of Koreans surveyed said "It doesn't matter or they don't care.

In addition, minority women's rights groups in the US claim that sex selective abortion bans may engender further discrimination via "stereotyping and racial profiling of Asian women" whose motivations for an abortion would be treated with suspicion.[249] Ultimately, they claim that the laws may in fact exacerbate gender discrimination.[250]

There is also anecdotal evidence that suggests that withholding such information from a woman who is highly motivated to have a child of a particular sex may be futile, and have adverse consequences.[251] In a UK study examining professionals' attitudes towards sex selection, participants discussed the implication of withholding information regarding fetal sex from pregnant women out of concern that the couple wished to have a child of a particular sex. One particular case involved a woman who was not told of the sex of the fetus and who subsequently terminated the pregnancy, as she feared she was carrying a female fetus. Ironically the foetus was male. One participant observed "… to me that was a very good lesson, in that sometimes you can try to intervene for the best of reasons, and actually it goes horribly wrong".[252] Another participant stated that: "[w]e're not contributing to the termination of a female fetus [by not disclosing sex], so therefore, in one sense, we're kind of squeaky clean … but as this poor woman comes back after her third late termination … probably done under not such ideal conditions …, you know, we feel less squeaky clean …"[253]

While this research illustrates how health professionals may feel morally implicated by decisions that patients may make, it also reflects the futility of withholding information in

some circumstances when trying to enforce a moral value that the patient does not share.

Even if there might be some interest in fetal sex selection in NZ (which is by no means apparent), access to abortion is dependent upon the grounds for lawful abortion being met. In the absence of a substantial risk that the future child will have a serious medical condition, lawful termination requires a belief that continuing the pregnancy would result in serious danger to maternal mental health.[254] This threshold test needs to be met before two consultants may certify an abortion. It is also pertinent that if a woman is sufficiently concerned about the future sex of a child as to seriously consider terminating an otherwise wanted pregnancy on that basis, it would seem morally preferable to enable this to occur earlier, rather than later, when the pregnancy is more advanced.

These arguments suggest caution before assuming that state imposed limits are legitimate and desirable. Ultimately, withholding information from *all* women because of the way that *some* women may respond to such information seems at best paternalistic, at worst punitive.

However, the view that the state has an interest in protecting fetal life is generally accepted amongst western liberal democracies. Although a complete prohibition on abortion is extremely rare, states often impose regulatory limits on the scope of lawful abortion. The following analyses the approach to abortion adopted in NZ compared with the United States and the considerations that informed these legal initiatives. The US provides a particularly interesting comparator, given that despite Supreme Court recognition of a Constitutional right to reproductive choice (at least in the case of previable pregnancies), legislators in some US states have sought to constrain the scope of reproductive liberty given advances in prenatal testing.

Regulatory approaches to abortion: United States

In the case of *Roe v Wade*, the US Supreme Court held that in the early stages of pregnancy, a woman's right to decide whether or not to terminate her pregnancy was protected under the Fourteenth Amendment's "concept of personal liberty" which the Court held conferred a right to privacy and respect for private life.[255] While the right to abortion was established in *Roe*, it did not extinguish the state's legitimate interest in the "potentiality of human life".[256] Consequently it held that *after* viability (then approximated at 24 weeks gestation), the state could regulate, or even proscribe abortion, *except* when termination was necessary to preserve the life or health of the mother.[257]

The Supreme Court was careful to distinguish any claimed fetal interests from personhood i.e. the fetus was not, at law, a legal person nor did it have legal rights.[258] Instead, it adopted a biological approach, whereby the strength of the state interest in the potentiality of human life grows as the "woman approaches term", becoming a compelling interest at viability.[259]

While US abortion law is largely a result of judicial interpretation of the US Constitution, New Zealand's current legal framework for abortion is a result of recommendations made in the 1970s by the Royal Commission of Inquiry on Contraception, Sterilisation and Abortion.[260]

New Zealand's legal framework: termination of pregnancy

The Royal Commission considered that from the moment of implantation, the fetus had a status entitling it to preservation and protection. This did not confer an absolute right to life, but could "yield in the face of compelling competing interests".[261]

The Commission accepted that abortion should be lawful when the pregnancy posed a "serious danger" to the life of the mother, or when the continuance of the pregnancy would result in serious danger to the mental health of the woman. However, it specifically recommended against permitting abortion on the basis of "psychological stress" that was "well accepted medically" to be "attendant upon normal childbirth".[262] Conversely, the Commission supported prenatal testing and diagnosis for serious disorders,[263] recommending that abortion be lawful if there is a "substantial risk that if a child were born it would suffer from such physical or mental abnormalities as to be seriously handicapped".[264]

In contrast, the Commission recommended against a specific provision authorising abortion on the grounds of rape because it could be the "subject of abuse", inferring that some women desperately seeking abortion might lie in order to obtain one. Hence, the Commission recommended that a claim of rape should be "taken into account" by doctors making the abortion decision, but should not be a ground for abortion in itself.[265]

Apart from instances where a pregnancy posed *serious* danger to a woman's life or health,[266] or in the case of fetal abnormality, the Commission only considered abortion justifiable in circumstances when there was an assumed absence of "fault" on the part of the woman.[267] Where the woman was considered causally "responsible" for a pregnancy—she could be compelled to carry a pregnancy that did not pose a serious risk to her life or health to term. Although the Commission ostensibly based its recommendations on the "sanctity" of fetal life, it arguably did not define sanctity in terms of inherent moral worth, but rather according to the circumstances of conception or the absence of fetal disability.

Unlike the US jurisprudence, NZ's Commission did not consider that the developmental stage of fetal life was relevant to a woman's interest in determining for herself whether to continue a pregnancy based on her individual circumstances. The Commission's recommendations were eventually codified by provisions introduced into the Crimes Act 1961.[268] These provisions, (using terminology that is at best out-dated if not offensive) provide that termination for fetal abnormality in the case of pregnancies under 20 weeks is only lawful if it is believed that "there is a substantial risk that the child, if born, would be so physically or mentally abnormal as to be seriously handicapped".[269] What constitutes a serious abnormality is not statutorily defined—although a common sense interpretation of "serious" suggests it would not extend to "trivial" or relatively minor conditions.

Perceptions of what is a minor or insignificant condition will not be homogenous among the general public. Clearly, there could be a tension between these statutory grounds for abortion, and less serious conditions identified in the course of NIPT, such as sex chromosome abnormalities. However access to termination is not limited to fetal

abnormality.[270] In the case of pregnancies *under* 20 weeks, an abortion is lawful if it is believed that "the continuance of the pregnancy would result in serious danger (not being danger normally attendant upon childbirth) to the life, or to the physical or mental health, of the woman or girl".[271] Despite these seemingly restrictive abortion provisions, it was stated in 2008 that New Zealand had "an abortion rate comparable to those of Canada and the USA, where women enjoy a constitutional right to abortion."[272] However, abortion rates in New Zealand have been consistently falling since 2007.[273] The vast majority of abortions are performed on mental health grounds (97.6% in 2013)[274] and the majority of terminations performed occur before the end of the 10th week of pregnancy.[275]

Although many jurisdictions have adopted "protectionist" policies regarding fetal life, the presumption that fetuses do not possess "rights" of personhood, in particular a right to life, has been endorsed in both international human rights law and in domestic jurisdictions.[276] Nevertheless in some countries, primarily the United States, the increase in prenatal screening capacity has reinvigorated the abortion debate.[277]

NIPT and US abortion politics

In the US, where many of the commercial NIPT tests were developed, the Supreme Court, rather than the legislature, has primarily determined the law regarding termination of pregnancy. As already noted above, the US Supreme Court held that on the basis of rights protected under the US Constitution, a woman may terminate a pregnancy for any reason up to the point of viability.[278] Despite this, the US anti-abortion lobby has not abated in its efforts to make significant dents in the seemingly inviolable US abortion law. Some states have subsequently introduced legislation that imposes specific requirements on informed consent and maternal decision-making. [279]

Although the US Supreme Court has recognised certain rights, they are not absolute. In *Roe*, Blackmun J held that even when fundamental rights are involved, regulation limiting these rights may be justified when there is a "compelling state interest".[280] As the woman "carries an embryo and, later, a fetus" the circumstances are distinguishable from other cases involving privacy.[281] Consequently:[282]

> ... it is reasonable and appropriate for a State to decide at some point that another interest, that of health of the mother or that of potential human life, becomes significantly involved. The woman's privacy is no longer sole and any right of privacy she possesses must be measured accordingly.

Blackmun J held that, after viability, the state "in promoting its interest in the potentiality of human life" may go so far as to "regulate, and even proscribe, abortion during that period except where it is necessary, in appropriate medical judgment" to preserve the life or *health* of the mother.[283]

Following anti-abortion agitation, the Supreme Court was required to reconsider *Roe* in *Planned Parenthood of Southeastern Pennsylvania v Casey*.[284] The Court confirmed the essential premise of *Roe*.[285] Although the Supreme Court has held that the state may

impose limits on when a woman abortion may seek an abortion (ie pre-viability) and on certain procedures,[286] it has not directly considered the issue of selective reproduction.[287] Nevertheless, it seems implicit that the Court in *Roe* and *Casey* did not consider it the state's prerogative to enquire into a woman's reasons for terminating a pregnancy pre-viability, although the Court in *Casey* upheld laws imposing mandated informed consent requirements to ensure decisions were well-informed.[288] While to some this may seem an innocuous requirement, some of the mandated disclosure laws passed by states have been criticised largely on the basis that "forcing a patient to receive information that is either unwanted or misleading is an affront, not an enhancement, to patient well-being".[289]

The state interests that have been found to justify pre-viability abortion restrictions, provided that such restrictions do not impose an "undue burden" on the woman, include "maintaining medical standards, preserving the mother's health, and protecting potential human life".[290] However, more recent US abortion jurisprudence demonstrates a more conservative approach.

In *Gonzales v Carhart*[291] the US Supreme Court upheld the Federal Partial-Birth Abortion Ban Act of 2003,[292] in direct contrast to its earlier decision in *Stenberg v Carhart*.[293] In *Stenberg*, a Nebraska statute provided that the procedure was *only* lawful when the woman's *life* was at risk. The Supreme Court invalidated the Act because it did not provide an exception for maternal *health*, a requirement formulated in Roe.[294] Nevertheless, the US Congress introduced a statute in 2003 in similar terms to the previously invalidated Nebraska law on the grounds that failing to prohibit the procedure implicitly approved it, which would "further coarsen society to the humanity of not only newborns, but all vulnerable and innocent human life, making it increasingly difficult to protect such life".[295] It also expressed concern for the reputation of the medical community. Significantly, the federal law targeted a particular method of abortion that some clinicians considered would, in rare circumstances, constitute the best option for a woman.[296]

Gonzales is in stark contrast to previous Supreme Court decisions that have held that although some activities may offend the moral sensitivities of significant parts of the community, this alone is insufficient to restrict the liberty interest of others.[297] In a strong critique of the judicial reasoning, Sonia Suter charges that legislating to ostensibly prevent "moral coarsening" of society is to be guided by a conservative gut instinct (i.e. the "wisdom of repugnance") rather than adopting a rational, rights-based approach as demanded by the Constitution.

US states: selective abortion bans

More recently, and largely as a result of developments such as NIPT, anti-abortion campaigns have specifically targeted selective reproduction—when a decision to continue or discontinue a pregnancy is determined by the presence of a particular fetal trait or congenital anomaly. Some US state legislatures have enacted laws directly prohibiting what has been termed "reasons-based"[298] or "motive-based"[299] abortion, although this seems an incongruous descriptor/moniker given that any abortion decision is surely based on reasons. The regulatory targets of "reasons-based" abortion restrictions encompass non-medical sex selection and abortion for fetal abnormality.[300] Given the Supreme Court abortion jurisprudence, these reason-based restrictions or bans are highly problematic.

Laws prohibiting sex-selective abortion have been introduced in at least nine US states.[301] In 2013, the State of North Dakota introduced legislation prohibiting abortion for fetal anomalies detected through prenatal testing. The law states that physicians are prohibited from performing an abortion solely because "the unborn child has been diagnosed with either a genetic abnormality or a potential for a genetic abnormality".[302] Indiana introduced a similar law in 2016,[303] although a federal district court judge subsequently granted an interim injunction preventing those provisions coming into force on the basis that they "directly contravene the principle established in *Roe v Wade*".[304] A similar bill in Missouri has been read a second time and referred to the House Children And Families Committee.[305]

Some of the new restrictions are limited to state-funded services. In the US there is a ban on Federal funding of abortion (which clearly has significant implications for people with limited funds or health insurance who wish to access abortion services).[306] In the absence of a threat to the woman's life, the state of Missouri prohibits state funded genetic counselling services from making a referral for an abortion.[307] The state of Tennessee prohibits government-funded NIPT for incurable conditions.[308]

In what is an extraordinary contravention of the doctrine of informed consent, Arizona and Oklahoma extend immunity to physicians who decline to disclose the existence of fetal anomalies to a pregnant woman.[309] The law allows providers to withhold information if it is believed the woman would seek an abortion if such information is disclosed. While in many jurisdictions a failure to inform a prospective parent of a genetic disorder would potentially ground a civil claim for wrongful birth, statutes passed in Arizona and Oklahoma (in 2012 and 2010 respectively) prohibit wrongful birth suits.[310]

Several states have also introduced conscience clauses for genetic counsellors permitting a counsellor to refrain from providing information about abortion. Virginia's law governing licensure of genetic counsellors allows counsellors to refuse to provide results regarding abnormalities (eg Down syndrome or Tay-Sachs Disease) if they think it will result in a woman terminating a pregnancy.[311] Licensing laws in both Virginia and Nebraska permit genetic counselors to elect not to discuss abortion with the women whom they are counseling—although this conscience-based non-disclosure must be made known to the patient and information regarding access to alternative counselors provided.[312] The Nebraska law specifically provides that the licensing of a genetic counselor is not "contingent upon his or her participation in counselling or referral with respect to abortion".[313]

It is apparent that state laws governing selective reproduction throughout the US are variable and in a state of flux—despite the fundamental liberty right declared in *Roe* and reaffirmed in *Casey*. What may be concluded is that, as the capacity for prenatal testing expands, some US states are employing various measures that implicate not only abortion rights but also the integrity of the patient-clinician relationship by placing constraints/waivers on information provision. Many of these regulatory measures erode the concepts of individual reproductive choice and the common law doctrine of informed consent, as well as non-directiveness.[314] Indeed they establish a concerning disregard for the concept of the duty of care in general.[315] The constitutionality of

the new reasons-based abortion bans has not yet been tested, but they are likely to be subject to challenge.[316] Indeed some commentators consider that attempts to trigger reconsideration of the Supreme Court's abortion jurisprudence is at the heart of many of these newly enacted state laws.[317]

Conclusion

While New Zealand's abortion law permits an abortion for fetal abnormality, the question is whether abortion should be limited to predetermined or defined serious disorders. This triggers questions regarding the scope of legitimate access to termination for fetal anomaly, which is largely affected by one's attitude to the fetus' relative moral status, and to abortion in general.

For those who consider that, subject to reasonable limitations, a decision whether or not to carry a pregnancy to term should be a matter of reproductive choice, state-imposed criteria determining the range of conditions for which a termination may be performed is an intrusion on the interest of reproductive liberty. However selective reproduction also triggers concerns by disability rights proponents. In 2012, NZ advocacy group Saving Down Syndrome lodged a complaint with the International Criminal Court in relation to the Ministry of Health screening for Down syndrome on the grounds that preventing the birth of children with Down syndrome is discriminatory.[318] The integration of expanded screening via NIPT must also be considered against a background of a flourishing disability rights movement. The combined ease of performing NIPT with the potential future expansion in testing capacity reignites claims made by the Disability Rights Critique of prenatal testing. A rich account of this is provided in a seminal work resulting from a two-year project run by the New York-based Hastings Centre.[319] The following considers the claims made against the backdrop of evolving reproductive testing.

The Disability Rights Critique of prenatal screening

The 'social' versus the 'medical' model of disability

Disability Rights arguments are generally premised on a concept of disability termed the "social" model of disability. This model conceptualises disability as externally imposed on people with impairments: that is, it is not impairment that disables individuals *per se*, but rather the inhospitable socio-political environments that people with impairments inhabit. Proponents of the social model posit that it is the discrimination experienced by disabled persons that disables. It follows that if people with impairment were adequately accommodated and supported, fewer people would experience disability.

The antithesis of the social model is the medical model of disability. The medical model is claimed to characterise disability as a personal "tragedy", rather than mere difference. According to this account, impairment is conceptualised as an anomaly, a defect inhering in an individual that may/must be "cured" or "normalised" by medical intervention.

Extreme versions of both the social model and medical model are problematic. The social model because, as even many persons with impairment concede, impairment is rarely a neutral condition and is often associated with specific challenges or

disadvantages.[320] Conversely the medical model fails to take into account that socio-political factors can significantly compound disabling conditions. For example, poor disability access to facilities compounds the disability experienced by those individuals with impaired mobility or those who are wheelchair-bound. This may prevent access not only to public spaces or hamper travel on public transport, it may also limit the range of vocational, sporting and other opportunities open to an individual.

Arguably the traditional characterisations of the "social" and "medical" models of disability reflect a problematic dichotomy captured by John Muller in the following:[321]

> Scholars speak of disability with reference to a pair of tired descriptive models. The medical model casts disability as a biological impairment synonymous with illness. By this view, disability is an undesirable deviation from normal functioning. The social model, by contrast, casts disability as a social construction like race. By this view, cultural practices transform differences into disabilities. Neither of these descriptive models necessarily incorporates a particular norm of justice or a particular notion of the value of disability. It has long been clear, however, that adherents of the social model tend to cast disability as a difference we should celebrate, and that adherents of the medical model tend to cast disability as a difference we should eliminate.

Political philosopher Richard Hull cogently argues that attempts to define disability "must differentiate between functional limitation and society when accounting for disadvantage".[322] Consequently, Hull distinguishes between "impairment induced disability" that is experienced as a result of impairments involving physical, mental or sensory functional limitations and "socially induced" disability". The latter is[323]

> … the loss or limitation of ability or opportunities for people with impairments to take part in the life of the community on an equal level with others due to of [sic] economic, political, social, legal, environmental and inter-personal barriers.

Hull's approach is attractive from a policy perspective; the experience or reality of impairment is not ignored, while the issue of equality is emphasised placing the issue of disability "firmly in the area of social justice".[324] Adopting a more nuanced account of disability means acknowledging that impairment can be associated with certain limitations and disadvantages, some of which may be mitigated by social and political assistance. It is this kind of nuanced account of disability and impairment that we adopt in this report.

Prenatal testing: the disability rights critique

The Disability Rights critique of prenatal testing challenges the stereotype of disability and the problematic assumptions about disability that they claim underlie its routinisation.[325] The Critique asserts that negative selection for fetal abnormality is, more often than not, premised on a misunderstanding of what life is like for those with disabilities and their families.[326]

Informational deficits

The concern regarding parental decisions being ill-informed, or based on assumptions and stereotypes of disability, have resulted in governmental and non-governmental initiatives being introduced elsewhere to address perceived knowledge deficits. The United States recently introduced federal law designed to improve the quality of information provided to pregnant women and families about "health conditions" that are diagnosed prenatally or up to a year postnatally.[327] Santin explains:[328]

> The federal Act authorizes the National Institutes of Health to: "collect, synthesize, and disseminate" information and data relating to Down syndrome [and other prenatally or postnatally diagnosed conditions] and to coordinate "support services for patients receiving a positive diagnosis for Down syndrome" in five ways, by (1) establishing telephone hotlines, (2) launching outreach programs that provide parents with up-to-date information regarding the potential of their child with Down syndrome, (3) expanding and developing "national and local peer-support programs," (4) creating a national registry of parents hoping to adopt individuals with Down syndrome, and (5) initiating education and awareness programs for healthcare providers who inform parents of test results relating to Down syndrome.

Despite introducing these provisions, the Act has not been funded or implemented. Further, the Act does not elaborate as to how this information should be provided, although some states have introduced laws in this regard.[329]

In the United Kingdom, a non-governmental initiative funded by the Wellcome Trust, provides web-based information and testimonials from individuals currently living with conditions that may be screened for prenatally.[330] In New Zealand, several non-governmental organisations provide information to prospective parents regarding the lived experience of disability. These include Parent to Parent[331] and the group Saving Down Syndrome.[332]

While the issue of *mis*information is a valid concern because it undermines decision-making, arguably this particular claim of the Disability Rights Critique is not sufficient to prevent adequately informed prospective parents from determining for themselves the impact that a particular condition or disability may have on a future child, as well as their own lives or wider family, and making decisions accordingly.

However, another distinct claim made by the Disability Rights movement is that selection against impairment-related traits, either as a result of prenatal diagnosis or PGD, *offends* those individuals living with similar impairments, potentially harming the disabled community as a group as well as society at large.

The expressivist objection to prenatal testing

The particular claim, known as the "expressivist" objection to selective reproduction, asserts that selection necessarily expresses negative or discriminatory attitudes towards, and ossifies negative attitudes about, the disabled community.[333] However there is now an extensive literature countering this particular strand of the Disability Rights critique which counters that it is plausible to value a person who is living with impairment, but to not want to be responsible for bringing about a future child with the same impairment.[334]

The lack of support objection

A related concern is that with increased prenatal testing and selection, there will be less support for the children who are born with impairments. However NIPT does not raise any new issues in this regard. Indeed this argument of dwindling support, which is premised on the assumption that fewer persons will be born with genetic anomalies, was made in the context of PGD. However, sociologist and disability advocate Tom Shakespeare in particular has argued that the potential consequential harm of genetic testing reducing the incidence of disability has not been realised. Rather, while prenatal testing and selective termination have increased, this does not appear to have caused deterioration in attitudes towards those with disabilities, or impacted negatively on the standard of care provided to disabled persons. He states, "the irony is that the increasing availability of genetic knowledge has coincided with the increasing acceptance of disability rights and slowly improving provision for disabled people".[335] It is also salient that the majority of impairment experienced by individuals is not caused by genetic anomalies, but are a result of aging, accidents, environmental toxins, or birth trauma. Further, Wertz and Fletcher conclude that:[336]

> It appears unlikely that society will have fewer people with disabilities in the future. As society ages, we can expect more, rather than fewer, people with disabilities of all types, including mental disabilities. It is therefore important to increase, rather than to contemplate decreasing, support for people with disabilities.

Determining the scope of selective reproduction

It is clear that NIPT enables greater screening capacity for disability or illness compared with traditional screening. In the future, it may become possible to test for less immediately serious conditions, such as predispositions to cancer syndromes or early onset neurological disorders such as Alzheimer's disease. NIPT also promises to provide other trait-based information that is not linked to disability or illness, such as athletic ability.

Although selecting against disability is often expected (e.g. by clinical staff,[337] friends, family members),[338] there is considerable opposition to parents seeking to choose a fetus based on non-medical traits, primarily sex selection. Indeed, much ink has been spilled debating the ethics of non-medical sex selection.[339] In some jurisdictions that have liberal abortion laws, some providers may refuse to perform sex-selective abortion. Other jurisdictions have enacted legislation that implicitly, if not explicitly, prohibits sex-selective abortion.[340]

The legitimate scope of parental choice is a major factor in debates about selective reproduction. Alicia Ouellette notes how current debates attempt to demarcate acceptable parental preferences:[341]

> While many scholars, lawmakers, and advocates oppose selection based on traits such as race, sex, or eye color, all but the most committed to the preservation of all embryonic and fetal life would allow selection against "serious conditions" or for "medical reasons," categories that include a wide range of conditions.[342] … The more immediate legal and ethical debate focuses on whether to adopt laws or policies that define as unacceptable other criteria for preimplantation and prenatal selection.

Given increasing genomic capacity, the current question is whether prospective parents should be able to access all available genetic information regarding their embryo or fetus, or whether such access to information should be limited and, if so, according to what criteria. This triggers questions regarding the appropriate scope of state intervention in individual decision-making:[343]

> Reproductive autonomy has two facets: personal and political. Reproductive autonomy can refer to the actual making of autonomous decisions about reproduction, guided by one's own values and commitments. It also speaks to the question of whether and to what extent constraints can be erected by the State around one's freedom to make reproductive decisions, based on the interests of the collective (or of others, external to the decision itself).

An argument made by those who would constrain parental choice is a concern that increased selection, particularly selection for non-medical traits, changes the traditional parental project by introducing a problematic selective mentality. On this account it is detrimental to the individual putative parent's character if they fail to act as a virtuous parent. In this case the agency cost associated with selection is the claimed loss of moral virtue associated with taking a particular action.[344]

The 'agency cost' of trait-based selection: parental preferences & parental virtue

Claims that there is a moral "cost" associated with trait-based selection are premised on certain conceptions of parental virtue, such as the virtue of "acceptingness".[345] In his influential critique of reproductive technology (which primarily involves enhancement technology but also encompasses selective reproduction), US philosopher Michael Sandel formulates certain parental virtues that he claims challenge arguments in favour of respecting individual reproductive choice.[346] These characteristics include humility, "openness to the unbidden", and unconditional love.

Significantly, Sandel's objection to reproductive liberty is not primarily based on harm to offspring. Rather his objection is that such choices express, and indeed promote, parental

traits that should be discouraged or subverted. These negative qualities are the "hubris" of the parents in "their drive to master the mystery of birth".[347] In contrast, Sandel urges applying what he terms the "ethic of giftedness" to pre-parental decision-making. He claims that to "appreciate children as gifts is to accept them as they come, not as objects of our design, or products of our will, or instruments of our ambition".[348]

However, it is clear that society already tolerates a sphere of parental privacy and choice when it comes to future children. In contemporary society, a woman is not required to continue a pregnancy when she discovers her fetus will be seriously impaired or suffer illness once born. This suggests that certain assumptions and exceptions are often made about parental virtue and norms of unconditional love. Further, parents who elect to terminate a pregnancy because of a diagnosis of serious fetal abnormality often report that they are guided by their own conception of parental virtue—for such individuals acting virtuously is not necessarily synonymous with "acceptingness" but rather follows deep reflection regarding the implications for a future child and their family.[349] Consequently, it is apparent that concepts of parental virtue differ amongst individuals.

In addition, the concept of unconditional love as militating against permitting selection is problematic in this context. Even if we accept a *prima facie* moral obligation on parents that they love their *existing* children unconditionally, it does not follow that prospective parents must unconditionally love potential, currently non-existent, future children. Indeed, it is open to debate whether it is possible to inculcate, never mind enforce, the value of unconditional love upon parents of children who are not *yet* born.

The essence of such non-harm based arguments is that permitting increased selection risks altering parental norms. A particular concern is that if we permit an extended range of choice, parents will be unable to adjust to a child that does not conform to parental aspirations which will undermine the parent-child relationship. However, Ronald Green challenges this assumption of parental disappointment, providing a more positive view of the evolving parent-child relationship which is explained as follows:[350]

> Green reasons, for example, that what we prospectively think we want in a child—perfect health, sharp intellect, even a particular sex—does not presuppose a lack of love when a child arrives that does not conform to those prospective putative preferences. He fashions what he describes as a psychological principle that: "Parental Love Almost Always Prevails" (PLAAP).[351] So, for example, the couple who chance another pregnancy in the hope that the future child will be a different sex to those children they already have is not thereby destined to reject the resultant baby that is an addition to their existing tribe of girls or boys. Nor does disability preclude parental love and devotion to a child. To assume otherwise is to underestimate the generally instinctive nature of parental love.[352]

Hence, there are two possible counters to concerns regarding the impact of selective reproduction on parental norms: the first is whether we can, or indeed should, force a prospective parent to accept a putative child regardless of the child's condition or traits;

the second is that permitting selection does not preclude a parent's unconditional love for a child once born if that child does not conform to parental expectations.

Prominent bioethicists Jeffrey Botkin and Thomas Murray suggest permitting some, but not all, parental choice. On these accounts, we should limit reproductive liberty to selection against conditions that implicate the well-being of prospective parents such as child-onset conditions that threatens parental interests. Both defend this demarcation on the grounds that "some information and choice is inimical to what good parents should consider and what a caring society should accept".[353] This approach charges the legislature/policy makers with determining a list of sufficiently serious conditions and, in so doing, inculcating a particular notion of the good parent.

However, there are problems/challenges associated with enforcing a vague concept of a "good" parent. In the normal course of life, society generally accepts a "good enough" parent and "good enough" parenting. Parents may make what some of us consider to be suboptimal choices—in which case it may be acceptable to dissuade or actively discourage some parental choices—but unless the threshold of harm to the child or others is met, parental discretion is generally widely respected.

Ultimately, the question is whether there is a good argument not to extend this deference to parental authority to the prenatal context. For some, the fact that a decision involves fetal life and who will exist makes it distinct from decisions about schooling, diet, lifestyle, or religion. For some, the degree of appropriate deference to parental preference will be assessed according to the quality of the trait in issue: ie selection against serious disorders may be acceptable but not "trivial" choices such as sex selection.

An assumption often made is that if the parental interest implicated by a trait is 'low' there is less reason to respect parental preferences. For example, US legal academic Erin Nelson notes that some choices attract greater "respect" than others: "not all reproductive decisions necessarily demand the same level of deference in law and policy".[354] However, it is clear that individuals may think differently about ill health, impairment, and the parental project in general. If there is no harm associated with non-medical trait selection, or at least no greater harm than that which occurs as a result of selective reproduction to avoid having an ill or impaired child, enforcing a prohibition on non-medical trait sex selection arguably erodes our ability/right to develop our own moral code and act as individual moral agents.

Indeed, prominent UK bioethicist John Harris counters the assumption that the acceptability of selection depends on the seriousness of the condition or trait. Harris argues that the more seemingly trivial a choice is—such as testing for sex—the more it may be described as "morally neutral". The same would go for other traits such as hair or eye colour. He describes these gene variants as morally neutral because he:[355]

> … assume[s] no reasonable person thinks it could be *morally* better to have one color of hair rather than another, nor for that matter to be one gender rather than another. Although this is often taken to be a difficult question and indeed the idea of parents being able to choose such things very often causes outrage, it seems to me to come to this: either such traits as hair color, eye color, gender, and the like

are important or they are not. If they are *not* important why not let people choose? And if they *are* important, can it be right to leave such matters to chance?

Alternatively, it could be claimed that permitting selection for an increasing range of traits will foster more permissive social attitudes to selective reproduction, thereby increasing the incidence of selection. Increasing selection choices in the aggregate could contribute to the medicalisation of conception and pregnancy and place increasing demands on already scarce professional resources. However, given that achieving pregnancy is not necessarily an easy process for many women, and once pregnant a woman may become invested and attached to the prenatal life that she is carrying, the strength of this concern may be weak.

Ultimately even if some preferences attract less respect, it is not clear that this alone constitutes sufficient reason to prohibit such selection, although it may speak to responding in ways that discourage such choices. The following considers additional arguments regarding imposing regulatory limits on the scope of parental liberty.

Should we limit trait-based selection? A Disability Rights-sensitive perspective

There are numerous factors in the debate regarding selective reproduction and the appropriate scope of parental choice and reproductive liberty. However, given the wide practice and general acceptance of selection for disability, imposing limits on trait-based selection has particular salience for the disability community.[356] While some commentators advocate drawing a line of sufficiently serious conditions that justify parental choice in terms of selection, others fear that this reinforces the very message that the disability rights critique challenges—which is the inherent "badness" of disability.

Ouellette claims that because of the pervasive challenges that persons with disability experience in terms of achieving equal opportunity and respect, drawing a line that permits deselection based on some traits but not others risks compounding this struggle.[357] Ouellette echoes the arguments articulated by Adrienne Asch, a prominent disability rights advocate, who directly challenges the idea that permitting selection *only* against disabling traits is value-free. She states that:[358]

> ... enumerating a set of testable genetic diseases tells people who currently have those conditions that it would be better if prospective parents went to considerable lengths to prevent the births of children with those conditions. Consequently, I can only urge people who support reproductive choice and also support disability inclusion and equality to oppose line-drawing efforts. It must become as acceptable to test for tone deafness or color blindness (if tests are ever developed) as it now is to test for certain forms of deafness and blindness. Undoubtedly, more prospective parents will terminate for the latter conditions than the former, but at least the decision will be those of the people raising children, and not society, in the form of its insurance carriers and clinicians as gate-keepers.

Ouellette reiterates the idea that endorsing tests for some characteristics but not others implies that some characteristics are more worthy than others of parental attention claiming that it:[359]

> … should be noted that the concern that disability-based selection perpetuates discrimination against persons currently living with disability is more acute with respect to laws[360] and professional policies[361] that distinguish disability-based selection from other kinds of trait-based selection, such as laws banning sex-based selection, than it is with individual choices ... pre-implantation and prenatal screening gives potential parents information and control in deciding whether and how to exercise their right to reproduce. Individual parents make selections decisions based on their own values. Private decisions about reproduction need not harm or show disrespect to individuals living with disabilities. By contrast, laws and policies that define as unacceptable selection based on specific traits (sex or race, for example) differ from individual family decisions. Such laws send an official message that some forms of equality and respect have priority over others. Proposals to prevent sex-based selection in fertility treatment, for example, prioritize "women's equality at the expense of the equality of individuals with genetic diseases, conditions, and characteristics that are deemed 'undesirable.'" Likewise, laws and policies that would deem selection acceptable for certain genetic or disabling traits (i.e., those that are especially serious or cause pain or reduce life expectancy), but not others, necessarily make a value judgment that some lives are valued over others.[362]

While some oppose line-drawing because it arguably legitimises selection against those conditions and potentially stigmatises them,[363] other arguments against line-drawing are premised on respect for reproductive choice. On this account even if many of us do not feel sympathetic to some trait-based choices, a genuine commitment to respect for reproductive liberty implies refraining from legal moralism. Hence, policy should be premised on a presumption of reproductive liberty—subject to considerations of harm. Ouellette observes:[364]

> … the similarities between sex and disability-based selection are more important than the differences. Much of what is viewed as undesirable or unwanted about a child of a given sex or with a particular disabling trait is socially constructed. Indeed, some parents view sex as a kind of disability. They might see female children as inferior for cultural or social reasons, and view their life options and value to the family as more limited than males. Like parents selecting based on disability status, parents selecting for a particular sex, may make choices for family or social reasons. If one such choice is acceptable, similar choices should also be allowed. The law should leave such decisions to prospective parents.

One of the arguments against state policy that restricts choices to selection against disability is that it is premised on public health principles that are arguably problematic in the reproductive context:[365]

> The decision to screen and test for Down syndrome but not for sex or some condition that physicians might not consider serious (eg, a predisposition to acne or dyslexia) reflects the value-laden judgements driving contemporary practice. Sometimes there is disagreement over what should be considered serious, such as a female fetus who is an unaffected carrier of haemophilia or adult onset disease. Many defenders of PND, PNS and PGD oppose the use of these interventions for sex selection except in the case of sex-linked conditions. If contemporary practices are aimed at promoting autonomy and fostering reproductive freedom, they should not be restricted to selecting against conditions physicians, insurers and governments have chosen. Individuals in authority to choose (parents and prospective parents) should decide what is important. To treat some characteristics differently from others undermines the professed importance of respecting and advancing reproductive freedom and reveals the discriminatory views that underlie social commitment to contemporary PNS, PND, abortion and PGD practices. What we have today is constrained reproductive freedom where the constraints are driven by the eugenic impulse and have a eugenic effect.

On this account, devolving reproductive choices to parents is not only synonymous with the concept of reproductive liberty and respecting individual choices regarding family formation, it is necessary to avoid "value-laden" judgments about what constitutes morally acceptable selective reproductive choices.

Immediate medico-legal and policy considerations

While the foregoing analysis has traversed the ethical and legal implications of NIPT, the following considers the immediate clinical context and the minimum national standards that should be established in NZ in regard to this technology.

The legally required standard of care

As noted above, prenatal screening and diagnosis is not without its challenges. Arguably, some of these challenges are compounded by the rapid commercial introduction of NIPT, which has significant implications for providers and the legal obligations owed to patients.

It is well established that clinicians have a legal duty to act with reasonable care and skill and are liable for any breach of that duty that results in injury or harm to a patient.[366] While this notion is uncontroversial, the legally required standard of care in any particular context is subject to specific legal principles and may quickly evolve as medicine develops, which arguably is the case with NIPT.

The standard of competence expected of a practitioner is assessed according to the standard of a reasonably competent practitioner skilled in that particular field of practice. Courts throughout the common law world have made it clear that, although evidence regarding professional practice is relevant, it is not the sole factor in informing judicial determinations regarding the legally required standard of care in any case.[367] As Bernard Dickens helpfully summarises:[368]

> Professional standards are established by evidence of professional education and training, and of general practice within a particular provider's specialty or profession. The standard of competence and skill the profession sets for its practitioners will be strongly influential. The legally required standard of care or skill remains a matter of law, however, and is not just what a profession finds satisfactory … Very exceptionally, courts may find that a standard of performance accepted in a particular profession falls below the level of protection to which the public is entitled.

As evidence mounts regarding NIPT's superior capacity to detect common trisomies it is likely that the requisite duty of care requires providers to inform women about the availability of NIPT and how to access it privately should they wish to. For clinicians providing or facilitating access to NIPT, part of the duty of care requires adequate information provision regarding available treatment or care, which logically extends to the performance (and limitations), interpretation and communication of test results.

Informed consent

Both the common law[369] and the Health and Disability Consumers' Code of Rights impose a legal duty on service providers to provide information that a reasonable person, in that person's circumstances, would expect to receive when accessing treatment services.[370] In the case of NIPT, the obvious information that should be imparted prior to testing concerns not only the range of tests that may be/are conducted, but also the implications of both a false-positive or false-negative result, as well as the on-going need for other screening tests such as a fetal anomaly ultrasound scan.[371]

Offering genetic screening, [372] obtaining consent to routine screening, as well as interpreting and communicating the relevance of test results must be consistent with the legally required standard of care. In a complex case, the standard of care expected of a non-specialist clinician would include referral for specialist genetic counseling when a situation is beyond the primary carer's expertise.

It is significant that many clinicians who refer patients for NIPT do not have sufficient understanding of genetics, or the limits of test results. The complexity of some genetic conditions and the relevant tests, and the potential repercussions of General Practitioners ordering complex genetic tests is indicated in a recent Australian decision involving interim damages in regard to historical genetic testing undertaken in 1999.[373] Norton et al note the significant informational implications of providers communicating NIPT results:[374]

> … given that pregnancy termination is a potential result of a positive test, and that cell-free DNA tests will now be provided through general prenatal practices rather than specialized prenatal diagnosis centers, obstetric providers will absorb more of the burden of discussing these complex results.

Due to the speed with which NIPT has evolved, it may be difficult for health professionals, particularly those who do not specialise in medical genetics, to be able to accurately convey the necessary information required for patients both pre and post testing.[375] Similar issues are already evident in paediatric practice where CMA testing has diffused rapidly into routine clinical usage.[376] Consequently this technology will have implications for providers and the scope of the standard of care expected of them.

The Genetic Services of Western Australia (GSWA) reinforced the issue of professional competence and workforce capacity when it recently reported its experience of integrating clinical NIPT when there are professional knowledge deficits. It stated:[377]

> … since NIPT has become available patients are being referred to GSWA for genetic counselling after both increased and low-risk NIPT results and are showing a lack of understanding about the results. Furthermore, several patients have been referred after entirely inappropriate use of NIPT, paid for by the patient, including NIPT in multiple situations where the mother or father is a known balanced translocation carrier (In house information, 2013) for chromosomes not analysed with NIPT at the time of the test being ordered.

To address these issues, the GSWA recommend introducing pilot programmes and developing appropriate educational materials and services so that the increased need for genetic counselling may be accommodated.

In 2015 Jessica Mozersky published the first ethnographic study of NIPT. She observed 100 counseling sessions for women deemed "high risk" due to their age or a positive prior screen. Of those 100, 35 consented to be interviewed after 24 weeks' gestation. Similar to the early study of women undergoing AFP screening by Press and Browner, Mozersky observed that:[378]

> Many fundamental ethical questions about prenatal screening, such as abortion or the value of disabled children, often do not emerge during clinical sessions, enabling most women to defer thinking about these issues until the future, when and if the need should arise. It may only be in the rare case when a woman receives a positive test result that she may be forced to confront ethical issues that she had up until then been able to avoid.

Significantly, Mozersky is careful not to suggest that informed consent was not obtained—noting the counselors she observed always explained the tests being performed and their limitations. Rather, she observed that there was no explicit discussion of abortion and disability. However, unlike some commentators, Mozersky questions whether "deferring" deep reflection about abortion or disability is always problematic. She suggests that NIPT provided reassurance for many of the participants regarding fetal health, for which they were grateful because it enabled them to avoid confronting the rare possibility that there may be health risks to the fetus. Indeed, she

suggests that putting off such deeper reflection "could be interpreted as a productive form of 'strategic ignorance'".[379] While it may be acceptable for individuals to determine the scope of information they are provided, this is qualitatively different to information being filtered by providers.

It certainly seems plausible that, although there should always be a level of awareness of the possibility that screening may detect an issue in a pregnancy, women may metaphorically elect to "face that bridge when they come to it" or to ascribe to the view that "what you don't know can't hurt you".[380] However, Mozersky also notes some of the disadvantages that may be associated with this approach:[381]

> This desire for reassurance may come at the expense of having contemplated the potential negative outcomes and limitations of testing. In the rare circumstance where women do not receive reassuring results, they may be unprepared and shocked by what NIPT can and cannot reveal. The routinization of NIPT as the latest and best available prenatal screening test does not necessarily create new ethical issues, but this study highlights ethical continuities following its arrival. However, the continued expansion of NIPT to include more conditions and women will increase the number of women who receive positive results, including false positives, and who may be shocked and unprepared as a result.

While informed consent is an on-going issue in the context of prenatal testing, its reiteration in the context of NIPT suggests the need for improvement, rather than an argument against the technology itself. Further, while informed consent must be obtained prior to any clinical procedure that, in the context of screening, includes the possibility of identifying a problem with fetal health, some women may not wish to dwell on that particular hypothetical scenario. As tests proliferate and become increasingly complex, the use of decision aids may assist in personalising information provision.

Recent research conducted in the Netherlands demonstrated that web-based decision aids significantly improved informed decision making regarding prenatal testing.[382] In a randomised controlled trial involving 261 women, half of the participants received ordinary prenatal care, while those in the intervention group were provided written and audiovisual information regarding available prenatal tests. This information encompassed traditional first trimester screening, NIPT and invasive diagnosis—essentially covering the entire screening and testing trajectory. One of the benefits of a web-based multimedia design is that the information is standardised and impartial. It can also be organised into discrete sections:[383]

> … for example from basic to advanced, or from prenatal testing to diagnostic testing, reflecting the different steps of the trajectory. This allows pregnant women and their partners to control the amount and content of the information provided and enables processing of information at their own pace, at a time and place they find convenient. This is especially important as couples face increasingly complex decisions.

Significantly, the decision aid included "values clarification exercises". These exercises encouraged participants to reflect on the potential harms and benefits of each particular prenatal test to enhance the ability to make a decision that was consistent with the individual's value-base. A decision was deemed to constitute an "informed choice" when "a woman has adequate relevant knowledge and her participation or non-participation is consistent with her values and attitudes towards undergoing prenatal testing".[384]

Out of 259 women, 146 (56.4%) decided to undertake prenatal screening, comprising less than two-thirds of the total group. Of those that did undergo screening, 91.8% undertook traditional screening, 4.8% undertook NIPT abroad (as it was not available locally) and 3.4% undertook both traditional screening and NIPT abroad. Significantly, the authors found that 82.3% of the women in the intervention group made an informed choice, compared to 66.4% in the control group concluding that the decision aids enhanced the consent process.

Similarly a US randomized trial that compared women's decisions following use of a decision making tool (a computerized interactive decision-support guide) designed to promote preference-based decision making with the decisions of women who received usual prenatal counselling found that those in the intervention group were more informed regarding the benefits and risk associated with prenatal testing, and less likely to have invasive diagnostic testing.[385] The use of such step-wise decision aids may be valuable in the current context where NIPT is not diagnostic, and further decisions must be made following a high chance result.

A significant issue for the future, should NIPT become a diagnostic test, is that there will be no "breathing space" between identifying a *potential* fetal abnormality, and obtaining a confirmatory *diagnosis*.[386] This transition to diagnostic testing capacity would require more extensive information provision prior to testing. Consequently, adequate information prior to NIPT and obtaining sufficiently informed consent to testing will be essential. This could be achieved by providing written information (electronic or hard-copy) and using innovative decision aids prior to testing.

These issues should inform the way that NIPT is integrated into current clinical practice given that commercial NIPT panels may become closer to diagnostic tests and may significantly extend the range of information routinely available regarding a pregnancy.

Disclosure of test results

It is clear that the new NIPT-based tests will potentially provide complex information. It is axiomatic that, in the ordinary clinical context, patients have a right to know the results of tests—which implies that they have the right to know the relevant implications of test results.[387] The significance of this is compounded when results often require careful interpretation and (at least) a rudimentary understanding of genetics. Some positive results may warrant access to a clinical geneticist or counsellor for specialist advice. However, in 2016, Genetic Health Services New Zealand (GHSNZ) employed only nine consultant clinical geneticists.[388] In many cases it is likely that responsibility for counselling patients regarding test results will fall on the general providers of obstetric care who facilitate NIPT. Given the complex nature of genetic testing and

the high stakes involved, an underlying medico-legal issue in this context concerns the implications of inadequate clinical care in the course of providing advice or interpreting genetic tests.

The tort of wrongful birth in NZ

Wrongful birth constitutes a claim that "but for" the defendant's negligence, the plaintiff would have elected not to conceive, or to continue, a pregnancy. Theoretically, a legal claim of wrongful birth is possible following negligent clinical care that results in the birth of a child with impairments.[389] The essence of a wrongful birth claim is illustrated in the following: [390]

> The nature of the tort of wrongful birth has nothing to do with whether a defendant *caused* the injury or harm to the child but rather, whether the defendant's negligence was the proximate cause of the parents' being *deprived of the option of avoiding* a conception or, in the case of pregnancy, making an informed and meaningful decision either to terminate the pregnancy or to give birth to a potentially defective [sic] child. (emphasis added)

Until recently, it was uncertain whether a civil suit could be brought against a provider on the basis of wrongful birth in New Zealand if a child is born following negligent clinical care or advice. The Supreme Court in *Allenby* have clarified this to some extent.[391]

Under New Zealand's no-fault accident compensation regime, a patient who suffers "treatment" injury as defined in the Accident Compensation Act 2001 is eligible for compensation. "Treatment injury" is defined as "personal injury" caused by treatment that is not an ordinary consequence of treatment.[392]

In *Allenby*, the Supreme Court held that a pregnancy that occurred following a negligently performed sterilisation would constitute personal injury for which ACC would provide cover.[393] However, the extent of cover for personal injury under the Act is likely to be limited to the physical consequences of the actual pregnancy. In *ACC v J*, the High Court held that ACC did not compensate for *all* of the consequences that arise from the covered injury.[394] Specifically, cover for the personal injury following negligent sterilisation did not extend to providing cover for childcare.[395]

It may be extrapolated that a pregnancy during which there is a negligent failure to diagnose/inform a regarding a fetal abnormality may be covered under the Act as treatment injury. In *C v Accident Compensation*[396] the Court of Appeal held that:

> … continuation of the pregnancy following the incorrect diagnosis and the consequential inability of the mother to implement her choice to terminate the pregnancy can constitute a physical injury suffered by the mother for the purpose of the definition of "personal injury".

In this context, the court indicated that cover under the ACC Act is dependent upon the claimants proving that the grounds for lawful abortion are met on the facts.[397] But while the pregnancy may constitute treatment injury and attract cover under the Act, the additional cost associated with raising a child born are unlikely to be covered under ACC.[398] This leaves open the possibility of a common law claim for damages. While courts have been reluctant to award damages for the cost of raising a healthy child in wrongful birth proceedings, the likelihood of success may be greater in the case of a child born with serious genetic impairment following negligent clinical care.[399]

In addition, the Health and Disability Commissioner Code of Health and Disability Services Consumers Rights (Consumers' Code of Rights) provides an avenue of additional civil liability for health care providers who are found to have breached a consumer's rights.[400]

Summary

This section highlights some of the ethical and legal issues that this technology triggers. While some of these are not new, NIPT has stimulated a wide-spread resurgence of some of these debates, with varying outcomes. It also considers the more immediate impact of NIPT's rapid commercial integration into clinical care prior to ensuring adequate provider knowledge, clinical support, and the formulation of robust clinical guidelines. It identifies several areas that need attention by professional bodies and clinicians to ensure the safe provision of NIPT.

One issue identified is the regulatory controls on NIPT tests that are manufactured by offshore companies that, at least in the case of the US, have been found to be inadequate in terms of premarket controls and postmarket surveillance and monitoring. At a minimum, there should be an international registry established to record and investigate false positive and negative results, just as occurred when amniocentesis was first introduced. In addition, specific quality assurance measures need to be considered and introduced as necessary, such as mandatory recording of fetal fraction and standardised reporting of results to providers.

Informed consent is a vital factor in this context and women need to be adequately informed of the risks, benefits and limitations of NIPT. This is especially relevant given that many of the test forms provided privately by companies on a user-pays basis permit a provider or patient to "opt in" or "opt out" of expanded testing, which includes sex chromosome abnormalities and subchromosomal abnormalities. This reinforces the need for providers to have adequate genetic literacy to provide adequate patient counseling regarding these tests. Because NIPT essentially outsources testing from genetics services, increased testing may put pressure on public services.

Although no professional guidelines have as yet been released for Australasia, the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) stress that NIPT is a screening, rather than a diagnostic test and have recently commissioned a Cochrane Review of NIPT.[401] The Human Genetics Society of Australasia and the Australasian Association of Clinical Geneticists recently endorsed a joint paper prepared by the European Society of Human Genetics and American

Society of Human Genetics on NIPT.[402] In 2016 the New Zealand Maternal Fetal Medicine Network (NZMFMN) released a brief *Statement on the use on Non-Invasive Prenatal Testing* that "NIPT has been shown to be a useful screening test in both low and high risk pregnancies".[403]

Ultimately, an issue that is still to be debated is how NIPT might be incorporated into a public screening programme, an issue complicated by the fact that there are different considerations between public screening (which is publicly funded and informed by broad public health principles) and individual privately funded requests for NIPT.

3.5 Incorporating NIPT into public screening programmes

Introduction

Although there has been widespread uptake of NIPT, its appropriate role in a public prenatal screening system is debated:[404]

> The role of NIPS in aneuploidy screening and prenatal diagnosis is evolving. This test has been called disruptive, a term used to describe innovations that displace existing technologies with something generally more efficient and worthwhile.[405] In many ways, NIPS fits that description … However, it also cannot provide information about the range of possible conditions based on multiple-marker screening (e.g., adverse pregnancy outcomes),[406] and it is much more expensive than current screening.

The rapid commercial integration of NIPT raises questions regarding a public NIPT screening programme and how it should be operationalised. Against the backdrop of a rapidly escalating technology, the central issues are: what conditions should be included in the evolving PNT landscape, and is it the same for NIPT that is accessed privately as opposed to a public screening programme (ie who should decide: policy makers or parents).

To answer this question, it is necessary to determine what public interest a screening programme legitimately serves. This requires acknowledging the sensitivities at stake, particularly given that it impacts women's reproductive interests and, potentially, fetal life. Another significant issue is that publicly funded prenatal screening services cannot feasibly be unrestricted and are necessarily subject to resource constraints. In some cases, prospective parents may wish to access prenatal testing for indications beyond those conditions for which testing is available in a public model.

What is public 'screening'

The objective of a public screening programme is to identify risk factors in a particular population to enable interventions aimed at prevention, or treatment, of a particular disease.[407] Consequently, screening is broadly defined as "a systematic and unsolicited offer" of medical/non-diagnostic test to a targeted group that are not known to be affected by the condition(s) tested.[408] Hence, population health screening is essentially a co-ordinated programme of risk surveillance aimed at averting negative health

outcomes.[409] Of course prenatal screening differs markedly from other public screening programmes, such as those for cervical or breast cancer. As de Jong and de Wert succinctly state:[410]

> Prenatal screening for foetal abnormalities such as Down's syndrome differs from other forms of population screening in that the usual aim of achieving health gains through treatment or prevention does not seem to apply. This type of screening leads to no other options but the choice between continuing or terminating the pregnancy.

The goal of prenatal screening is not (at least not ostensibly) to reduce the burden of disease in a community, but rather to identify the presence of fetal anomalies in order to facilitate informed reproductive decisions.[411] On this account, the objective of PNS is solely providing choice, rather than promoting a public health imperative.[412] However, some critics claim that public screening programmes are more aligned with traditional public health objectives and are motivated by eugenic goals, rather than with promoting reproductive liberty per se.[413]

In many ways, the decision to publicly fund, or not fund, prenatal screening attracts paradoxical claims. On one hand, funding such programmes could be criticised as encouraging eugenics. Publicly funding a panel of tests could be perceived as state endorsement of "responsible" reproduction. On this account, a woman who foregoes testing is deemed irresponsible at best, or subversive at worst. If, on the other hand, access to publicly funded screening is not provided, policy makers may be criticized as limiting access to screening to the affluent, reinforcing social and gender inequality. This is not to suggest that publicly funded programmes are indeed motivated by eugenic goals, nor that all women are coerced into undergoing testing. However, prenatal screening constitutes challenging territory for policy makers as well as clinicians, particularly if they are concerned regarding the potential for legal action if testing is not offered and a condition is not detected prenatally.

An alternative rationale for publicly funded prenatal screening constitutes what Stephen Wilkinson dubs the "Public Health Pluralism" model.[414] The public health pluralist considers that providing choice is one aspect of a state-sponsored prenatal screening programme, but also considers that there are other more important goals, such as improving population health (by reducing the incidence of disease and disability in newborns as well as well as health and welfare spending), maternal health and fetal health.[415]

The model adopted for the purposes of this analysis is that while facilitating choice is a primary goal of screening, screening objectives also legitimately include promoting certain public interests. These interests include ensuring safety and efficacy/reliability of screening, preventing foreseeable harms to women and promoting fetal health, as well as balancing the cost-benefits of a public screening programme.[416]

Public screening principles

As already noted, NIPT has been developed as a screening test outside of public screening programmes. As such, test panels have not been subjected to the kind of analysis ordinarily applied to screening tests. Rather commercial companies are providing tests as the technology allows/develops and aggressively marketing them direct to consumers.[417]

The framework first outlined by Wilson and Jungner in the 1960s specified several requirements/aspects of a responsible screening programme, which has been refined over time. The NZ National Health Committee has formulated the following criteria for assessing screening programmes, although arguably they do not translate easily to the prenatal context:[418]

1. The condition is a 'suitable' candidate for screening. [*not defined*]
2. There is a suitable test. [i.e. *safe, accurate*]
3. There is an effective and accessible treatment or intervention for the condition identified through early detection. [*implicitly encompasses termination of pregnancy in the prenatal context*].
4. There is high-quality evidence, ideally from randomised controlled trials, that a screening programme is effective in reducing mortality or morbidity.
5. The potential benefit from the screening programme should outweigh the potential physical and psychological harm caused by the test, diagnostic procedures and treatment.
6. The health care system will be capable of supporting all necessary elements of the screening pathway, including diagnosis, follow-up and programme evaluation. [i.e *it is not ethical to provide screening without access to diagnosis and treatment, including abortion*]
7. There is consideration of social and ethical issues. [i.e. *public interest considerations that encompass maternal and fetal interest*]
8. There is consideration of cost-benefit issues. [i.e. *public interest considerations when publicly funded*]

In regard to prenatal screening specifically, the following criteria have been endorsed by some groups:[419]

(1) A disorder of sufficient severity to warrant screening;

(2) A high frequency of carriers in the screened population;

(3) The availability of an inexpensive and dependable test with low false-negative and false-positive results;

(4) Access to genetic counseling for couples identified as carriers;

(5) The availability of prenatal diagnosis; and

(6) The acceptance and voluntary participation by the population targeted for screening.

Given this, the following considers the current uptake of screening in NZ, the potential ways that NIPT could be incorporated into a public screening system, and the associated advantages and disadvantages. The following assumes that the range of tests would be the same as is currently performed in traditional screening: i.e. screening for trisomies 21, 18 and 13.

Current uptake of prenatal screening in NZ

Prenatal screening is already a routine feature of antenatal care, with invasive testing being less common. However, the uptake of prenatal screening and testing varies between countries. Around 70% of US women currently elect to undergo prenatal screening.[420] Statistics from the year 2012/13 indicate that around 60% of pregnant women undergo screening in New Zealand.[421] Of those women who received an increased risk result following first trimester screening (risk >1:300), 66% underwent diagnostic testing, although the rate was lower for women who received an increased risk following second trimester screening (48%).[422] Clearly, an increased risk screening result does not correlate directly with undergoing invasive diagnosis and gestational age may influence decisions regarding invasive diagnosis.

NIPT provides significant "relative" benefits in comparison to traditional screening: it may be performed early in pregnancy; reduces the number of false positive results compared with traditional screening for common trisomy's, which in turn reduces the number of unnecessary invasive procedures. As companies continue to develop NIPT, it is likely that the range of conditions that may be screened will increase. Somewhat ironically, this expansion will have adverse implications for some of the "relative" benefits because it may increase the number of invasive procedures performed when a false positive is returned for a rare condition.

Options for integrating publicly-funded NIPT

A major issue in prenatal screening is how NIPT will be integrated within, or be available in addition to, the national screening system. The following outlines several options and their associated implications.

NIPT as a first-tier test

Providing NIPT as a first-tier test involves offering NIPT to all pregnant women instead of the current combined screening system. However, this would require significant public resources. In addition, NIPT is not a stand-alone test.

Traditional screening approaches that include ultrasound for nuchal translucency and maternal screening may identify chromosomal abnormalities that are not currently detectable with NIPT (although this may change in the future). Ultrasound scans are necessary to screen for fetal abnormalities such as neural tube or cardiac abnormalities. Thus, for women wishing to undertake comprehensive screening, good practice requires that maternal AFP tests and fetal ultrasound scans are offered to those undertaking first tier NIPT to ensure risk assessment for neural tube or ventral wall defects.[423]

Ultimately, a small proportion of NIPT tests will fail due to issues such as inadequate fetal DNA, failed sequencing, or other factors such as high maternal body mass index (BMI).[424] In this context traditional screening or invasive diagnosis should be offered.[425]

NIPT as a second-tier test

Some professional bodies have recommended NIPT as a second-tier option for women who are assessed at increased risk due to advanced maternal age or a prior aneuploid pregnancy, or women who are identified as high risk following screening programmes. Given NIPT's lower false positive rates for the common trisomy's, this option could theoretically reduce the rate of invasive testing overall. However, one of the associated trade-offs is that NIPT does not currently have the same testing capacity as invasive PND, which enables comprehensive testing to be performed on fetal cells.[426]

Invasive diagnostic testing, especially using chromosomal microarray technology, has the capacity to detect a significant range of chromosomal abnormalities.[427] To illustrate, Danish researchers recently published the results of a retrospective study of a cohort of women with singleton pregnancies who had undergone combined first-trimester screening. [428] Of those 193,638 women, 5.3% subsequently had invasive genetic testing using microarrays, and 11% received an atypical/abnormal karyotype result. The authors noted that 23.4% of the atypical results (which were likely to be "clinically significant") would not have been identified by targeted NIPT.[429] Because NIPT does not detect all of the chromosomal abnormalities identifiable by invasive diagnostic testing and karyotyping, some clinicians suggest that invasive screening should be offered to women considered to be at *very* high risk of fetal abnormality (>1:10). [430]

It has also been suggested that the occurrence of submicroscopic imbalances may actually be higher than the incidence of common aneuploidy.[431] Although some commercial NIPT providers are offering testing for microdeletion syndromes, NIPT clearly provides less coverage than current microarray technology.[432] Consequently, some clinicians advise that women who are at increased risk of having a fetus with an atypical/abnormal karyotype should be counselled accordingly if considering NIPT.[433] However, there are other issues associated with using microarray technology given the extensive range of information that may be derived, some of which is of uncertain utility. The issues associated with microarrays in PND are discussed further in the next section of this report.

While invasive diagnostic testing provides additional information, it is also associated with a risk of miscarriage. However women balance this trade-off differently. As Hewison notes, some "women prioritize diagnostic reassurance over miscarriage risk, and those who do may not all be persuaded by the revised screening risk and hence might still press for an invasive test."[434] An alternative screening strategy combines traditional screening, NIPT as well as invasive diagnostics screening, which responds to some of these issues.

A third option: triaging traditional screening, NIPT and amniocentesis (contingent NIPT)

An alternative approach utilises the spectrum of screening and invasive diagnostics, combining traditional combined first trimester screening (cFTS), NIPT and invasive diagnosis depending on whether a woman is considered low, intermediate or at high risk of having an aneuploid pregnancy.

On this approach, all women would undergo traditional screening. For women who are assessed as very low risk of having a fetus with Trisomy 21 (e.g. ≤ 1 in 1000), no further testing is considered necessary. Those women in the intermediate risk category (e.g. a risk between 1 in 101 and 1 in 999) would be offered NIPT as a second tier-screening test. It is estimated that this would reduce NIPT to 7.1% of the pregnant population, but would still provide "significant improvement in the overall detection of trisomy 21".[435] In contrast, women found to have a very high risk of trisomy (e.g. ≥1 in 100) would be offered the option of invasive diagnostic testing. At this threshold, it is thought that the majority of potentially clinical significant "atypical" anomalies would be detected by amniocentesis, but the proportion of invasive tests performed would also be reduced by approximately 50%.[436]

These thresholds are flexible, depending on the objective of policy-makers.[437] Petersen et al explain:[438]

> The cut-offs used to describe low-, intermediate- and high-risk groups can be *altered according to the priorities of health policy*. Those wanting to prioritize the overall detection rate for trisomy 21 would set a higher risk limit (e.g. 1 in 3000) for the intermediate tier who are offered NIPT. Those wishing to prioritize minimization of the risk of miscarriage would set a higher risk threshold (e.g. 1 in 10) for invasive testing. Those wishing to focus on the detection of atypical chromosomal abnormalities would use a more complex formula for defining the high-risk group that would proceed to invasive testing.

Given these different policy options, it is informative to see how some jurisdictions propose to incorporate NIPT into public screening.

Proposed UK approach to NIPT

Some countries such as Canada and the Netherlands are currently assessing the relative benefits of introducing NIPT.[439] The UK has been at the forefront in developing NIPT as a technology largely due to the government funded RAPID Project, an acronym standing for "Reliable Accurate Prenatal Non-invasive Diagnosis (RAPID)". As a result, the UK is on the cusp of introducing NIPT into its public prenatal screening system.

The RAPID study offered NIPT to women undergoing screening whose risk for having a fetus with Down syndrome was assessed as >1:1000 following traditional serum screening.[440] Women with a higher risk of >1:150 were offered NIPT or invasive prenatal diagnosis. All women who received positive NIPT test results were offered invasive diagnostic testing. Overall, 1,164 women accepted NIPT for T21 and or T18/T13. A total of 89 invasive tests were performed, 29 of which were preceded by NIPT. Of those invasive tests, 32 pregnancies were diagnosed with T21.

In the case of traditional combined screening, over 10 invasive procedures must generally be performed to detect one pregnancy with T21.[441] However, in the RAPID study, the ratio of invasive procedures to each pregnancy diagnosed with T21 was 2.8 invasive tests to 1 diagnosis. The authors conclude that the improved ratio "is a reflection

of a reduction in uptake in IPD in women with risks greater than 1:150 [following a negative NIPT result] and increased detection from the offer of NIPT to women with risks of 1:151-1:1000".[442]

The results of RAPID were used to project the outcome in terms of several specific factors (i.e. detection rates, the impact on the number of invasive tests performed, and cost) if NIPT was to be implemented based on three different risk thresholds: risk >1:150; risk >1:500; and lastly risk >1:1000.

Table 5: Chitty L. et al *RAPID Non-invasive Prenatal Testing (NIPT) Evaluation Study: A Report for the UK National Screening Committee Executive summary* (2015) at 6.

Table 3.2 (p.85) Summary comparisons of the outcomes for the proposed screening pathway including NIPT compared to the current NHS DS screening pathway in the England and Wales population

Testing strategy	DS detected compared to current	Less IPD compared to current	Less IPD related miscarriage compared to current	Additional cost of implementing NIPT testing strategy (test cost - £250)
>1:1000 No direct IPD	176 more	4,805 less	24 less	£7,809,000 more
>1:500 No direct IPD	152 more	4,826 less	25 less	£3,365,000 more
>1:150 No direct IPD	102 more	4,870 less	25 less	£337,000 less

The UK National Screening Committee (UK NSC) also commissioned a systematic review. The systematic review constructed an economic model comparing NIPT as a second stage screen for pregnant women with an elevated risk of trisomy 21 with NIPT as a first-stage test for any woman.[443] It found that using NIPT as a second stage screen for women with a risk >1:150 was more cost-effective than using it as a first stage screen, as well as more effective than existing combined screening (serum test and ultrasound) in reducing invasive tests overall. The Nuffield Council on Bioethics Background Report summarises the review findings in the following manner:[444]

> The model showed that NIPT as a second-stage screen [rather than a primary screen] would result in similar numbers of trisomies detected, 43 fewer miscarriages of unaffected pregnancies (because fewer women would choose invasive testing than currently do) at approximately the same cost as currently (ie with existing first and second trimester combined screening); whereas NIPT as a first-stage screen test would cost an extra £105 million to the NHS, and would result in more invasive tests than NIPT as a second-stage screen.

In January 2016, the UK NSC recommended that NIPT be implemented as a second-tier test option for trisomies 21, 18 and 13 if first or second trimester screening suggests there is a high risk of fetal abnormality, with a threshold risk of ≥1:150.[445] However, it should be noted that although the model indicated that implementing NIPT as a first stage screen would result in more invasive tests compared to a second-stage screen, this is because more women would undergo NIPT overall. Nevertheless, the number

of invasive tests if NIPT was a first-screen test would still be comparatively less than currently occurs following traditional first and second trimester screening.[446] It was projected that if NIPT replaced combined testing as a first-tier test there would be 38 less test-related miscarriages of healthy pregnancies following invasive testing and 117 extra trisomies detected, but this would be achieved at significantly greater cost.[447]

The UK strategy is designed to expose fewer women to the risk of miscarriage, as well as reducing the incidence of "missed cases"[448] although this strategy has not been maximised, potentially because of resource implications. However, there are also limitations associated with NIPT (such as a lower positive predictive value in the general obstetric population) as discussed in section 3.3 above. Further, cFTS may assist with detecting additional chromosomal anomalies not currently detected by NIPT and may also provide information regarding adverse pregnancy outcomes, such as pre-eclampsia.[449] Ultimately, implementing NIPT as a second stage screen (i.e. retaining the current >1:150 risk threshold) may minimise potential disruption to existing screening programmes, while allowing the offer of NIPT to those at increased risk and provides an opportunity to explore current uncertainties.[450] The UK NSC recommended that the initial implementation of NIPT as a systematic population screening programme be evaluated and reviewed by the UK NSC before any decision is made to fully roll out NIPT within the public NHS Fetal Anomaly Screening Programme.[451]

Extended public prenatal screening?

As already noted, commercial companies are steadily extending NIPT panels. Given established public screening principles that attempt to balance risks and benefits of screening, policy makers and professional bodies are likely to exercise considerable caution before increasing the range of conditions that may be identified by a single blood test within a routine screening programme. Because of the potential drawbacks of population screening, specifically false positives that may trigger unnecessary invasive procedures and additional stress, Munthe observes that:[452]

> The presupposition of a consensus on PNT as a servant of patients cannot therefore be taken for granted when designing policies for the new PNT landscape. Rather, policies need to be shaped to reinforce that norm.

All population-based screening tests include complex trade-offs. Screening may provide medical benefits associated with early identification or psychological benefit as a result of reassurance regarding fetal health, which must be balanced against the burden associated with false positive or uncertain findings, as well as costs to a health system.[453] In the context of prenatal screening, this requires careful analysis.[454]

The American College of Medical Genetics (ACMG) advises that selecting disease-causing targets for inclusion in a general population-based screening programme (ie where there is no family history of a condition) should be developed subject to clear criteria (as is the case for newborn screening[455]) rather than merely including every condition possible.[456]

In 2013, the ACMG provided policy advice regarding expanded population-based screening in the preconception and prenatal context. It advised that a condition may be included in a population screening programme if it is of "a nature that most at-risk patients and their partners identified in the screening program would consider having a [invasive] prenatal diagnosis to facilitate making decisions surrounding reproduction".[457]

The implicit rationale for this recommendation, which effectively limits screening to a condition for which most parents would potentially consider terminating a pregnancy, is not immediately clear. It may be motivated by a desire to limit the range of prenatal screening to avoid an increase in pregnancy termination for less serious conditions. However, it is apparent that women vary greatly in respect to what they wish to know/not know regarding fetal health and how they respond to that information.

Emerging empirical data challenges the assumption that extending the scope of screening will invariably lead to an increase in pregnancy termination. Indeed, motives for seeking information may be more complex. In one such study, researchers sought to interrogate general assumptions often made by experts about the principles that should inform prenatal screening from the perspective of the target population—the women undergoing screening.

The researchers surveyed 95 women in Northern California who had given birth to a healthy child in the previous year.[458] The participants (a mostly highly educated but racially/ethnically diverse group) were interviewed to determine their attitudes regarding prenatal testing and termination for various congenital disorders.

The study focused on specific conditions that the researchers considered represented archetypal disorders for which prenatal testing is available or may become available in the future. These conditions were Down syndrome (DS), phenylketonuria (PKU), congenital heart disease (CHD), spinal muscular atrophy (SMA), fragile X syndrome (FraX) and cystic fibrosis (CF)). The conditions varied in respect of severity, treatability, cognitive and physical impairment and life expectancy, as summarised in the following table.[459]

Table 6: Conditions and associated characteristics as presented to participants

Table 1. Disorders and key characteristics presented to participants.

Disorder	Main features	Treatment *
Down syndrome	ID, typical facial features, medical issues; life expectancy, 60 s	As needed; none for ID
Fragile X	ID, facial features, behavioral/autistic issues; normal life expectancy	None
PKU	Metabolic disorder, ID without rx, good outcome with treatment, rx somewhat time consuming/intense; normal life expectancy	Dietary
CHD	Outcomes vary, usually no other abnormalities; somewhat shortened to normal life expectancy	Surgical
SMA	Severe hypotonia, respiratory failure; death by age 2	None
Cystic fibrosis	pulmonary/pancreatic dysfunction, significant medical problems; life expectancy, late 30 s	Medical

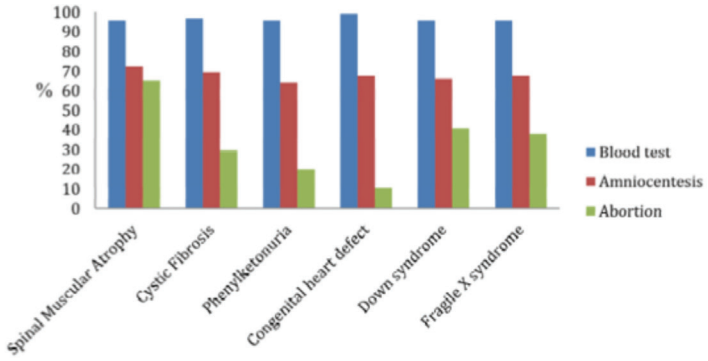
* Refers to medical treatment, as opposed to educational interventions; ID = intellectual disability; PKU = phenylketonuria; CHD = congenital heart defect; SMA = spinal muscular atrophy; rx = treatment.

It was found that participant's choice to undertake screening or invasive amniocentesis was broadly consistent, regardless of the condition being screened, with 95% of women indicating that they would undertake screening for *all* of the conditions listed. In contrast, decisions regarding termination varied across the group, and were largely dependent on the implications of the condition.

For example, termination was less commonly considered for treatable conditions such as PKU and congenital heart defects. However more than half of the participants were inclined to terminate a pregnancy in the case of SMA, a condition that is lethal in childhood. The results are illustrated in the figure on the next page.

Figure 11[460]

Figure 1. Proportion of patients indicating they would definitely or probably undergoing screening (blood test), diagnostic testing (amniocentesis) or pregnancy termination for each condition.



Significantly, the figure demonstrates that the choice to undertake screening and amniocentesis is fairly consistent across all of the various conditions. However, decisions regarding termination varied significantly across the conditions.

The research suggests that reasons for undertaking prenatal testing are diverse. Unlike the common perception that the goal of prenatal genetic testing is to identify fetal anomalies with the intention of terminating an affected pregnancy, most participants in this study did not share this view of testing.[461] The authors note that:[462]

> While previous studies have retrospectively evaluated differences in the rate of termination of pregnancy for disorders of increased severity or those that include intellectual disability,[463] few to no data exist on how women compare or value testing for different categories of conditions and whether they associate a desire for testing with an inclination toward termination for a given condition.

Given this, the common assumption that prenatal screening should be limited to conditions for which a woman would be likely to terminate a pregnancy, or that is considered severe enough by clinicians to warrant a termination, is open to challenge.[464] Emerging empirical evidence suggests that some women want to know a significant range of information, with information valued for different reasons.

While more similar research on this issue would be helpful, this single study questions the orthodoxy of limiting testing to conditions that it is assumed most women would elect to terminate.

The future of population-based prenatal screening: public policy & private choices

It is clear that prenatal screening and testing capacity will expand exponentially in the near future. However, there are tensions between what information women might wish to know prenatally, and the generalised principles and inherent constraints that apply to publicly funded population-based screening programmes.

Swedish philosopher Christian Munthe predicts that in time current predetermined test/screening panels will be abandoned in favour of "individualised" approaches to screening. This model would "decentralise" decisions regarding what conditions are sufficiently serious to justify screening, making it a matter for individual judgment, rather than a matter for policy makers. Munthe envisions an approach that ensures women are made aware of PNT, but would place the onus on individuals to decide whether or not to access screening. Prospective parents would choose the type of information they are willing to receive following WGS from a range of predetermined categories. The only restriction Munthe recommends is not returning variants that are of unknown significance.[465] Individuals would be free to make decisions that fit with their own values, assuming they are sufficiently informed regarding the nature and implications of tests.[466] He claims this promotes the value of reproductive liberty, and is more sensitive to the disability rights critique which opposes an official "list" of conditions for which prenatal testing (and termination) is appropriate.[467]

Clearly, such an individualised approach would be prohibitively expensive to sustain publicly given the need to adapt testing and to provide adequate counseling. However, Munthe acknowledges this as an argument against publicly funding such a regime on the basis that "mere promotion of reproductive autonomy will hardly serve to justify such costs in a public priority-setting context".[468] Accordingly, he makes a more radical proposal:[469]

> Focusing on the new PNT as a source of liberation and self determination thus rather drives a notion of it as a reproductive information technology to be used by people outside publicly funded services. If offered to honour reproductive autonomy and liberty without creating additional drawbacks, the new PNT signals a time to end the mass-screening efforts of national health services.

However, Munthe does not suggest that all public screening be abolished. Rather he argues that public funds should support access to PNT for a narrow range of conditions for conditions where:[470]

> … no conceivable extent of societal adaption [sic] or support will reduce the burdens for parents sufficiently to make access to PNT a mere luxury product. These, then, may be included in a justifiable publicly funded new PNT offer.

Munthes approach determines the scope of public funding according to a principle of the "parental burden" approach. It is premised on a two-track system: a privatised PNT model where individuals determine what conditions they wish to test for, with public funding only available for particularly serious and untreatable conditions. However, this still requires policy makers to determine what conditions impose parental burdens that cannot be ameliorated with adequate social support.

Although he does not expand on what would constitute sufficiently serious conditions, Munthe identifies sex-chromosomal disorders such as Klinefelter or Turner syndrome, or conditions that are associated with cognitive-behavioural difficulties (using examples of fragile X or Down syndrome), as falling outside the range of a justifiable public funding "package".[471] For serious but treatable conditions where individuals may have "reasonable life-spans, decent quality of life and autonomy", Munthe claims that public resources would be better used to promote social inclusion and support than selection.[472] In contrast, he argues that commercial PNT should be available without restrictions, apart from those mandated by professional standards, for those who wish to fund it themselves.

3.6 Conclusion

In the case of common aneuploidies, NIPT has been proven to have better test characteristics than traditional combined first trimester screening, not just in elevated risk pregnancies, but potentially also in the general patient population. While in some countries NIPT is accessed privately (or paid for by private insurers) as a first tier test, other countries such as the UK have recommended offering NIPT as a 2nd tier test within a publicly-funded prenatal screening programme.

One of the controversial aspects of NIPT is the way in which commercial companies have aggressively marketed tests and extended NIPT screening panels to include additional trisomies, sex chromosome anomalies as well as microdeletion syndromes before having clear evidence regarding the positive predictive values of these less common anomalies.[473] Leaving those issues aside, it is arguable that if one agrees with the concept of screening (i.e. to facilitate reproductive choice and/or enable early post natal intervention once a child is born), there would need to be a good reason to limit NIPT to screening for the common trisomies currently targeted in traditional screening. Consequently, relevant factors for policy makers and consumers in this extended screening landscape include:

- the accuracy of a particular test as well as the incidence of that condition and the corresponding positive predictive value/negative predictive value;
- achieving sufficient institutional knowledge among providers to enable adequate pre-test counseling;
- ensuring access to post-test genetic counselling as necessary;

In the absence of standardised guidelines for NIPT, the following outlines proposed policy recommendations for NZ.

(Immediate) Policy Recommendations for NIPT

1. **Duty of Disclosure:**
    - NIPT is **not** a diagnostic test but is a more sensitive screening test for the three main trisomies traditionally targeted in serum screening: ie trisomy 21; trisomy 18; and trisomy 13.
    - NIPT does not identify anatomical/structural anomalies or neural tube defects. Consumers should be offered a fetal ultrasound scan and α-fetoprotein if undergoing NIPT.
    - Some commercially available NIPT tests screen for additional conditions, such as chromosome abnormalities, and sex chromosome abnormalities.
    - An explanation of the kinds of conditions that are included in a screening test should be provided, with the option to accept or decline additional tests.
    - If NIPT is performed to determine fetal sex, women should be made aware of the possibility of detecting incidental sex chromosome aneuploidies.[474]
2. **Test Requirements: institutional quality assurance initiatives:**
    - Gestational age should be provided when samples are obtained (fetal ultrasound).
    - Laboratory should report the methodology used for testing (eg NGS).[475]
    - Reporting of results should be standardised using the terminology: "high risk/low risk" or alternatively "high chance/low chance" of aneuploidy.[476]
    - Mandatory reporting of fetal fraction with results and minimum level for reporting.
    - Procedures for a "no call" result, ie discussion with the consumer regarding other screening tests or invasive diagnosis.
3. **Professional Requirement: institutional quality assurance (Australia / New Zealand):**
    - Institute Monitoring and Reporting Mechanisms in relation to:
    - Test failures: provide reason for test failure (if ascertainable);
    - Report incidence of false positives, false negative (include the specific condition, specific company providing test).[477]
4. **Professional Requirement: when offering NIPT:**
    - **Offers of testing should be non-coercive.**
    - **Explanation of the nature of screening:** the offer of NIPT should be accompanied by information regarding the nature of a prenatal screening test: ie that screening is not diagnostic. Instead, it enables the identification, among otherwise apparently healthy pregnancies, of those that are at a particular risk of having a specific condition.[478] Some results may warrant considering subsequent invasive diagnostic testing to confirm/preclude a condition.
    - **The possible outcomes should screening indicate a fetal anomaly should be discussed:** e.g. access to genetic counselling to assist with decision-making regarding any further testing and ultimately the future of the pregnancy.

5. **Informed consent to testing: an explanation regarding:**

The range of tests performed on the NIPT panel:

- General information regarding the clinical features of the conditions screening is undertaken to detect;
- Variable sensitivity of tests for different conditions (e.g. sensitivity may be 99% for Down syndrome but is less for trisomy 13 and trisomy 18) and the corresponding risk of receiving a false negative result;
- PPV: the less common the condition, the less likely a "high risk" result will be a "true" positive;
- Specific consent to "additional" tests (e.g. sex chromosome abnormalities).

Return of Results:

- Return of results timeline;
- How results are interpreted: e.g. a low-chance, high-chance result;
- Explanation of the possibility of false positive results and the corresponding need to perform invasive testing if wanting to confirm a high risk/high chance aneuploidy result.
- In the event of a high chance result, the laboratory provides a patient-specific PPV or a population-derived PPV if the patient-specific PPV is unavailable.[479]

Limitations of NIPT:

- NIPT tests only test for the conditions specified on the panel and will not identify all possible fetal anomalies.
- NIPT does not identify structural or neural tube defects. A fetal anomaly scan and serum α-fetoprotein are necessary to screen for structural or neural anomalies.
- NIPT is not as comprehensive, or as accurate, as invasive prenatal diagnosis such as amniocentesis. Some patients may elect to undertake invasive diagnosis in preference to NIPT in some circumstances such as increased risk or maternal anxiety regarding fetal health.

Incidental Findings:

- In rare cases, NIPT may indicate a maternal condition, such as a sex chromosome abnormality or maternal cancer.

Positive result:

- In the event of a positive result a specialist referral should be made available.

Invasive diagnostic testing:

- Invasive diagnostic testing using microarrays may yield more genomic information than NIPT, which may be relevant to some women carrying a high risk pregnancy or if fetal structural anomalies are identified on ultrasound.

6. **Option for follow-up testing in the event of a high risk/high chance of aneuploidy result is discussed:**

- chorionic villus sampling (tests tissue from the villi of the chorion) — performed after 11 weeks' gestation or

- amniocentesis (fetal skin cells sampled from the amniotic fluid) — performed after 15 weeks' gestation.

The Bigger Picture: the Likely Trajectory of NIPT

While NIPT has attracted a significant degree of scrutiny and even a measure of alarm in some quarters, much of this relates to the continuing evolution of genomics and the capacity for NIPT to extend the range of conditions exponentially. In 2011, Stanford Law Professor Henry Greely observed that the potential trajectory of current NIPT could be virtually unlimited, stating:[480]

> There seems to be no technical barrier, given increasingly cheap genotyping and sequencing, to being able to test one sample simultaneously for chromosomal abnormalities; for single-gene diseases, such as cystic fibrosis, sickle-cell anaemia, and Tay-Sachs disease; and for various non-disease genetic traits such as sex.

Greely considered that the ultimate impact of this new non-invasive technology would depend on two major "drivers". First, whether it is a "cost effective" test and therefore likely to be funded either by insurance companies or by public health systems. A second potential driver is if NIPT comes to be considered the legally required standard of prenatal care, whereby NIPT may become the default position to avoid possible law suits alleging "wrongful birth" claims.[481] Five years later, it is clear that both of these phenomena, in conjunction with aggressive marketing, are driving the uptake of NIPT. More recently, two proponents of the new genomics capture the rapidity of global expansion, stating: [482]

> … non-invasive prenatal screening for aneuploidy using massively parallel sequencing (MPS) of maternal plasma is the fastest growing genetic or genomic test in the history of medicine.

Although the scope of NIPT is currently limited, the range of tests being provided by commercial companies continues to expand. Arguably, a significant factor in NIPT's future development depends on the technology progressing to the point that NIPT becomes a *diagnostic* test, rather than a *screening* test, that scans the entire fetal genome. (Currently, it is only possible to perform *diagnostic* NIPT for a limited range of single gene disorders.)[483] For the most-part therefore, a "high chance" NIPT result is not a definitive result. However, it is expected that the increased analytical capacity that is being integrated into the general clinical genetics context will eventually be applied to NIPT and that NIPT may become a diagnostic rather than a screening tool.[484]

Proof-of-concept studies have established that non-invasive "fetal genome-wide molecular karyotyping" (examining all 22 pairs of chromosomes and the sex chromosomes) and even whole genome sequencing to identify single gene disorders may theoretically be performed. However, whole genome sequencing is not straight

forward, requiring analysis of the maternal/paternal DNA as well as fetal DNA, and is associated with high rates of false positives.[485] Analysing the entire fetal genome easily and accurately by noninvasive means is dependent on retrieving actual fetal cells (i.e. not cffDNA), which is currently associated with significant challenges.[486] Despite this, there is an emerging consensus that the evolution to non-invasive comprehensive genomic screening is "only a matter of time'.[487] Most recently, it has been claimed that:[488]

> NIPT is already becoming a screening test and replacing less accurate biochemical tests. Increased sequencing depth will allow the accurate detection of genetic disorders, eventually reaching the resolution of current array analyses on invasive prenatal samples. Several groups have demonstrated proof-of-principle that non-invasive cfDNA analysis enables the reconstitution of the total fetal genome sequence …

Although non-invasive whole genome sequencing is not yet clinically feasible, the capacity for extensive screening is increasing steadily.[489] Researchers recently published the results of a study that expanded conventional cffDNA-based NIPT to genome-wide screening (distinct from whole genome sequencing).[490] This resulted in the detection of additional clinically relevant chromosomal abnormalities that would have gone undetected by conventional NIPT, such as rare autosomal trisomies and segmental chromosomal imbalances (increasing the detection rate by 7.4%). The authors reported that genome-wide cffDNA screening provides significantly greater sensitivity (capacity to detect a disease if it is present) compared with standard NIPT, while also maintaining a high specificity (capacity to exclude the disease if it is not present). While the authors considered the results suggested introducing genome-wide cffDNA as a routine prenatal test was plausible, this had to be balanced against the risk of overdiagnosis and an increased number of false positives that may lead to increased invasive diagnosis and maternal anxiety.

Clearly as NIPT technology develops, it is plausible that NIPT might become the screening equivalent of current microarray technology in the context of invasive prenatal diagnosis. Given that it provides an indicator of the types of challenges that may arise if similar testing becomes possible using NIPT the following chapter provides a review of the clinical implementation of microarray testing in invasive prenatal diagnostics.

Endnotes

1. B Katz Rothman The Tentative Pregnancy: How Amniocentesis Changes the Experience of Motherhood (Penguin Books, New York, 1986); RR Rapp Testing Women, Testing the Fetus: the Social Impact of Amniocentesis in America (Routledge, New York, 2000). The earliest recorded amniocentesis procedures were performed in the mid-1950s. These procedures were performed after it was discovered that in some cell types, cell nuclei reveal could reveal sex differences. Fuchs and Riis examined amniotic fluid (collected from women who either underwent artificial rupture of membranes to induce pregnancy or, alternatively, instances where pregnancy was surgically "interrupted") to determine if the fluid contained enough sufficiently well-preserved fetal cells to determine fetal sex. See F Fuchs and P Riis "Antenatal Sex Determination" (1956) 177 Nature 330.
2. J King "And Genetic Testing For All … The Coming Revolution in Non-Invasive Prenatal Genetic Testing" (2011) 42 Rutgers Law J599.
3. H Greely, "Get Ready for the Flood of Fetal Gene Screening" (2011) 469 Nature 289.
4. J Daar, "One Small Step for Genetics, One Giant Leap for Genocide?" (2011) 42 Rutgers Law Journal 705.
5. The discovery of cell free nucleic acids was made in 1947. These acids result from the degradation of nuclear DNA contained in hematopoietic cells (stem cells) when these cells have undergone programmed cell death. HC Fan, YJ Blumenfeld, U Chitkara et al "Noninvasive diagnosis of fetal aneuploidy by shotgun sequencing DNA from Maternal Blood" (2008) 105 Pro Natl Acad Sci 16266. Ultimately scientists will be attempting to identify whole fetal cells – if they can isolate intact whole fetal cells then diagnostic testing, rather than screening, can be performed.
6. A Thompson "Noninvasive Prenatal Testing" (2015) 314 JAMA 198.
7. A Mauron "Choosing among possible persons: The ethics of prenatal selection in the postgenomic age" (2015) 338 C. R. Biologies 566 at 569.
8. While NIPT may theoretically be done at seven weeks, it may result in a lower fetal fraction when it is conducted before 10 weeks.
9. This is in relation to: trisomy 21, trisomy 18, trisomy 13, monosomy X. See P Devers, A Cronister, K Ormond et al "Noninvasive prenatal Testing/Noninvasive Prenatal Diagnosis: the Position of the National Society of Genetic Counselors" (2013) 22 J Genet Counsel 291 at 293.
10. MA Lutgendorf, KA Stoll, DM Knutzen et al "Noninvasive prenatal testing: limitations and unanswered questions" (2014) 16 Genet Med 281at 282. Many of the initial studies were performed in women at high risk of having a fetus with chromosomal abnormalities. However studies are being rolled out in the general population of pregnant women (often referred to at the average or "low risk" obstetric population).
11. M Vanstone, K Yacoub, S Windsor et al "What Is "NIPT"? Divergent Characterizations of Noninvasive Prenatal Testing Strategies" (2015) 61 A JOB Empir Bioeth 54.
12. Many available NIPT testing panels have already been expanded to include additional chromosomal conditions (such as sex chromosome abnormalities) as well as microdeletions and microduplication syndromes.
13. MA Minear, S Alessi, M Alysse et al "Noninvasive Prenatal Genetic Testing: Current and Emerging Ethical, Legal, and Social Issues" (2015) 16 Annu Rev Genomics Hum Genet 369 at 372.
14. M Allyse, MA Minear, E Berson et al "Non-invasive prenatal testing: a review of international implementation and challenges" (2015) 7 Int'l J Women's Hlth 113 at 115.
15. S Taylor-Phillips, K Freeman, J Geppert et al "Systematic review and cost-consequence assessment of cell-free DNA testing for T21, T18 and T13 in the UK – Final report." July 2015; United Kingdom National Screening Committee United Kingdom National Screening Committee non-invasive prenatal testing (NIPT) recommendation (Jan 2016) http://legacy.screening.nhs.uk/fetalanomalies.
16. NIPT is already marketed with array CGH by at least one commercial entity. See C Munthe, "A New Ethical Landscape of Prenatal Testing: Individualizing Choice to Serve Autonomy and Promote Public Health: A Radical Proposal" (2015) 29 Bioethics 36 at 38.

17. J Klitzman, MW Snyder, M Ventura et al "Noninvasive Whole-Genome Sequencing of a Human Fetus (2012) 4 Science Translational Medicine 137ra76.
18. Z Deans, A Newsom, A Clarke "For Your Interest? The Ethical Acceptability of Using Prenatal Testing to Test "Purely for Information"" (2015) 29 Bioethics 19.
19. An increased risk indicated by screening permits access to diagnostic testing (eg amniocentesis) via the public health system.
20. www.nsu.govt.nz.
21. Commercial NIPT is offered by the following: Labtests (Auckland: Sequenom MaterniT21); Southern Community Labs (Otago); Canterbury Health Laboratories (Christchurch) as well as Genea Oxford Women's Health (Christchurch); and Insight-Ascot Radiology (Auckland).
22. RANZCOG College Communiqués: DNA-based Noninvasive Prenatal Testing for Fetal Aneuploidy (April, 2015).
23. Ibid.
24. See W Dondorp, G de Wert, Y Bombard et al "Non-invasive prenatal testing for aneuploidy and beyond: challenges of responsible innovation in prenatal screening" (2015) 23 Eur J Hum Genet 1438.
25. Ibid.
26. New Zealand Maternal Fetal Medicine Network: "Statement on the use on Non-Invasive Prenatal Testing (NIPT)" (NZFMN, Jan 2016). www.healthpoint.co.nz
27. C Munthe "Permissibility or Priority? Testing or Screening? Essential distinctions in the Ethics of Prenatal Testing" (2017) 17 American Journal of Bioethics 30.
28. We deliberately adopt the term "policy" rather than "regulatory" as we do not presume that a specific legal framework is required rather than the existing medico-legal framework that governs the provision of clinical care.
29. LS Penrose "Maternal age, order of birth and developmental abnormalities" (1939) 85 J Ment Sci (now known as Brit J Psych) 1141 at 1142.
30. J Lejeune, M Gautier, R Turpin "Etude des chromosomes somatiques de neuf enfants monoliens" (1959) 248 C R Hebd Seances Acad Sci 1721.
31. Meiotic nondisjunction is the failure of two members of a chromosome pair to separate from one another during meiosis, causing both chromosomes to go to one cell.
32. RL Berkowitz, J Roberts, H Minkoff "Challenging the Strategy of Maternal Age-Based Prenatal Genetic Counseling" (2006) 295 JAMA 1446 at 1447.
33. M Loane, H Dolk, J Morris et al "Total and livebirth prevalence of Down syndrome and other trisomies in Europe 1990-2007: impact of increasing maternal age, prenatal screening and termination of pregnancy" (2012) 21 Eur J Hum Gen 27.
34. C Vassy, S Rosman, B Rousseau, "From policy making to service use. Down's syndrome antenatal screening in England, France and the Netherlands" (2014) 106 Soc Sci Med 67.
35. NMTH Crombag, YE Vellinga, SE Kluijfhout et al "Explaining variation in Down's syndrome screening uptake: comparing the Netherlands with England and Denmark using documentary analysis and expert stakeholder interviews" (2014) 14 BMC Hlth Serv Res 1.
36. Crombag et al note that screening is free for all pregnant women in Denmark and England, whereas in the Netherlands DSS is only reimbursed for women over 36 years, or at high prior risk for fetal anomalies. Women younger than 36 years of with no prior risk are required to pay €160,00.
37. R Salonen "Prenatal chromosome analysis today: Screening by maternal age or serum test?" (1993) 72 Acta Obstet Gynecol Scand 146.
38. E Pergament and D Pergament "Reproductive Decisions after Fetal Genetic Counselling" (2012) 26 Best Pract Res Clin Obstet Gynaec 517 at522.
39. KL Wilson, JL Czerwinski, JM Hoskovec et al "NSGC Practice Guideline: Prenatal Screening and Diagnostic Testing Options for Chromosome Aneuploidy" (2013) 22 Journal of Genetic Counseling 4
40. HS Cuckle and NJ Wald "Maternal serum-alpha-fetoprotein measurement in antenatal screening for anencephaly and spina bifida in early pregnancy" (1977) 309 Lancet 1323. NA Press and CH Browner "Why women say yes to pre-natal diagnosis" (1997) 45 Soc Sci Med

979. NDTs occur in the first month of pregnancy. Spina bifida, where the spinal column does not close completely and usually causes some form of paralysis, and anencephaly, where most of the brain and skull do not develop properly with most babies being stillborn or dying shortly after birth, are the most commonly reported serious birth defects. J Woo "A short history of amniocentesis, fetoscopy and chorionic villus sampling" www.ob-ultrasoundnet/amniocentesis.html [accessed 15 October 2015].

41. IR Merkatz, HM Nitowsky, JN Macri et al "An association between low maternal serum α-fetoprotein and fetal chromosomal abnormalities" (1984) 148 Am J Obs Gyn 886.
42. HS Cuckle, NJ Wald, RH Lindenbaum "Maternal serum alpha-fetoprotein measurement: a screening test for Down syndrome" (1984) 1 Lancet 926 at 929.
43. In 1987 and 1988 it was discovered that measuring levels of human chorionic gonadotropin (hCG) and unconjugated estriol (uE3, an estrogen that is produced in significant amounts only during pregnancy) were found to improve the sensitivity of serum screening. Identifying elevated hCG levels resulted in detection of 68% of pregnancies that were chromosomally abnormal, with a false positive rate of 1.35%. (See MH Bogart, MR Pandian, OW Jones "Abnormal maternal serum chorionic gonadotropin levels in pregnancies with fetal chromosome abnormalities" (1987) 7 Prenatal Diagn 623.) In the late 1990s, hCG and uE3 were used in conjunction with AFP as a second trimester triple screen, increasing detection rates for trisomies 21 and 18 to approximately 80%. ACOG "Practice Bulletin No 77: Screening for Fetal Chromosomal Abnormalities" (2007) 109 Obstet Gynecol 217 at 218.
44. While there is a risk that it may cause preterm labour, the risk of miscarriage following amniocentesis is believed to be less than 0.5%. CVS can be performed earlier than amniocentesis or PUBS and samples placental tissue. The risk of miscarriage from the procedure is low (0.5-1.0%) and there is a slight risk of leakage of amniotic fluid or Limb Reduction Deficits. It can occur between 10-15 weeks gestation. PUBS examines blood drawn from the umbilical cord, providing rapid chromosome analysis. It is only used when amniocentesis or CVS cannot be performed or yielded unclear results as it carries a significant risk to the fetus of complications from hemorrhaging. Fetal biopsy is the sampling of fetal skin, liver or muscle tissue to diagnose disorders that could not be diagnosed by CVS or amniocentesis, such as certain hereditary skin disorders or problems with the proper development of epidermal appendages. This would typically be performed between 17-20 weeks gestation. Many of these conditions can now be diagnosed using NGS DNA analysis of amniotic fluid for known mutations.
45. N Press and C Browner, "Collective silences, collective fictions: How Prenatal Diagnosis became part of Routine Prenatal Care" in K Rothenberg and E Thomson (eds) Women and Prenatal Testing: Facing the Challenges of Genetic Technology, (Ohio State Univ Press, Columbus, 1994) at 202.
46. Ibid.
47. Id at 203.
48. B Katz Rothman The Tentative Pregnancy: Prenatal Diagnosis and the Future of Motherhood (Penguin Books, New York, 1986).
49. Id at 101.
50. Wertz, D and J Fletcher "Feminist Criticism of Prenatal Diagnosis: a Response" (1993) 36 Clin Obs Gyn 541 at 544.
51. Ibid.
52. E Parens and A Asch (eds) *Prenatal Testing and Disability Rights* (Georgetown University Press, Washington DC, 2000).
53. D Wertz and J Fletcher "Feminist Criticism of Prenatal Diagnosis: a Response" (1993) 36 Clin Obstet Gynecol 541.
54. J Mozersky "Hoping Someday Never Comes: Deferring Ethical Thinking About Noninvasive Prenatal Testing" (2015) 6 A JOB Empirical Bioethics 31.
55. American College of Obstetricians and Gynecologists "Practice Bulletin No 77: Screening for Fetal Chromosomal Abnormalities" (2007) 109 Obstet Gynecol 217 at 218.
56. Id at 219.
57. D Chitayat, S Langlois, RD Wilson "Prenatal screening for fetal aneuploidy in singleton pregnancies" 33 J Obstet Gynaec Can 736 II-2E.

58. KL Wilson, JL Czerwinski, JM Hoskovec et al "NSGC Practice Guideline: Prenatal Screening and Diagnostic Testing Options for Chromosome Aneuploidy" (2013) 22 J Gen Couns 4 at 4.
59. NSU Antenatal Down Syndrome screening in New Zealand 2007: A Report of the Down Syndrome Screeing Advisory Group to the National Screening Unit (Wellington, Ministry of Health, 2007) at 20.
60. P Stone "Prenatal Testing for Aneuploidy and other Conditions in New Zealand: time for Action Again" (2016) 129 New Zealand Medical Journal 77 citing NSU *Antenatal Screening for Down Syndrome and Other Conditions: Monitoring Report* 1 July 2010 to 30 June 2013 (National Screening Unit. Ministry of Health). https://www.nsu.govt.nz/ health-professionals/ante-natal-screening-down-syndrome-and other-conditions/ procedures-guidelines-3.
61. First and second semester screens are funded, although some sonographers charge an additional fee for ultrasound scanning in addition.
62. These analytes are: beta-human chorionic gonadotrophin (β-hCG); unconjugated oestriol (uE3); alpha-fetoprotein (AFP); and inhibin A (DIA). <http://www.health.govt.nz/your-health/pregnancy-and-kids/pregnancy/weeks-14-30/screening-tests-and-scans-week-14-30>
63. KL Wilson, JL Czerwinski, JM Hoskovec et al "NSGC Practice Guideline: Prenatal Screening and Diagnostic Testing Options for Chromosome Aneuploidy" (2013) 22 J Genet Couns 4 at 5.
64. YWM Lo "Non-invasive testing using massively parallel sequencing of maternal plasma DBA: from molecular karyotyping to fetal whole-genome sequencing" (2013) 27 Reprod Med Online 593.
65. The previous gold-standard (using four second-trimester maternal serum markers) only had a sensitivity rate of approximately 80%, with a 5% false positive rate AR Gregg, IB van den Veyver, SJ Gross et al "Noninvasive Prenatal Screening by Next-Generation Sequencing" (2014) 15 Annu Rev Genom Hum Genet 327 at 328.
66. YWM Lo "Non-invasive testing using massively parallel sequencing of maternal plasma DBA: from molecular karyotyping to fetal whole-genome sequencing" (2013) 27 Reprod Med Online 593.
67. Purwosunu, Yuditiya and others "Clinical Potential for Noninvasive Prenatal Diagnosis Through Detection of Fetal Cells in Maternal Blood" (2006) 45 Taiwanese J Obstet Gynecol 10.
68. See ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/NCT00064597.
69. A Thompson, "Noninvasive Prenatal Testing" (2015) 314 JAMA 198.
70. AR Gregg, IB van de Veyver, SJ Gross et al "Non-invasive prenatal screening by next-generation screening" (2014) 15 Annu Rev Genomics Hum Genet 327 at 328.
71. YWM Lo "Non-invasive testingj using massively parallel sequencing of maternal plasma DBA: from molecular karyotyping to fetal whole-genome sequencing" (2013) 27 Reprod Med Online 593.
72. M Vanstone, C King, B DeVrier et al "Non-Invasive Prenatal Testing: Ethics and Policy Considerations" (2015) 6 American Journal of Bioethics 515.
73. ME Norton, B Jacobsson, GK Swamy et al "Cell-free DNA Analysis for Noninvasive Examination of Trisomy" (2015) 372 New England Journal of Medicine 1589.
74. L Hui, "Non-invasive Prenatal Testing for Fetal Aneuploidy: Charting the course form Validity to Clinical Utility" (2013) 41 Ultrasound Obstet Gynecol 2.
75. Ibid.
76. Ibid. If a woman who is RhD-negative conceives an RhD-positive fetus with an RhD-positive partner, the maternal and fetal blood types are "incompatible". Consequently, if fetal blood cells come into contact with maternal blood cells an immune response is triggered and antibodies are developed against what are recognized as "foreign" (fetal) cells—a process called "alloimmunization". Administering anti-D (RhIg–immune globulin) either during or immediately after pregnancy generally prevents alloimmunisation and the subsequent risk of Haemolytic Disease of the Newborn. "NIPD for the RHD gene in alloimmunised pregnant women allows early identification of fetuses at risk of haemolytic disease without the need for diagnostic amniocentesis for fetal blood group."

77. S Morain, MF Greene, MM Mello "A new era in noninvasive prenatal testing" (2013) 369 N Engl J Med 499.
78. Ibid.
79. L Hui, "Non-invasive Prenatal Testing for Fetal Aneuploidy: Charting the course form Validity to Clinical Utility" (2013) 41 Ultrasound Obstet Gynecol 2
80. ME Norton, B Jacobsson, GK Swamy et al "Cell-free DNA Analysis for Noninvasive Examination of Trisomy" (2015) 372 New England Journal of Medicine 1589. The study was a prospective, multicentre, blinded study conducted at 35 international centres, that compared cfDNA testing with standard screening during the first trimester in routine prenatal populations. Results showed that NIPT for trisomy 21 had higher sensitivity, a lower false positive rate, and higher positive predictive value compared with standard screening ie NT and biochemical analytes (ie not combined first trimester and second trimester screening). Although Trisomy 21 was the primary outcome evaluated, trisomy 19 and trisomy 13 were also evaluated as secondary outcomes. The authors stated that the "lower false positive rate and higher positive predictive value support the use of cffDNA testing in risk assessment for trisomies 18 and 13".
81. One study that involved 2049 women indicates that NIPT for trisomy 21 and 18 may perform well in routine (ie average/low risk) first-trimester population ie with similar detection rates. Hui 2013 citing KH Nicolaides, A Syngelaki, G Ashoor et al "Noninvasive prenatal testing for fetal trisomies in a routinely screened first-trimester population" (2012) 207 Am J Obstet Gynecol 374; Another study involved a large multicentre study involving a cohort of 4002 pregnant women who were primarily, but not solely, in the high-risk category. See ME Norton, H Brar, J Weiss et al "Non-Invasive Chromosomal Evaluation (NICE) Study: results of a multicenter prospective cohort study for detection of fetal trisomy 21 and trisomy 18" (2012) 207 Am J Obstet Gynecol e371.
82. AR Gregg, IB van de Veyver, SJ Gross et al "Non-invasive prenatal screening by next-generation screening" (2014) 15 Annu Rev Genomics Hum Genet 327 at 333.
83. J Helgeson, J Wardrop, T Boomer "Clinical outcome of subchromosomal events detected by whole-genome nonvasive prenatal testing" (2015) 35 Prenatal Diagnosis 999.
84. MA Minear, S Alessi, M Alysse et al "Noninvasive Prenatal Genetic Testing: Current and Emerging Ethical, Legal, and Social Issues" (2015) 16 Annu Rev Genomics Hum Genet 369 at 373.
85. NL Vora and BM O'Brien, "Noninvasive prenatal testing for microdeletion syndromes and expanded trisomies: proceed with caution" (2014) 123 Obstet Gynecol 1097.
86. Id at 1098.
87. AR Gregg, BG Skotko, JL Benkendorf et al "Noninvasive prenatal screening for fetal aneuploidy, 2016 update: a position statement of the American College of Medical Genetics and Genomics" (2016) 18 Genet Med 1056. This statement replaced an earlier statement: AR Gregg, SJ Gross, RG Best et al "ACMG statement on noninvasive prenatal screening for fetal aneuploidy" (2013) 15 Genet Med 395.
88. W Dondorp, G de Wert, Y Bombard et al "Non-invasive prenatal testing for aneuploidy and beyond: challenges of responsible innovation in prenatal screening" (2015) 23 Eur J Hum Genet 1438.
89. TK Lau, SW Cheung, PS Lo et al "Non-invasive prenatal testing for fetal chromosomal abnormalities by low-coverage whole-genome sequencing of maternal plasma DNA: review of 1982 consecutive cases in a single center" (2014) 43 Ultrasound Obs Gyn 254 at 262.
90. MT Mennuti, S Chandrasekaran, N Khaled et al "Cell-free DNA screening and sex chromosome aneuploidies" (2015) 35 Prenat Diagn 980.
91. Carole Samango-Sprouse, Colleen Keen, Teresa Sadeghin and Andrea Gropman "The benefits and limitations of cell-free DNA screening for 47, XXY (Klinefelter syndrome)" (2017) 37 Prenatal Diagnosis 497.

92. MT Mennuti, S Chandrasekaran, N Khaled et al "Cell-free DNA screening and sex chromosome aneuploidies" (2015) 35 Prenat Diagn 980.
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4. NIPD as a valid expansion of personal choice. Concerns included the "trivialisation of testing" and the implications of commercial/ direct-to-consumer tests."

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performed, (13.0 vs 15.7 weeks; $p < 0.01$), with women more likely to undertake chorionic villous sampling (59.6% vs 41.5%; $p < 0.01$). The gestational age when termination was performed was also lower (14.2 vs 17.2; $p < 0.01$), and terminations after 16 weeks were less likely in the post-NIPT cohort (25.0% vs 61.0%; $p < 0.01$), 18 weeks (7.7% vs 39.0%; $p < 0.01$), or 20 weeks (3.9% vs 12.2%; $p = 0.23$)." See Sarah Lassey, Emily Reiff, Lori Dobson, Bryann Bromley, Louise Wilkins-Haug, Deborah Bartz and Sarah Little "The influence of noninvasive prenatal testing on gestational age at time of abortion for aneuploidy" (2017) 37 Prenatal Diagnosis (epub ahead of print).

239. RV van Schendel, JH Kleinveld, WJ Dondorp et al "Attitudes of pregnant women and male partners towards non-invasive prenatal testing and widening the scope of prenatal screening" (2014) 22 Eur J Hum Genet 1345 citing P Schielen "Quality control parameters of Dutch Down's syndrome screening laboratories" (2010) RIV M Report No: 230083003/2012.
240. RV van Schendel, JH Kleinveld, WJ Dondorp et al "Attitudes of pregnant women and male partners towards non-invasive prenatal testing and widening the scope of prenatal screening" (2014) 22 Eur J Hum Genet 1345. Participants were asked what conditions they thought should be included in NIPT tests, and who should decide. The majority of women considered that NIPT should be offered for life-threatening conditions (89%), severe physical conditions (79%), or severe mental conditions (76%), with fewer considering that prenatal screening should also be offered for late-onset disorders (29%). Interestingly (41%) of participants would prefer to be able to choose what tests are performed from a list of conditions; 31% preferred a 'closed offer' or 'set' range of tests; and 26% preferred choosing between categories of disorders determined by disease type and severity. In terms of who should decide what conditions NIPT should detect, 40% considered that pregnant women (and their partners) should decide; 31% considered that a special commission should decide (with stakeholder contribution including government representatives, healthcare professionals, patient organisations, and pregnant women); 23% considered that healthcare professionals should determine testing panels; and 2% considered that the government or the patient–consumer organisations should determine the scope of NIPT.
241. RM Farrell, PK Agatisa, MB Mercer et al "Balancing Risks: the Core of Women's Decisions About Noninvasive Prenatal Testing" (2015) 6 Am J Bioeth 42.
242. Nuffield Council on Bioethics Non-invasive Prenatal Testing: Ethical Issues (Nuffield Council, March, 2017). http://nuffieldbioethics.org/.
243. Only 28.4% did not report fetal sex, while 22.7% of laboratories always reported fetal sex and the remaining 48.9% reported fetal sex on request. See Zandra Deans, Stephanie Allen, Lucy Jenkins, Farrah Khawaja and others "Recommended practice for laboratory reporting of non-invasive prenatal testing of trisomies 13, 18 and 21: a consensus opinion" (2017) Prenatal Diagnosis 1 at
244. However it should be noted that the law governing preimplantation genetic diagnosis prohibits selecting embryos on the basis of sex for non-medical reasons. Human Assisted Reproductive Technology Act, s 11.
245. S Barot "A Problem-and-Solution Mismatch" (2012) 15 Guttmacher Policy Review 18.
246. World Health Organization Preventing Gender-Biased Sex Selection: An Interagency Statement OHCHR, UNFPA, UNICEF, UN Women and WHO (2011).
247. R Dworkin Life's Dominion (New York, Knopf, 1993) 441.
248. B Citro, J Gilson, S Kalantry et al "Replacing Myths with Facts: Sex-selective abortion Laws in the United States" (2014) University of Chicago.
249. S Barot "A Problem-and-Solution Mismatch" (2012) 15 Guttmacher Policy Review 18 at 21.
250. Id at 22.
251. Kathryn Ehrich and others "Choosing Embryos: Ethical Complexity and Relational Autonomy in Staff Accounts of PGD" (2007) 29 Sociology of Health and Illness 1091.
252. Kathryn Ehrich and others "Choosing Embryos: Ethical Complexity and Relational Autonomy in Staff Accounts of PGD" (2007) 29 Sociology of Health and Illness 1091 at 1099.
253. Id.
254. Crimes Act, s 187A(a).

255. *Roe v Wade* 410 U.S. 113 (1973) at 153.
256. 410 U.S. 113 (1973) at 159.
257. 410 U.S. 113 (1973) at 164.
258. D Fox "The state's interest in potential life" (2015) 42 J Law Med Ethics 345.
259. *Roe v Wade* 410 US at 162-63. Fox posits four distinct legal justifications for curtailing reproductive liberty based on the states "interest in potential human life": 1) To protect from destruction, which becomes a compelling interest at the point of viability; 2) To protect from prenatal harm that will crystallise at birth; 3) To promote moral ideals and social values; and 4) To prevent adverse social effects. He claims the latter two interests are not concerned with saving prenatal life, but rather to impose moral values and are illegitimately subsumed under the state's interest in the "potentiality of human life" prerogative.
260. D McMullin Royal Commission of Inquiry on Contraception, Sterilisation and Abortion in New Zealand, *Contraception, Sterilisation and Abortion in New Zealand: Report of the Royal Commission of Inquiry* (Government Printer, Wellington, 1977).
261. Id at 192.
262. Id at 270.
263. Id at 206.
264. Id at 211.
265. While rape has always been a crime under the Crimes Act 1961, section 128(3) originally conferred spousal immunity on a husband who raped his wife, unless the couple were legally separated or divorced and no longer living together. Marital rape only became a criminal offence with the enactment of the Crimes Amendment Act 1985.
266. This is subsumed within the legal concept of self-defence under the Doctrine of Double Effect. Thomas Aquinas is credited with conceptualising the principle of double effect when discussing the permissibility of self-defense. He stipulated that the Doctrine is dependent on the harmful conduct being proportionate to the threat. *Summa Theologica* (II-II, Qu. 64, Art.7).
267. Paula Abrams has argued that a state's "willingness to authorize exemptions from abortion restrictions base on incest, rape, severe birth defects, physical harm to woman, etc., strongly suggests that the legislative goal of protection of potential life is fraught with assumptions about women's behavior as it relates to reproductive function. Exemptions for rape and incest establish a "fault" standard whereby women who involuntarily engage in intercourse are excused. The exemptions for severe birth defects reflect a state conclusion that the protection of potential life does not prevail in all circumstances. An exemption based on physical harm to the woman suggests that a woman's only legitimate interest in not carrying a pregnancy to term must be grounded in physical damage". See P Abrams "The Tradition of Reproduction" (1995) 37 Arizona Law Rev 453 at 499 citing R Siegel "Reasoning from the Body: A Historical Perspective on Abortion Regulation and Questions of Equal Protection" (1992) 44 Stanford Law Rev 261 at 365.
268. See Crimes Amendment Act 1977, s 6 which inserted 187A into the Crimes Act 1961. Abortions after 20 weeks are only lawful if necessary to save the life of the woman or to 'prevent serious permanent injury to her physical or mental health'. See Crimes Act 1961, s 187A (3).
269. Crimes Act 1961 s 187A(1)(aa). For pregnancies under 20 weeks, an abortion may be performed if it is believed that that "there is a substantial risk that the child, if born, would be so physically or mentally abnormal as to be seriously handicapped".
270. Contraception, Sterilisation and Abortion (CSA) Act 1977 (ss 29, 33, 37) require that a woman must obtain authorisation from two "certifying consultants" who confirm that the proposed abortion is to be performed for one of the indications permitted under section 187A of the Crimes Act 1961. The CSA Act makes it an offence also to perform an abortion otherwise than in a licensed institution (s 37).
271. Crimes Act 1961, s 187A(1)(a)). Abortions after 20 weeks are only lawful if necessary to save the life of the woman or to "prevent serious permanent injury to her physical or mental health. See Crimes Act 1961, s 187A(3).
272. *Right to Life New Zealand Inc v The Abortion Supervisory Committee* [2008] 2 NZLR 825 at [3] per Miller J.

273. This has been attributed to Government-funding of long-term contraceptive implants. Report of the Abortion Supervisory Committee Annual Report (Ministry of Health 2014) at 5. A Government may legitimately actively support reduced abortion rates, while maintaining policies that are consistent with pro-choice values. Arguably, promoting the state interest in protecting fetal life is best achieved by preventing the number of unwanted pregnancies and reducing the number of abortions performed overall, rather than imposing restrictive abortion laws.
274. Report of the Abortion Supervisory Committee (Ministry of Health, Wellington, 2014). Although the Abortion Supervisory Committee has certain duties under the Contraception, Sterilisation and Abortion Act 1977, it is not empowered to review or scrutinise individual decisions of certifying consultants to authorise or refuse an abortion. *Right to Life Inc v Abortion Supervisory Committee* [2012] NZSC 68.
275. In 2014, 70 per cent of abortions were performed before the end of the 10th week of pregnancy. 18 per cent of abortions were performed after 12 weeks of pregnancy. Statistics New Zealand, Abortion Statistics: Year ended December 2014, http://www.stats.govt.nz/browse_for_stats/health/abortion/AbortionStatistics_HOTPYeDec14.aspx
276. Vo v France (2005) 40 EHRR 12; see New Zealand Right to Life New Zealand Inc v The Abortion Supervisory Committee [2008] 2 NZLR 825; *Roe v Wade* 410 U.S. 113 (1973).
277. R Rebouche "Non-Invasive Testing, Non-Invasive Counselling" (2015) 43 J Law Med Ethics 228.
278. *Roe v Wade* 410 U.S. 113 (1973) at 153. (A woman's right to decide whether or not to terminate her pregnancy, at least during the first trimester, was protected under the Fourteenth Amendment's "concept of personal liberty" which conferred a right to privacy. After the first trimester and until the end of the second trimester, the state could regulate in the interests of maternal health or, after viability, to protect fetal health).
279. Planned Parenthood of Se. Pa. v Casey, 505 U.S. 833 (1992) 878.
280. 410 U.S. 113 (1973) at 155.
281. 410 U.S. 113 (1973) at 159.
282. 410 U.S. 113 (1973) at 159.
283. 410 U.S. 113 (1973) at 164.
284. 505 U.S. 833 (1992).
285. 505 U.S. 833 (1992) at 851. The court state that "these matters, involving the most intimate and personal choices a person may make in a lifetime, choices central to personal dignity and autonomy, are central to the liberty protected by the fourteenth Amendment. At the heart of liberty is the right to define one's own concept of existence, of meaning, of the universe, and of the mystery of human life. Beliefs about these matters could not define the attributes of personhood were they formed under compulsion of the State."
286. *Gonzalez v Carhart* 550 U.S. 124 (2007). See for a discussion S Suter "The 'Repugnance' Lens of *Gonzales v Carhart* and Other Theories of Reproductive Rights: Evaluating Advanced Reproductive Technologies" (2008) 76 George Washington Law Rev 1514.
287. V Koch "Legal issues in Prenatal and Preimplantation Genetic Diagnosis" in J Galst, M Verp (eds) *Prenatal and Preimplantation Diagnosis: The Burden of Choice* (Springer, New York, 2015) at 163.
288. *Planned Parenthood of Se. Pa. v Casey*, 505 U.S. 833 (1992) 878. (The Court stated that even though a woman had a right to choose up until viability "it does not at all follow that the State is prohibited from taking steps to ensure that this choice is thoughtful and informed". The Court adopted a test of "undue burden" so that a state could legitimately regulate aspects of abortion in the interests of both the woman and the fetus pre-viability. Such regulations would only be invalid if "its purpose or effect is to place substantial obstacles in the path of a woman seeking an abortion before the fetus attains viability").
289. J Daar "Distinctions in Disclosure: Mandated Informed Consent in Abortion and ART" (2015) 43 J Law Med Ethics 255 at 257.
290. *Roe v Wade* 410 US 113, 149-50 (1973)
291. 550 U.S. 124 (2007).
292. In 1996 and 1997 attempts were made by Congress to ban partial-birth abortion. Both times President Clinton vetoed the congressional legislation, and the Senate did not override the veto. The Act of 2003 was signed into law by President Bush.
293. 530 U.S. 914 (2000) per Breyer, Stevens, O'Connnor, Souter, Ginsburg JJ's.

294. The clinical term for a partial birth abortion is "intact dilation and extraction", a procedure performed mostly, if necessary, in late abortions carried out in the second trimester. It will generally be performed for a late-term pregnancy that is terminated because of serious fetal abnormality or the health of the woman is such that she cannot continue with the pregnancy.
295. 550 U.S. 124 (2007) at157.
296. Although Congress accepted evidence that there was never any necessity to perform a partial birth abortion in the interest of the health of the woman (so a health exception was not justified) there was, however, as noted in *Gonzales*, "a substantial body of medical opinion presented to Congress in opposition". 550 U.S. 124 (2007) at 176.
297. *Lawrence v Texas* 539 U.S. 558 (2003).
298. J King "And Genetic Testing For All … The Coming Revolution in Non-Invasive Prenatal Genetic Testing" (2011) 42 Rutgers Law J599.
299. J Gillette "Pregnant and Prejudiced: the Constitutionality of Sex-and Race-Selective Abortion Restrictions (2013) 88 Wash L Rev 645.
300. V Koch "Legal issues in Prenatal and Preimplantation Genetic Diagnosis" in J Galst, M Verp (eds) *Prenatal and Preimplantation Diagnosis: The Burden of Choice* (Springer, New York, 2015) at 163.
301. These States include Arizona, Illinois, Kansas, North Carolina, North Dakota, Oklahoma, Pennsylvania and South Dakota. B Citro, J Gilson, S Kalantry et al "Replacing Myths with Facts: Sex-selective abortion Laws in the United States" (2014) University of Chicago 2 at 21.
302. A new section (14-02.1-04.1) inserted into the North Dakota Century Code provides that: "Notwithstanding any other provision of law, a physician may not intentionally perform or attempt to perform an abortion with knowledge that the pregnant woman is seeking the abortion solely: (1) On account of the sex of the unborn child; or (2) Because the unborn child has been diagnosed with either a genetic abnormality or a potential for a genetic abnormality."
303. House Bill 1337 which was signed into law in March 2016 (HEA No. 1337). The Digest to the Indiana General Assembly states that the bill prohibits "a person from performing an abortion if the person knows that the pregnant woman is seeking the abortion solely because of: (1) the race, color, national origin, ancestry, or sex of the fetus; or (2) a diagnosis or potential diagnosis of the fetus having Down syndrome or any other disability. Provides for disciplinary sanctions and civil liability for wrongful death if a person knowingly or intentionally performs a sex selective abortion or an abortion conducted because of a diagnosis or potential diagnosis of Down syndrome or any other disability". https://iga.in.gov/legislative/2016/bills/house/1337#digest-heading. Cf *Chaffee v Seslar*, 786 N.E.2d 705 (Ind. 2003).
304. *Planned Parenthood of Indiana and Kentucky et al. v. Commissioner, Indiana State Dept. of Health et al* (Case 1:16-cv-00763-TWP-DML). The judge stated "a state may not prohibit a woman from making the ultimate decision to have an abortion prior to fetal viability".
305. Missouri Abortion Ban for Sex Selection and Genetic Abnormalities Act of 2016 (HB 1815).
306. US President Barack Obama (who holds overtly pro-choice personal views) set back access to abortion for those disenfranchised women who are unable to pay for termination procedures when he agreed to pass an Executive Order (13535) prohibiting (with few exceptions) the use of federal funds for abortion. G Annas "The Real Pro-Life Stance – Health Care Reform and Abortion Funding" (2010) N Engl J Med e56(1).
307. R Rebouche "Non-Invasive Testing, Non-Invasive Counselling" (2015) 43 J Law Med Ethics 228 at 232. Mo. Rev. Stat. § 191.320 (2011). Missouri also has a statute prohibiting wrongful birth claims: V.A.M.S. 188.130 (1986).
308. R Rebouche "Non-Invasive Testing, Non-Invasive Counselling" (2015) 43 J Law Med Ethics 228 at 232. Tenn. Code Ann. § 65-5-504(a)(1) (2010).
309. R Rebouche "Non-Invasive Testing, Non-Invasive Counselling" (2015) 43 J Law Med Ethics 228 at 232.Okla. Stat. Ann. Tit. 63, §§ 1-738.2, -741-.12 (2011).
310. The tort of wrongful birth is accepted by just under half of all US states. D Pergament and K Ilijic "The Legal Past, Present and Future of Prenatal Genetic Testing: Professional Liability and Other Legal Challenges Affecting Patient Access to Services" (2014) J Clin Med 1437.
311. V Koch "Legal issues in Prenatal and Preimplantation Genetic Diagnosis" in J Galst, M Verp (eds) *Prenatal and Preimplantation Diagnosis: The Burden of Choice* (Springer, New York, 2015) at 163.
312. R Rebouche "Non-Invasive Testing, Non-Invasive Counselling" (2015) 43 J Law Med Ethics

228 at 233. The Nebraska Genetic Counselling Practice Act and the Virginia Bill protect the counselor from disciplinary or recriminatory action if the counselor informs the woman of their refusal to counsel or refer for abortion and provides information regarding alternative licensed genetic counselors.

313. Rachel Rebouche, "Non-Invasive Testing, Non-Invasive Counselling" (2015) 43 J Law Med Ethics 228 at 234.
314. Ibid.
315. In the Minnesota case of *Molloy v Meier* (2004) the plaintiffs brought proceedings after clinicians (a paediatrician, a paediatric neurologist and a neurologist) failed to diagnose Fragile X in their child and they conceived a second child with the condition. The plaintiff parents were able to recover for wrongful birth, despite the prohibition on such claims, because they claimed that they would have avoided conception, rather than undergoing a termination of pregnancy. The Minnesota Supreme Court held that: "a physician's duty regarding genetic testing and diagnosis extends beyond the patient to biological parents who foreseeably may be harmed by a breach of that duty." *Molloy v Meier* 679 N.W.2d 719 (Minn. 2004).
316. J Gillette "Pregnant and Prejudiced: the Constitutionality of Sex-and Race-Selective Abortion Restrictions (2013) 88 Wash L Rev 645; R Rebouche, K Rothenberg "Mixed Messages: The Intersection of Prenatal Genetic Testing and Abortion (2012) 55 How. Laward J 983
317. Rachel Rebouche, "Non-Invasive Testing, Non-Invasive Counselling" (2015) 43 J Law Med Ethics 228.
318. www.savingdownsyndrome.org
319. E Parens and A Asch Prenatal Testing and Disability Rights (Hastings Center Studies in Ethics).
320. Tom Shakespeare Disability Rights and Wrongs (Routledge, London and New York, 2006) at 43.
321. John Muller, "Disability, Ambivalence, and the Law" (2011) 37 American Journal of Law and Medicine 469 at 470.
322. R Hull "Defining Disability – A Philosophical Approach" (1998) 4 Res Publica 199 at 204.
323. Ibid, at 209.
324. Ibid, at 210.
325. E Parens and A Asch (eds) *Prenatal Testing and Disability Rights* (Georgetown University Press, Washington DC, 2000) at ix; at ix; see also A Asch "Disability Equality and Prenatal Testing: Contradictory or Compatible" (2003) 30 Florida State Univ Law Rev 315.
326. E Parens and A Asch "The Disability Rights Critique of Prenatal Genetic testing: Reflections and Recommendations" in E Parens and A Asch (eds) *Prenatal Testing and Disability Rights* (Georgetown University Press, Washington DC, 2000) at 20.
327. See Prenatally and Postnatally Diagnosed Awareness Act (United States Public Law 110-134, 2008). See P Reilly "Commentary: The Federal 'Prenatally and Postnatally Diagnosed Conditions Awareness Act" (2009) 29 Prenat Diagn 829; R Dresser "Prenatal Testing and Disability: A Truce in the Culture Wars?" (2009) Hastings Center Rep 7.
328. T Santin "Is Down Syndrome Doomed? How State Statutes can Help Expectant Parents Make Informed Decisions about Prenatal Down Syndrome Diagnoses" (2012) 6 J Enviro Pub Hlth 241 at 260.
329. Eg Pennsylvania's Down Syndrome Prenatal and Postnatal Education Act. Missouri, New Jersey, Alabama and Virginia have also introduced laws requiring healthcare providers to supply certain information.
330. T Shakespeare "The Social Context of Individual Choice" in D Wasserman, J Bickenbach, R Wachbroit (eds) *Quality of Life and Human Difference* (Cambridge Univ Press, New York, 2005) at 234. See <www.antenataltesting.info>.
331. www.parent2parent.org.nz
332. www.savingdownsyndrome.org
333. Soren Holm claims that there are at least three distinct expressivist objections. The first involves expressivist claims associated with a politically approved social practice (ie state funded prenatal diagnosis and screening). The second involves expressivist claims associated

with the choices of individuals. He claims that the third aspect is whether the expressivist claim is that the selection choices expresses a discriminatory message to individuals, or merely suggests a negative attitude towards the disability. See S Holm "The Expressivist Objection to Prenatal Diagnosis: Can it be Laid to Rest?" (2008) 34 J Med Ethics 24.

334. A Ouellette "Selection against Disability: Abortion, ART, and Access" (2015) J Law Med Ethics 211 at 215; J Malek "Deciding Against Disability: Does the Use of Reproductive Genetic Technologies Express Disvalue for People With Disabilities?" (2010) 36 J Med Ethics 217; S Wilkinson *Choosing Tomorrow's Children* (Oxford University Press, Oxford, 2010).
335. T Shakespeare *Disability Rights and Wrongs* (Routledge, London and New York, 2006) at 96. See also T Murphy "When Choosing the Traits of Children is Hurtful to Others" (2010) 37 J Med Ethics 105 at 108.
336. Wertz, D and J Fletcher "Feminist Criticism of Prenatal Diagnosis: a Response" (1993) 36 Clin Obs Gyn 541 at 552.
337. For example women who underwent microarray testing reported that they did not feel supported in continuing a pregnancy diagnosed with 22q112 delection which is associated with a variable phenotype. OM Vanakker, C Vilain, K Janssens et al "Implementation of genomic arrays in prenatal diagnosis: The Belgian approach to meet the challenges" (2014) 57 Eur J Med Genet 151.
338. CI Hickerton, M Aitken, J Hodgson et al " Did you find that out in time?": new life trajectories of parents who choose to continue a pregnancy where a genetic disorder is diagnosed or likely" (2012) 158A Am J Med Genet Part A 373.
339. S Wilkinson *Choosing Tomorrow's Children* (Oxford Univ Press, Oxford, 2010) at 209; H Strange and R Chadwick "The Ethics of Nonmedical Sex Selection" (2010) 18 Hlth Care Anal 252; R Brownsword "Happy Families, Consenting Couples, and Children with Dignity: Sex Selection and Saviour Siblings" (2005) 17 Child Fam Law Q 435; L Purdy "Is Preconception Sex Selection Necessarily Sexist?" (2007) 15 Reprod BioMed Online 33; B Steinbock "Sex Selection: Not Obviously Wrong" (2002) 32 Hastings Center Rep 23; D Wertz "Ethical and Social Issues in Prenatal Sex Selection: A Survey of Geneticists in 37 Nations" (1998) 46 Soc Sci Med 255; V Seavilleklein and S Sherwin "The Myth of the Gendered Chromosome: Sex Selection and the Social Interest" (2007) 16 Cambridge Q Healthc Ethics 7; R McDougall "Acting Parentally: An Argument Against Sex Selection" (2005) 31 J Med Ethics 601; P Herissone-Kelly "The 'Parental Love' Objection to Nonmedical Sex Selection: Deepening the Argument" (2007) 16 Cambridge Q Healthc Ethics 446.
340. G de Wert and W Dondorp "Preconception Sex Selection for Non-medical and Intermediate Reasons: Ethical Reflections" (2010) 2 Facts, Views and Vision in ObGyn 267–277. There is no express prohibition on sex-selective abortion in New Zealand legislation, however it does not fall easily within any of the current exceptions to the prohibition on abortion and it is an offence to perform PGD to select sex in the absence of a sex-linked disorder (HART Act, s 11).
341. A Ouellette "Selection against Disability: Abortion, ART, and Access" (2015) J Law Med Ethics 211 at 213.
342. See E Parens and A Asch, "The Disability Rights Critique of Prenatal Genetic Testing: Reflections and Recommendations" (1999) 29 Hastings Center Rep S1-S22 at S16.
343. Erin Nelson Law, *Policy and Reproductive Autonomy* (Hart Publishing, Oxford, 2013) at 36.
344. R McDougall "Acting Parentally: an Argument Against Sex Selection" (2005) 31 J Med Ethics 601 at 605.
345. R McDougall "Acting Parentally: an Argument Against Sex Selection" (2005) 31 J Med Ethics 601 at 603.
346. M Sandel The Case Against Perfection: Ethics in the Age of Genetic Engineering (Belknap Press, Cambridge, 2007) at 45.
347. Id at 46.
348. Stephen Wilkinson *Choosing Tomorrow's Children* (Clarendon Press, Oxford, 2010) at 27.
349. R Fitzgerald, M Legge, J Park "Choice, Rights, and Virtue: Prenatal Testing and Styles of Moral Reasoning in Aotearoa/New Zealand" (2015) 29 Med Anthrop Q 400 at 410; C Farelly "Virtue Ethics and Prenatal Genetic Enhancement" (2007) 1 Studies Ethics, Law Tech

<www.bepress.com/selt/vol1/iss1/>.

350. J Snelling "Parental Preferences and Procreative Choices: Reproductive Liberty and the Regulation of Preimplantation Genetic Diagnosis" (PhD thesis), University of Otago, 2012 at 133.
351. R Green *Babies by Design* (Yale University Press, New Haven, 2007) at 114.
352. Id at 115. Green acknowledges that there are exceptions to the general principle of PLAAP. However, evidence suggests that failure to bond with a child is more likely to be a result of other factors such as a parent's personal problems or problems within the marriage.
353. A Asch "Disability Equality and Prenatal Testing: Contradictory or Compatible?" (2003) 30 Florida State Univ Law Rev 315 at 338.
354. Erin Nelson *Law, Policy and Reproductive Autonomy* (Hart Publishing, Oxford, 2013) at 69.
355. John Harris *Enhancing Evolution: The Ethical Case for Making Better People* (Princeton Univ Press, Princeton, 2007) at 146.
356. A Ouellette "Selection against Disability: Abortion, ART, and Access" (2015) J Law Med Ethics 211 at 214.
357. Ibid.
358. A Asch "Disability Equality and Prenatal Testing: Contradictory or Compatible?" (2003) 30 Florida State Univ Law Rev 315 at 339.
359. A Ouellette "Selection against Disability: Abortion, ART, and Access" (2015) J Law Med Ethics 211 at 218.
360. See, e.g., Ariz. Rev. Stat. Ann. § 13-3603.02(A) (2014) (prohibiting the performance of an abortion on the basis of the unborn child's sex); 720 Ill. Comp. Stat. 510/6(8) (2014) (prohibiting sex-based abortions); S.B. 141, 85th Leg., Reg. Sess. (Kan. 2013) (prohibiting sex-based abortions); N.C. Gen. Stat. § 90-21.121 (2014) (prohibiting sex-based abortions).
361. Position statement, American College of Obstetricians and Gynecologists, available at <http://www.acog.org/Resources_ And_Publications/Committee_Opinions/Committee_ on_Eth- ics/Sex_Selection> (last visited May 4, 2015).
362. Ibid.
363. A Ouellette "Selection against Disability: Abortion, ART, and Access" (2015) J Law Med Ethics 211 at 219.
364. Ibid.
365. A Iltis "Prenatal Screening and Prenatal diagnosis: Contemporary Practices in Light of the Past" (2016) 42 J Med Ethics 334.
366. *Bolam v Friern Hospital Management Committee* [1957] 1 WLR 582. For a discussion see J Manning "The Required Standard of Care for Treatment" in P Skegg and R Paterson (eds) *Health Law in New Zealand* (2nd ed, Thomson Reuters, Wellington, 2015) 102.
367. Elias J in *B v Medical Council of NZ* endorsed the approach adopted by the Australian High Court in *Rogers v Whitaker* when it stated: "Whether a medical practitioner carries out a particular form of treatment in accordance with the appropriate standard of care is a question in the resolution of which responsible professional opinion will have an influential, often a decisive role to play; whether the patient has been given all the relevant information to choose between undergoing and not undergoing the treatment is a question of a different order". Although Elias observed that in "the case of diagnosis or treatment, conduct which falls short of the mark will be assessed substantially by reference to usual practice of comparable practitioners" it was implicit that, even in the circumstance of diagnosis and treatment, common practice will not always be determinative. *B v Medical Council of NZ* (HC AK HC11/96, 8, July 1996, Elias J) p 17. This approach has been apparent in subsequent proceedings. *Martin v Director of Proceedings* (HC AK CIV-2006-404-005706, 2 July 2008 per Courtney J) (the court preferred one expert testimony to the other and were willing to extend judicial scrutiny into the realm of diagnosis and treatment; *Ambros v ACC & Ors* (HC, AK Civ 2004-404-3261, 21 March 2005, per Harrison and Heath JJ) (High Court was not satisfied by the evidence of four cardiologists that the medical management of did not constitute Medical Error."
368. B Dickens "Ethical and Legal Aspects of Noninvasive Prenatal Gentic Diagnosis" (2014) 124 Int'l J Gyn Obs 181.
369. See *Rogers v Whitaker* (1992) 175 CLR 479 (HCA) which was adopted in *B v Medical Council of*

NZ (Unreported, HC Auckland, HC11/98/7/96 Elias J) and applied in ACC proceedings; see *Matich v ACC* 27/2/95, (ACC Appeal Authority, Auckland, Decision No 163/95 PJ Cartwright); see also *Montgomery v Lanarkshire Health Board* [2015] UKSC 11 in which, for the first time, a UK court adopted this "reasonable patient" test.

370. The Health and Disability Commissioner (Code of Health and Disability Services Consumers; Rights) Regulations 1996 (SR 1996/78). This includes, in Right 4(1), the "right to have services provided with reasonable care and skill" and in 4(2) the right to have services provided that are consistent with "legal, professional, ethical, and other relevant standards". Right 6(1) provides that "Every consumer has the right to the information that a reasonable consumer, in that consumer's circumstances, would expect to receive … including the right to results of tests and procedures" (Right 6(1)(f), 6(1)(g)).
371. In *Harman v Director of Proceedings* HC (Civ 2007-404-003732) Wild J stated that in relation to both the common law and the Code of Rights that "[a]lthough the focus on effective communication is ubiquitous, the usual articulation is that a medical practitioner must "enable" understanding" … "The [former] Health and Disabilities Commissioner, Mr Ron Paterson, has emphatically stated that this standard is not the same as having to "ensure" that the patient understands, and nor is it necessary that the patient possesses actual understanding. Instead he states that 'Doctors are required to facilitate understanding, but cannot be expected to guarantee patient understanding, and the law makes no such requirement' (R Paterson "Informed Consent in New Zealand: Medical Myths" (2003) 116 NZMJ 1183)".
372. *Waller v James* [2015] NSWCA 232. The court held that the doctor had a duty of care in respect of an IVF patient whose husband had anti-thrombin deficiency to ensure that the parents understood that ATD is a hereditary condition and the importance of accessing genetic counselling. While the doctor failed to discharge his duty of care in this respect, the wrongful birth claim failed on the basis of legal causation because the injury was not caused by the genetic condition.
373. *Eastbury v Genea Ltd* (formerly Sydney IVF Ltd) [2015] NSWSC 1834.
374. M Norton, N Rose, P Benn "Noninvasive prenatal testing for fetal aneuploidy: Clinical assessment and a plea for restraint" (2013) 121 Obs Gyn 847 at 848.
375. MA Minear, S Alessi, M Alysse et al "Noninvasive Prenatal Genetic Testing: Current and Emerging Ethical, Legal, and Social Issues" (2015) 16 Annu Rev Genomics Hum Genet 369 at 375.
376. P Das, D Jones "Chromosomal microarray testing in children: Experience from a NZ secondary care hospital" (2014) 50 Journal of Paediatrics and Child Health 574.
377. S Long and J Goldblatt, "Noninvasive prenatal testing (NIPT) in Western Australia; Considerations in clinical practice" (2014) 54 Austr NZ J Obs Gyn 487 at 489.
378. J Mozersky "Hoping Someday Never Comes: Deferring Ethical Thinking About Noninvasive Prenatal Testing" (2015) 6 A J Empir Bioethics 31.
379. Ibid. Mozersky cites L McGoey "The logic of strategic ignorance" (2012) 63 Brit J of Sociol 533. McGoey utilises the logic of strategic ignorance in the context of industry and politics whereby ignorance is exploited to deny liability or to command resources. In this context, ignorance may be strategically beneficial for persons in positions of power or authority.
380. L McGoey "The logic of strategic ignorance" (2012) 63 Brit J of Sociol 533 at 554.
381. J Mozersky "Hoping Someday Never Comes: Deferring Ethical Thinking About Noninvasive Prenatal Testing" (2015) 6 A J Empir Bioethics 31at 31. Mozersky also notes the inherent paradox of screening for many women: "no matter how accurate NIPT may be, it is never enough information. No test can definitively determine whether a baby will be healthy (or the severity of a potential disability …), yet this is exactly the reassurance women appear to desire more than anything else from testing, and they cling to after receiving good results".
382. L Beulen, M van den Berg, B Hw Faas et al "The effect of a decision aid on informed decision-making in the era of non-invasive prenatal testing: a randomised controlled trial" (2016) 24 Eur J Hum Genet 1409.
383. Id at 1415.
384. Id at 1409.
385. Miriam Kuppermann, Sherri Pena, Judith Bishop, Sanae Nakagawa "Effect of Enhanced

Information, Values Clarification, and Removal of Financial Barriers on Use of Prenatal Genetic Testing
A Randomized Clinical Trial" (2014) 312 JAMA 1210.

386. H Skirton, L Goldsmith, L Jackson et al "Offering prenatal diagnostic tests: European guidelines for clinical practice" (2014) 22 Eur Hum Genet 580 at 584.
387. The Code of Rights, right 6 (1)(f).
388. Personal communication, Dr Joanne Dixon, National Clinical Director, Genetic Health Service NZ March 2016. There are also two vocational training positions in NZ, but only one vocational trainee currently.
389. *Parkinson v St James and Seacroft University Hospital NHS Trust* [2002] QB 266.
390. *Keel v Banach* 24 So.2d 1022, 1029 (Ala. 1993) cited in Klein RD, Mahoney MJ "Medical Legal Issues in Prenatal Diagnosis" (2007) 34 Clin Perinatol 287.
391. See *Allenby v H and Ors* [2012] NZSC 33; *Cumberland v Accident Compensation Corporation* [2013] NZCA 590.
392. Accident Compensation Act 2001, s 32, s 29.
393. *Allenby v H and Ors* [2012] NZSC 33.
394. *Accident Compensation Corporation v J* [2016] NZHC 1683.
395. "Once a mother has recovered physically from her pregnancy and giving birth to her child, she will not be 'unable' to work because of her pregnancy… [Her] inability to work is almost certainly not going to be because of the… effects of the pregnancy but… [because of] factors such as childcare arrangements, the unavailability of the other parent and parenting choices."
396. *Cumberland v Accident Compensation Corporation* [2013] NZCA 590 at [34].
397. As contained in the Crimes Act 1961 and the Contraception Sterilisation and Abortion Act 1977.
398. Once born, a child may have independent cover under ACC for treatment injury if the personal injury child suffered is a direct result of (negligent) obstetric care/antenatal injury that occurred during the pregnancy or birth, for example hypoxic brain damage directly caused by negligent care.
399. Although the High Court of Australia has held that the costs of rearing a healthy, but unplanned, child are recoverable (*Cattanach v Melchior* (2003) 199 ALR 131) the United Kingdom has followed a different path based on policy grounds (*McFarlane v Tayside Health Board* [1999] 4 All ER 961). The House of Lords has reaffirmed that such costs are not recoverable (*Rees v Darlington Memorial Hospital NHS Trust* [2003] 4 All ER 987), but where the birth has resulted in the birth of a disabled child, there may be a greater chance of damages being recovered, see *Parkinson v St James and Seacroft University Hospital NHS Trust* [2002] QB 266. See S Todd, "Damages for Wrongful Birth" (2001) 4 NZ Law Rev 534. "*Parkinson* provides for a fair and just solution to a difficult question. Distinguishing between children who are normal and children who are disabled might be thought to be invidious, but arguably the extra expenses fall outside the ordinary and inextricable calculus of benefits and burdens associated with the birth of a child. As Hale LJ observed, the analysis treats a disabled child as having exactly the same worth as a non-disabled child. It affords him the same dignity and status. It simply acknowledges that he costs more." It remains to be seen which common law approach NZ courts would courts adopt.
400. Should it be found that a provider has breached the Code, the Health and Disability Commissioner has a range of (limited) powers. These include: making a recommendation (e.g. that the provider apologise); reporting the opinion to a relevant person including a registration authority; or referring to the Director of Proceedings to determine if proceedings in the Health Practitioners Disciplinary Tribunal or the Human Rights Review Tribunal proceedings are justified.
401. Royal Australian and New Zealand College of Obstetricians and Gynaecologists "College Communiqués: DNA-based Noninvasive Prenatal Testing for Fetal Aneuploidy" (28 April 2015) http://www.ranzcog.edu.au/womens-health/college-communiques/1357-dna-based-noninvasive-prenatal-testing-for-fetal-aneuploidy.html.
402. W Dondorp, G de Wert, Y Bombard, D Bianchi and others: Noninvasive Prenatal Testing for Aneuploidy and Beyond: Challenges of Responsible Innovation in Prenatal Screening" (2015)

23 European Journal of Human Genetics 1438.

403. New Zealand Maternal Fetal Medicine Network: "Statement on the use on Non-Invasive Prenatal Testing (NIPT)" (NZFMN, Jan 2016). www.healthpoint.co.nz.
404. AR Gregg, IB van de Veyver, SJ Gross et al "Non-invasive prenatal screening by next-generation screening" (2014) 15 Annu Rev Genomics Hum Genet 327 at 339.
405. CM Christensen The Innovator's Dilemma: When New Technologies Cause Great Firms to Fail (Harvard Bus. Sch. Press, Boston, 2013).
406. PA Benn, A Borrell, R Chiu et al (2013) "Position statement from the Aneuploidy Screening Committee on behalf of the Board of the International Society for Prenatal Diagnosis" 33 Prenat Diagn 622.
407. The NZ National Health Committee defines screening as "a health service in which members of a defined population, who either do not necessarily perceive they are at risk of, or are already affected by, a disease or its complications, are asked a question or offered a test, to identify those individuals who are more likely to be helped than harmed by further tests or treatment to reduce the risk of a disease or its complications". National Health Committee *Screening to Improve Health in New Zealand: Criteria to assess screening programmes* (Wellington: Ministry of Health, 2003) at 29.
408. A de Jong and G de Wert "Prenatal Screening: An Ethical Agenda for the Near Future " (2015) 29 Bioethics 46 at 47.
409. C Burton-Jeangros, S Cavalli, S Gouilhers et al "Between tolerable uncertainty and unacceptable risks: how health professionals and pregnant women think about the probabilities generated by prenatal screening" (2013) 15 Hlth Risk Soc 144.
410. A de Jong and G de Wert "Prenatal Screening: An Ethical Agenda for the Near Future " (2015) 29 Bioethics 46.
411. Screening also often extends beyond testing for certain traits or anomalies to testing for maternal or fetal conditions that may adversely affect a pregnancy such as infectious diseases or Rhesus antigen status.
412. Stephen Wilkinson, "Prenatal Screening, Reproductive Choice, and Public Health" (2015) 29 Bioethics 26.
413. Asch "Why I Haven't Changed My Mind about Prenatal Diagnosis" in Erik Parens and Adrienne Asch Prenatal Testing and Disability Rights (Georgetown University Press, Washington DC, 2000) at 253; Adrienne Asch "Disability Equality and Prenatal Testing: Contradictory or Compatible?" (2003) 30 Florida State University Law Review 315 at 339.
414. S Wilkinson "Prenatal Screening, Reproductive Choice, and Public Health" (2015) 29 Bioethics 26 at 27.
415. Eg Angus Clarke delineates three objectives of centralised policy for PNT: "1) avoiding healthcare costs associated with children with disabilities; 2) avoiding suffering of the child born; and 3) promoting reproductive choice". A Clarke "Prenatal Screening: Paradigms and Perspectives" in P Harper and A Clarke (eds) Genetics, Society and Clinical Practice (Abingdon, Oxon, 1997).
416. J Hewison, "Psychological Aspects of Individualized Choice and Reproductive Autonomy in Prenatal Screening" (2015) 29 Bioethics 9.
417. B MurdochV Ravitsky, U Ogbogu et al "Non-invasive prenatal testing and the unveiling of an impaired translation process" (2017) 39 J Obs Gyn Canada 10.
418. National Health Committee Screening to Improve Health in New Zealand: Criteria to assess screening programmes (Wellington: Ministry of Health, 2003) at 49.
419. ME Norton, S Nakagawa, M Kuppermann "Women's attitudes regarding prenatal testing for a range of congenital disorders of varying severity" (2014) 3 J Clin Med 144.
420. J Daar, "One Small Step for Genetics, One Giant Leap for Genocide?" (2011) 42 Rutgers Law J 705 at 710. Around 2% of US women undertake invasive diagnostic testing such as amniocentesis or chorionic villus testing.
421. NSU *Antenatal Screening*

for Down Syndrome and Other Conditions: Monitoring Report 1 July 2010 to 30 June 2013 (National Screening Unit. Ministry of Health) at vi.

422. Id at 24.
423. AR Gregg, IB van de Veyver, SJ Gross et al "Non-invasive prenatal screening by next-generation screening" (2014) 15 Annu Rev Genomics Hum Genet 327 at 340.
424. Ibid.
425. Professional bodies, such as the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) emphasise that NIPT should not be a unitary test but rather an adjunct to other screening modalities. They recommend that all women should be offered a first-trimester ultrasound scan, regardless of their intention to undergo NIPT. LJ Salomon, Z Alfirevic, F Audibert et al (International Society of Ultrasound in Obstetrics and Gynecology (ISUOG)) "ISOUG consensus statement on the impact of non-invasive prenatal testing (NIPT) on prenatal ultrasound practice" (2014) 44 Ultrasound Obstet Gynecol 122.
426. AR Gregg, IB van de Veyver, SJ Gross et al "Non-invasive prenatal screening by next-generation screening" (2014) 15 Annu Rev Genomics Hum Genet 327 at 339.
427. RJ Wapner, CL Martin, B Levy et al "Chromosomal microarray versus karyotyping for prenatal diagnosis" (2012) 367 N Engl J Med 2175.
428. OB Petersen, I Vogel and al, C Ekelund et "Potential diagnostic consequences of applying non-invasive prenatal testing: population-based study from a country with existing first trimester screening" (2014) 43 Ultrasound Obstet Gynecol 265 at 268.
429. Specifically NIPT for trisomy 21, 18, 13 and sex chromosome aneuploidy.
430. OB Petersen, I Vogel and al, C Ekelund et "Potential diagnostic consequences of applying non-invasive prenatal testing: population-based study from a country with existing first trimester screening" (2014) 43 Ultrasound Obstet Gynecol 265 at 265.
431. E Norwitz and B Levy "Noninvasive Prenatal Testing: The Future is Now" (2013) 6(2) Rev Obs Gyn 48 at 60.
432. AR Gregg, IB van de Veyver, SJ Gross et al "Non-invasive prenatal screening by next-generation screening" (2014) 15 Annu Rev Genomics Hum Genet 327 at 335.
433. OB Petersen, I Vogel and C Ekelund et al "Potential diagnostic consequences of applying non-invasive prenatal testing: population-based study from a country with existing first trimester screening" (2014) 43 Ultrasound Obstet Gynecol 265.
434. J Hewison "Psychological Aspects of Individualized Choice and Reproductive Autonomy in Prenatal Screening" (2015) 29 Bioethics 9.
435. OB Petersen, I Vogel and al, C Ekelund et "Potential diagnostic consequences of applying non-invasive prenatal testing: population-based study from a country with existing first trimester screening" (2014) 43 Ultrasound Obstet Gynecol 265 at 268.
436. Id at 268.
437. Argyro Syngelaki, Eugene Pergament, Tessa Homfray, Ranjit Akolekar, Kypros H. Nicolaides "Replacing the Combined Test by Cell-Free DNA Testing in Screening for Trisomies 21, 18 and 13: Impact on the Diagnosis of Other Chromosomal Abnormalities? (2014) 35 Fetal Diagn Ther 174.
438. OB Petersen, I Vogel and al, C Ekelund et "Potential diagnostic consequences of applying non-invasive prenatal testing: population-based study from a country with existing first trimester screening" (2014) 43 Ultrasound Obstet Gynecol 265 at 268.
439. MA Minear, S Alessi, M Alysse et al "Noninvasive Prenatal Genetic Testing: Current and Emerging Ethical, Legal, and Social Issues" (2015) 16 Annu Rev Genomics Hum Genet 369 at 381.
440. L Chitty and others *RAPID Non-invasive prenatal testing (NIPT) evaluation study: A Report for the UK National Screening Committee Executive Summary* (2015) at 3..
441. Traditional screening in the UK also has a risk cut-off of >1:150 for invasive testing.
442. L Chitty and others *RAPID Non-invasive prenatal testing (NIPT) evaluation study: A Report for the UK National Screening Committee Executive Summary* (2015) at 3.
443. See S Taylor-Phillips, K Freeman, J Geppert et al *Systematic review and cost-consequence assessment*

of cell-free DNA testing for T21, T18 and T13 in the UK – Final report. July 2015 http://docplayer.net/42246154-Systematic-review-and-cost-consequence-assessment-of-cell-free-dna-testing-for-t21-t18-and-t13-in-the-uk-final-report.html.

444. V Ravitsky "Nuffield Council on Bioethics Background Paper: Non-Invasive Prenatal Testing (NIPT) Identifying key clinical, ethical, social, legal and policy issues" (2015) at 22.
445. See United Kingdom National Screening Committee *United Kingdom National Screening Committee non-invasive prenatal testing (NIPT) recommendation* (Jan 2016) http://legacy.screening.nhs.uk/fetalanomalies.
446. See S Taylor-Phillips, K Freeman, J Geppert et al *Systematic review and cost-consequence assessment of cell-free DNA testing for T21, T18 and T13 in the UK – Final report.* July 2015; D Bianchi, L Parker, J Wentworth et al "DNA Sequencing versus Standard Prenatal Aneuploidy Screening" (2014) 370 N Engl J Med 799; P Brady, N Brison, K van den Bogaert et al "Clinical Implementation of NIPT: Technical and Biological Challenges" (2015) Clin Genet 523. However, the positive predictive values are expected to be lower in the group of women at low risk compared with those at increased risk of aneuploidy. The positive predictive values for the general population will also be dependent upon the specific test characteristics and further studies are warranted before NIPT is routinely offered to all women..
447. See S Taylor-Phillips, K Freeman, J Geppert et al *Systematic review and cost-consequence assessment of cell-free DNA testing for T21, T18 and T13 in the UK – Final report.* July 2015 at 14. The cost per case detected was approximated at £14,764 if NIPT is implemented as a secondary screen compared with £84,709 if NIPT was implemented as a primary screen.
448. J Hewison, "Psychological Aspects of Individualized Choice and Reproductive Autonomy in Prenatal Screening" (2015) 29 Bioethics 9 at 12.
449. Andrew McLennan, Ricardo Palma-Dias, Fabricio Da Silva Costa, Simon Meagher et al "Noninvasive prenatal testing in routine clinical practice – An audit of NIPT and combined first-trimester screening in an unselected Australian population" (2016) 56 ANZJOG 22.
450. V Ravitsky "Nuffield Council on Bioethics Background Paper: Non-Invasive Prenatal Testing (NIPT) Identifying key clinical, ethical, social, legal and policy issues" (2015) at 23.
451. United Kingdom National Screening Committee *United Kingdom National Screening Committee non-invasive prenatal testing (NIPT) recommendation* (Jan 2016) http://legacy.screening.nhs.uk/fetalanomalies.
452. C Munthe "A New Ethical Landscape of Prenatal Testing: Individualizing Choice to Serve Autonomy and Promote Public Health: A Radical Proposal" (2015) 29 Bioethics 36 at 39.
453. BA Bernhardt, D Soucier, K Hanson "Women's experiences receiving abnormal prenatal chromosomal microarray testing results" (2013) 15 Genetics in Medicine 139.
454. NC Rose, P Benn, A Milunsky "Current controversies in prenatal diagnosis 1: should NIPT routinely include microdeletions/microduplications?" (2015) 36 Prenat Diagn 10. Arguments both for and against expanded prenatal screening are presented.
455. The European Society of Human Genetics; the international paediatric platform of P3G; the Human Genome Organisation and the UK PHG Foundation support a targeted approach in NBS programmes (using targeted sequencing or gene panels). They consider the responsible use of WGS-based genetic testing within a public health programme such as NBS should be mediated on the basis of its public health potential, rather than being technology driven. While this approach will reduce the number of incidental findings, they consider findings that identify serious conditions for which prevention or treatment may be instituted should be reported to parents. Bartha Knoppers, Ma'n H Zawati, and K Senecal, "Return of Genetic Testing Results in the Era of Whole-Genome Sequencing" (2015) 16 Nature Reviews Genetics 553.
456. WW Grody, BH Thompson, AR Gregg et al "American College of Medical Genetics and Genomics ACMG position statement on prenatal/preconception expanded carrier screening" (2013) 15 Genet Med 482. The ACMG states that the principle of nonmaleficence dictates that disorders that are screened for prior to conception or prenatally should be of a kind that most individuals participating in the screening program would consider undergoing prenatal diagnosis in order to inform the reproductive project.
457. In regard to disorders with variable expressivity or incomplete penetrance, or conditions that may only have a mild phenotype, the ACMG considers screening should be optional.

In addition, the ACMG specifically states that before screening for a particular mutation, its incidence in a population should be known so that advice may be given regarding residual risk for those who test negative. Further it states that there must be a clinical link between the mutation and the disorder. WW Grody, BH Thompson, AR Gregg et al "American College of Medical Genetics and Genomics ACMG position statement on prenatal/preconception expanded carrier screening" (2013) 15 Genet Med 482.

458. ME Norton, S Nakagawa, M Kuppermann "Women's attitudes regarding prenatal testing for a range of congenital disorders of varying severity" (2014) 3 J Clin Med 144.
459. Id at 147.
460. Id at 149.
461. Id at 150.
462. Id at 145.
463. BL Shaffer, AB Caughey, ME Norton "Variation in the decision to terminate pregnancy in the setting of fetal aneuploidy" (2006) 26 Prenat Diagn 667; AJ Peller, MN Westgate, LB Holmes "Trends in congenital malformations, 1974–1999: Effect of prenatal diagnosis and elective termination" (2004) 104 Obs Gyn 957; KB Schechtman, DL Gray, JD Baty et al "Decision-making for termination of pregnancies with fetal anomalies: Analysis of 53,000 pregnancies" (2002) 99 Obs Gyn 216.
464. ME Norton, S Nakagawa, M Kuppermann "Women's attitudes regarding prenatal testing for a range of congenital disorders of varying severity" (2014) 3 J Clin Med 144 at 145.
465. C Munthe "A New Ethical Landscape of Prenatal Testing: Individualizing Choice to Serve Autonomy and Promote Public Health: A Radical Proposal" (2015) 29 Bioethics 36 at 43.
466. Ibid.
467. Id at 40.
468. Id at 43.
469. Ibid.
470. Id at 44.
471. Ibid.
472. Ibid.
473. Blake Murdoch, Vardit Ravitsky, Ubaka Ogbogu, Sarah Ali-Khan et al "Non-invasive Prenatal Testing and the Unveiling of an Impaired Translation Process" (2017) 39 JOGC 10.
474. Rosemary E. Reiss, Marie Discenza, Judith Foster, Lori Dobson, Louise Wilkins-Haug "Sex chromosome aneuploidy detection by noninvasive prenatal testing: helpful or hazardous?" (2017) 37 Prenatal Diagnosis 515 at 519.
475. Zandra Deans, Stephanie Allen, Lucy Jenkins, Farrah Khawaja and others "Recommended practice for laboratory reporting of non-invasive prenatal testing of trisomies 13, 18 and 21: a consensus opinion" (2017)37 Prenatal Diagnosis 1.
476. Id.
477. Tanja Schlaikjær Hartwig, Louise Ambye, Steen Sørensen and Finn Stener Jørgensen "Discordant non-invasive prenatal testing (NIPT) – a systematic review" (2017) 37 Prenatal Diagnosis 1.
478. HS Cuckle, NJ Wald, RH Lindenbaum "Maternal serum alpha-fetoprotein measurement: a screening test for Down syndrome" (1984) 1 Lancet 926.
479. AR Gregg, BG Skotko, JL Benkendorf et al "Noninvasive prenatal screening for fetal aneuploidy, 2016 update: a position statement of the American College of Medical Genetics and Genomics" (2016) 18 Genet Med 1056.
480. H Greely, "Get Ready for the Flood of Fetal Gene Screening" (2011) 469 Nature 289 at 290.
481. Ibid. "Much of the social impact – and the impact on the medical system – will depend on how widely such testing is used. Some of that will depend on those who fund health care and whether they see this testing as yet another cost or as a way to save money by avoiding the births of high-cost children. Part of the impact will depend on the legal system. If a test is clinically available and a physician does not offer it to a patient, at least in the United States, a physician could be liable through a "wrongful birth" suit for the health costs of a child whose

birth might have been prevented."

482. L Chitty and D Bianchi "Next generation sequencing and the next generation: how genomics is revolutionizing reproduction" (2015) 35 Prenat Diagn 929.
483. NIPD for single gene disorders is limited to conditions inherited paternally or that are de novo (eg Achondroplasia thanatophoric dysplasia and Apert syndrome). Currently NIPD is not offered for conditions that are maternally inherited because if the mother is a gene-carrier there will be a high level of the mutation in the maternal blood.
484. A Mauron "Choosing among possible persons: The ethics of prenatal selection in the postgenomic age" (2015) 338 C R Biologies 566.
485. YM Lo, KC Chan, EZ Chen et al "Maternal Plasma DNA Sequencing Reveals the Genome-Wide Genetic and Mutational Profile of the Fetus" (2010) 2 Sci Translational Med; YM Lo "Non-invasive prenatal testing using massively parallel sequencing of maternal plasma DNA: from molecular karyotyping to fetal whole-genome sequencing" (2013) 27 Reprod BioMed Online 593.
486. AR Gregg, BG Skotko, JL Benkendorf et al "Noninvasive prenatal screening for fetal aneuploidy, 2016 update: a position statement of the American College of Medical Genetics and Genomics" (2016) 18 Genet Med 1056.
487. W Dondorp, G Page-Christiaens, G de Wert "Genomic futures of prenatal screening: ethical reflection" (2016) 89 Clin Gen 531.
488. JRVermeesch, T Voet, K Devriendt "Prenatal and pre-implantation genetic diagnosis" (2016) 17 Nature Rev Genet 643 at 646.
489. RB Lefkowitz, JA Tynan, T Liu et al "Clinical Validation of a Non-Invasive Prenatal Test for Genome-Wide Detection of Fetal Copy Number Variants" (2016) 215 Am J Obs Gyn (2016) 227; AH Yin, CF Peng, X Zhao et al "Noninvasive detection of fetal subchromosomal abnormalities by semiconductor sequencing of maternal plasma DNA" (2015) Proceed Nat'l Acad Sci 14670. The study utilised a "semiconductor-sequencing platform") to perform genome-wide NIPT analysis in the case of structural anomalies detected on ultrasound. The average age of gestation of the study participants was 24 weeks. Researchers were able to detect subchromosomal abnormalities (ie deletions or duplications/CNVs) using DNA from the maternal plasma, although limited to deletions or duplications (>5 Mb) and resulted in a significant false positive rate. Although less accurate than invasive chromosomal microarray testing using fetal DNA, the study demonstrated that sequencing maternal plasma DNA could reliably identify chromosomal deletions and duplications with relatively high resolution, while avoiding the necessity of an invasive procedure. However confirmatory testing (using fetal DNA obtained by invasive testing) was still necessary to identify false-positive results. Researchers consider that, in the future, comprehensive NIPT screening it has the potential to become the prenatal 'standard of care'.
490. Francesco Fiorentino, Sara Bono, Francesca Pizzuti, Sara Duca, Arianna Polverari, Monica Faieta, Marina Baldi, Laura Diano, Francesca Spinella "The clinical utility of genome-wide non invasive prenatal screening" (2017) 37 Prenatal Diagnosis 1.

Chapter Four

A comparator to future NIPT: prenatal microarrays

4.1 Introduction

Reproductive genomics is said to be on the cusp of enormous change. Commentators recently observed (somewhat polemically) that[1]

> … behind the scenes, the contours of a revolution are taking shape. The two main ingredients for this are already present, although still at distinct stages of the screening trajectory: the use of cell-free DNA (cfDNA) from maternal plasma for non-invasive testing for common aneuploidies and the use of high-resolution genomic technologies at the follow-up stage.

Consequently this chapter examines recent developments in prenatal testing following amniocentesis or chorionic villus testing, specifically chromosomal microarray (CMA) technology. CMA essentially enables more extensive tests to be performed at much higher resolution, identifying genomic variants not previously discernable with conventional analysis. Although a significant development, its integration into clinical prenatal practice has not been without challenge. The following section briefly reviews the current prenatal screening and testing landscape, before considering the issues raised by prenatal CMA following amniocentesis.[2]

4.2 The prenatal screening/diagnosis landscape

An increasingly extensive spectrum of prenatal investigations are now available. The individual clinical context may influence the type of screening or diagnostic interventions that a woman and her provider elects to undertake.[3] These include:

a. An otherwise healthy pregnancy, with no red flags or established risk factors.

b. Generic maternal risk for foetal aneuploidy/abnormality, such as AMA.

c. A foetal anomaly identified during routine screening (with/without generic risk factors).

d. A heritable condition identified in the family.

A minority of women who have a routine pregnancy may not wish to undergo prenatal screening. Alternatively, a pregnant woman may undertake either traditional first/second trimester screening or in more recent times may access NIPT on a user-pays basis. Some women who have a high chance of having an aneuploid pregnancy due to age, or who have received an abnormal result following conventional screening, may be offered/recommended NIPT as a second-tier test.

As discussed in the previous section, NIPT is more accurate than traditional testing. It may also screen for additional trisomies as well as sex chromosome anomalies and some microdeletion/duplication syndromes. Nevertheless, some clinicians encourage invasive

procedures such as amniocentesis with high-resolution testing, not only for those women with an elevated risk. Srebniak and colleagues state that:[4]

> patients seeking rapid, reliable and high-resolution diagnostics (rather than a screening test) benefit from invasive prenatal array testing. It has been shown recently by several authors that a pathogenic submicroscopic abnormality is found in 0.5–2% of uneventful pregnancies. The prevalence of submicroscopic pathogenic findings is sufficiently high as to justify invasive sampling.

Some women without any particular risk factors may wish to undertake invasive diagnosis (amniocentesis) to investigate fetal health more fully. Regardless of the indication for invasive diagnosis, it is increasingly claimed that, if undertaking invasive tests, all women should be informed of the option of CMA.

What is Chromosomal Microarray Analysis (CMA)?

CMA is located on a continuum of increasingly sophisticated tests, from conventional karyotyping to whole genome and whole exome sequencing. Briefly, conventional karyotyping of fetal cells obtained by amniocentesis/chorionic villus sampling enables "identification of all numerical and structural chromosome abnormalities that are visible by microscope" (>3-5 Mb)."[5] Such chromosomal deletions or duplications are virtually always linked with intellectual and physical impairment in a child, with varying levels of severity. In comparison, CMA enables significantly more sensitive tests to be performed.[6] CMA identifies both large (5-10 Mb) and sub-microscopic DNA variations (<5 Mb). These sub-microscopic DNA variations are variously referred to as "microdeletions" or "microduplications", or simply "copy number variations".[7]

There are various types of microarrays. Some microarrays target specific areas of a chromosome (e.g. bacterial artificial chromosomes or BAC). Others, such as array comparative genomic hybridization (aCGH) platforms and single nucleotide polymorphism (SNP) arrays[8] may be designed to target specific areas or, alternatively, may cover the entire genome.[9] Significantly, CMA do not detect balanced chromosomal rearrangements, or many mutations responsible for single gene disorders (ie small point mutations).[10]

What are 'Copy Number Variations" (DNA deletions/duplications)?

Recent research indicates that copy number variations play a major role in influencing individual traits. Generally individuals carry two copies of most genes – one inherited maternally and one paternally, although structural alterations in a chromosome can lead to the gain or a loss of one copy of a gene. For example when a fragment of DNA is lost either during copying or when the genes are "shuffled" during meiosis, a deletion may occur or, alternatively a duplication occurs if an additional copy of a gene is gained.

Deletions and duplications involving more than 1,000 nucleotides are called copy number variants (CNVs). The difference in the copy number of a gene can increase or decrease the level of that gene's activity.[11] If a copy of a gene is deleted, the cell may produce less protein, which may contribute to the development of disease/illness.[12]

Because of its increased sensitivity, CMA is more successful at characterising CNVs than conventional karyotyping.[13] A 2014 study that compared CMA with standard karyotyping in 1082 pregnancies with abnormal ultrasound results found that CMA identified clinically relevant CNVs not previously identified by conventional testing in 6% of cases.[14] In the case of women with AMA and/or a "high chance" serum screen but without fetal abnormalities detected on ultrasound, CMA increased detection of clinically significant findings by 1.7%.[15] In this latter group CNVs linked with psychiatric disorders and cognitive impairment were identified in 1:125 pregnancies. These kinds of CNVs occur randomly, and are not associated with maternal age. As a result, commentators suggest that all pregnancies have a 1:125 risk for these kinds of conditions, concluding that "there is no such thing as a low-risk pregnancy!"[16]

Although use of microarrays following invasive diagnostic testing was initially only performed if clinically indicated, its integration into prenatal medicine is increasing. The literature reflects a distinct shift from the traditional screening paradigm involving follow-up invasive testing for anomalous results toward broader testing, with or without identifiable risk indicators. It is possible that prenatal identification of clinically significant CNVs may continue to expand in the future given the number of association studies being conducted. Further, prenatal testing may extend beyond use of CMA.[17]

The following considers the implications of integrating CMA in prenatal diagnostics.

Prenatal microarrays: the range of potential findings?

As already noted, prenatal microarrays are qualitatively different from traditional prenatal screening. CMAs are diagnostic tests that extend beyond common aneuploidies to detecting submicroscopic CNVs. CMA may generate large amounts of genomic information of varying types. Although CMA enables more extensive testing, there are trade-offs associated with increased sensitivity.

Even though a CNV may be directly associated with a specific condition, its severity may be highly variable (variable expressivity). In addition, some CNVs detected will be of uncertain clinical significance. CNVs, which are increasingly being linked with common complex disorders, may be categorised into three groups depending on their health impact as follows:[18]

Benign CNVs: variants that are commonly found in the normal population.

Pathogenic CNVs: one of the recurring genomic conditions that have a well-defined phenotype or a known phenotypic effect.[19]

Unclassified CNV: a variant of unknown significance that cannot be classified as either benign or pathogenic.

Microarrays may be used to scrutinise targeted genomic regions or to undertake broad-scope genome-wide analysis. If untargeted microarray testing is performed following a high-risk screening result, testing is not restricted to the genomic area associated with a suspected anomaly and additional information may be derived. Additional information may fall into any of the following broad categories:[20]

(1) CNVs that cause a well-described and clinically significant anomaly that is not related to the initial indication for which testing was performed i.e. an unexpected diagnosis or "incidental finding";

(2) CNVs that are associated with a condition that has variable expressivity and heterogenous clinical features that, if identified prenatally, have an unquantifiable risk of resulting in a child with an abnormal phenotype (often called "susceptibility loci (SL) for neurodevelopmental disorders"); and

(3) Variants of unknown clinical significance (VOUS).

As a result of the range of potential findings, use of CMA in invasive prenatal diagnosis poses challenges for informed consent, genetic counselling and reproductive decision making. Each of these types of finding is discussed more fully below.

Incidental findings in prenatal CMA

When a particular anomaly or irregularity triggers diagnostic testing, an "incidental finding" is any finding that is not causative of the issue for which prenatal testing is performed. Consequently, if invasive prenatal testing is performed due to an increased chance for trisomy, any other finding may be considered incidental.[21]

However, in cases where there is no specific indicator for testing apart from seeking "reassurance" of fetal health, any finding may be considered "incidental". If a finding is associated with a known condition, it is categorised as clinically significant. Pathogenic or "disease-causing" incidental findings may be further categorised into several subgroups: early-onset diseases that are either treatable or untreatable, and late-onset diseases that are either treatable or untreatable.[22]

There may be considerable uncertainty regarding the potential impact of an incidental finding. Even if there is a known association between a specific gene variant(s) and a particular disease, the *probability* of a disease occurring in an individual may not be known with any degree of accuracy.

Challenging categories

A particularly challenging aspect of microarray testing is the identification of CNVs that are associated with neurodevelopmental disorders. Uncertainty of outcome is pervasive in regard to these types of CNVs which are associated with variable expressivity (the condition may or may not develop) and heterogeneity (a diverse range) of clinical symptoms.

Susceptibility loci for neurodevelopmental disorders

Neurodevelopmental or neurocognitive disorders result from disorders of brain function or the central nervous system. They encompass conditions such as mild intellectual disability, developmental delay, autism spectrum disorders, speech and learning problems, epilepsy, and schizophrenia.[23] CNVs associated with neurodevelopmental disorders have only recently been identified by association studies, although there is clearly still considerable uncertainty associated with these results.[24] Consequently the clinical significance of these types of CNVs, and whether or not to report them, is debated.

Because many CNVs are not fully penetrant, the likelihood that the condition will occur in the individual will vary according to multiple factors, such as the interaction of other genes or environmental factors. These types of CNVs are best described as "susceptibility loci" (SL). Significantly they and are found in 1-3% of pregnancies tested prenatally.[25] SL may be seen in healthy parents and healthy controls. Consequently, SL pose significant challenges for providers and patients. The following illustrates the diversity of clinical responses to prenatally identified SL:[26]

> Although there are guidelines[27] and such findings may be classified as pathogenic[28], some classify such CNVs as VOUS.[29] The phenotypes of SL carriers seems to vary from normal to severely affected and the phenotypes of control individuals carrying SL were shown recently to be intermediate between affected carriers and non-carrier control individuals[30], so the presence of an abnormal phenotype seems to be dependent on a 'second hit'.[31] Nevertheless, the classification of such findings seems to be controversial and there is no internationally recognized policy regarding whether to report them. [32]

Evidence suggests that SL associated with neurodevelopmental disorders are identified more often in fetuses with ultrasound abnormalities, compared with those with normal ultrasounds (3.6% vs 0.8%[33] and 1.4% vs 0.55%).[34] Despite this association, the risk of developing a particular neurodevelopmental condition is still largely indeterminate[35] and the prognosis for a fetus is uncertain.[36] Determining the implications of a SL in the prenatal context is particularly difficult:[37]

> As increasing numbers of cases and controls are studied for CNVs, we are discovering many additional examples of these "predisposing," or "susceptibility," loci. Microarray analysis is now recommended as a first-tier test for many pediatric neurodevelopmental disorders … as the use of microarrays in prenatal settings increases, fetuses without a known family history of these CNVs will be identified as carriers. This can lead to counseling dilemmas and parental anxiety, especially in low-risk pregnancies, because the associated neurodevelopmental phenotypes cannot be ascertained prenatally and it is difficult to quantify the risk to the fetus.

As a result, some clinicians suggest a cautious approach to returning SL results, taking into account any accompanying ultrasound anomalies and/or a family history of developmental disorder.

Specifically, a group of Belgian practitioners recently formulated professional guidelines, recommending that any decision to return a SL result should be assessed in conjunction with the ultrasound scan and family history. Given that there is likely to be less risk if the variant is inherited from a parent who has not developed the condition, the authors observe:[38]

> Theoretically the possible pathogenicity of these variants can be influenced by the presence of a second CNV or ethnic background, but sound data is lacking to date. In most cases, it will remain difficult, if not impossible, to determine whether the child will have manifestations and to provide reliable risk figures for clinically significant manifestations or on the severity of manifestations. As such, no practical information can be given during counselling with the consequence of putting parents in a moral dilemma (so-called toxic knowledge). For all these reasons, it was decided not to report these variants.

The rationale given for not reporting SL is based on research conducted by Barbara Bernhardt et al who adopted the metaphor of "toxic" information to describe how some women experienced receiving information that was of uncertain significance.[39] However, the Belgian guidelines identify seven specific CNVs that are associated with a high risk of a severe disorder and/or are associated with a structural malformation detectable by ultrasound that they advise may be returned to a woman if it is expected to influence the management of the pregnancy. Nevertheless, not all SL are reported to prospective parents by the Belgian group, which they consider may court some medico-legal risk:[40]

> … it remains an open question what our legal position would be in case a child in whom a susceptibility factor for autism was not returned is later diagnosed with autism. However, we feel that potential legal implications should not be the only determinant of what we consider good clinical practice.

In this context, the clinical view of what constitutes "good clinical practice" is influenced by the degree of risk and severity associated with the condition, the presence or absence of a family history of the condition, and whether there is a co-existing structural anomaly present in the fetus.

Not all clinicians adopt the same approach to reporting SL to prospective parents, as illustrated by a Dutch group of clinicians and researchers.[41] They sought to evaluate pregnancy outcomes after prenatal detection of an SL, reviewing 4043 cases where prenatal (SNP) microarrays were performed following invasive testing. Some, but not all, of the women presenting for invasive diagnosis had anomalies detected on fetal ultrasound. Each patient received pre-test counselling and had the option to decline disclosure of a SL if it was detected, with some patients taking up the option of non-disclosure for this category of finding.

Out of the 4043 cases, 59 SL were detected in 57 fetuses (1.4%). The protocol required the laboratory to report the results to a clinical geneticist, who was responsible for discussing the results with the referring clinician and the prospective parents.

When a SL was detected, the clinical geneticist informed the patient immediately regarding the nature of the finding and offered an appointment for counselling. Post-test

counselling involved explaining the (unquantifiable) risk of the future child developing neurodevelopmental problems such as autism, hypotonia, or mild intellectual disability.[42] Case reports from the literature were made available to the patients, as well as patient leaflets provided that were sourced from the website "Unique".[43] Counselling also included the reasons why the SL was considered actionable during pregnancy (i.e. because it might result in additional ultrasound scanning for any "missed" anomalies) or actionable after birth (i.e. early intervention if symptoms emerge). Testing was also offered to parents, some of whom subsequently self-identified their own symptoms.

While the authors noted that abnormal prenatal results with unclear outcomes are not a new issue in prenatal diagnosis, they emphasised the importance of post-test counselling being provided to patients by an experienced clinical geneticist. They stated:[44]

> All geneticists involved in prenatal counseling in our team already had experience in this type of posttest counseling. Our experience is in agreement with Rooryck and colleagues,[45] who reported that if the posttest counseling is carried out by an experienced clinical geneticist, most patients understand the variability of clinical phenotypes and are able to cope with it. We did not observe panic reactions or pregnancy terminations exclusively because of SL disclosure as suggested before.[46] In our cohort, two pregnancies (case 35 and 36) without ultrasound anomalies were terminated after releasing information about SL. However, in these cases, the SL was only one of factors contributing to the decision of termination. In both cases the patients had already high anxiety about the pregnancy and were already considering TOP.

The authors reported that out of 34 cases with SL that also had anomalies on ultrasound, 8 opted for termination of pregnancy. The authors specifically noted that the presence and the anomalies detected on ultrasound "is one of the most important factors that influences decisions on pregnancy termination", with the presence of an SL less of a factor.[47]

For this group of clinicians, the boundary marker for reporting results to parents was informed consent and prenatal and postnatal "actionability". It was reported that patients generally elected to be informed of the presence of an SL if detected. However the clinicians also noted that providing pretest information regarding the possibility of a SL and the choice whether or not to receive such a result (ie an option for non-disclosure) was also vital.

Susceptibility to psychiatric illness

Although there is no single genetic determinant for psychiatric illness, the extent of the genetic contribution to its development is also under widespread study.[48] The Psychiatric Genomics Consortium (PGC), consisting of collaborators from over 80 institutions, recently reported it had identified 108 genetic locations at which the DNA sequence of individuals diagnosed with schizophrenia generally differed from the DNA sequence of individuals without schizophrenia.[49] While many of the variations discovered are common, people with schizophrenia were found to have more of them, with each

contributing to the overall risk of developing the illness.[50] Significantly, the researchers developed an algorithm to calculate a score for the relative risk that each variant contributed to schizophrenia.

Given that some of these conditions may be more prevalent in some families, prospective parents may seek reproductive genetic counselling. A Canadian specialist genetic counselling service emphasises the current (limited) contribution genetics makes to the development of psychiatric illness, and that genetic tests cannot currently confirm or refine a psychiatric diagnosis:[51]

> **Testing for single nucleotide polymorphisms:** Though it is likely that we have yet to identify all single nucleotide polymorphisms (SNPs) that are associated with psychiatric illness, there are many that have already been described.[52] SNPs can be detected using strategies including next-generation sequencing methods and panel-based testing. Typically, each SNP individually confers only a very small contribution to vulnerability to psychiatric illness, so testing for single variants of this kind is of minimal clinical utility. However, the derivation of polygenic risk scores (combining information for many associated SNPs) for psychiatric disorders is an area of increasing interest.[53] At present, these approaches have predictive values comparable to analysis of a detailed three-generation psychiatric family history, but ultimately, as and when they surpass this threshold, may be used more clinically.

When done pre-symptomatically the most a genetic test can provide is probabilistic, not definitive, information:[54]

> **… Testing for copy number variations:** Several copy number variations (CNVs) have been identified that can contribute to development of psychiatric disorders,[55] and they can be detected using different techniques including chromosomal microarray and next generation sequencing methods. However, no CNV has yet been identified that directly causes psychiatric illness in a fully penetrant manner.[56] For example, 22q11.2 deletion syndrome carries one of the highest likelihood ratios of developing some form of psychiatric illness[57], including an ~30% chance of schizophrenia spectrum disorders, but even for this CNV, penetrance for psychiatric disorders seems to be incomplete.[58] Cumulatively, CNVs are common in the population and are not necessarily pathogenic; thus, the relevance to the aetiology of psychiatric illness of most that can be detected is uncertain.

The incidence of 22q11.2 deletion, which mostly occurs randomly as a *de novo* event, may be up to 1 in 1000 pregnancies.[59] As well as being associated with a range of physical anomalies detectable on ultrasound, presence of the deletion may also increase the risk of maternal and fetal complications, such as intrauterine growth retardation and prematurity. Although predicting cognitive or neuropsychiatric outcomes in individuals

is not possible, there is emerging evidence that in the case of 22q11.2DS, there is a clinically significant increase risk of schizophrenia in adolescence/early adulthood associated with preterm birth (<37 weeks).[60]

To summarise, an increasing number of "susceptibility loci" have been discovered that predispose an individual to developing a neurodevelopmental disorder (such as autism) or neuropsychiatric illness (e.g. schizophrenia). Theoretically these susceptibility loci may be identified prenatally. Some parents may wish to be made aware of a SL, particularly if there is a family history of the condition as it may influence their reproductive or parental decision-making.[61] However the risk of developing, and the severity of a condition associated with a SL varies, and is influenced by other genetic and environmental factors.

There is no common approach to testing or reporting SL, indeed even classification of these kinds of variants differ: while some classify them as SL, others classify them as variants of unknown significance (VOUS). Although there is no consensus, some clinical guidelines recommend that SL are not disclosed to prospective parents because of the lack of predictive certainty, unless there are exceptional circumstances such as a familial history of a neurodevelopmental or neuropsychiatric condition or co-existing structural anomalies detected on ultrasound.

It is uncertain what the legal duty of care requires when a SL is identified.[62] If it is not disclosed to the parent and a child subsequently develops a condition like autism, it could be claimed that the parents lost a chance to institute neurodevelopmental treatment/intervention at the earliest opportunity after the child was born.[63] Alternatively it could be claimed that the parents lost a chance not to continue the pregnancy.

In the medico-legal context, the standard of information provision that is legally required to be provided to a patient is the information that a reasonable person, in that person's circumstances, would expect to receive. Given the lack of predictive capacity associated with SL and that the age of onset and severity of these complex conditions are highly variable, it is difficult to intuit what a reasonable person would expect to be told in this context. It could be argued that the risks of providing information may be skewed against disclosure, although this may be considered paternalistic. However, if there is a family history of a condition such as autism there would be more scope to claim that a reasonable person in that situation would expect to receive that information.[64] Ultimately providing information regarding the potential for a SL to be identified in pre-test counseling, with the option to decline to receive those results, is most conducive to promoting and respecting individual patient autonomy, provided the information is provided in conjunction with access to genetic counselling.

Variants of Unknown Significance (VOUS)

CMA may identify gene variant(s) that are not yet identified in the genomics literature or in databases (such as ClinGen or DECIPHER) and have unknown health implications.[65] So-called Variants of Uncertain Significance (VOUS) are discovered in around 2% of prenatal CMAs.[66] It is unclear how clinicians and prospective parents respond to such information. Given the absence of standardised guidelines there is a range professional approaches to VOUS:[67]

As whole genome arrays with higher resolution are designed, more findings of uncertain clinical significance will be identified.[68] This has led to the suggestion that these not be reported to the patient.[69] Others have found this approach too paternalistic and believe that with counseling, patients are capable of understanding uncertain or inconclusive results. Alternatively, as part of the pretest counseling and consent process, patients choose whether they wish to be made aware of uncertain laboratory results. At present, there is no consensus on the best approach or practice guidelines.

While some health care providers are reluctant to report prenatal VOUS,[70] empirical data suggests that patients (at least initially) wish to be informed of any clinically relevant incidental findings as well as VOUS.[71]

Research also indicates that some women may consider termination on the assumption that a VOUS is deleterious, which is concerning in the case of a wanted pregnancy when the variant may have not have any effect.[72] Clearly access to genetic counselling is important to ensure sufficient understanding when VOUS are returned to prospective parents.

As genomic testing becomes more integrated among the general population, more individuals will become aware of their genetic make-up, including any VOUS they may carry. This is already having an impact on the reproductive decision-making context, where some prospective parents may consider undertaking preimplantation genetic diagnosis following the diagnosis of a VOUS in a parent or sibling with an undiagnosed illness or syndrome.

VOUS and reproductive "risk-reduction": a new indication?

At least one case report involves two couples in Israel who considered undertaking PGD after a VOUS was diagnosed in one of the immediate family members.[73]

One case involved a man with a familial history of Lynch syndrome (a familial colorectal cancer syndrome) who had undertaken whole exome sequencing, which revealed that he carried a MLH1 missense variant. Although the variant was not previously reported to be pathogenic, algorithms predicted that it could be damaging. After further analysis of the family it was determined that there was a high probability that the variant was associated with the gastrointestinal cancers developed by the family and PGD was provided.

In another case a couple requested PGD after their daughter, who had pervasive developmental disorder and intellectual disability, was found to have a microduplication (chr:Xp.22.3) and a microdeletion (chr:17q21.31). In this case PGD was declined, as the maternally inherited X-linked microduplication was also present in the mother's healthy brother and daughter, and the chr17 microdeletion was a *de-novo* (spontaneous) event and therefore unlikely to be causative of the condition. PGD in this context would have been unnecessary.

A new reproductive era?

It is well established that CMA has greater capacity to detect fetal genetic anomalies than traditional testing. A 2016 review cites evidence that CMA increases detection of disease-causing copy number variants (CNVs) results by 6-8% compared with traditional testing following an abnormal ultrasound and, in cases with normal ultrasounds, CMA increases detection rates of CNVs by 1-2%.[74] Given this increased diagnostic "yield", the authors conclude "there is a general consensus that chromosomal microarrays should be the first-tier cytogenetic test for prenatal diagnosis".[75]

Internationally genetics services have introduced CMA into invasive prenatal testing cascades when anomalies have been discovered on routine serum or ultrasound screening. However CMA may not necessarily be limited to elevated risk. There is now support for expanding the offer of CMA to *all* patients who choose to undergo invasive testing in the general obstetric literature because CMA may identify pathogenic anomalies in otherwise apparently healthy pregnancies:[76]

> For patients of any age with a normal ultrasound and karyotype, the chance of a pathogenic copy number variant is greater than 1%, similar to the age-related risk of aneuploidy in the fetus of a 38 year old. This risk is 4-fold higher than the risk of trisomy 21 in a woman younger than 30 years and 5- to 10-fold higher than the present accepted risk of a diagnostic procedure. Based on this, we contend that every patient, regardless of her age, be educated about these risks and offered the opportunity to have a diagnostic procedure with array comparative genomic hybridization performed.

Over the last few years, professional organisations have begun to recommend routine CMA whenever invasive diagnostic testing is performed.

International integration of CMA

In 2013 the American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine initially recommended that CMA be deployed as a first tier prenatal cytogenomic test for pregnancies with one or more major fetal structural abnormalities identified on ultrasound.[77] The ACOG now recommends that CMA is considered for any woman undergoing an invasive procedure for any reason, including women carrying "structurally normal" fetuses.[78]

Eight clinics in Belgium routinely use CMA when performing invasive PNT for any indication, not just in the case of abnormal ultrasounds or screening results, but also to provide reassurance of fetal health.[79] Ultimately it appears that we are entering a new era of prenatal genomics where, according to one narrative, there is no such thing as a low-risk pregnancy. This is an era of more sensitive tests and as a result increased risks/uncertainty. Borrowing social scientist Anthony Giddens terminology, this new era of genomics is one of generated, or "manufactured", uncertainty/risk'.[80] This extended genomic capacity may have both positive and negative repercussions for the individuals involved.

Although CMA is increasingly being used in the prenatal context and will likely become a first-tier test for invasive prenatal testing in the future,[81] its merits have been debated. Although CMA provides significantly more genetic information, not all of the implications of this information are well understood, nor will it necessarily be experienced as helpful by prospective parents.[82] Reminiscent of the way in which amniocentesis changed the experience of pregnancy when it was first introduced,[83] it seems that the narrative of pregnancy may be changing once again.

As a result of genomic advances, pregnancies are likely to be subject to more genetic analysis/risk surveillance. While this may be welcomed by some (perhaps even the majority of) women/prospective parents, it is associated with a risk of receiving a range of genetic information, some of which will be probabilistic or of uncertain significance. Prospective parents may be presented with information not previously available and will have to consider how it is relevant for them and their prospective child.

4.3 How do prospective parents experience and navigate CMA testing?

Research regarding womens' experience of expanded testing using CMA is only now emerging, although there is considerable evidence of womens' experience of receiving an abnormal prenatal screen.

Currently many women undergoing invasive diagnosis by amniocentesis do so after receiving an abnormal prenatal test result or in the case of elevated risk. Research indicates that prospective parents can experience a range of emotions such as anxiety, grief, hopelessness, guilt and anger following prenatal diagnosis of a fetal anomaly.[84] Indeed some studies suggest that psychological distress, including posttraumatic stress, depression, and anxiety are common in this context.[85] The distress experienced may be influenced by the gestational age when the finding is made, the severity of the anomaly (actual or potential), and uncertainty regarding the diagnosis and/or prognosis.[86] Prospective parents may face decisional conflict, between continuing a wanted pregnancy and concerns regarding the potential birth/quality of life of a child with additional and potentially complex needs.[87]

CMA is not only offered when a fetal anomaly has been detected on ultrasound but "is being used increasingly for other indications, including advanced maternal age, increased risk after maternal serum marker screening, and maternal anxiety."[88]

Although there are few studies regarding the uptake of prenatal CMA, some studies suggest that the majority of women at increased risk choose to undertake CMA in addition to conventional testing. In one such study, 45 out of 53 high-risk couples chose to undergo amniocentesis following genetic counselling, with 73% choosing to undergo CMA to enable more extensive testing.[89] Reasons given by those who declined CMA included a fear of increased anxiety when waiting for results or because the conditions were considered rare.

A recently published Dutch study also provides some evidence that, if given a choice, women/couples at increased risk of aneuploidy in pregnancy are more likely to choose screening or invasive testing using high-resolution micro arrays, rather than lower resolution arrays that are comparable to conventional chromosome analysis.[90]

The study examined 82 couples undergoing PNS and 59 undertaking invasive PND. The majority of participants in each group (94% of PND and 69% of PNS group) preferred the high-resolution arrays because they identified more pathogenic variants. Some of the participants, but more of those in the PND group, also chose to be informed of results indicating susceptibility for neurodevelopmental disorder (84% of PND and 44% of PNS group). The authors observed that "pregnant couples value information to the extent that they are willing to bear the uncertainty caused by SL".[91] However, none of the participants received a SL result, consequently it was uncertain how couples would experience and navigate such a result.

Significantly, the study suggests that the desire for additional fetal health information was not restricted to those undergoing invasive diagnostic testing. Further, most couples wished to determine for themselves the scope of testing and subsequent information disclosure (79%).[92] The authors subsequently concluded that it "seems justified" to offer women a choice in both the resolution of array and disclosure of SL when undergoing PND.

The clinicians emphasized the need to obtain consensus in classifying and reporting gene variants to prospective parents, ultimately favouring a model of individualised choice stating:[93]

> Therefore, we should discuss not whether to implement array, but rather how to deal with the difficulties: how to improve the classification and interpretation of findings and how to achieve consensus in reporting VOUS, SL and late-onset (un)treatable disorders if encountered unexpectedly. It is the responsibility of all specialists in clinical genetics to ensure detection of pathogenic findings without violating patients' (and their future children's) autonomy and their right 'not to know', and without causing future stigma and discrimination. We are only one step away from next-generation sequencing in prenatal clinics.

Ultimately recent research suggests that although most prenatal CMA results will be normal, between 1.6 and 6% of cases will identify a CNV of "known or probable clinical significance" that would not have been identified in conventional testing.[94] CMA findings also frequently encompass disorders that are less severe or have more variable phenotypes.

Few social science studies of CMA have been published, although a 2013 study by Bernhardt and colleagues provided important insights into women's experiences of prenatal CMA.[95] The researchers recruited 23 women who were undergoing amniocentesis or chorionic villus sampling following an abnormal ultrasound/prenatal screening result or due to AMA who were offered CMA in addition to traditional testing. The 23 participants who underwent traditional testing were invited to undertake further

CMA designed to detect more than 80 known deletion/duplication syndromes.[96] Any result considered potentially clinically relevant was reported to the participants, but CNVs classified as likely benign were not.

The authors followed up all of the women that had received abnormal results exploring: the women's reasons for undertaking prenatal testing and enrolling in the study; their understanding of CMA; the process of receiving results and subsequent decision making; and their emotional responses and needs during that time. They identified five key themes that "dominated" the women's experiences of the research.

The women's reasoning process was essentially that once they had made the decision to undertake invasive fetal testing, there seemed to be no reason not to undertake CMA. Essentially the opportunity to access broader testing seemed too good to pass up. However, some women who received normal results following conventional chromosome testing but subsequently received the abnormal CMA results reported being "blindsided" by the later results. This suggests that the women did not appreciate the increased sensitivity of CMA compared with conventional testing, or alternatively, assumed that they would be in the group that not receive an abnormal result. A pragmatic solution to this issue could be to return all of the results at the same time.

A positive aspect of CMA for some participants was that it definitively identified the genetic cause of a fetal structural anomaly that had been identified on ultrasound. Being able to confirm the presence of a genetic anomaly assisted in any decision to continue or terminate a pregnancy.[97]

Significantly most of the women who participated in the study were unaware that some information derived by CMA would be uninterpretable. This highlights the range of informational deficits that can occur with new tests. For some, this "unknown" was referred to as "toxic" knowledge because it caused them to worry about their baby's health, anxiety which lasted after the birth of their child.[98]

Some of the women who received abnormal results reported that they were left confused by variants that were of uncertain significance, or the risks unquantifiable. The authors noted that the difficulty of reproductive decision-making was compounded when CMA returned a VOUS and information regarding the associated effect on phenotype was limited or absent. As explained in the following quote this is made more difficult in the prenatal setting than the postnatal: [99]

> Unlike the postnatal situation in which microarray testing is ordered to explain a child's phenotype, these women were not able to interpret the findings in light of their child's observable health and development. Both the phenotypic range associated with many CNVs, and the lack of precise probability of a medical issue being present challenged a woman's ability to imagine how her child might be affected. Although some uncertainty associated with prenatal microarray testing could be reduced by the use of targeted arrays,[100] uncertainty will still remain because of the variability of phenotype of even well-described conditions such as the 22q11.2 microdeletion syndrome.[101] In our study, among the six

> women whose fetuses were diagnosed with deletions involving the DiGeorge region, two chose to terminate and four continued their pregnancies. Most of these women described their decision making as tortured, and women continuing their pregnancies experienced considerable uncertainty about the development of their child after delivery.

Clearly even in cases where disorders could be well described such as the 22q11.2 deletion syndrome, its variable severity made decision-making difficult. The lack of time to decide whether to continue a pregnancy also increased the stress that some of the women experienced. Significantly, several women who continued their pregnancies following identification of 22q11.2 microdeletion syndrome reported that their providers were not supportive of their decision. Despite this, only two of six couples elected to terminate the pregnancy. It is interesting to consider whether, if the same condition was identified in an ex vivo embryo, the same woman would have chosen to transfer the embryo and, if so, whether clinicians would facilitate her choice. Ironically women are likely to have greater control over their reproductive decisions when already pregnant, compared with women undergoing PGD.

In some cases, testing indicated that one of the parents was an unknown carrier of a chromosomal deletion or duplication identified in the fetus, which generated different responses in the participants. On one hand, some parents considered that it provided a reassuring indication that the foetus would be unaffected and some were relieved by this (although evidence suggests that a child may nevertheless develop the condition). However other parents felt "pathologised" because they found out that they carried a genetic anomaly that, in some individuals manifests as a physical or intellectual abnormality. Some of the themes found in the Bernhardt study have been replicated in other research.

A UK study exploring the experiences of twenty-five pregnant women with a fetal abnormality detected on ultrasound who subsequently underwent traditional karyotyping as well as CMA found that VOUS presented challenges for clinicians and participants.[102] However identification of a VOUS did not result in any terminations of pregnancy.[103] Three of the participants reported that, after receiving normal test results following traditional testing, they were not emotionally prepared for receiving abnormal CMA results—again suggesting that they may not have understood the difference between the tests or assumed they would not be in the group that received a positive result. Indeed, the authors observed that[104]

> women and their partners struggle to recall the details of genetic testing and the differences between genetic tests. Often women have only just had a diagnosis of an abnormal scan and under stressful circumstances it is unsurprising that little information is retained.

Another more recent study conducted in the US involved 29 women (and their 12 male partners) who received positive CMA results.[105] The authors found that in general women understood the nature and implications of CMA results, while men were less well informed. The authors outlined the reasoning process that the participants adopted and how they navigated a positive result:[106]

> After participants received positive CMA results and collected information, they assessed the extent to which they felt capable of parenting a child with phenotypic involvement. They imagined the best and worst case outcomes, personal values, as well as their expectations, capabilities, and limitations as parents, to make decisions about pregnancy termination. In light of this highly individualized process and the limited window to terminate, an accurate understanding of risk is vital. Consistent with previous research, participants who believed they had resources to identify and manage problems early were more confident in proceeding with their pregnancy.

This extract highlights the social justice aspect of reproductive choice, where access to resources influenced decision making regarding continuing or terminating a pregnancy. Given the complexities of genomic testing, CMA not only requires adequate information provision and counseling, but also a process for managing and reporting the information derived from tests.

4.4 Approaches to reporting prenatal CMA results

Currently there is no consensus regarding how, and when, prenatal CMA should be implemented or the kinds of arrays used. Some professional groups and institutional bodies have formulated policies governing classification, interpretation and reporting of CMA results. Theoretically all test results could be returned, although there is little evidence if this approach. Reporting results is subject to various professional practices that are broadly outlined in the following categories.

A restricted parental choice model

A group of Dutch physicians have formulated a consent form that permits a woman to choose what information she receives following testing from four categories:[107]

(1) only outcomes that explain the ultrasound abnormality or also

(2) findings likely to lead to health effects early in life,

(3) findings likely to lead to health effects later in life, and/or

(4) findings likely to affect their own health."

This approach permits prospective parents to elect to receive clinically significant results, including later-onset conditions. It also enables disclosure of information that may have significance for the parent's health. Significantly, it enables a woman to limit the extent of information that she receives. The underlying value informing this model is respect for reproductive liberty.

Return of results according to the likelihood of pathogenicity

An alternative approach is for clinicians to prospectively determine the range of results that are mandatorily reported to prospective parents. This model is exemplified by a Belgian group encompassing eight medical diagnostic laboratories that formulated a national consensus regarding the classification and reporting of prenatal CMA results.[108] Patients receive an information leaflet prior to testing which includes a description of the results that would be returned and those that are not returned—which is not subject to parental choice.[109]

When determining what variants should be routinely reported, the group drew on the ACMG's list of mandatory tests formulated in the context of clinical genomic testing. The ACMG recommend that in the case of "clinically indicated" whole genome/exome sequencing in both paediatric and adult patient populations, genomic tests should include analysis of 56 specified genes that are causative of 30 conditions. These conditions include cancer predisposition syndromes, as well as genetic vascular and heart syndromes, some of which are late-onset. All of these conditions have actionable interventions with early detection, but are not currently subject to population screening.[110] As discussed previously in Chapter 1, this list is controversial because of its mandatory nature, but even more so in the prenatal context. Although the ACMG extended its recommendations to testing performed in the paediatric context, it expressly did not include prenatal testing.[111]

As well as routinely reporting genes on the ACMG list, the Belgian group also returns some CNVs. Unclassified variants of uncertain significance, or risk loci that are associated with uncertain penetrance or variable expression, are not routinely reported.[112]

The Belgian consensus, which requires mandatory return of results including late onset conditions contained on the ACMG list[113] is controversial given that it does not take into account the parents' wishes regarding the kinds of incidental findings that are reported.[114] Applying this approach in the prenatal context has been criticised:[115]

> … in prenatal and pediatric settings, this may lead to severe ethical and psychosocial implications, especially because some findings may lead to future discrimination of individuals known to carry late-onset diseases (both treatable and untreatable), and thereby undermine the child's rights. The decision 'to report or not to report' seems to be highly individual and the majority (~80%) of genetic counselors and geneticists believe that the parents should be given a choice as to what kinds of unexpected diagnoses are returned to them, after extensive pretest (or even preconception) counseling. Since many genetic diseases are very rare, an appropriate balance between informing about all possibilities and preventing unnecessary anxiety in the future parents has to be found.

The value informing the Belgian approach is one of pure clinical utility; if the prognosis of an early or late-onset condition may be improved by preventive measures or early treatment, it is reported. The Belgian group departs from the traditional approach to predictive testing of minors, that recommend against testing for late-onset disorders. The reason for this is because "the information may be important for the parent and other family members in case of an inherited CNV, which lead us to conclude that the parents should be informed about these results." However predictive testing for untreatable late-onset disorders, such as Alzheimer disease or CADASIL is only offered if there is a family history and following counselling.

Significantly, parents are required to receive incidental findings that are not necessarily relevant to the indication for which testing is performed, and includes both early and late-onset conditions. Patients are informed that the test results are interpreted by reference to the currently available scientific knowledge—but that the current information may be subject to change as genomic associations become increasingly better understood.[116]

In the United Kingdom, the Joint Committee on Genomics in Medicine recently released recommendations governing the use of microarrays in pregnancy.[117] The Joint Committee is comprised of members representing the Royal College of Physicians, the Royal College of Pathologists and the British Society of Genetic Medicine with members representing the Public Health Genomics Foundation, the Royal College of Obstetricians and Gynaecologists, British Maternal and Fetal Medicine Society and the Genetic Alliance.

In broad terms the Committee recommends that a variant be reported if it "will potentially inform the management of the pregnancy, or of the family, in the clinical context in which CMA was done or in the future". Although this refers to pathogenic variants related to the indication for CMA, it specifically states that it may also encompass:

- neuro-susceptibility loci that have a high penetrance and are associated with a risk of a severe phenotype; (ie associated with severe neurodevelopmental, psychiatric or cognitive impairment)
- neuro-susceptibility loci that are associated with an increased incidence of anomalies that are detectable by ultrasound scan to enable further scanning;
- unsolicited (or incidental) pathogenic findings that fulfil the "above criteria" e.g. a known cancer predisposition gene such as *BRCA1*.

The Committee also states that when reporting a clinically actionable pathogenic incidental finding, it should be made clear that the finding is not associated with the presenting problem, but genetic counselling should be considered when appropriate. Significantly it does not allude to any patient choice in respect of what results are reported, although this may be implicit by reference to returning results that may inform the management of the pregnancy.

The Joint Committee recommend that *incidental* findings not associated with a potential condition in the future child or that have no clinical actionability for that child or its family in the future should not be reported. This precludes reporting a VOUS that is not linked to a potential phenotype, or low penetrance neuro-susceptibility loci, as well as non-treatable incidental pathogenic variants.[118] The Committee provides a list of reportable and non-reportable variants.[119] The Committee have also appointed an expert advisory group to advise in individual cases on variants that have uncertain pathogenicity, comprised of 2 scientists and 2 clinicians.

4.5 New Zealand: Professional Guidelines

Prenatal chromosomal microarray technology has been integrated into New Zealand and Australian maternal fetal medicine services over the last few years.[120] In 2016 the Human Genetics Society of Australasia and the Royal Australian and New Zealand College of Obstetricians and Gynecologists released a joint Committee Statement outlining professional guidelines, including recommendations for CMA, entitled *Prenatal screening and diagnosis of chromosomal and genetic abnormalities in the fetus in pregnancy*.[121]

The Committee Statement recommends CMA as a "first tier" chromosome test when a structural fetal abnormality has been identified on ultrasound. [122] It also notes that CMA identifies a greater number of pathological chromosomal anomalies in the case of a normal ultrasound. However, it specifically acknowledges that:[123]

> The diagnostic advantage of microarray is tempered by the fact that microarray can detect variants of uncertain significance that may cause genetic counselling dilemmas and patient concern and distress.[124] The test therefore should only be offered in the context of pre-test and post-test counselling, especially when fetal ultrasound is normal. Patients who receive abnormal or uncertain microarray results should have access to a formal genetic counselling service staffed by genetic counsellors and/ or clinical geneticists.

The statement notes that CMA identifies both large (5-11 Mb) and sub-microscopic (<5-10Mb) variations, but does not identify most single gene disorders or balanced chromosomal rearrangements.[125] Further it provides that laboratories should be accredited, need appropriately trained staff to analyse and report microarray data, and have access to a clinical geneticist to assist with interpreting/reporting rare or complex findings.[126] Currently three laboratories in New Zealand provide prenatal CMA, and all use the same reporting criteria.[127]

There is little empirical research available regarding the integration of CMA in Australia and New Zealand. An exception is one Australian study that investigated the utility of high resolution microarrays to assist in diagnosing pregnancies with abnormalities detected on ultrasound.[128] The study involved 107 women who had abnormal fetal ultrasounds who underwent CMA. Of 107 pregnancies, 7 fetuses were diagnosed with a CNV of uncertain significance, and 10 with a pathogenic CNV. Significantly the authors reported that, in regard to the impact of CMA on reproductive decision making[129]

> It has been our experience that a pregnant woman's decision to terminate a pregnancy is often based on the severity of the ultrasound-detected abnormality and not on the results of the microarray alone. Concerns about microarray technology causing unnecessary anxiety with regrets for late termination of a potentially normal fetus were not supported in this study.

This observation is significant given concerns that CMA may increase termination rates. Although one couple terminated a pregnancy where there was a 90-95% "assurance of a normal pregnancy outcome", the authors observed that "this is in keeping with the spectrum of decision-making following genetic counselling of uncertain findings".[130]

Although only one small study, it reaffirms that a main indicator for pregnancy termination in the case of fetal abnormality is the severity of the condition identified. Anecdotally it has been observed that a significant number of NZ women who have indicators for invasive diagnostics and CMA decline invasive testing.[131]

4.6 Discussion: clinical, ethical and legal implications

Although prenatal diagnosis is an accepted part of prenatal care, CMA raises additional issues. CMA is increasingly being implemented in invasive diagnostic testing for pregnancies with ultrasound abnormalities, as well as in the case of pregnancies at elevated risk of aneuploidy. Adopting expanded, untargeted testing is driven by several reasons:[132]

> In sum, the thrust of these debates and developments is toward wider testing at the follow-up stage, partly reflecting the fact that targeted testing may not always suffice to find a diagnosis, but partly also as a deliberate move to use what is formally diagnosis as a platform for broad-scope screening for clinically relevant abnormalities that would otherwise go undetected. Although this may as well be driven by scientific interests, the implicit justification seems that not using the opportunity to find more abnormalities rather than less amounts to providing suboptimal care to women who have already agreed to prenatal testing.

It is clear that CMA has progressed through various stages of its technological career: it is no longer a research-based innovation, and is now approximating the required "standard of care". As such it is a "game changer", potentially transforming invasive prenatal diagnosis to identify a suspected foetal anomaly to a multi-purpose diagnostic/screening tool.

Genome-wide (non-targeted) CMA conflates diagnosis and screening, normally two distinct endeavours. Screening programmes are generally population-based and each condition is subject to risk-benefit analyses derived from the Wilson and Jungner principles, which is not the case with CMA. CMA identifies a range of conditions that may be of variable severity, may be early-onset or late-onset, and some of which may only have a statistical likelihood of actually occurring rather than a certainty. Some findings may be associated with physical, cognitive, or psychiatric conditions.

Scholars who frequently contribute ethical commentaries on the implications of expanded genomics suggest two disadvantages associated with opportunistic screening in CMA. First it may pose a "screening trap" for women who are insufficiently informed of the nature of CMA and result in outcomes for which the woman is unprepared.[133] Alternatively, they suggest that it may create inequity as women who don't undergo invasive testing are effectively 'excluded from access to this further round of screening",[134] a concern that presupposes that expanded genomic screening is, and will be perceived by women as, a beneficial procedure. When considering expanded screening, an important preliminary question is what women information women want, and why they value that information. As Hewson observes, current information is limited in this respect:[135]

> Do we know what conditions women in the general population would like to be tested for? Test uptake rates – and termination rates – are known to differ between conditions *for which testing is currently available and permitted*, but since real tests for specific conditions are only offered in specific – and highly variable – circumstances, like-with-like comparisons of actual uptake figures cannot be interpreted with any confidence.

In summary, there are several themes apparent in the literature on CMA. The first is the assumption often made by prospective parents and clinicians that more information is better than less. From this it could be extrapolated that some women elect additional testing in the belief that it provides greater control over a pregnancy outcome, or that "knowledge is power". While this assumption may be true of testing that provides definitive diagnoses, the severity of some conditions may differ significantly amongst individuals and clinicians may not be able to predict where the future child may fall on that spectrum. Further, the potential genomic variants detected can include predispositions to complex disorders—when there is no certainty that a condition will develop in the future individual. The reality is that prenatal genomic testing may not provide certainty and, contrary to assumptions, may be anathema to any sense of "control" given potentially ambiguous results. Although prospective parents will engage with, and experience risk and uncertainty differently, it is likely that it will be challenging for many. Ironically the search for greater knowledge may not lead to more clarity:[136]

> Prenatal screening is a good illustration of 'manufactured uncertainty' (Giddens 1994), in which 'more and better knowledge produces new decision-making situations and more risks to make wrong decisions.

Evidence suggests some couples are often unprepared for positive CMA results following normal karyotyping results and have difficulty processing uncertain results, struggling in the quagmire of the unknown.[137] The themes of unquantifiable risk and uncertainty are common in the clinical literature on prenatal CMA. However, uncertainty is not solely a problem for genetic test results.[138] Routine ultrasound scans may also reveal findings that are of uncertain significance, such as anatomical variations that are suggestive, but not determinative, of fetal anomaly. Indeed some research suggests that prospective parent's

perception of risk is similar regarding uncertain ultrasound and genetic test results.[139] Nevertheless the degree of risk and uncertainty associated with some genomic results are important factors in prenatal CMA and any woman undergoing prenatal CMA should be prepared for the possibility of uncertain or ambiguous results. While people deal with uncertainty differently, it may also be impacted by the degree and quality of professional support available. However, the fact that knowing more may be difficult to deal with is generally not in itself a reason not to provide information in the first place. Ultimately some women are prepared to receive uncertain information, despite the anxiety it may invoke.

The issue of informed consent in clinical reproductive genomics, specifically the extent of information that should be imparted prior to testing and the extent of information that should be returned *after* testing, has been a long-contested subject. There has been significant concern expressed in the clinical and ethical literature regarding informed consent to prenatal genetic testing.[140]

Yet it is arguable that some commentators overstate the requirements of a legally effective consent in this context, wrongly assuming that being fully informed requires disclosure of every condition tested and every possible eventuality. However, while consent needs to be "sufficiently" informed—it does not require that an individual is informed of every conceivable outcome, particularly if it would be unduly burdensome on the recipient of the information. When obtaining informed consent to a procedure, a patient must be provided with all *material* information that is relevant to that decision. The test of materiality encompasses all of the information that a *reasonable* person in *that* person's circumstances would expect to *receive*.[141] Given the complexity of modern genetic testing, information provided in generic terms is likely to suffice, such as the categories of conditions that are being tested for, and the implications of a positive result.[142] This is necessary to avoid overloading with superfluous information.

The nature of genomics means that informed consent is not restricted to obtaining consent to actual testing but is an on-going process. Given that individual reproductive decision-making is often reliant upon the test results that a patient receives following genomic analysis, the legal requirement of receiving sufficient information to inform decision-making remains a live issue throughout the clinical encounter. A major issue in CMA is dealing with the information derived and return of results.

Returning results: what boundary markers for information?

Two cardinal principles underpinning clinical genetic testing are clinical validity and clinical utility. Clinical validity is the capacity of the test to identify what it is testing for, and clinical utility is the capacity of the test to provide clinically useful information.[143] For clinicians, the issue of what information to report back to patients generally depends on the type of information derived and its clinical utility. "Clinical utility" is generally understood as:[144]

> the likelihood that a given intervention (in this case, genetic information) will lead to an improved health outcome or to whether a test can provide information about diagnosis, treatment, management, or prevention of a disease that will be helpful to a consumer.

In the prenatal context, clinical utility also encompasses information that may be relevant to a parental decision to continue a pregnancy or not.[145] Employing the boundary marker of clinical utility is partly premised on a concern to avoid causing unnecessary harm, such as the harmful effects of anxiety following the discovery of a VOUS or an ambiguous test result. Classifying results as reportable and unreportable based on clinical utility may also be driven by a concern to prevent overwhelming patients with information. However, using "clinical utility" as the sole boundary marker for return of results is not without issues.

Although some results may have limited clinical utility, some prospective parents undergoing prenatal diagnosis may only wish to receive results that fall into specific categories, such as conditions that are life-threatening and/or early onset. They may not wish to be informed that their child (and by implication one of the parents if it is an inherited mutation) has a predisposition to developing an adult onset cancer syndrome, such as the *BRCA1*, *BRCA2* mutations that predisposes to breast, ovarian and bowel cancer.[146] Conversely, parents may want to receive information that, in medical terms, has no clinical utility, including non-medical traits. Indeed knowing the sex of a foetus may have utility for parents, although there is no clinical utility in testing for sex in the absence of a risk of a sex-linked disorder.

While some guidelines accommodate parental preferences regarding the clinical information they wish receive, there is also an emerging view that parents should not have such a discretion to decline disclosure of clinically significant test results. A group of prominent geneticists and bioethicists argue in favour of a "moral duty to know" claiming that[147]

> if there is such a thing as a 'parental right not to know,' it cannot cover findings that, even though they are unsolicited, are of clinical relevance, in the sense of requiring treatment, prevention, or surveillance.

In support of this assertion they cite recommendations made by the European Society of Human Genetics (ESHG) which state that health professionals are responsible for promoting the "interests of the minor if the decision of the minor's parents or legal guardian's is not to the direct benefit of the minor".[148] The authors argue that permitting parents to decline information regarding relevant incidental findings that are not related to the condition being tested is ethically unsound:[149]

> the issue here is not one of parental autonomy, but of parental and professional duties of beneficence. To suggest otherwise is to make a mockery of the principle of respect for autonomy.

Yet there are several troubling aspects to this position—which has nevertheless been adopted by some European groups.

Clearly at the prenatal stage there is no legal "minor", although there is a possible future child whose interests should plausibly be taken into account. However the fact the fetus does not have legal personhood is relevant for at least two reasons: first, subordinating the interests of the parent in not knowing for those of the foetus is problematic from a public policy perspective. Some of the information derived may not involve definitive diagnoses, but rather involve predictions of risk. Some parents may wish to parent without knowing that there are certain conditions that their child may, or may not, develop. Such knowledge could be anxiety provoking, or may have implications for insurance for the child after birth. It seems anomalous that paediatric guidelines caution against testing children for some late-onset conditions, yet a pregnant woman could be compelled to receive the same information regarding their foetus if presymptomatic treatment or surveillance could be instituted in child-hood. (Significantly the authors do not include *BRCA1*, *BRCA 2* mutations in this category as surveillance measures are generally not recommended until early adulthood. However these mutations are on the ACMG list of mandatory tests and disclosure in whole genome sequencing in paediatrics and inform the some of the European guidelines).

Public policy reasons may also militate against mandatory disclosure to parents, as being compelled to receive unwanted genetic information regarding a foetus may deter prospective parents from undertaking any invasive diagnosis that may indicated for other reasons.

According to this particular/mandated approach to returning results, prospective parents are deemed not only to be the guardians of their future child's future health, but also their wider family members. The authors state:[150]

> it will often be the case that not just the interest of the child is at stake, but also the health and/or reproductive interests of the parents themselves and, possibly, of other relatives. Although, in principle, the parents have a right not to be informed about findings about themselves, this again does not overrule their parental responsibility to be given information that reveals a serious and treatable condition in their child. Nor can they be granted the right to decide that the possible health and/or reproductive interests of other family members need not be taken into account.

While such policies justify the mandatory return of results on the basis that it may be for the 'benefit of family' members, there is currently no legal obligation to pass on such information to family members.[151] Although the "benefit of the family" view may militate in favour of providing a prospective parent with the choice of receiving incidental information, arguably this should not be imposed nor obligatory.[152]

It should be noted that rejecting any claimed parental duty to know incidental prenatal information does not mean that the information should forever be unavailable. Once a test has been performed, it is plausible that the results could be stored and accessed if the child developed symptoms at a later stage, or if the parents subsequently changed their mind. This effectively means that the clinicians and parents negotiate the scope of non-disclosure, which may subsequently be revisited.

Conversely, the authors state that prospective parents do not have a right to be informed if it is discovered incidentally that a fetus has a mutation linked to a late-onset untreatable disorder, e.g. Huntington Disease. This restriction is imposed ostensibly because disclosure would undermine the child's so-called "right to an open future".[153] The crux of the "open future" concept is that the future adult the child will become has a right to make their own autonomous choices regarding significant matters, such as whether to undergo genetic testing for a late onset untreatable disorder, and parents are trustees of that right to future autonomy. Arguably this policy would only be defensible if clinicians knew that such information would not affect a parental choice to continue the pregnancy.

Ultimately the approach advocated by Dondorp et al arguably signals a distinct shift toward genetic determinism and arguably reflects some troubling paternalism, although ostensibly premised on the interests of the future child and the wider family. The central imperative is promoting public health, rather than acknowledging and respecting a zone of parental discretion.[154]

Current approaches

Currently there are three main approaches to prenatal testing and subsequent information provision.[155] One approach devolves decision making to the prospective parents as to what kinds of clinical information they do or do not want to receive following testing—this is essentially a negotiated agreement based on parental preferences.[156] This permits women the option of avoiding information that, in the Bernhardt study, was experienced as "toxic". Another is to return all information, including incidental findings and VOUS, to prospective parents, however, for some prospective parents this may be overwhelming. An alternative approach is to only return results that are clinically significant. Hence both causal and incidental findings are reported, but VOUS or benign CNVs are not.[157] For some groups this would include reporting some susceptibility loci/CNVs associated with neurodevelopmental or psychiatric conditions.[158] Interestingly, some groups adopt arbitrary "cut-offs" for reporting, such as one Belgian group do not routinely report CNVs that pose a less than 25% risk of the individual developing the condition.[159]

Determining which of these approaches is preferable must be measured against the backdrop that, by its nature exercising "choice" in the reproductive context is complex. Elisabeth Hildt provides an analysis of the implications of increasing the scope and range of information that may be provided to prospective parents. She refers to five dimensions of increased choice (originally formulated by Dworkin) that may impact upon individual freedom in this context.[160] These are:[161]

1. the financial cost associated with acquiring information as well as the emotional cost of acquiring information;
2. the responsibility assumed for choices made, particularly in relation to avoidable disability;
3. the pressure to conform to social expectations of responsible choices;
4. the exercise of choice itself;
5. increased choice may alter attitudes to pregnancy that may be associated with welfare decline.

As well as being emotionally charged, decision making may also be influenced by the socio-political environment in which it is exercised. Women do not make individual choices in a social vacuum, and all decisions are implicated to some extent by one's environment. Others' expectations may impact women's choices. For example some critics claim that CMA is essentially a "search and destroy" exercise, and that it encourages perfectionist parental expectations.[162] Conversely "legitimising" certain technologies, by clinically endorsing testing or providing public funding, can influence conceptions of the "good" parent. Hence some women may feel that they need a good reason to decline expanded screening. [163]

While this is not a reason against providing CMA, it highlights that significance of the way in which testing is offered and the social/political context in which it is offered. Some women will consider invasive diagnosis/screening is inconsistent with their personal moral framework and their conception of parenthood, particularly if they hold particular views regarding the sanctity of fetal life. Further, evidence indicates that some women's experience of CMA is not always positive. The technological imperative should not obscure the fact that declining screening, or choosing to only receive certain types of information, is a legitimate exercise of reproductive choice.

Conclusion

There is considerable evidence in the international literature that, when given the opportunity, many parents elect to undertake more expansive invasive prenatal testing than that provided traditionally, particularly if there are elevated risks associated with a particular pregnancy or fetal abnormalities identified on ultrasound.[164] Information is often sought not only when it would be determinative of a decision to carry a pregnancy, but also when it may have implications for a future child's health or well-being. Several studies have reported that parents prefer to be able to choose to receive information regarding a potential genetic or susceptibility identified in a fetus, which may reflect greater general acceptance of the ubiquity of genetic vulnerability and a willingness to know more, rather than less for multiple reasons. Others caution that "unfiltered" prenatal information may create intense parental anxiety and alter the parent-child dynamic.[165] Similar concerns regarding the effect of genetic information, particularly in regard to parent-child dynamics, occurred in the context of childhood testing as has discussed in Chapter II, where concerns regarding harmful psychosocial effects of paediatric genetic testing have largely not been reflected in the (pre-genomic) empirical literature. However, CMA expands the scope of potential information that may be derived significantly, including VOUS and variants associated with susceptibility to neurodevelopmental conditions.

Clearly while the new era of prenatal genomics trigger a range of ethical and legal issues, some of these issues are familiar. The notion of genetic determinism, as well as debates regarding the appropriate scope of reproductive autonomy versus medical "paternalism" are all factors in this discourse. A pervasive issue is the assumed association of expanded prenatal diagnosis with termination. However, it is questionable whether CMA increases the incidence of termination. The available empirical research suggests that it may be useful to help inform a decision when a fetal anomaly has been

identified on ultrasound, but it seems that in the post-CMA era the factors that influence a decision whether to continue a pregnancy continue to be the nature, severity and likelihood of a condition developing. Further, it is also debatable whether the possibility that a woman may terminate on the basis of certain information is sufficient, on its own, to justify withholding information. Arguably the issue of whether termination is a proportionate response to the nature or severity of a risk/condition identified is an issue for the individual woman/couple and their clinician.[166] Clearly underlying all of these debates are competing views regarding philosophies of (responsible) reproduction and parenthood, as well as the state's role in reproduction.

This analysis suggests that one of the major risks in this context is to make assumptions about what women want to know, and provide a one-size-fits all approach. It also suggests that women should have a choice regarding the categories of results returned to them following expanded screening and diagnosis. This could be facilitated by a negotiated agreement that moderates the return of results, but enables revisiting tests at a later stage if there are subsequent concerns regarding a child's health or development. This approach presupposes an account of autonomy that aids the exercise of genuine choice by being provided with good, understandable information and the opportunity to discuss issues as needed with an adequately trained practitioner.[167]

Developing adequate clinical capacity to address these issues should be a priority for maternal and fetal health services given the likely trajectory of technology. It is possible that, in the future, the current capacity of prenatal CMA will be replicated in NIPT, transforming it from a screening to a diagnostic test. This could significantly increase the number of women receiving additional genetic information should they choose to access expanded non-invasive prenatal diagnosis.

In the meantime, Dondorp et al predict invasive diagnostics will expand exponentially:[168]

> Finally, it seems a logical next step to use next-generation sequencing (NGS) for comprehensive genome scanning in all foetuses that undergo invasive prenatal testing, as soon as doing so is technically logistically and financially feasible. This will make it possible to test the fetus for an even wider array of genetic conditions and risk factors. And given proof of principle regarding the analysis of the entire fetal genome in maternal plasma it is to be expected that this will not remain confined to the invasive testing stage.
>
> Clearly, there is no good reason why prenatal genetic screening should remain limited to Downs's syndrome or to the three common trisomies. And indeed, ultrasound is already a much wider form of screening. However, is the fact that we can soon test the fetus 'for everything', including for later onset disorders and risk factors for common diseases, a sufficient reason for doing so? If the dynamics of the field is not to be determined by the 'technological imperative', a debate about the scope of prenatal screening is urgently needed.

Whole genome sequencing is likely to reveal a significant amount of information. Specifically studies suggest that performing WGS on an individual is likely to reveal "a nontrivial number of clinically significant (or possibly clinically significant) findings", some of which are associated with serious genetic illness but may, or may not, cause ill-health in all individuals that carry them.[169] Yet it remains an open question whether prospective parents have any interest in such extensive sequencing. Current studies involving WGS and newborn babies suggest that parents have little interest in genome-wide screening of their newborn.[170] In particular researchers in the BabySeq study found that after discussions with a genetic counsellor, the vast majority of parents declined to participate due to concerns regarding privacy, uncertain results, and implications for insurance.[171] Researchers are assessing the clinical utility of newborn WGS and whether the information is beneficial or has negative effects on the child and the family.

This and the previous chapters, have sought to traverse the clinical and ethical and legal implications of expanded prenatal screening and diagnosis. In particular, it has sought where possible to include insights from those whose interests are directly implicated by such technologies: those of women and children. The following chapter extends this analysis, by considering the additional implications of the new genomics on preimplantation genetic testing.

Endnotes

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4. M. I Srebniak and others "Whole-genome array as a first-line cytogenetic test in prenatal diagnosis" (2015) 45 Ultrasound Obstet Gynecol 363 at 367.
5. E Bunnik and others "The New Genetics and Informed Consent: Differentiating Choice to Preserve Autonomy" (2013) 27 Bioethics 348.
6. E Bunnik and others "The New Genetics and Informed Consent: Differentiating Choice to Preserve Autonomy" (2013) 27 Bioethics 348.
7. LG Shaffer, MP Dabell, AJ Fisher et al. "Experience with microarray-based comparative genomic hybridization for prenatal diagnosis in over 5000 pregnancies" (2012) 32 Prenat Diagn 976–985.
8. M. I Srebniak and others "Whole-genome array as a first-line cytogenetic test in prenatal diagnosis" (2015) 45 Ultrasound Obstet Gynecol 363 at 363. "Both array-CGH and SNP arrays can detect unbalanced (sub)microscopic chromosomal abnormalities, but SNP arrays also provide genotype information (based on the A and B alleles) at multiple SNP loci throughout the genome, which makes it the preferred microarray method. The main reason that we favor SNP arrays (although non-SNP arrays, i.e. array-CGH, are as effective in detecting submicroscopic CNVs) is that this can be used as a rapid stand-alone test, while a non-SNP array has to be supplemented with rapid aneuploidy detection (RAD) and testing for maternal cell contamination in all cases. A SNP array detects all relevant unbalanced aberrations, detects additional aberrations not detectable by non-SNP arrays, and recognizes samples contaminated with maternal tissue or with low mosaicism within the same experiment. Moreover, the B-allelic frequency plot supports the CNV findings and the need to validate the findings is minimized".
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10. HGSA/RANZCOG "Prenatal screening and diagnosis of chromosomal and genetic abnormalities in the fetus in pregnancy" C-Obs 59 (Endorsed March 2015, amended May 2016) at 13.
11. DNA learning centre. http://www.dnalc.org/view/552-Copy-Number-Variants.html
12. One of the most common conditions that result from a CNV is Down Syndrome, resulting from an additional whole chromosome.
13. L Shaffer, M Dabell and J Rosenfeld "Experience with Micorarray based comparative Genomic Hybridization for Prenatal Diagnosing Over 5000 Pregnancies" (2012) 32 Prenatal Diagnosis 976.
14. The study used data from the US National Institute of Child Health and Human Development microarray trial. See J Donnelly, L Platt, A Rebarber and others "Association of Copy Number Variants with Specific Ultasonographically Detected Fetal Anomalies" (2014) 124 Obstet Gynecol 83; R Wapner and others "Chromosomal microarray versus Karyotyping for Prenatal Diagnosis" (2012) 367 N Engl J Med 2175.
15. R Wapner and others "Chromosomal microarray versus Karyotyping for Prenatal Diagnosis" (2012) 367 N Engl J Med 2175.
16. R Wilson, D Ledbetter and E Pergament "Current Controversies in Prenatal Diagnosis 3: the Ethical and Counselling Implications of New Genomic Technologies: all Pregnant Women Should be Offered Prenatal Diagnostic Genome-wide Testing for Prenatally Identified Fetal Congenital Anomalies" (2015) 35 Prenatal Diagnosis 19 at 20.
17. The authors of a recent review state: "Most developmental disorders are not caused by CNVs, however, but by single-nucleotide variants (SNVs) or insertions or deletions (indels). Whole-exome sequencing (WES) studies of children and adults with developmental disorders have shown a diagnostic yield of about 25%. Hence, the use of WES in the prenatal setting is being explored." Joris Robert Vermeesch, Thierry Voet and Koenraad Devriendt "Prenatal and pre-implantation genetic diagnosis" (2016) 17 Nature Reviews Genetics 643.

18. Olivier Vanakker and others "Implementation of genomic arrays in prenatal diagnosis: The Belgian approach to meet the challenges" (2014) 57 European Journal of Medical Genetics 151 at 153.
19. Olivier Vanakker, and others "Implementation of genomic arrays in prenatal diagnosis: The Belgian approach to meet the challenges" (2014) 57 European Journal of Medical Genetics 151 at 153.
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165. G Donley, S Hull and B Berkman "Prenatal Whole Genome Sequencing: Just Because We Can, Should We? (2012) Hastings Center Report 28 at 33.
166. Certifying consultants appointed under the Contraception Sterilisation and Abortion Act 1977 are responsible for determining whether one of the grounds for lawful abortion provided in the Crimes Act 1961 are met. An abortion under 20 weeks will be lawful if two consultants certify that 'there is a substantial risk that the child, if born, would be so physically or mentally abnormal as to be seriously handicapped' (s 187A(1)(aa)). In the recent annual Report of the Abortion Supervisory Committee (2015 p 20) it was reported that 97.3% of abortions were performed under the mental health provisions, specifically that "the continuance of the pregnancy would result in serious danger … to the life, or to the physical or mental health, of the women." (s 187A1(1)(a)).
167. For a discussion of a two-stage informed consent process see S Chen, D Wasserman "A Framework for Unrestricted Prenatal Whole-Genome Sequencing: Respecting and Enhancing the Autonomy of Prospective Parents" (2017) 17 AJOB 3 at 7.
168. W Dondorp, Page-Christiaens and G de Wert "Genomic Futures of Prenatal Screening: Ethical Reflections" (2016) 89 Clinical Genetics 531 at 534.
169. G Donley, S Hull, B Berkman "Prenatal Whole Genome Sequencing: Just Because we Can, Should We?" (2012) Hastings Center Report 28 at 33.
170. Jocelyn Kaiser "Baby genome screening needs more time to gestate" (2016) 354 Science 398.
171. Jocelyn Kaiser "Baby genome screening needs more time to gestate" (2016) 354 Science 398 at 399.

Chapter Five

The future of Preimplantation Genetic Testing

5.1 Introduction

It has been 28 years since Preimplantation Genetic Diagnosis (PGD) was first successfully performed in the United Kingdom.[1] The technology, which identifies deleterious mutations in an embryo created using in vitro fertilisation (IVF), was developed so that couples with a known-risk of transmitting a serious genetic disorder to their offspring could avoid doing so. PGD has provided a valuable alternative for such prospective parents who wish to have a genetically related child. In this case, the only alternative is to undertake prenatal testing and terminate a pregnancy if the fetus subsequently tests positive for the condition, an experience that many prospective parents understandably wish to avoid.

The controversy that initially surrounded PGD was fuelled by similar arguments witnessed in the abortion debates, primarily the morality of creating and destroying nascent human life, further complicated by the ethics of "choosing" one's child. Despite anxieties regarding clinicians and parents "playing God",[2] creating "designer babies"[3] and its implication for existing people living with disabling conditions,[4] PGD has become part of mainstream medicine.

PGD: initial projections and current trajectory

When first introduced, PGD's potential trajectory was projected to be narrowly restricted to detecting single gene mutations associated with serious genetic disorders that manifest at birth or in early childhood, or to detecting mutations that cause devastating late-onset disorders, such as Huntington disease.[5] However as the molecular bases of a multitude of monogenic disorders have been discovered in the intervening years, the capacity of preimplantation testing has increased exponentially, particularly over the last two decades. This has occurred against a background of evidence that indicates, in the case of a singleton pregnancy, that the risk to the future child resulting from embryo biopsy appears to be no greater than the risk associated with IVF/ICSI in the case of singleton pregnancies.[6] Further, recent research indicates that cognitive and psychosocial development is similar to those children born following natural conception.[7]

Over time, the scope of PGD has expanded considerably. It may be used to detect mutations associated with late-onset conditions to which a person may be predisposed, but not certain, to develop. In these circumstances whether a disease manifests in an individual depends upon the interaction of multiple genetic and/or environmental factors, but ultimately the condition is caused by a unitary gene mutation that exerts a major effect on health. A paradigmatic example of "susceptibility" mutations are those mutations that predispose an individual to developing cancer later in life, such as the *BRCA 1* or *BRCA 2* gene mutations that predisposes an individual to developing breast, ovarian and bowel cancer. Although not all people who have a susceptibility mutation will develop the disease, for those who do it may potentially be life threatening.[8]

In terms of non-disease-related traits, PGD may also be used to determine an embryo's sex or to identify an embryo's HLA tissue type (i.e. human leukocyte antigen testing). Embryonic HLA tissue typing has been performed in situations where a family has an existing sick child who is in need of a stem cell transplant, but there is no available tissue-matched donor. The embryo is tested to determine if it could be a prospective matched stem cell donor, thereby creating a so-called 'savior sibling'.[9]

A less well known technology that has evolved alongside PGD is preimplantation genetic *screening* (PGS).

Preimplantation Genetic Screening (PGS): PGD's less well-known counterpart

While PGD is concerned with identifying genetic mutations, PGS identifies structural or numerical chromosomal abnormalities, (eg an additional or a missing chromosome).[10] Given that chromosomal abnormalities or "aneuploidy" is well known to be associated with implantation failure or spontaneous pregnancy loss (miscarriage) and is also known to increase with advanced maternal age (AMA), it was theorised that screening embryos to select chromosomally normal or "euploid" embryos in these obstetric circumstances would increase the likelihood of successfully conceiving and carrying a pregnancy to term.[11] Because PGS is used in an attempt to increase the success of IVF in certain high-risk obstetric groups rather than to select a particular "type" of child, it escaped the same intensity of scrutiny when PGD was first debated. International data indicates that PGS now constitutes the major indication for which PGD is performed.[12]

Despite the seemingly plausible assumption that PGS may improve implantation rates, PGS has been controversial given scant evidence that it actually increases the "take home baby rate" in high risk groups, and evidence that it may actually reduce it.[13] Although still contentious, some recent studies involving new testing methodologies suggest that PGS may now be associated with better pregnancy outcomes than in ordinary IVF, which is discussed further below.

Ultimately developments in testing techniques, as well as advances in IVF and embryology, promise to alter the nature of PGD and PGS in the future. The remainder of this chapter focuses on the confluence of factors that make comprehensive preimplantation genetic testing a likely development in the future. It concludes by providing an overview of the issues that this prospect raises, and the questions that it poses for patients, providers and policymakers.

5.2 A confluence of events

The convergence of several technological advances has steadily expanded the scope of PGD and PGS. These include advances in embryo biopsy techniques, advances in embryology and vitrification, as well as ever-increasing sensitivity and capacity of tests.

Advances in embryology

The traditional approach to embryo biopsy involves biopsying an embryo 3 days after fertilisation to remove 1-2 cells from the inner cell mass for genetic analysis (i.e. blastomere biopsy). The results inform which, if any, embryo(s) is transferred to the woman's uterus. However, a paradigm shift in biopsy technique is occurring, whereby embryos are biopsied 5 days after fertilisation (i.e. blastocyst biopsy).

While a 3-day embryo generally contains only 8 cells, a 5-day blastocyst contains around 130 cells. These cells are distributed between the inner cell mass (which subsequently develops into the fetus) and the surrounding trophectoderm cells (which subsequently develops into the placenta and fetal membranes). Biopsying the trophectoderm enables 5-10 cells to be removed for analysis, significantly more in comparison to 1-2 cells in the case of a day 3 biopsy. This mitigates some of the technical problems associated with only having limited DNA for analysis, which may also lead to misdiagnosis.[14]

An additional advantage of trophectoderm biopsy (TEB) is that aspirating cells from the trophectoderm, rather than the inner cell mass, poses less risk of negatively impacting embryo development.[15] Further, the increasing use of vitrification to cryopreserve embryos after biopsy also allows unlimited time for subsequent genetic analysis and diagnosis.[16]

Although fewer embryos generally survive to blastocyst stage and therefore less embryos are biopsied and available for transfer, some studies indicate that implantation rates for biopsied blastocysts are higher than embryos biopsied at day 3.[17] Given these advantages, it is predicted that most PGD centres will move to trophectoderm biopsy in the future.[18] The change in the type and timing of embryo biopsy, in association with the introduction of advanced analytics, has significant implications for the future of preimplantation genetic testing.[19]

From traditional testing to advanced analytics: PGD

Traditionally testing for a DNA sequence associated with known a single gene mutation such, as cystic fibrosis or Huntington Disease, involved a technique called polymerase chain reaction (PCR). PCR copies and amplifies a targeted gene sequence. However, if one or both alleles fail to amplify in this process, there is a risk of misdiagnosis.

Newer testing protocols use whole genome amplification (WGA) of embryonic cells, rather than amplifying a targeted gene sequence. When WGA is performed on multiple cells obtained following trophectoderm biopsy, the incidence of allele drop out is significantly alleviated.[20] Significantly WGA also enables simultaneous testing for a number of different gene sequences, with less risk of misdiagnosis. Consequently, the combination of trophectoderm biopsy, whole genome amplification and advanced testing techniques have significantly contributed to the evolution of PGD. It enables more than one single gene disorder to be tested at a time.

From traditional testing to advanced analytics: PGS-version 2

Although PGS is technically a "screening" tool, as opposed to a diagnostic test performed for a particular condition, PGS involves testing embryonic DNA and is capable of providing definitive diagnoses, such as the presence of an additional chromosome (trisomy) or a missing chromosome (monosomy). Prior to 2007, the technique used for chromosome analysis was fluorescent in situ hybridization (FISH).[21] This technology only enabled a limited number of chromosome pairs to be analysed. Because traditional PGS was limited to scrutinising around half of the full complement of chromosomes, some aneuploidies were undetected. PGS in its initial form was subsequently found not to improve, or even adversely effect, pregnancy outcomes.[22]

Early developments in PGS involved a technique called comparative genomic hybridisation (CGH) which enables all 24 chromosomes to be analysed at once.[23] Subsequently, "array CGH" (aCGH) was developed, which provides a more rapid method of comprehensive chromosomal screening.[24] While both array-CGH and single nucleotide polymorphism microarrays (SNP arrays) can determine the number of chromosomes in a DNA sample, SNP array also enables simultaneous testing for genetic diseases, including single gene and, at least theoretically, multigenic disorders.[25] SNP arrays may also detect small deletions and duplications.[26] Currently four different methods are used to perform PGS: aCGH, SNP array, quantitative polymerase chain reaction (qPCR), and next-generation sequencing (NGS).

Trials investigating the effect of TEB with comprehensive chromosome analysis using microarrays to select chromosomally normal or "euploid" embryos have been reported to yield encouraging results on subsequent implantation and pregnancy rates,[27] although some of these studies have been subject to criticism.[28]

A recent review examined whether, what is now often described as "PGS-version 2", improves IVF outcomes in good-prognosis IVF patients (i.e. patients without a history of recurrent miscarriage/ implantation failure / advanced maternal age).[29] The review included 3 randomised controlled trials, comparing PGS-version 2 with routine IVF care. PGS-version 2 resulted in higher implantation rates and ongoing pregnancy compared with the control group. The authors concluded enthusiastically that "PGS-version 2" may become the standard of care for infertile couples requiring IVF, although qualified this with the observation that further RCTs would be required before it is introduced into routine clinical practice.[30] In another recent review commentators observed that[31]

> As a consequence of the technological advancements in single-cell DNA amplification and single cell genome analysis, PGD and PGS methods now enable faster, more accurate analyses and have the potential of increasing IVF success rates.
>
> PGS is suggested not only to improve the success rates of embryo survival in patients with advanced maternal age, but also to improve the efficacy of IVF in general. Currently, a randomized clinical trial is underway to compare the outcomes of standard IVF treatment with aneuploidy screening to assist embryo selection.[32] If proof-of-concept studies are confirmed, genome-wide aneuploidy screening may well become standard practice for all IVF embryo transfers.

Ultimately, if clinical trials confirm that PGS-version 2 increases implantation rates compared to standard assessments of embryo morphology, it is foreseeable that there will be significant pressure to introduce it into routine IVF practice.[33] There would be a professional incentive to provide it, and a public demand to access PGS as an adjunct to routine IVF and PGD, signalling a move away from recommending PGS based on a predetermined risk threshold. However, it currently remains uncertain whether PGS improves IVF outcomes.[34] Nevertheless, as the resolution of microarray and Next Generation Sequencing (NGS) technology steadily increases, the scope of testing not only for aneuploidy to improve IVF success, but to screen for health-related conditions, will potentially increase.

NGS comprises a group of technologies that permit rapid sequencing of large segments of DNA, potentially extending to sequencing an individual's entire genome.[35] Two "state of the art" reviews predict that NGS will eventually be integrated into PGD. Specifically, Stern cites several studies that demonstrate that "NGS-based PGD can be performed accurately and with high throughput", which he claims likely heralds a move from current PGS technology to NGS analysis, particularly as the cost of sequencing continues to decline.[36] Brezina and Kutteh note how NGS may be utilised in the preimplantation context:[37]

> Next generation sequencing can also be used for 23 chromosome pair preimplantation genetic screening.[38] This technique amplifies embryonic DNA and compares millions of fragmented DNA sequences with a reference genome (human hap-map hg19). This technique can evaluate specific DNA sequences along each chromosome and also determine single (or multiple) gene mutations. Next generation sequencing can therefore be used concurrently for preimplantation genetic screening and preimplantation genetic diagnosis when parental genetic mutations are present.

Simlarly Dahdouh and colleagues note that NGS technology[39]

> has been used on trophectoderm biopsies for single gene disorders,[40] and at the single blastomere level for aneuploidy screening.[41]With next-generation sequencing technology, cost effective genetic testing has emerged by sequencing in simultaneous clinical scenarios, for monogenetic disease and chromosomal translocations coupled with complete chromosome analysis. Nevertheless, further studies with large sample sizes will be needed before the introduction of this technology into routine clinical practice.

Given evidence that it is possible to perform comprehensive embryo screening either in conjunction with PGD to diagnose a known genetic condition or as a stand-alone procedure to improve IVF success,[42] the very thing that in the was considered not to be remotely possible in the early debates on PGD now appears to be a realistic prospect.[43]

That is, obtaining a complex set of genetic diagnoses following PGD and/or PGS, as opposed to merely identifying the presence or absence of a particular deleterious mutation or a chromosomal abnormality. The following considers the kind of additional information that may be discovered.

Susceptibility (complex) conditions and uncertainty

While most clinical reports of next generation sequencing (NGS) studies involve the identification of large chromosomal changes, aCGH, SNP-array and NGS may also identify small subchromosomal copy number variations (CNVs <10 Mb), as well as aneuploidy.[44] As discussed in previous chapters, CNVs may be associated with a range of serious syndromes, or may be benign.

As well as identifying CNVs associated with known conditions, it is also possible that variants of unknown clinical significance will be identified. As prominent researcher Dagan Wells notes, employing technology with increasing resolution and genome coverage to the extent that it reliably detects clinically significant CNVs has significant implications for clinical practice because it[45]

> will inevitably result in the occasional identification of alterations that are of unknown phenotypic impact. As a consequence, there will be uncertainty concerning the status of some of the embryos tested, resulting in significant challenges for patient counselling. It is not yet clear how often such incidental findings will be observed in Preimplantation embryos.

It seems that as well as identifying large chromosomal aneuploidies and smaller CNVs, single-cell NGS may be used to identify a range of genetic mutations in an embryo in the future. As well as testing chromosomes, SNP-array is also capable of testing for specific genetic diseases using a method called haplotyping, which involves comparisons with a parental reference sample.[46] Consequently these two technologies enable PGD to be conducted using methods that were initially designed for PGS.

While targeted testing for a mutation or variant identified in a parent seems plausible, there is good reason to question whether broad scope untargeted testing is a realistic prospect in the future.[47]

The (un)reliability of gene-disease associations

NGS generally involves broad "indication-blind" testing. A significant issue for the future development of preimplantation NGS is the paltry extent of genomic knowledge relative to the enormous variation of the human genome. While an increasing number of gene-disease associations have been made, some of these associations may not be reliable.[48] In 2012 Donley and colleagues noted that[49]

> the function of more that 90 percent of annotated genes in the human genome is unknown, as is the function of 99.8 percent of the noncoding regions. In other words, only a small number of the genetic markers that whole genome sequencing will produce have been studied enough to substantiate their

connection to disease. Although the scientific community is in the budding stages of research on many new markers, preliminary results are often subject to change, as is illustrated by a number of published genomic discoveries that have subsequently been retracted after additional evidence has come to light. As the nascent field of genomics continues to develop, much of the data generated from prenatal wgs over the next few years (or even decades) will be of questionable utility at the time they are generated, and even findings that seem clinically relevant could be subject to later retraction or revision. Reflecting this scientific uncertainty, some commentators and scientific leaders have articulated restrained optimism about the speed with which genomic medicine will be clinically useful.

The challenges noted above are made clear in a 2014 study that sought to determine whether, should embryonic whole genome sequencing (WGS) be implemented at some time in the future, it would be technically feasible to use NGS to accurately distinguish between unharmful gene variants and disease-causing mutations at the preimplantation stage.[50]

The researchers selected several severe Mendelian diseases with known molecular bases/gene mutations, as well as mutations annotated in the Human Genome Mutation Database (HGMD), that were known to be damaging. These were compared with the DNA samples of genome-sequenced individuals, that were mostly obtained from publicly available genome databases. The authors hypothesised that if the identified mutations were sufficient to cause the early-onset disease and are therefore of predictive value in the context of embryo screening, these known gene mutations should *not* be found in apparently healthy adults.

Significantly, the authors reported that "more than 40% of individuals who can be considered healthy have mutations that are predicted to be damaging in genes associated with severe Mendelian disorders or are annotated as disease causing".[51] Similar results have been found in other studies.[52] Indeed, it is well known that James Watson, famous for co-discovering the double helix nature of DNA and who was one of the first individuals to have their whole genome sequenced should, according to his results suffer from 2 serious illnesses, Usher syndrome and Cockayne syndrome, but does not. Ultimately this means that some embryos identified with Mendelian mutations will not necessarily result in a future individual developing the associated disease, but it will be difficult to identify those that will particularly in the absence of a family history of the condition.[53]

An issue highlighted in the Winande study also included false-positive entries, or errors, in the mutation database. During the course of the study a mutation thought to be causative for a disease resulting in congenital blindness was reclassified in the HGMD as only having a tenuous association with the disease.[54] These studies highlight the problems associated with analytic validity and utility in the context of opportunistic screening of ex vivo embryos.

An additional challenge arises from the fact that even if testing enables identification of specific gene variant(s) associated with disease, the implication for a prospective individual may not be known in advance. As already noted previously, some variants suggest a susceptibility to develop a disease, such as a predisposition to cancer. Because

the gene is not fully "penetrant" the *probability* of the disease occurring in an individual may not be known with any degree of accuracy.[55] This uncertainty may be more difficult in the case of complex, or multifactorial, conditions:[56]

> Uncertainties are far greater for gene variants associated with common diseases like diabetes, common cancers, and heart disease.[57] The 'uncertainties are due in part to the evolving science: information on genetic associations for common disease is still being accumulated. Little is known about many variants, and errors in assignment of risk are present in current databases. In addition, risk prediction for common diseases is inherently limited due to the multifactorial nature of these conditions, which are influenced not only by genetics, but also by lifestyle, childhood environment, and other exposures.' Even the genetic component is complex because risk for most common diseases is associated with changes in many different genes, each associated with very small increments of risk.

Possible routes to implementing comprehensive embryo screening

As noted earlier in this report, there is an increasing public and professional awareness of genomic testing across the lifespan. Consequently, there are various ways that comprehensive embryo testing could become integrated into clinical practice.

First, it is possible that "universal" pre-conception genetic testing may evolve in the future.[58] As links are increasingly being made between genetics and male/female reproductive failure, couples experiencing infertility or subfertility may be advised to undertake preconception genomic screening by fertility providers or, alternatively they may undertake direct-to-consumer genetic tests of their own volition.[59] In addition, couples who are fertile and not at any particular risk of having a child with a disease-related condition may undertake preconception screening prior to attempting to become pregnant naturally. The results of preconception tests would enable what some have referred to as "smart combinations of genetic testing" on embryos.[60] This would involve IVF and preimplantation testing that is "tailored" to the particular couple. PGD could be performed for any single gene disorder that is indicated following parental preconception testing, as well as comprehensive chromosomal screening for aneuploidy.[61]

An alternative route to implementation would involve the routine offer of PGS to all women undergoing IVF (should the evidence establish that it actually improves the take home baby rate). PGS could also be added offered as an add-on to PGD that is being performed for a known familial condition.

For couples undergoing routine IVF who may need to choose a single embryo from several, comprehensive screening to inform that choice may seem logical. It is also plausible that comprehensive chromosomal testing might also appeal to people who are not infertile, but wish to undertake comprehensive embryo screening either in an attempt to reduce the time taken to achieve a pregnancy, or to screen embryos for abnormalities.

Implication of increased information: trade-offs and difficult decisions

As the sensitivity of testing increases and more conditions may be identified, it is possible that embryos will have a less than "perfect" or unblemished genetic profile. The Health Council of the Netherlands noted presciently in 2010 the potential challenge given[62]

> the possibility that each embryo may have a number of genetic abnormalities, either related to degrees of viability in the womb or to health, be it congenital or later in life, may lead to the fact that difficult or even impossible trade-offs will have to be made by the couple or by the professionals involved.

This possibility raises issues as to who is ultimately responsible for determining whether an embryo is transferred to a woman in this situation. This decision is particularly complicated in the preimplantation context, given the considerable uncertainty regarding the effect of a variant or mutation on the future child's health.

Further, decision making is even more complicated in the preimplantation context than the prenatal genetic context where a pregnancy is established. Although decisions in prenatal testing are still challenging, there is an ultrasound to aid in determining the effect of some genetic variants, which is not the case in the context of ex vivo embryos. Further clinicians may be more directly involved in decision making and have a greater capacity to influence, or in some cases control, decisions regarding embryo transfer. This is distinct from a situation that involves the possible termination of a fetus, where it is generally accepted that reproductive decision making is the prerogative of the pregnant woman.

It is apparent that some clinicians and professional organisations consider that they are "co-responsible" for the welfare of the child born following PGD. Best Practice Guidelines released by the European Society of Human Reproduction and Embryology (ESHRE) in 2005 to establish professional norms regarding embryo selection and transfer attempted to define "acceptable" and "unacceptable" practice.[63] The guidelines provided that transferring embryos carrying autosomal recessive mutations, or female carriers of a recessive X-linked disorder, was "acceptable". This was presumably because there are no direct health implications for the future individual, although there may be reproductive implications. However, the guideline implicitly suggests that transferring carrier embryos was less preferable than transferring non-carriers. Yet arguably transfer decisions should presumptively be made on the basis of which embryo has the best chance of successfully implanting, with carrier status a lesser consideration. In contrast, the guidelines recommended against transferring undiagnosed embryos or embryos with monogenetic disorders. The guidelines espoused that it was acceptable for health practitioners to object conscientiously to transferring an embryo that is likely to result in the birth of an affected child. In this context, the professional body considered that non-directive counselling simply did not apply.[64]

As testing capacity subsequently evolved and an increasing range of conditions with variable severity could be diagnosed, ESHRE was required to revisit its policy in 2014. As noted earlier, developments have enabled detection of less immediately serious conditions, such as the *BRCA1* and *BRCA2* mutations that predispose to breast, bowel and ovarian cancer in adult life. Applying a "no-transfer" policy could preclude prospective parents attempts from achieving parenthood in cases where, despite undertaking PGD, there are no mutation-free embryos available for transfer. Yet precluding the transfer of an embryo with a late-onset susceptibility mutation is arguably a disproportionate response to the potential risk to a future child's health if prospective parents consent to transfer such an embryo. Consequently, ESHRE stated that its policy "to never transfer either an affected embryo" or a "high risk" embryo after what they term "failed" PGD "needs reconsideration".[65]

ESHRE considered that given expanding testing capacity, not *all* conditions should preclude transfer if the prospective parents are fully informed and consent. However. it advised doctors not to transfer an embryo if there is a "high risk of serious harm." "High risk" and "serious harm" are not defined, and are open to debate, particularly if a decision will preclude parenthood when a future child will, although impaired, nonetheless have a life worth living.

It is plausible that some clinicians may also be concerned that parents may subsequently regret a decision to transfer an embryo it the child subsequently suffers ill-health and may hold them morally, if not legally, responsible. Yet such concerns could be managed by robust counselling and informed consent processes, whereby it is established that prospective parents have been provided with sufficient information to make such a choice.

The principle that generally informs clinical views regarding the acceptability of embryo transfer in this context is often claimed to be premised on promoting the "welfare of the child", rather than on the principle of reproductive liberty. While this may not be based on the historical eugenic ideology of improving society, it nevertheless adopts a particular conception of parental duty, or virtue, based on a future child's well-being.[66] However, this conflates a welfare test with the embryos genetic profile, when well-being may be implicated by a range of factors and is not merely dictated by genetics. Further, the notion that non-selection improves an individual child's welfare is problematic if it is accepted that refusing to transfer an embryo issue does not promote an individual's welfare, it only prevents conception and the potential birth of a particular child. If we consider that an embryo has a unique genetic identity, any selection choice does not alter the life of any actual child once born, it merely alters which individual is born. It follows that if a child is born with a sufficient level of well-being that it may be considered to have a life worth living, there is no harm visited on that child by their parent's choice to implant the embryo and carry it to term. No "person-affecting" harm is committed in this situation, because no individual/victim is made worse off.

Ultimately it is debatable whether clinicians should be the final arbiters of such choices, or whether these decisions fall within the range of private decisions that prospective parents might make in conjunction with medical advice, taking into account what kind of life they are prepared to be responsible for bringing about and parenting. It is possible that a professional's conception of "reproductive responsibility" may not be consistent with a couple seeking to conceive a child.

5.3 The future of PGD/PGS and IVF: high resolution NGS

Looking towards the future, the extensive diagnostic potential of preimplantation NGS makes its increasing use likely. Significantly, NGS is reported to be less expensive than traditional PGS, although only a small number of laboratories are capable of performing such testing. One of the first clinics to provide, and advertise, PGD/PGS-NGS was Polish clinic Invicta, which states on its website that it provides testing for all 24 chromosomes (22 pairs and x and y chromosomes) chromosomes and for any known single gene disorder. NGS is also being adopted by some of the larger private companies in the US (e.g. Progenesis).[67] Reports of the first live birth of a child following NGS appeared in the US in 2013.[68] More recently scientists from the University of Oxford's Biomedical Research Center were involved in NGS research that resulted in the birth of a child in May 2016.[69]

However, as higher resolution NGS testing platforms are developed, concerns have once again been raised regarding the efficacy of PGS-version 2, due to the discovery of higher rates of embryo mosaicism than previously thought. This discovery means that embryos may not be able to be neatly categorised as normal (euploid) or non-normal (aneuploid), and challenges previous assumptions regarding embryo stability.

An unexpected outcome of high resolution NGS (hr-NGS) in PGS: an emerging new category of embryo

Traditionally, single cell PGS was premised on the presumption that generally all of the cells in an embryo are chromosomally identical, although in rare cases mosaicism may occur (i.e. when an embryo contains more than one cell line, each of which has a different chromosomal make-up). Consequently if a biopsied cell was found to be chromosomally euploid or alternatively aneuploid, it was generally presumed that all of the cells had the same chromosomal make-up.

However, research indicates this is not the case, and more embryos than previously thought may be mosaic. Significantly, some early mosaic embryos may still give rise to a healthy pregnancy. Some commentators who are critical of providing routine PGS in IVF cite evidence of several PGS cases where a woman subsequently miscarried a pregnancy diagnosed as euploid, which was subsequently found to be aneuploid; and other cases where relatively good prognosis patients have undergone repeated IVF/PGS cycles, but never achieved embryo transfer because all of the embryos were diagnosed as aneuploid.[70] A concern that some patients may be discarding embryos unnecessarily resulted in some clinicians transferring such embryos, reporting "surprisingly high normal live birth rates and so far, no miscarriages".[71] The following explains the potential reasons underlying this.

In the case of advanced maternal age, chromosomal aneuploidy typically occurs due to problems during meiosis (the process when sperm and eggs are produced) and is generally present in all of the embryonic cells (i.e. "uniform" aneuploidy). However, a significant percentage of embryos created by IVF may exhibit chromosomal mosaicism, which generally occurs after fertilisation. Mosacism is the presence of two or more cytogenetically distinct cell lines, each with a different chromosomal makeup.[72] Mosaic

embryos may have some chromosomally normal (euploid) cells, while some cells may contain chromosomal aneuploidy ("partial" aneuploidy), or there may be a mix of aneuploid cell lines. Chromosomal mosaicism is not related to maternal age and may also occur for other reasons, one potential cause being the IVF treatment/process itself.[73]

Trophectoderm biopsy in conjunction with high-resolution next generation sequencing (hr-NGS) has increased the capacity to identify mosaicism. Significantly, it detects more mosaic embryos than testing using microarray technology (29% vs. 5%).[74] It has been estimated that these technologies, which do not analyse individual cells but analyses the biopsy as a single entity providing an overall result, may be able to detect a mosacism level as low as 20%.[75] Significantly, research indicates that the actual incidence of mosaicism is far greater than previously thought, with preliminary data suggesting 10-30% of trophectoderm biopsies are found to be mosaic.[76]

Unsurprisingly, preliminary research suggests that embryos identified as mosaic following trophectoderm biopsy implant less often than euploid embryos, and those that do implant have a higher rate of miscarriage.[77] Despite this, there is evidence that some embryos diagnosed as mosaic may result in a successful healthy pregnancy.[78] One reason for this is that an embryo may self-correct as it develops. Alternatively, it may be because the cells in the trophectoderm do not reflect the cells in the inner cell mass, which subsequently develops into the fetus. The clinical significance of identifying chromosomal mosaicism is delineated in the following:[79]

> First, embryos may have robust mechanisms of self-correction … Second, TE cells may not always represent the cells of the inner cell mass, and other embryonic tissues may be comprised of cell lines that differ from the biopsied cells. Finally, the distribution of abnormal cells in an embryo can vary depending on the timing of mutational events and the degree of proliferation of aneuploid versus euploid cells (Spinner and Conlin, 2014). *Therefore, embryos deemed mosaic by PGS have the potential to develop into a fetus that is chromosomally normal, chromosomally abnormal, or mosaic to a lesser, greater, or similar degree to that predicted by the biopsy results* (Greco et al., 2015).

While most trophectoderm biopsy results indicate either normal for all chromosomes or abnormal (one or more aneuploidies), a proportion may indicate possible chromosomal mosaicism.[80] The possible implication of mosaicism ranges from none, to effects on placental function and/or the birth of a child that is clinically affected. This raises significant challenges.

The first guidelines to directly address the issue of mosaicism were recently released by the Preimplantation Genetic Diagnosis International Society (PGDIS). It recommends classifying embryos into three distinct categories following trophectoderm biopsy: 1. euploid (normal); 2. mosaic; 3. aneuploid. However, given that NGS can only detect mosaicism over a 20% threshold, the PGDIS defines the "euploid" group as mosaicism below 20%. Hence, even embryos classified as euploid following trophectoderm biopsy

may be partially mosaic (up to 20%).[81] While this classification may guide embryo selection, some patients may only have mosaic embryos available. In this event the PGDIS advises that, in the absence of fully euploid embryos, embryos classified as mosaic may be considered for transfer if a patient elects that option following appropriate counselling.[82] However it also provides recommendations regarding which kinds of mosaic embryos should be prioritized if transfer is contemplated.

Given the absence of being able to provide clear risk information regarding the outcome for embryos displaying mosaicism, counselling patients is particularly challenging in this context.[83] Providing such screening in conjunction with PGD, or as a stand-alone procedure, requires informing the patient of the potential for mosaic results, the potential outcomes, and prenatal testing options. The PGDIS provides that the following options should be discussed if a woman/couple is considering transferring an embryo that is mosaic:[84]

> a. A further cycle of IVF with aneuploidy testing to increase the chance of identifying a normal euploid blastocyst for transfer b. Transfer of a blastocyst with mosaic aneuploidies for low risk chromosomes only, after appropriate genetic counseling if available c. Appropriate monitoring and prenatal diagnosis of any resulting pregnancy, preferably by early amniocentesis (> 14 weeks gestation).

When informed of these possibilities, some patients may elect not to pursue PGS.[85] The invasiveness and expense of PGS, in conjunction with the possibility of uncertain results and "the burden of decision-making" regarding embryos diagnosed as mosaic may significantly reduce the appeal of PGS.[86]

Ultimately, providing PGS-version 2 as a routine clinical service remains debatable.[87] In a recent review, Gleicher and Orvieto reiterate that it is questionable whether a single trophectoderm biopsy (TEB) can accurately assess the embryos chromosomal status.[88] Further, they observe that a single TEB cannot provide reliable information because it does not represent the whole TE, and in turn, the TE does not reliably reflect the ICM which subsequently becomes the fetus. Further, embryos may be able to "self-correct downstream" from the blastocyst, meaning that some embryos may be discarded that could potentially have been successfully implanted and carried to term. Given these uncertainties, they argue that PGS should be restricted to research protocols. Peter Braude's salient observation several years ago remains pertinent in this context:[89]

> The question still to be answered is whether the test being offered to patients purportedly to improve their chance of success is robust enough to allow the discarding of some of their embryos, especially when at advanced maternal age they may have very few anyway ... Responsible practice requires responsible clinicians and embryologists who are prepared to test their results in proper clinical trials as the minimum standard before offering PGS.

In summary, the conclusion of current Randomised Controlled Trials are necessary to conclusively determine whether, and in what patient groups, PGS improves the time it takes to achieve a healthy pregnancy. Further, attempts to increase the chance of reproductive success by always eliminating aneuploidy no longer appears tenable, and some women may find that there is no chromosomally "risk-free" embryo available for implantation, creating challenging transfer decisions for clinicians and patients.

5.4 Approaches to NGS: information disclosure

While traditional testing has generally been performed in the case of increased risk and is targeted to interrogating a particular of the genome (PGD) or, alternatively, to detect common trisomies (PGS), NGS constitutes broad/untargeted testing. There is as yet no established policy for NGS performed in the preimplantation context. Different groups have adopted different approaches. The following considers policy adopted by a multidisciplinary professional group, compared with that adopted by the UK Human Fertilisation and Embryology Authority (HFEA) pursuant to the Human Fertilisation and Embryology Act 1990.

Professional approach: embryo selection and information disclosure

In the context of PGD performed in the presence of known genetic risk in conjunction with PGS, some commentators have mooted sequencing the whole genome, but only reporting particular areas.[90] A Belgian multidisciplinary group recently reported the principles it applies to guide selection and/or prioritisation of embryos following single cell (day 3) PGD with genome-wide haplotyping. This testing strategy provides information regarding the Mendelian disorder for which PGD is performed, as well as identifying additional mutations and numerical and structural chromosome anomalies genome-wide.

When determining transfer decisions, common aneuploidies that occur prior to fertilization (eg 13, 18, 21) are contraindicated for embryo transfer. However, the group notes that although chromosomally normal embryos were prioritized, transferring embryos with abnormalities that occur after fertilization is not contraindicated, given evidence that some non-normal embryos may implant and develop normally. In terms of broad scope (untargeted) embryo screening for mutations and variants that are unrelated to the condition for which PGD is indicated, the authors noted studies indicating the limited analytic and clinical validity of identifying single gene mutations in the embryonic context. Also noted was the potential to identify variants of unknown significance and the potential to identify non-medical traits. Ultimately the policy adopted was said to be guided by[91]

> The basic ethical principle for embryo selection and transfer is that the embryos may not be selected based on features that the society considers as normal nor on characteristics that the couple may indicate as desired for their future child (De Wert et al., 2014). Only clinically relevant information leading to known severe diseases can be used for embryo selection and embryo transfer prioritization (Shenfield et al., 2003). Hence, genetic risk factors or genetic lesions at the DNA sequence level other than the reason of referral are currently not considered during embryo selection and prioritization.

The policy was developed by a multidisciplinary team of clinical geneticists, fertility specialists and ethicists, although it does not appear that the group included fertility service users. The policy clearly sets out the principles used to inform embryo selection, and justifies its selection criteria for embryo transfer according to developments in PGS research and WGS studies. An interesting feature of the guidelines is that it clearly states how embryos are to be prioritized for transfer, and the information that is, and is not disclosed to prospective parents. However, the policy may conflict with parental preferences to be informed of incidental findings, particularly potentially clinically relevant findings.[92]

The authors note that their policy is one approach among many potential approaches in the absence of an international consensus on implementing novel embryo testing technology. In contrast the UK Human Fertilisation and Embryology Authority (HFEA) has adopted a different policy approach.

Legal Approaches to NGS: the United Kingdom

The United Kingdom have been at the forefront of IVF and PGD. It is also one of the first jurisdictions to directly address advances in genomic testing in policy. The following sets out the general mechanics of the Human Fertilisation and Embryology Act 1990 (the HFE Act) before analysing the UK approach to NGS.

HFE Act 1990 and the Code of Practice (8th ed)

The HFE Act establishes certain prohibitions regarding embryos,[93] and authorises the HFEA to act as an arms-length licensing and policy-making body.[94] The HFEA may grant clinics a license to perform approved activities in the course of providing "treatment services".[95] Treatment services are defined as "medical, surgical or obstetric services provided to the public … for the purpose of assisting women to carry children".[96] The activities for which the HFEA may grant treatment licences are specified in Schedule 2 of the Act.[97]

The Act stipulates standard conditions that automatically apply to all licences authorized by the HFEA.[98] It specifically provides that a "woman shall not be provided with treatment services unless account has been taken of the welfare of any child who may be born as a result".[99]

The Act also specifies the purposes for which embryo testing may be licensed, and explicitly prohibits PGD for social sex selection.[100] Paragraph 1ZA of schedule 2 to the Act provides that the HFEA may not authorise embryo testing unless it is for one of the purposes specified.[101] With the exception of Preimplantation HLA tissue typing, PGD is regulated by the HFEA on a condition-by-condition basis.[102] The HFEA has responsibility for determining, according to statutory criteria provided, the conditions for which PGD may be performed. [103] The HFEA also maintains a *Code of Practice* to inform its licensing decisions and establish necessary standards for fertility clinics. The HFEA is responsible for reviewing a condition and, if approved, it is placed on an official list.[104] Once approved, a licenced clinic may perform PGD for any of the conditions appearing on that list.

The provisions governing preimplantation genetic testing in paragraph 1ZA distinguish between testing that is performed for screening purposes (PGS), and testing to identify a causative mutation that an embryo is known to be at-risk of inheriting (PGD).

Preimplantation genetic screening (PGS)

As already noted, the overriding objective of PGS is to enable identification and selection of embryos that have the greatest chance of successfully implanting in a woman's uterus and being carried to term. Hence the HFE Act permits testing for the purposes of:

> (a) establishing whether the embryo has a gene, chromosome or mitochondrion abnormality that may affect its capacity to result in a live birth.[105]

On the face of it this provision could enable any woman to access PGS, although PGS has traditionally been used in instances of recurrent miscarriage or advanced maternal age. Given advances in genomics and PGS, the HFEA's Scientific Clinical Advances Advisory Committee (SCAAC) undertook a review of PGS technologies in 2015. It noted that, on the basis of clinical trials of PGS-version 2 in 'good prognosis' IVF patients that[106]

> There has been a shift in our understanding of the role of PGS. It should no longer be considered as a means for increasing the pregnancy rate per cycle, particularly in women of advanced maternal age, who are likely to have no normal embryos to transfer after PGS. The current view is that PGS should not be considered as a means of deselecting aneuploid embryos, but rather for ranking embryos in order of quality and using this information to prioritise embryo transfer.[107] The end goal for fertility treatment of achieving a pregnancy is not the only marker of success. Achieving a pregnancy in the shortest possible time, with the fewest number of miscarriages is also highly desirable and PGS may help in this regard.

The above quote acknowledges that new testing techniques may result in an increasing number of embryos being identified with a chromosomal abnormality, particularly in women with AMA. However, this may not necessarily preclude transfer, but it may inform prioritisation of the embryos for transfer. The SCAAC considered that the requirement in the *Code of Practice* that clinics 'must validate the use of PGS for each category of patient to which they offer it' was outdated in regard to modern clinical practice and technology.[108] However that requirement has not been amended in the *Code of Practice*.

The SCAAC went on to consider the implications of modern genetic technologies such as aCGH, SNP-array and NGS, stating[109]

> 5.12. … many of the newer PGS technologies are able to generate very detailed genetic information, including the presence of segmental aneuploidies as small as 14Mb in size. However, for findings of this nature it will often be unclear a) whether the genetic abnormality would affect an embryo's capacity to result in a live birth, and b) what the clinical relevance would be (ie whether or not it would cause a genetic disease). As such, this raises both legal and ethical concerns.

It is implicit in the above that the range of information derived from NGS extends beyond the current boundary markers imposed by the Act, which is to identify gene, chromosome or mitochondrion abnormalities that may affect an embryo's capacity to result in a live birth. However, the SCAAC states:

> 5.13. The Executive has sought legal advice on this matter and has been advised that as the additional data created by some newer PGS techniques is a by-product of the primary test, it cannot be said that they constitute a breach of the requirements set out in the Act. However, concerns still remain. Why would clinics choose to carry out tests that could produce data that are currently impossible to interpret? Is it proper that clinical decisions are made on data of this sort, and when they are, can clinics be considered to be subverting the legislation?
>
> 5.14. *Leaving aside the ethics of carrying out genetic testing which may generate uninterpretable data*, practically what should clinics do with such results? The current practice of embryo testing laboratories is to flag all anomalies to the requesting centre and to highlight when there are abnormalities present for which clinical significance cannot be determined. It is then the decision of the treating clinician, genetic counsellor or other qualified professional to determine whether the embryo should be transferred in accordance with the law/with the aid of a local ethics board.[110] In the view of the Executive, it is only acceptable to carry out genetic tests that can generate data of unknown clinical significance if patients receive patient information and are offered counselling prior to PGS, which sufficiently explains what the potential finding may be and what they mean.

Significantly, stakeholder views regarding handling and sharing information was also sought. In a subsequent HFEA meeting the Regulatory Policy Manager detailed a summary of these views that indicated the following:[111]

> Patients would want access to any information generated through embryo testing, however ambiguous the finding may be;
>
> Patients should see an expert in interpreting genetic information and discuss their options in the light of the information generated;
>
> Patients should be able to opt out of receiving any additional genetic information that embryo testing might find;
>
> Genetic information which could not help select an optimal embryo for transfer should not be tested for.

Subsequently the HFEA amended its Code of Practice reflecting developments in NGS.

HFEA Code of Practice (Amended July 2016)

It seems that the HFEA has sought to makes its policy consistent with other areas of genomic medicine. It states that it's approach to managing information generated by new testing techniques is informed by general guidelines on genomic testing "and should be referenced when providing guidance to the sector".[112] These guidelines include policy endorsed by Genomics England, as well as best practice guidelines issued by the Joint Committee on Medical Genetics (encompassing the Royal College of Physicians, the Royal College of Pathologists and the British Society for Human Genetics) and by the Association of Clinical Genetic Science.[113] These guidelines address consent and confidentiality in clinical genetic practice (Joint Committee) and targeted NGS (Association of Clinical Genetic Science).[114]

The HFEA Code of Practice consequently requires that clinics inform patients undergoing PGS of:[115]

> (a) the procedure and risks associated with the procedure
>
> (b) that more robust clinical and laboratory trials are needed to assess whether or not PGS significantly increases live birth rates
>
> (c) the failure and misdiagnosis rates associated with PGS for aneuploidy, including the fact that false results can be positive or negative
>
> (d) the concept of mosaicism, and the effect that this could have on the accuracy of results
>
> (e) that PGS techniques are capable of detecting segmental aneuploidies [ie CNVs] which may generate results where the clinical significance is not known
>
> (f) that there is no guarantee against a miscarriage occurring, despite PGS for aneuploidy being performed, and
>
> (g) the financial and emotional costs where treatment fails and there is no live birth following PGS for aneuploidy.

Significantly, in the case of women undergoing PGS who do not wish to be given any additional genetic information such as CNVs (segmental aneuploidies), the Code provides that the "centre should follow, where possible, guidelines around PGD for non-disclosure".[116] These non-binding guidelines referred to were previously formulated to accommodate prospective parents at risk of a serious, untreatable late-onset condition (such as Huntington disease) to undergo IVF/PGD to ensure a child is not born with the mutation, without finding out their own disease status. In this context if an embryo tests positive it confirms the presence of the mutation in the parent, consequently the parent is not informed of the embryonic test results, but is reassured that any embryos transferred will not have the mutation. The Code of Practice guidelines permit centres to withhold test results in exceptional circumstances when the following conditions are met:[117]

(a) that patients are given the opportunity to receive genetic counselling on the implications prior to giving consent,

(b) that protocols are established to limit, as far as possible, the risk of unwanted disclosure to the patients.

The Code recommends that centres document the reasons for not disclosing results along with a written informed consent including:[118]

(b) a statement from the people seeking treatment confirming that they have been given the opportunity to receive genetic counselling and that they have, prior to giving consent, received information: (i) on the risks of inadvertent disclosure.

Rather than adopting an essentialist approach to preimplantation testing, the HFEA have arguably endorsed a constrained parental choice model that draws on guidelines for genomic testing in the wider context, and implemented measures to address issues associated with non-disclosure. This approach requires skill in genetic counseling and obtaining informed consent.

Preimplantation Genetic Diagnosis

In regard to preimplantation genetic diagnosis, the HFE Act provides that the HFEA may licence PGD if "there is a particular risk that the embryo may have any gene, chromosome or mitochondrion abnormality" that poses a "significant risk" of a future individual having or developing "a serious physical or mental disability or illness or any other serious medical condition".[119] Similarly, sex selection is permitted in the case of a "particular" risk of a child having or developing a gender-related "serious physical or mental disability", "serious illness" or "any other gender-related serious medical condition".[120]

Given the absence of a statutory definition the HFEA provides guidance to assist the Licence Committee determine whether a "particular" risk exists in any given situation. The HFEA *Explanatory Note* requires the Committee to take into account whether or not the abnormality is heritable and the relevant mode of inheritance, which the HFEA describes as "an objectively measurable criterion", such as a one in two chance or one

in four chance of an embryo having that abnormality.[121] While the applicable provision authorises testing in the case of a "particular" risk, it extends the scope of permissible testing further, allowing preimplantation testing not only for that abnormality but also for any *other* gene, chromosome or mitochondrion abnormality, subject to express limits.[122] A licence cannot authorise testing unless the Authority is satisfied[123]

> 1ZA(2)(1)
>
> (a) in relation to the abnormality of which there is a *particular* risk, and
>
> (b) in relation to *any other abnormality* for which testing is to be authorised under sub-paragraph (1)(b)
>
> that there is a *significant* risk that a person with the abnormality will have or develop a *serious physical or mental disability*, a *serious illness* or any other *serious medical condition*.

As the arbiter of what constitutes a "significant" risk of a "serious" disability in the absence of a statutory definition, the HFEA *Explanatory Note* states that determining "significance" requires an assessment of a mutation's "penetrance" (i.e. the likelihood of an individual with the mutation developing the relevant condition).[124] If penetrance is variable, it instructs the Licence Committee to assess the condition according to the *highest possible risk*.[125]

The *Explanatory Note* also specifies factors to be considered when determining a condition's "seriousness". If the symptoms of the condition are variable, the HFEA clearly urges the Licence Committee to consider the *worst possible case-scenario*.[126] The *Explanatory Note* clearly encourages a generous interpretation of the statutory provision, encouraging its greatest possible application.

Of significance in this context is that under paragraph 1ZA(1)(b) multiple testing may be performed in the course of PGD, not just of a known causative single gene mutation, but also *for any other genetic or structural chromosomal abnormality*.[127] Consequently, testing may be performed for a monogenic disorder such as cystic fibrosis, as well as additional genetic testing to identify any other genetic conditions or chromosomal aberrations an embryo may have.[128] Access to PGD to test for a single gene disorder however still initially requires evidence of a particular risk, either as a result of parents undertaking expanded screening where a previously unknown mutation is detected, or if there is a family member with the condition. As of 2016, the list of conditions licensed by the HFEA extends to almost 400.[129] Some licensing decisions indicate a significantly more generous interpretation of the statutory provisions than others.[130]

In summary, while it was initially assumed that the extent of add-on testing in the course of PGD would be necessarily restricted given the limited amount of analysis that can be performed on one or two cells, this is arguably no longer the case. However, a limiting factor is that any condition for which embryo testing is performed must be expressly considered and approved by the HFEA.[131] Nevertheless, it is clear that if whole genome analysis becomes available at the preimplantation stage, the potential scope of preimplantation gene testing will increase exponentially.

Embryos with known genetic abnormalities

As noted earlier, it is possible that PGD may not result in any mutation-free embryos, and as higher resolution/genome wide screening develops, the incidence of "failed" PGD/PGS may increase when there are no mutation-free or chromosomally euploid embryos. Although the UK HFE Act contains statutory provisions that govern embryo selection in the case of failed PGD, the primary rationale for introducing these provisions was to prevent PGD being used to deliberately select embryos with mutations associated with disabling traits, such as Deafness.

Section 13(5) of the Human Fertilisation and Embryology Act 1990 (as amended) provides that the welfare of any child who may be born as a result of treatment services must be taken into account, and also imposes limitations on transferring embryos known to have a genetic mutation. Section 13(9) provides that embryos "known to have a gene, chromosome or mitochondrion abnormality involving a *significant risk* that a person with the abnormality will have or develop" a serious physical or mental disability, a serious illness, or any other serious medical condition "*must not be preferred* to those that are not known to have such an abnormality". Section 13(10) extends this restriction to preferring embryos with a particular sex-related risk of serious disability or illness. But although the Act seeks to prevent the *preferential* selection of an embryo with a known genetic anomaly, it stops short of imposing a full-blown prohibition on the selection of such embryos.

Although the primary rationale for introducing sections 13(9) and (10) was to prevent PGD being used to select embryos with mutations associated with disabling traits, such as Deafness, it was also introduced to respond to the issue of "failed PGD". As noted, this involves situations when PGD is undertaken to identify a particular mutation, but all of the resulting embryos are identified as having that particular mutation.[132] Such a scenario could involve PGD performed to identify *BRCA1* or *BRCA2* mutations (which are associated with the development of breast and ovarian cancer in later life) but which results in all of the embryos being identified as carriers of the mutation. Although the Act essentially prohibits performing PGD with the *objective* of selecting an embryo with a disease or illness-related gene variant, the *Code of Practice* provides an exception to the prohibition on transferring embryos known to have an abnormality. In such situations, the HFEA *Code of Practice* states that section 13(9) and 13(10) of the Act:[133]

> … applies *only* where there is at least one other embryo suitable for transfer that is not known to have the characteristics. Where there is no other embryo suitable for transfer, an embryo with these characteristics may be transferred.

This policy is implicitly informed by the so-called (and ethically contested) principle of "procreative beneficence". This posits that if a putative child would have a disability if born, and if that outcome is reasonably avoidable by substituting another child in that child's place, substitution is the morally preferable course of action.[134] The HFEA *Code of Practice* imposes additional obligations on fertility service providers in these circumstances, stating that:[135]

> The use of an embryo known to have an abnormality … should be subject to consideration of the *welfare* of any resulting child and should *normally* have approval from a clinical ethics committee.
>
> If a centre decides that it is appropriate to provide treatment services to a woman using an embryo known to have an abnormality … it should document the reason for use of that embryo.

Two important points may be made regarding these provisions. First it essentially imposes a hierarchy of selection. For those who are sensitive to Disability Rights arguments, this conveys a problematic attitude to the value of disabled persons lives. Second, for those who consider this is primarily a prospective parent's decision, it codifies a particular concept of reproductive "responsibility", which arguably has problematic and eugenic overtones. Although such a decision directly implicates prospective parental interests, the HFEA clearly imposes a "gatekeeper" role on the third parties identified: specifically the fertility service and the ethics committee.

NZ law: HART Act 2004 and the HART Order 2005

Clinical PGD has only been available in New Zealand since 2005. Initially this involved "transport" PGD, whereby biopsied samples were analysed in an Australian laboratory.[136] While it is now performed locally, the only NZ clinic with the capacity to perform NGS to identify large chromosomal abnormalities (i.e a loss or gain of one or more chromosomes) is Auckland private fertility clinic, Repromed.

The regulatory framework governing assisted reproductive technology is established by the Human Assisted Reproductive Technology Act 2004. The Act contains a prohibition on non-medical sex selection, but otherwise establishes an Advisory Committee on Assisted Reproductive Technology (ACART) that is responsible for formulating guidelines and giving advice to the Minister involving assisted reproductive procedures and research. It also establishes an Ethics Committee on Assisted Reproductive Technology which is responsible for considering applications to perform assisted reproductive procedures that must be ethically approved in accordance with ACART guidelines before they may be performed.

The Act provides general principles that any person exercising powers or performing functions under the Act must be guided by. Section 4 of the Act stipulates that:

> (a) the health and well-being of children born as a result of the performance of an assisted reproductive procedure or an established procedure should be an important consideration in all decisions about that procedure:
>
> (b) the human health, safety, and dignity of present and future generations should be preserved and promoted:
>
> (c) while all persons are affected by assisted reproductive procedures and established procedures, women, more than men, are directly and significantly affected by their application, and the health and well-being of women must be protected in the use of these procedures:

(d) no assisted reproductive procedure should be performed on an individual and no human reproductive research should be conducted on an individual unless the individual has made an informed choice and given informed consent

(e) …

(f) the needs, values, and beliefs of Māori should be considered and treated with respect:

(g) the different ethical, spiritual, and cultural perspectives in society should be considered and treated with respect.

Section 6 of the Act enables an assisted reproductive procedure to be declared to be an "established procedure", subject to certain requirements, by Order in Council. An "established procedure" may be performed routinely without the need for prior ethical approval. The Minister of Heath may recommend that such an order be passed on the basis of advice tendered by ACART. If ACART recommends that an assisted reproductive procedure should become an established, it must provide a report explaining the procedure, an assessment from published and peer reviewed research of its known risks and benefits, and whether in the opinion of ACART, the known risks to health fall within a level of risk that is acceptable. The current HART Order 2005 came into effect over a decade ago.

The Order currently permits PGD to diagnose conditions that have a 1:2 or a 1:4 chance of transmission (i.e. Mendelian inheritance) and that may cause a future individual to be "seriously impaired", which is not defined.[137] The Order also provides that PGD may be performed to test for non-familial chromosomal disorders (aneuploidy testing) when the woman is of AMA, or has experienced recurrent implantation failure or miscarriage.

Given that many women accessing ART are over 35, or alternatively may have history of recurrent miscarriage, many women will qualify for PGS in New Zealand under the HART Order.[138] The Order otherwise precludes "good prognosis" IVF patients routinely accessing PGS. If PGS-version 2 is found to improve IVF success rates, (which as yet is not definitively determined) the Order may need to be revisited so that all women seeking IVF have the option to undertake PGS if they are prepared to consent to an invasive embryo biopsy and to meet the additional expense. This would require ACART to advise the Minister that the Order be modified on the basis of evidence regarding risks and benefits, and would require consideration of additional factors associated with newer technology.[139]

As high resolution NGS develops internationally, and if it is introduced into New Zealand, clinics will need to address the additional complexity associated with increased screening and diagnostic capacity. This includes determining what information will be derived from tests, what information prospective parents may access, processes for obtaining consent and providing disclosure of information, and how information is stored. ACART would need to consider whether the non-disclosure model adopted

by the UK HFEA should be replicated, or whether an alternative approach should be adopted. Clinics may also be faced with clinical challenges, such as cases where all of the resulting embryos have a deleterious mutation or chromosomal abnormality of some kind which complicates selection and transfer decisions. Counseling will need to include the possibility of false positive and negative results, as well as the need for follow up testing. The approach to dealing with additional or unexpected results, such as sex chromosome aneuploidy and incidental findings, also needs to be considered.

What may be extrapolated from empirical research in other contexts is that preference for information will differ amongst parents, levels of understanding will not be homogenous, and the effect of information may vary amongst recipient(s). Responses to information regarding predisposition to illness or variants of uncertain significance will vary, and may be adaptive or maladaptive.[140] However the NZ fertility consumer network, which are an engaged and active group of stakeholders, are likely to be extremely interested in technological advances in this field and both willing and able to contribute their views to policy development in this area.

At present, the current HART Order 2005 permits PGD to test for a single gene disorder when there is a known risk of inheritance, and would permit testing for multiple single gene disorders, provided there is evidence that the disorder has been identified in the family.[141] PGS is permitted for women undergoing IVF who are of advanced reproductive age, or have suffered from recurrent implantation failure or miscarriage.[142] These procedures may be accessed as routine clinical procedures.

However, the evolving era of higher resolution NGS tests is likely to extend to New Zealand in the future. This arguably creates additional issues that ACART will be wise to contemplate in advance, to ensure that clinical integration of newer testing technologies is well-considered and consistent with the HART Act 2004 principles. Given all of these developments internationally and the constantly evolving challenges, facilitating discussion amongst NZ stakeholders (including scientists in the field, clinicians, ethicists, lawyers and fertility service consumers) in the near future is desirable.

Conclusion

PGS and PGD both involve the analysis of embryonic cells obtained by biopsy, but while PGS has traditionally been performed in an attempt to improve the chance of a successful pregnancy, PGD is concerned with identifying a particular genetic mutation in an embryo. Consequently, these two technologies originally had distinct aims, with PGS less contentious given that it was concerned with achieving the birth of a child, rather than the birth of a particular child. However subsequent developments have altered the nature of PGS and PGD.

The current context

The development of high resolution genome-wide micro-arrays and NGS technology has extended testing capacity in both the PGD and PGS context. These technologies enable comprehensive screening of all chromosomes and, in the case of PGD, extends testing capacity beyond identifying a single monogenic disorder.

Historically PGS to detect and discard embryos with chromosomal anomalies was performed on the assumption that it would improve IVF success rates in specific patient groups, but was subsequently discredited given evidence that it provided little benefit and in some cases decreased the take-home baby rate. However, subsequent developments in biopsy methods and testing processes, in conjunction with microarray technology and NGS methods, has once again raised the spectre of improving implantation rates by detecting, ranking and discarding embryos with chromosomal aneuploidies. Indeed proponents of the new methods predicted that such technology could become the standard of care for all IVF patients. However this enthusiasm must be tempered by two important factors.

First, it is likely that with ever-deepening microarray and NGS technology there will be an increasing capacity to generate additional genomic information, such as identifying additional genetic mutations associated with both serious illness and less serious conditions or of unknown effect, as well as CNVs that are associated with serious conditions but which may have variable impact and severity, or be of unknown effect. In this sense, PGS may not only be performed to improve IVF success by detecting aneuploidies that reduce the chance of successful conception and birth, but also provide information regarding an embryos prospective future health. However broad scope PGD/PGS is not a panacea. Some of this information will difficult to interpret clinically, particularly at the embryonic stage where there is no fetal ultrasound to assist in identifying any physical effects of certain mutations and chromosomal variations. As discussed in the previous chapter, the clinical significance of susceptibility loci (CNVs) associated with neurodevelopmental and neuropsychiatric conditions is also both highly variable and uncertain, and there is debate about whether such variants should even be reported to prospective parents.

Another significant factor is that while there is emerging evidence that PGS using high resolution microarrays and NGS for aneuploidy *may* improve IVF success rates, its clinical utility is debated given a lack of definitive evidence that it actually reduces time to conceive and results in more life births and it is associated with burdens of cost and additional embryo interventions. More recently, NGS testing on trophectoderm biopsies has revealed an unexpected rate of mosaicism as a result of higher resolution testing. For some critics, this confirms that the central premise underlying PGS is flawed. They suggest that due to the unstable biological nature of embryos and the fluidity of embryonic development, deselecting embryos on the basis of aneuploidy leads to an unacceptable rate of false positive and false negative results, ultimately negating its clinical utility.

In the past, single cell PGS resulted in a binary result, i.e. either an embryo was normal/euploid or abnormal/aneuploid, and the decision whether or not to transfer was made accordingly. However, developments in high resolution NGS has resulted in the emergence of a new/intermediate category of embryo: the mosaic embryo. Mosaic embryos currently occupy a "middle ground" in terms of transferability. Embryos that are diagnosed as mosaic have an uncertain prognostic outcome often depending on the chromosome that is affected, ranging from no effect on a future fetus who will likely be born healthy, to causing fetal demise or, if successfully carried to term may cause illness

or impairment in a future child. Given this, high resolution NGS/PGS is now provided on the basis that it may reduce the time taken to achieve a pregnancy by selecting the embryo most likely to implant successfully and result in a healthy birth. Hence proponents of PGD/PGS-NGS characterise PGS as a tool for "ranking" embryos, rather than as a tool for eliminating non-viable/aneuploid embryos. Clearly some women who find that all of their embryos are mosaic face difficult and complex decisions regarding embryo transfer, and potentially ongoing anxiety regarding fetal health when such embryos are transferred. The psychological and emotional toll on prospective parents who receive ambiguous mosaic results cannot be underestimated, and it is likely to alter the experience of pregnancy and childbirth in this context.[143] Ultimately whether newer PGS technology improves IVF outcomes by enabling better selection or ranking of embryos is currently the subject of clinical trials.

Ultimately the main themes that have emerged from this literature review involve issues of clinical validity and how the increasing information that expanded testing will provide may be experienced by patients and managed by professionals; as well as conceptions of reproductive responsibility and the appropriate scope of parental liberty. Some prominent bioethicists have argued that all parents have an obligation to undertake IVF and PGD if they are aware of a pre-existing genetic vulnerability. This argument derives from Derek Parfit's response to the "non-identity" principle.

The non-identity principle posits that, due to each individual's unique genetic identity, choosing to create a life that is likely to have poorer prospects than a possible alternative life does not generally harm the individual born. Given the only alternative for that individual is non-existence, unless their life is so miserable that it is not worth living, no individual is harmed by the choice to bring them into the world. Hence even if an individual born has poorer life prospects than a hypothetical other person who might have been born in their place in the future, there is no victim of harm. However, Parfit claims that it is intuitively wrong, even if not harmful, to fail to choose the most optimal life if there is capacity to choose between potential lives.[144] Along similar lines Savulescu and Kahane claim that parents have a duty of "procreative beneficence" (PB). They assert:[145]

> … we believe that unless the risks and costs are substantial, parents ought to select the most advantaged child … we believe that PB instructs women to seriously consider *IVF* if natural reproduction is likely to lead to a child with a condition that is expected to reduce well-being significantly, even if that condition is not a disease. This is clearest if natural reproduction is likely to result in a child disposed to, say, clinical depression or autism. But we believe that reproducers also have strong reasons to seek to prevent even an innate tendency to negative affect, or the severe impairment in social skills associated with Asperger's syndrome.

Similarly, it has been claimed in the context of genetic predispositions/susceptibility to cancer, that procreative beneficence requires a woman to undergo PGD.

In contrast, it has been argued elsewhere that imposing such an obligation is both naiive and overstates the capacity of genetics to determine an individual's well-being.[146] Further it:[147]

> … may harm women by constraining reproductive choice and impairing their autonomy; it imposes a technology burden on society and encourages a social bias towards those conditions. Promoting medicalisation and geneticisation of conception in this way constitutes both a social harm and a gender harm.

While the concept of procreative beneficence may justify prospective parents choosing to undertake PGD on moral grounds, it seems harder to justify imposing a duty to undertake PGD and choose the best embryo based on predicted health status. It has been argued that the principle of procreative beneficence:[148]

> exemplifies genetic determinism at its most extreme. A conscientious application of its logic could lead individuals to endure multiple cycles of *IVF*—driven by the imperative of procreative beneficence and the prospect that there may be a "better" embryo yet to come.

As well as imposing a burden on women, this interpretation of procreative beneficence is also troubling from a human rights perspective.[149] To suggest that creating a world with less disability/greater "well-being" is a matter of moral obligation, rather than pure preference seems dubious, transforming reproduction in to a public rather than a private endeavour.[150] What constitutes a sufficiently serious condition to warrant such a parental duty is a particularly challenging issue, that has been subject to sustained analysis.[151] While it is widely accepted that prospective parents may reasonably wish to avoid conceiving a child with a particular condition, it is a far greater leap to suggest that they are morally obliged to do so. Arguably it "renders the private a matter of public concern by removing the reproductive project from the privacy of individuals to the concerns of the collective".[152]

While Savulescu and Kahane suggest that procreative beneficence is a moral duty, they stop short of claiming it should be a legal duty.[153] However, bioethicist Janet Malek and lawyer Juding Daar claim that parents who choose to undertake IVF who know that there is a substantial risk the future child may inherit a serious disorder are arguably under a legal duty to use PGD.[154] Malek and Daar argue for a "relational view" of identity rather than (Parfitian) genetic identity. They claim that "for the purposes of reproductive decision making, the morally relevant characteristics of a future child are not genetic, but are instead related to the role that future child will play in the world".[155] On this account the prospective parent can improve the well-being of their "relational" or "notional" child by selecting against impairment. However again this only seems to provide a moral justification for parents who choose to use PGD, rather than a reason to require them to undertake an emotionally and physically costly procedure when selection is not consistent with their own values, and a child will still have a life worth living.

It is clear that concepts of genetic/parental responsibility are not homogenous. Some prospective parents may choose not to access testing when they are at-risk of transmitting a condition because it is not consistent with their individual concept of what it is to act "parentally".[156] This is emphasised, in particular, by empirical research involving individuals with serious genetic disorders or parents of children living with disabling conditions.[157] Yet as testing becomes more pervasive and subject to external expectations, it is possible that the likelihood of those with differing conceptions of reproductive responsibility having those views respected will be reduced if the concept of procreative beneficence becomes entrenched in policy and practice.

There is some irony in the two broad themes associated with expanded genomics: on the one hand, there is concern that, in some instances, parents may want to know too little about a future child's health and that genetic/parental responsibility presupposes obtaining health-related information. However much of the additional information that may be derived at the embryonic stage is uncertain and likely cause anxiety regarding future fetal health, making pregnancies even more tentative than in the past. On the other hand, there is concern that parents might want to know too much about a future child, particularly when it concerns non-health traits because it is generally thought to be contrary to acting "parentally". Ultimately, most prospective parents who elect such testing are generally seeking assurance that their baby will be "healthy enough", rather than seeking a perfect made-to-order baby. However, the public concern that prospective parents may seek PGD for "trivial" traits is pervasive.

Ultimately it seems that one of the main issue triggered by these technologies is how they are integrated into clinical practice. It remains to be seen how the increasing medicalisation of assisted reproduction and the potential shift to controlled conception as a result of expanded PGS will impact future women's' experience of pregnancy, childbirth, and child-rearing.

There are contrasting clinical approaches to expanded preimplantation screening and diagnosis. One professional group providing genome-wide PGD/PGS has developed a comprehensive and transparent approach to the way it ranks embryos according to chromosomal status. It limits disclosure of incidental information generated, and only reports information relevant to the condition being tested for. In contrast, the UK has adopted an approach that reflects the general approach taken to clinical genomic testing.

The UK approach is premised on educating prospective parents regarding the potential range of results, permitting them to elect not to receive certain categories of information, and imposes duties on providers to prevent inadvertent disclosure of unwanted information. However, as a result of the statutory framework, a decision to transfer an embryo with a known abnormality is not solely a decision for the parents and their clinician. The clinician must take account of the welfare of the future child that may result, and a transfer decision should "normally" have approval from a clinical ethics committee. Hence the locus of decision making is moved from the individual/couple to third parties.

Clearly these issues are the subject of debate internationally, where technological advances are being made continually, using increasingly high resolution tests. However, not all NGS platforms are the same, and vary in terms of what they are capable of detecting. NGS is not routinely used in New Zealand clinics, with only one fertility clinic currently providing NGS for eligible patients.

However, it is likely that, over time, more NZ fertility providers will provide increasingly sensitive embryo screening if current international clinical trials confirm that PGS/NGS successfully reduces the time it takes for a woman to conceive, and increases the live birth rate. Ultimately there are many issues that will need to be addressed by providers, patients, and ACART alike. Some of the broad questions to contemplate include:

- Does the technology used meet minimum requirements of clinical utility and validity?
- Are the risks of proportionate/disproportionate to the benefits?
- What information do prospective parents want to know, and is it the same for all parents?
- Do prospective parents have a duty to know certain information – should parents be able to "opt out" of receiving certain results?
- Who decides what information is to be disclosed following testing – should this be professionally predetermined, based on a shared/negotiated agreement with clinicians or, alternatively, should the scope of genomic screening be predetermined by regulators or policy-makers?
- What approach should be adopted to categorising ("binning") results: ie types of conditions, risk and severity?
- How will sufficiently informed consent, including the range of testing and the implications of results, be obtained?
- How will access to extended information be experienced by prospective parents; does it have the capacity to enhance or diminish the reproductive experience?
- Can the risk of psychosocial harm from preimplantation testing, such as increased anxiety, be mitigated?
- How is information best provided to prospective parents?
- What effect will extended testing have on the subsequent parent-child relationship?

The future

As noted in chapter 1 of this report, the latest development in NGS involves whole genome sequencing (WGS) and whole exome sequencing (WES). WGS has the capacity to examine the genetic variation in the entire DNA of an individual, while WES only measures variation in the DNA that code for proteins.[158] Although not currently a reality in the preimplantation context due to its prohibitive expense, UK scientist Dagan Wells recently claimed that "it is anticipated that accurate derivation of an embryo's entire genome sequence prior to transfer to the uterus will become feasible in the coming months or years".[159]

However there is reason to be ambivalent about opportunistically trawling an embryo's genome. First, research suggests that there is a significant disjunction between the presence of a disease-causing gene mutation and ill health in an individual. That is, some healthy individuals have been found to have mutations that are annotated in genomic databases as causing serious disease, providing proof that genotype-phenotype associations are more complex than currently understood, and embryos carrying mutations associated with serious conditions could be discarded unnecessarily. Ultimately, it is questionable whether whole genome sequencing will even appeal to prospective parents. As noted previously in the preceding chapter, a US study involving genome-wide screening of newborn infants reported that few parents were interested in accessing screening. In addition, it failed to identify some (metabolic) conditions that would have been detected by new born screening.[160] The factors that influenced parental refusal of screening included concerns about privacy, the potential for unclear results, and implications for insurance—concerns that may similarly be levelled at the preimplantation stage.

Endnotes

1. Alan Handyside and others "Pregnancies from Biopsied Human Preimplantation Embryos Sexed by Y-specific DNA Amplification" (1990) 344 Nature 766; Alan Handyside and others "Pregnancies from Biopsied Human Preimplantation Embryos Sexed by Y-Specific DNA Amplification (1989) Lancet 347.
2. Allen Buchanan and others *From Chance to Choice: Genetics and Justice* (Cambridge University Press, Cambridge, 2000).
3. Sonia Suter "A Brave New World of Designer Babies?" (2007) 22 Berkeley Technology Law Journal 897 at 923.
4. Timothy Murphy "When Choosing the Traits of Children is Hurtful to Others" (2010) 37 Journal of Medical Ethics 105 at 107; J Lindemann Nelson "Hurts, Insults and Stigmas: a Comment on Murphy" (2011) 37 Journal of Medical Ethics 66.
5. PGD has generally been used to detect single gene disorders such as cystic fibrosis or haemophilia, as well as identifying the few chromosomal abnormalities that are known to be hereditary. Robertsonian translocations may be inherited, but the majority of other chromosomal abnormalities are sporadic.
6. Sesh Sunkara and others "Pre-term birth and low birth weight following preimplantation genetic diagnosis: analysis of 88,010 singleton live births following PGD and IVF cycles" (2017) 32 Hum Reprod 432-438; Inge Liebaers and others "Report on a Consecutive Series of 581 Children Born After Blastomere Biopsy for Preimplantation Genetic Diagnosis" (2010) 25 Human Reproduction 276 (581 children – up to 2 months post birth); J Chang, S Boulet, G Jeng, L Flowers, D Kissin "Outcomes of in vitro fertilization with preimplantation genetic diagnosis: an analysis of the United States Assisted Reproductive Technology Surveillance Data, 2011-2012" (2016) 105 Fertil Steril 394-400.
7. Although long-term studies have yet to be performed given that the oldest children born following PGD are less than 27 years of age, recent research indicates that children's cognitive and psychosocial development following PGD is comparable to children conceived naturally or after ICSI. C Winter and others "Psychosocial development of full term singletons, born after preimplantation genetic diagnosis (PGD) at preschool age and family functioning: a prospective case-controlled study and multi-informant approach" (2015) 30 Human Reproduction 1122 (152 children). C Winter and others "Cognitive and psychomotor development of 5-to 6-year-old singletons born after PGD: a prospective case–controlled matched study" (2014) 29 Human Reproduction 1968.
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10. Chromosomal abnormalities include not only the presence of additional chromosomes, as in Trisomy 21 (causing Down Syndrome) but also structural aberrations such: as reciprocal translocation; Robertsonian translocation; inversions and deletions as well as numerical aberrations such as: 47 XXY (Klinefelter Syndrome); 47 XYY; Sex chromosomal mosaicism; and Male meiotic abnormalities. See Anonymous "Preimplantation Genetic Testing" (2004) 111 British Journal of Obstetrics and Gynaecology 1165.
11. Kristien Hens, Wybo Dondorp, Joep Geraedts and Guido de Wert "Preimplantation Genetic Screening for the Single Embryo: Aims and Responsibilities" in E Scott Sills (ed) *Screening the Single Euploid Embryo: Molecular Genetics in Reproductive Medicine* (Springer, 2015) chapter 27.
12. J Traeger-Synodinos, E Goossens "Data from ESHRE PGD Consortium" (2013) 28 Hum Reprod 28, S1.
13. Sebastiaan Mastenbroek and others "In Vitro Fertilisation with Preimplantation Genetic Screening" (2007) 357(1) New England Journal of Medicine 9; P Brezina and W Kutteh "Clinical Applications of Preimplantation Genetic Testing" (2014) 349 BMJ g7611; Joyce Harper, Emily Jackson, Karen Sermon and others "Adjuncts in the IVF laboratory: where is

the evidence for 'add-on' interventions?" (2017) 32 Human Reproduction 485.

14. These problems are due to "mosaicism" where more than one chromosomal makeup is present in the embryo. Consequently if only one cell is biopsied it may not accurately represent the embryonic DNA, and a misdiagnosis may occur.
15. Evidence suggests that biopsy at cleavage stage may cause slower development and/or embryo death. P Brezina, and W Kutteh "Clinical Applications of Preimplantation Genetic Testing" (2014) 349 BMJ g7611.
16. Martín, Julio and others "The impact of next-generation sequencing technology on preimplantation genetic diagnosis and screening" (2013) 99 Fertility and Sterility 1504.
17. H Stern "Preimplantation Genetic Diagnosis: Prenatal Testing for Embryos Finally Achieving Its Potential" (2014) 3 J Clin Med 280 at 287 citing: R Scott, K Upham, E Forman, T Zhao, N Treff, "Cleavage-stage biopsy significantly impairs human embryonic implantation potential while blastocyst biopsy does not: a randomized and paired clinical trial (2013) 100 Fertil Steril 624-630.
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Online 62. The authors reported successfully identifying small subchromosomal CNVs (<10 Mb) in biopsied embryos (blastocysts), as well as aneuploidy. The retrospective study reviewed 34 biopsies using NGS (CNVseq). Five blastocysts were identified as carrying a CNV (<10Mb), three were benign and two involved microdeletions associated with serious disease syndromes (Sotos syndrome and 7p terminal deletion syndrome).

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85. Andria Besser and Emily Mounts "Counselling considerations for chromosomal mosaicism detected by preimplantation genetic screening" (2017) Reproductive Biomedicine Online 369 at 372.
86. Ibid.
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90. H Stern "Preimplantation Genetic Diagnosis: Prenatal Testing for Embryos Finally Achieving Its Potential" (2014) 3 J Clin Med 280.
91. E Dimitriadou and others "Principles guiding embryo selection following genome-wide haplotyping of preimplantation embryos" (2017) 32 Human Reproduction 1-11.
92. Conrad Fernandez and others "Attitudes of Parents toward the Return of Targeted and Incidental Genomic Research Findings in Children" 16 (2014) Genet Med 633. (The study reported that over 80% of parents surveyed said that they would want to know all IF information found on their children, even for non-treatable conditions.)
93. HFE Act, s 3.
94. HFE Act, s 5.
95. HFE Act s 11(1) states that "The Authority may grant … (a) licences under paragraph 1 of Schedule 2 to this Act authorising activities in the course of providing treatment services …" Paragraph 1(3) of Schedule 2 provides that: "a licence under this paragraph cannot authorise any activity unless it appears to the Authority to be necessary or desirable for the purpose of providing treatment services".
96. HFE Act, s 2 (as amended).
97. Paragraph 1, Schedule 2, HFE Act. These activities include: bringing about the creation of embryos in vitro (a), procuring, keeping, testing, processing or distributing embryos (b), other practices designed to secure that embryos are in a suitable condition to be placed in a woman (d), placing any permitted embryo in a woman (e).
98. HFE Act, s 13.
99. HFEA Act, s 13(5).
100. Paragraph 1ZB of Schedule 2 of the Act.
101. HFE Act 1990, schedule 2, (1)(a)-(d). Paragraph 1ZA was inserted into schedule 2 of the Act by the Human Fertilisation and Embryology Act 2008.
102. In the past the HFEA Code of Practice provided that a clinic could only perform embryo testing for conditions, chromosomes or traits (or combinations of these) and specific tests listed in the Annex to their Licence, or as specifically approved by a Licence Committee on a case-

by-case basis. See J Snelling and others *Law and Regulation in Choosing Genes for Future Children: Regulating Preimplantation Genetic Diagnosis* (Dunedin, Human Genome Research Project, 2006) at p 283.

103. HFE Act 1990, s 11(1)(a).
104. See PGD Conditions Licensed by the HFEA. Available at www.hfea.org.uk.
105. Paragraph 1ZA(1)(a) of Schedule 2 of the HFE Act.
106. Scientific and Clinical Advances Advisory Committee *Preimplantation Genetic Screening* (HFEA, 10 June 2015) at [5.6].
107. This view was presented at both ESHRE's PGS conference and at the embryo testing SCAAC focus meeting.
108. Scientific and Clinical Advances Advisory Committee *Preimplantation Genetic Screening* (HFEA, 10 June 2015) at [5.7].
109. Scientific and Clinical Advances Advisory Committee *Preimplantation Genetic Screening* (HFEA, 10 June 2015).
110. This information was obtained at the embryo testing SCAAC focus meeting.
111. HFEA Meeting-Agenda, "Governance and Transparency (9/1/2016) 789" at p 12.
112. Human Fertilisation and Embryology Authority "Embryo testing: testing for more than one condition at a time HFEA (20/01/2016) 783" in HFEA (ed) *Authority Meeting-Agenda*, (HFEA, London, 2016) at 6.
113. Royal College of Physicians, the Royal College of Pathologists and the British Society for Human Genetics "Consent and confidentiality in clinical generic practice: Guidance on genetic testing and sharing genetic information" (A report of the Joint Committee on Medical Genetics): www.bsgm.org.uk/media/678746/consent_and_confidentiality_2011.pdf
114. Association for Clinical Genetic Science. Practice guidelines for targeted next generation sequencing analysis and interpretation: www.acgs.uk.com/media/774807/bpg_for_targeted_next_generation_sequencing_may_2014_final.pdf
115. Human Fertilisation and Embryology *Authority Code of Practice* (8th ed, London, revised July 2016) at [9.3].
116. Human Fertilisation and Embryology *Authority Code of Practice* (8th ed, HFEA, London, revised July 2016) at [9.6].
117. Ibid at [10.11].
118. Ibid at [10.12].
119. HFE Act 1990, schedule 2, paragraph 1ZA(1)(b).
120. HFE Act 1990, schedule 2, paragraph 1ZA(1)(c).
121. Human Fertilisation and Embryology Authority (2010) "Preimplantation Diagnostic Testing ("PGD") Explanatory Note for Licence Committee" (HFEA, 2010) at [4]. Available at www.hfea.org.
122. HFE Act, schedule 2, 1ZA(1)(b).
123. HFE Act, schedule 2, 1ZA(2)(1)(b).
124. Ibid at [5].
125. Ibid at [5.4] (emphasis added).
126. Ibid at [5.5] (emphasis added).
127. HFE Act, schedule 2, 1ZA(1)(b).
128. Legal advice received by the HFEA confirms that once the 'particular' and significant threshold is met for one condition, additional conditions that satisfy the 'significant' risk criteria may be performed regardless of whether there is a particular risk. Human Fertilisation and Embryology Authority "Embryo testing: testing for more than one condition at a time HFEA (20/01/2016) 783" in HFEA (ed) Authority Meeting-Agenda, (HFEA, London, 2016) at 5.
129. Human Fertilisation and Embryology Authority PGD Conditions licensed by the HFEA (2013). [Online] Available at www.hfea.org.uk.
130. J Snelling and C Gavaghan "PGD Past and Present: is the HFE Act 1990 now 'Fit for Purpose'? in K Horsey (ed) *Revisiting the Regulation of Human Fertilisation and Embryology* (Routledge, 2015) pp 80-97.
131. Human Fertilisation and Embryology Authority Code of Practice (8th ed, London, 2009) at

T88 and T89.

132. I Karpin and K Savell *Perfecting Pregnancy: Law, Disability, and the Future of Reproduction* (Cambridge University Press, New York, 2012) at 186.
133. Human Fertilisation and Embryology Authority (2009) HFEA Code of Practice (8th ed, London) at 10C.
134. Julian Savulescu and Guy Kahane "The Moral Obligation to Create Children With the Best Chance of the Best Life" (2009) 23 Bioethics 274. This theory is a derivative of philosopher Derek Parfit's famous 'Claim Q', which held that: "if in either of two outcomes the same number of people would ever live, it would be bad if those who live are worse off, or have a lower quality of life, than those who would have lived". D Parfit *Reasons and Persons* (Oxford, Oxford University Press, 1984) at 360.
135. HFEA *Code of Practice* (9th edition, 2016) at [10.17], [10.18].
136. J Snelling "Law and Regulation" in Human Genome Research Project *Choosing Genes for Future Children: Regulating Preimplantation Genetic Diagnosis* (Dunedin, 2006) at 329.
137. HART Order 2005, clause 6, part 2 of the Schedule.
138. Richard Fisher, Fertility Associates, ART Symposium, February 10, 2017. The average age of women receiving IVF at Fertility Associates is 37.8 years, while the majority of women are over 40 years.
139. HART Act, s 35(1)(b)(iii).
140. See discussion in chapter II. See also Stacy Gray and others "Social and behavioral research in genomic sequencing: approaches from the Clinical Sequencing Exploratory Research Consortium Outcomes and Measures Working Group" (2014) 16 Genetics in Medicine 727.
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143. Kira Peikoff "In IVF, Questions About 'Mosaic' Embryos" (United States, *The New York Times*, April 18 2016) https://www.nytimes.com/2016/04/19/health/ivf-in-vitro-fertilization-pregnancy-abnormal-embryos-mosaic.html
144. D Parfit *Reasons and Persons* (Clarendon Press, Oxford, 1984) at 360. "If in either of two outcomes the same number of people would ever live, it would be bad if those who live are worse off, or have a lower quality of life, than those who would have lived".
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147. Jeanne Snelling "Preimplantation Genetic Diagnosis for Susceptibility Conditions: A New Frontier or a Logical Extension?" (2008) 16 Journal of Law and Medicine 263 at 274.
148. Jeanne Snelling "Parental Preferences and Procreative Choices: Reproductive Liberty and the Regulation of Preimplantation Genetic Diagnosis" (unpublished PhD thesis, 2012, University of Otago) at 356.
149. Jeanne Snelling "Parental Preferences and Procreative Choices: Reproductive Liberty and the Regulation of Preimplantation Genetic Diagnosis" (unpublished thesis, 2012, University of Otago) at 356.
150. Colin Gavaghan *Defending the Genetic Supermarket: Law and Ethics of Selecting the Next Generation* (Routledge Cavendish, London, 2007) at 88.
151. Allen Buchanan and others *From Chance to Choice: Genetics and Justice* (Cambridge University Press, Cambridge, 2000).
152. See Thomas Baldwin "Choosing Who: What is Wrong with Making Better Children?" in John Spencer and Antje du Bois-Pedain (eds) *Freedom and Responsibility in Reproductive Choice* (Hart Publishing, Oxford and Portland Oregon, 2006) at 15, 16. Baldwin defends what he calls the weak version of procreative beneficence, which is that "[i]t is always permissible to make children in ways which are likely to make their lives better than the lives of those children who would otherwise have been born". This is also more compatible with reproductive liberty.
153. For a critique of the principle of Procreative Beneficence see Rebecca Bennett "When Intuition is Not Enough. Why the Principle of Procreative Beneficence Must Work Much

Harder to Justify Its Eugenic Vision" (2013) 28 Bioethics 447.

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Appendix One

The ACMG Guidelines 56 Conditions

Gene	Phenotype	Age of Onset	Inheritance	Presentation
BRCA1	Hereditary breast, ovarian cancer	Adult	AD	Familial early onset cancer resulting from heterozygous germline mutations in the *BRAC1* gene on chromosome 17q21.31. Affects both female and male family members, younger onset than sporadic breast or ovarian cancer and frequently bilateral. May also be indicated in pancreatic cancer.
BRCA2	Hereditary breast, ovarian cancer	Adult	AD	Familial early onset cancer resulting from heterozygous germline mutations in the *BRAC2* gene on chromosome 13q12.3. Affects both female and male family members. Risk of ovarian cancer greater than for the general population, but less than observed in *BRCA1* mutations. Significant increase in risk for other cancers has been demonstrated.
TP53	Li-Fraumeni syndrome	Child / adult	AD	Clinically and genetically heterogeneous inherited cancer syndrome which presents with a variety of tumour types, the most common being soft tissue sarcomas and osteosarcomas, breast cancer, brain tumours, leukaemia and adrenocortical carcinoma. It is caused by heterozygous mutation in the p53 gene on chromosome 17p13.1. Classic Li-Fraumeni syndrome is defined as a proband with a sarcoma before age 45 and 1 additional first- or second-degree relative with any childhood cancer or a sarcoma at any age.
STK11	Peutz-Jeghers syndrome (also known as polyposis, Hamartomatous intestinal polyps-and-spots syndrome)	Child / adult	AD	A heterozygous mutation in the serine/threonine kinase STK11 gene on chromosome 19p13. It is characterised by melanocytic macules (benign, well defined oval brown to black patch) of the lips, lining of the mouth and digits; multiple hamartomatous polyps (gastrointestinal polyps), and an increased risk of various neoplasms. Affected females are prone to ovarian tumours.

Gene	Phenotype	Age of Onset	Inheritance	Presentation
MLH1	Lynch syndrome I (HNPCC2)	Adult	AD	Hereditary, nonpolyposis colorectal cancer resulting from heterozygous mutations in the MLH1 gene on chromosome 3p22.2. Lynch syndrome I is site-specific colonic cancer. Early-onset colon cancer with a dominant pattern of inheritance, an excess of multiple primary cancers and significantly improved survival when compared stage-for-stage with other colorectal cancers.
MSH2	Lynch syndrome II	Adult	AD	Heterozygous mutations in the MSH2 gene on chromosome 2p21p16 results in hereditary nonpolyposis extracolonic cancer, particularly carcinoma of the stomach, endometrium, biliary and pancreatic system, and urinary tract. MSH2 is homologous to the E coli.MutS gene and is involved in DNA mismatch repair (MMA). Alteration of MSH2 is involved in Muir-Torre syndrome (subject to breast, colorectal, genitourinary tract cancers, and skin lesions such as keratocanthomas and sebaceous tumours) and mismatch repair cancer syndrome (MMRC).
MSH6	Lynch syndrome (G/T mismatch binding protein – GTBP)	Child / adult	AD	MHS6 germline mutation on chromosome 2p16.3 causing hereditary nonpolyposis colorectal cancer, as well as endometrial and pancreatic cancers. Children often present with café-au-lait spots in mismatch repair cancer syndrome.
PMS2	Lynch syndrome (Mismatch repair gene PSM2)	Adult	AD	Mutation of the PMS2 gene phenotype on chromosome 7p22.1. milder phenotype of colorectal cancer than in MLH1 and MSH2 mutations. Mismatch repair syndrome (also known as brain-tumour polyposis syndrome-1 or Turcot syndrome) is characterised by the concurrence of a primary brain tumour and multiple colorectal adenomas and is associated with mutations in the PMS2 gene.

Gene	Phenotype	Age of Onset	Inheritance	Presentation
MUTYH	Multiple colorectal adenomas, Autosomal recessive colorectal adenomas with pilomatricomas	Adult	Somatic mutation (in progress)	Germline mutation of the MYH gene on chromosome 1p34.1 causing colorectal cancer.
VHL	Von Hippel Lindau syndrome (VHL)	Child / adult	AD	Heterozygous mutation in the VHL gene on chromosome 3p25.3, with a potential phenotypic variation in the cyclin D1 gene on chromosome 11q13. VHL is a dominantly inherited familial cancer syndrome predisposing to a variety of malignant and benign neoplasms of the retina and hemangioblastoma of the cerebellum. It may also cause metastatic renal cancer.
MEN1	Multiple Endocrine Neoplasia Type 1	Child / adult	AD	Heterozygous mutations of the MEN1 gene on chromosome 11q13.1. MEN1 is a nuclear scaffold gene that regulates transcription and is considered to act as a tumour suppressor gene. Germline missense mutations can cause hyperthyroidism and endocrine carcinomas.
RET	Multiple Endocrine Neoplasia Type 2 (RET Protooncogene, Hirschsprung Disease)	Child / adult	AD	Heterozygous mutations in the RET oncogene on chromosome 10q11 indicated in Hirschsprung's disease, a hereditary congenital blockage of the large intestine and multiple endocrine neoplasms, including medullary thyroid carcinoma (MTC), pheochromocytoma, and parathyroid adenoma. MEN2B, characterised by MTC plus ganglioneuromas of the lips, tongue and colon without hyperparathyroidism.
RET	Familial medullary thyroid cancer	Child / adult	AD	A mutation of the RET oncogene on chromosome 10 causing a malignant tumour of follicular epithelial cells of the thyroid. It may also be indicated in certain renal abnormalities

Gene	Phenotype	Age of Onset	Inheritance	Presentation
PTEN	PTEN hamartoma tumour syndrome (Bannayan-Riley-Ruvalcaba syndrome)	Child / adult	AD	PTEN gene encodes a ubiquitously expressed tumour-suppressor phosphatase that antagonises the P13K signalling pathway. Mutation of PTEN on chromosome 10q23 is indicated in a number of syndromes which present with macrocephaly, pseudopapilladema, and multiple hemangiomas. Clinical features include high palate, scaphocephaly, lipomas, and hemangiomas. Many of the lipomas spontaneously regress with age. There seems to be a prevalence of males affected.
RB1	Retinoblastoma	Child	SMU, AD	Hereditary retinoblastoma caused by a heterozygous germline mutation on one allele and a somatic mutation on another allele of the RB1 gene on chromosome 13q14. It is an embryonic neoplasm that almost always presents in early childhood and is often bilateral.
SDHD	Parangliomas 1 (PGL1)	Child / adult	AD (genomic imprinting)	A mutation in the SDHD gene on chromosome11q23.1 causing parotid body tumours and occur equally in men and women when inherited
SDHAF2	Parangliomas 2 (PLG2)	Child / adult	AD	A mutation in the SDHAF2 gene (which encodes a protein necessary for the flavination of SDHA) on chromosome 11q12 causing familial parangliomas of the head and neck.
SDHC	Parangliomas 3 (PLG3)	Child / adult	AD	A mutation in the SDHC gene on chromosome 1q23 (which encodes subunit C of the succinate dehydrogenase complex) causing familial parangliomas of the head and neck.
SDHB	Parangliomas 4 (PLG4)	Child / adult	AD	A mutation in the SDHB gene on chromosome 1p36.3 (which encodes the iron sulphur subunit of the succinate dehydrogenase causing multiple catecholamine-secreting head and neck paragangliomas and retroperitoneal pheochromocytomas.

Gene	Phenotype	Age of Onset	Inheritance	Presentation
TSC1 / TSC2	Tuberous sclerosis complex	Child	AD	Tuberous sclerosis complex is caused either by a heterozygous mutation of the TSC1 gene on chromosome 9q34 or a mutation of the TSC2 gene on chromosome 16p13. It is an autosomal dominant multisystem disorder characterised by hamartomas in multiple organ systems, including the brain, skin, heart, kidneys and lungs. Central nervous system manifestations include epilepsy, learning disorder, behavioural difficulties and autism. There is a wide clinical spectrum, with some patients having minimal symptoms and no neurological disabilities.
WT1	Wilms tumour 1 (nephroblastoma)	Child	AD	Wilms tumor (WT) 1 is caused by a mutation in the WT1 gene on chromosome 11p13. WT is one of the most common solid tumours of childhood, with a prevalence of 1:10,000 accounting for 8% of childhood cancers. Germline mutations account for only about 5% of tumours, most are sporadic, although in familial cases, it is autosomal dominant with incomplete penetrance and variable expressivity.
NF2	Neurofibromatosis type 2 (NF2)	Child / adult	AD	A mutation of the NF2 gene (also called merlin) on chromosome 22q12.2. It is an autosomal dominant multiple neoplasia syndrome characterised by tumours of the eight cranial nerve, meningiomas of the brain, and schwannomas (tumours of the nerve sheath) of the dorsal roots of the spinal cord. It may cause deafness and/or blindness and occurs in 1:25,000 live births.
COL3A1	Ehlers-Danlos syndrome (EDS IV), vascular type	Child / adult	AD	EDS IV is caused by a heterozygous mutation of the COL3A1 gene on chromosome 2q31. It is characterised by joint and dermal manifestations, although less significant than in other forms of EDS. EDS IV manifests as proneness of spontaneous rupture of the bowel and large arteries, including subarachnoid haemorrhaging.

Gene	Phenotype	Age of Onset	Inheritance	Presentation
FBN1	Marfan syndrome	Child / adult	AD	Marfan syndrome is caused by a heterozygous mutation of the FBN1 gene on chromosome 15q21.1. It is a hereditary disease of the fibrous connective tissue with high clinical variability. Clinical features include increased height, disproportionately long limbs and digits, anterior chest deformity, mild to moderate joint laxity, scoliosis and a high, arched palate. Often patients have problems with their vision and cardiovascular systems.
TGFBR1	Loeys-Dietz syndrome type 1	Child / adult	AD	Loeys-Dietz syndrome (LDS) is caused by a heterozygous mutation of the TGBRF1 gene on chromosome 9q22.33. It is an autosomal dominant aortic aneurism syndrome with widespread systemic involvement, including craniofacial defects (cleft palate, hypertelorism).
TGFBR2	Loeys-Dietz syndrome type 2	Child / adult	AD	Loeys-Dietz syndrome is caused by a mutation of the TGBRF2 gene on chromosome 3p24.1 and characterised by immunological disorders, including food allergies, asthma, eczema and rhinitis. Similar to LD1, vascular disease is a major concern with LDS2.
SMAD3	Loeys-Dietz syndrome type 3	Child / adult	AD	LDS3 is caused by a heterozygous mutation of the SMAD3 gene on chromosome 15q22.33 causing aortic aneurism combined with early onset osteoarthritis.
ACTA2	Familial aortic aneurysm Thoracic 6 (AAT6)	Child / adult	AD	Heterozygous mutation of the ACTA2 gene on chromosome 10q23.31 can cause ascending or descending aortic aneurysm. Clinical features include livedo reticularis and iris floculli. Pregnancy in women with AAT6 is associated with a risk of aortic dissection with minimal aortic dilation. Considered less deadly than LDS and similar to treated Marfan syndrome.
MYLK	Familial aortic aneurysm Thoracic 7 (AAT7)	Child / adult	AD	Heterozygous mutation of the MYLK gene on chromosome 3q21.1 may cause aortic dissection with or without aortic aneurysm.

Gene	Phenotype	Age of Onset	Inheritance	Presentation
MYH11	Familiar aortic aneurysm Thoracic 4 (AAT4)	Child / adult	AD	Thoracic aortic dissection and/or aneurism with patent ductus arteriosus can be caused by mutations in the myosin heavy chain 11 gene on chromosome 16p13.11.
MYBPC3	Familial hypertrophic cardiomyopathy 4 (CMH4)	Child / adult	AD	CMH4 is caused by heterozygous, homozygous or compound heterozygous mutation in the gene encoding cardiac myosin-binding protein C on chromosome 11p11.
MYH7	Familial hypertrophic cardiomyopathy 1 (CMH1)	Child / adult	AD	CMH1 is caused by a heterozygous mutation of the gene MYH7 on chromosome 14q12. Hereditary ventricular hypertrophy in early stages produces a presystolic gallop due to an atrial heart sound. Progressive ventricular outflow may cause palpitation associated with arrhythmia, congestive heart failure, and sudden death.
TNNT2	Dilated cardiomyopathy 1D (CMD1D)	Child / adult	AD	Heterozygous mutation of the gene encoding cardiac troponin T (TNNT2) on chromosome 1q32 causing familial dilated cardiomyopathy. It has also been associated with left ventricular noncompaction, hypertrophic cardiomyopathy, and restrictive cardiomyopathy.
TNNI3	Familial hypertrophic cardiomyopathy 7 (CMH7)	Child / adult	AD	Heterozygous mutation in the TNNI3 gene on chromosome 19q13.42 causing hypertrophic cardiomyopathy.
TPM1	Familial hypertrophic cardiomyopathy 3	Child / adult	AD	Form of familial hypertrophic cardiomyopathy linked to chromosome 15q2 caused by a mutation in the alpha-tropomyosin gene.
MYL3	Familial hypertrophic cardiomyopathy 8	Child / adult	AR (in progress)	Caused by a homozygous or heterozygous mutation in the MYL3 gene on chromosome 3p21.31. This is a rare variant of familial hypertrophic cardiomyopathy that causes mid-left ventricular thickening.
ACT1	Familial hypertrophic cardiomyopathy 11	Child / adult	AD	Heterozygous mutation of the ACT1 gene on chromosome 15q14. Appears to be a less life-threatening variation of hypertrophic cardiomyopathy.

Gene	Phenotype	Age of Onset	Inheritance	Presentation
PRKAG2	Familial hypertrophic cardiomyopathy 6	Child / adult	In progress	Heterozygous mutation of the gene which encodes the gamma-2 regulatory subunit of AMP-activated protein kinase. Mutation of the PRKAG2 gene also causes the Wolff-Parkinson-White preexcitation syndrome in isolation or in association with hypertrophic cardiomyopathy.
GLA	Fabry disease	Adult	XL	Fabry disease is caused by a mutation in the GLA gene encoding alpha-galactosidase A on chromosome Xq22. Deficiency of the lyosomal enzyme alpha-galactosidase A leading to systemic accumulation of globotriaoslyceramide (Gb3) and related glycosphingolipids in the plasma and cellular lysosomes of vessels, nerves, tissues, and organs throughout the body. It causes progressive renal failure, cardiac disease, cerebrovascular disease, small-fibre peripheral neuropathy and skin lesions.
MYL2	Familial hypertrophic cardiomyopathy 10	Child / adult	In progress	Mutation of the MYL2 gene on chromosome 12q24.11.
LMNA	Dilated cardiomyopathy 1A (CMD1A)	Child / adult	AD	Heterozygous mutation in the lamin A/C gene on chromosome 1q21. Allelic disorders include the autosomal dominant form of Emery-Dreifuss muscular dystrophy and Hutchinson-Guilford progeria syndrome. Dilated cardiomyopathy is characterised by cardiac dilation and reduced systolic function. CMD is the most common form of cardiomyopathy and accounts for more than half of all cardiac transplants performed in patients between 1 and 10 years of age.
RYR2	Catecholaminergic polymorphic ventricular tachycardia	Child / adult	AD/AR	Heterozygous mutation of the cardiac ryanodine receptor gene on chromosome 1q43 causing an arrhythmic disorder of the heart characterised by a reproducible form of polymorphic ventricular tachycardia induced by physical activity, stress, or catecholamine infusion, which can deteriorate into ventricular fibrillation. CPVT can be inherited as an autosomal dominant or recessive trait. Clinical penetrance of the disease ranges from 25 – 100%, with an average of 70-80%.

Gene	Phenotype	Age of Onset	Inheritance	Presentation
PKP2	Arrythmogenic right-ventricular cardiomyopathy	Child / adult	AD	Heterozygous mutations in the PKP2 gene, which encodes plakophilin-2, an essential armadillo repeat protein of the cardiac desmosome, on chromosome 12p11. The disease causes replacement of ventricular myocardium with fatty and fibrous elements, preferentially involving the right ventricular wall.
DSP	Arrythmogenic right-ventricular cardiomyopathy 5	Child / adult	AD	Heterozygous mutation in the TMEM34 gene on chromosome 3p25 causing right ventricular cardiomyopathy. This ARVD subtype is a sex-influenced lethal arrhythmogenic cardiomyopathy, with a unique ECG finding, left ventricular dilation, heart failure, and early death.
DSC2	Arrythmogenic right-ventricular cardiomyopathy 11	Child / adult	AD	ARVD11 is caused by a heterozygous mutation in the desmocollin-2 gene (DSC2; 125645) on chromosome 18q. Homozygous mutation in the DSC2 gene causes arrhythmogenic right ventricular cardiomyopathy associated with mild palmoplantar keratoderma and woolly hair.
TMEM 43	Arrythmogenic right-ventricular cardiomyopathy 8	Child / adult	AD	ARVD8 is caused by a heterozygous mutation in the gene encoding desmoplakin on chromosome 6p24.3.
DSG2	Arrythmogenic right-ventricular cardiomyopathy 10	Child / adult	AD	ARVD10 is caused by a heterozygous mutation in the gene encoding desmoglein-2 on chromosome 18q12.
KCNQ1	Long QT syndrome 1 (Ward-Romano syndrome)	Child / adult	AD	Long QT syndrome caused by a heterozygous mutation in the KQT-like voltage-gated potassium channel-1 gene on chromosome11p15. Congenital long QT syndrome is characterised by a prolonged QT interval and polymorphic ventricular arrhythmias that may result in recurrent syncope, seizures or sudden death.
KCNH2	Long QT syndrome 2	Child / adult	AD	Caused by a mutation in the HERG gene on chromosome 7q35-q36. There is evidence that mutation in the KCR1 gene on 12p11 confers reduced susceptibility to acquired long QT syndrome-2.

Gene	Phenotype	Age of Onset	Inheritance	Presentation
SCN5A	Brugada syndrome 1 (BRGDA1)	Child / adult	AD	A heterozygous mutation in the SCN5A gene on chromosome 3p22 causing an ST segment elevation in the right precordial leads and a high incidence of sudden death in patients with structurally normal hearts. The syndrome normally manifests during adulthood, with a mean age of sudden death of 41 +/- 15 years, but it also occurs in infants and children.
LDLR	Familial hypercholesterolemia	Child / adult	AD	Heterozygous mutation in the low density lipoprotein gene on chromosome 19p13 causing elevation of serum cholesterol bound to low density lipoprotein, which increases deposits of cholesterol on the skin, tendons and coronary arteries.
PCSK9	Autosomal dominant hypercholesterolemia 3	Child / adult	AD	Heterozygous mutation in the PCSK9 gene on chromosome 1p32 causing hypercholesterolemia.
APOB	Autosomal dominant hypercholesterolemia 4	Child / adult	AD	Heterozygous mutation in the apolipoprotein B gene on chromosome 2p24.1 causing a reduction in LDL clearance due to a defect in the structure of LDL that reduces its affinity for receptors.
RYR1	Susceptibility to malignant hyperthermia King-Denborough syndrome	Child / adult	AD	Heterozygous mutation in the ryanodine receptor gene on chromosome on 19q13 causing a musculoskeletal disorder predisposing individuals to death from anaesthesia. Malignant hyperthermia is characterised by any combination of hyperthermia, skeletal muscle rigidity, tachycardia or arrhythmia, respiratory and metabolic acidosis, and rhabdomyolysis.
CACNA1S	Susceptibility to malignant hyperthermia 5	Child / adult	In progress	Heterozygous mutation in the CACNA1S gene on chromosome 1q32 causing malignant hyperthermia.

Source: www.omim.org

Appendix Two

The role of the family in genomics and disclosure for third party benefit

A trend that is becoming increasingly apparent in the genomics literature and that has specifically informed some professional guidelines like those of the ACMG is toward justifying genomic disclosure not only for the benefit of the individual, but for close family members.

In their comprehensive review of policy and guidance on research and clinical WGS, Knoppers and colleagues note that some guidelines mention the implications of communicating some incidental findings to family members. "Even in the absence of specific criteria, some policies allow the communication of incidental findings to family members on a case-by-case basis."[1] Significantly, some organisations such as the United Kingdom's Foundation for Genomics and Population Health (PHG Foundation) recommend that when discussing the possibility that incidental findings may be returned in the informed consent process, participants should also be informed that results may also be relevant to family members and that "potential disclosure will be made to these family members under certain circumstances".[2] Accordingly, participants are informed, and implicitly accept, that familial disclosure may be an outcome of testing.

Significantly, some courts have rejected claims that clinicians owe a duty of care to disclose genetic information to genetic relatives of patients diagnosed with serious genetic illnesses.

In the UK case of *ABC v St George's Healthcare NHS Trust & Ors,*[3] the defendants sought to strike out a claim brought by a woman who claimed that she should have been informed of her father's diagnosis of a serious heritable genetic illness. The facts of the case involved a man who, after being convicted of manslaughter (on the grounds of diminished responsibility) for the shooting and killing of his wife, was subsequently diagnosed with the neuro-degenerative disorder, Huntington's Disease. As a result of these events, the daughter was undergoing family therapy and was known to the defendant clinicians/hospital.

As HD is serious and untreatable and children have a 50% risk of inheriting the disorder, the man's clinicians sought his consent to disclose his condition to his daughter, who was pregnant at the time. The man refused disclosure, although a clinician later informed the daughter of her father's condition accidentally. The daughter was diagnosed as having the condition after she had her child.

The claimant brought an action claiming that the failure to inform her of her father's genetic condition was (a) actionable in negligence or alternatively (b) violated her right under Article 8 of the European Convention on Human Rights. The claimant stated that she would have undertaken prenatal genetic testing if informed, and would have terminated her pregnancy if the fetus tested positive for HD. She also claimed for psychiatric damage.

Based on the criteria set out in *Caparo v Dickman*[4] for establishing a duty of care, the defendants accepted that: 1) injury to the claimant was reasonably foreseeable if the defendants did not inform her of her father's condition and 2) there was sufficient

proximity between the defendants and the claimant to ground a duty of care.[5] However, despite the defendants conceding the issue of proximity, the judge held that proximity was not established on the facts. Just because the claimant was attending the hospital for family therapy did not establish a special relationship for the purposes of tort law, nor was there an assumption of responsibility in respect of the claimant such that would ground a duty to disclose information to her which the clinicians held under a duty of confidence to her father.[6] The case is currently on appeal[7] with a hearing expected in 2017 after the defendant's successful strike out application was overturned by the Court of Appeal.[8]

In another more recent case, *Smith v University of Leicester NHS Trust*,[9] the defendants were successful in having an action in negligence struck out on the grounds that a duty of care did not exist between the hospital and the patient's relatives who were not patients.[10]

Australia

Australia has enacted law that permits disclosure by a clinician to a family member in certain situations.[11] In 2006, it introduced an amendment to the federal Privacy Act 1988 with further reforms becoming effective in 2014.[12] A health professional may:[13]

> … disclose genetic information about his or her patient to a genetic relative of that patient where the disclosure is necessary to lessen or prevent a serious threat to an individual's life, health or safety, even where the threat is not imminent.

The Australian National Health and Medical Research Council has developed guidelines to assist practitioners in situations where a patient refuses to disclose information to relatives.[14] Acting in accordance with the guidelines protects the practitioner from being liable for any breach under the *Privacy Act 1988* (Cth).[15] These guidelines provide the following:[16]

> **Guideline 1**
> Use or disclosure of genetic information without consent may proceed only when the authorising medical practitioner has a reasonable belief that this is necessary to lessen or prevent a serious threat to the life, health or safety of a genetic relative.
>
> When consent [to disclosure] is withheld, the authorising medical practitioner will first need to determine whether there is a serious threat to genetic relatives, taking into consideration:
>
> - the nature of the condition, its associated risks and treatment or care options; and
> - the probability that a genetic relative may also have the condition or be a carrier of
>
> the relevant mutation.
>
> If a serious threat to the life, health or safety of genetic relatives is identified, it should then be determined whether the potential to lessen or prevent the threat exists. Considerations include:
>
> - whether the condition is preventable or manifestations treatable (eg whether the relatives can benefit from the information); and

- if the disease is incurable, whether knowledge of the condition would allow optimal management.

Before making a non-consensual use or disclosure of information, the authorising medical practitioner must form a reasonable belief that such an act is necessary to lessen or prevent the identified threat to genetic relatives. It must be determined whether a means other than use or disclosure exists to lessen or prevent the threat. The decision to use or disclose without consent must be made in good faith, with the health practitioners involved in the decision-making drawing on their experience, training and expertise.

The Guidelines make it clear that although health practitioners have an ethical duty to advise a patient to disclose their genetic status to relatives, practitioners "are under no legal obligation to disclose the information to genetic relatives themselves, whether consent is given or not. As the law currently stands, there is no valid basis to suggest that a doctor could be liable for non-disclosure."[17]

New Zealand

The law in New Zealand regarding disclosure of medical information is governed by both case law and statute law, although this analysis focuses on the legislative framework. Clinicians are subject to the Privacy Act 1993 and the Health Information Privacy Code (HIPC).[18] These legal instruments provide that clinicians may *only* disclose information in certain restricted circumstances.

While the HIPC previously permitted non-consensual disclosure of information to an appropriate person if it is necessary to prevent or lessen a serious and **imminent** threat, amendments introduced in 2013 now permit disclosure of health information under Rule 11(2) if:

> … the health agency believes on reasonable grounds that it is either not desirable or not practicable to obtain authorisation from the individual concerned and that— …
>
> (d) the disclosure of the information is necessary to prevent or lessen a serious threat to—
>
> (ii) the life or health of the individual concerned or another individual;

The definition of "serious threat" in the Privacy Act 1994 (which is likely to inform the provisions in the HIPC) is:[19]

> … a threat that an agency reasonably believes to be a serious threat having regard to all of the following:
>
> (a) the likelihood of the threat being realised; and
>
> (b) the severity of the consequences if the threat is realised; and
>
> (c) the time at which the threat may be realised.

It is possible that, even though the amended provision does not specifically refer to genetic information, disclosure of genetic information to an at-risk relative may be lawful

Appendix Three

Scope of national, international (multijurisdictional) WGS-based testing policy guidelines

under the HIPC in rare situations. However, this would provide a discretion, rather than a duty, to disclose in limited circumstances.

The following tables are replicated from a review that was published in *Nature Reviews Genetics* of policy guidance formulated by national and regional bodies governing WGS-based genetic testing and the return of genetic testing/research results.[20] The policy documents reviewed encompassed position papers, reports, guidelines or consensus statements that had been produced by international or national governmental and non-governmental health organisations, bioethics committees or professional associations.

Table 1 | **Policy landscape for WGS-based genetic testing**

Jurisdiction	Domains	Scope	Contexts	Populations	Issues addressed
Canada (CCMG)	Clinical application in monogenic diseases, 2015 (REF. 10)	National	Clinic	Adult and paediatric	Provide criteria for return of results, consent, counselling and confidentiality versus communication to family members
Denmark (Danish Council of Ethics)	Genome testing: ethical dilemmas, 2012 (REF. 13)	National	Research and clinic	Adult and paediatric	Consent, counselling and confidentiality versus communication to family members
Europe (ESHG)	WGS in health care, 2013 (REF. 38)	Regional	Clinic	Adult and paediatric	Provide criteria for return of results, consent and counselling
Germany (German National Ethics Council)	Genetic diagnostics, 2013 (REF. 27)	National	Research and clinic	Adult and paediatric	Provide criteria for return of results, consent, counselling and confidentiality versus communication to family members
Multijurisdictional (P^3G)	Population biobanks, 2013 (REF. 43)	International	Research	Adult	Provide criteria for return of results and consent
Multijurisdictional (P^3G)	WGS in paediatric research, 2014 (REF. 11)	International	Research	Paediatric	Provide criteria for return of results, consent and confidentiality versus communication to family members
Multijurisdictional (P^3G, ESHG, HUGO and PHG Foundation)	WGS in newborn screening, 2015 (REF. 41)	International	Clinic	Paediatric	Provide criteria for return of results, consent, counselling and confidentiality versus communication to family members
United Kingdom (MRC and Wellcome Trust)	Health findings, 2014 (REF. 17)	National	Research	Adult and paediatric	Provide criteria for return of results, consent and counselling
United Kingdom (PHG Foundation)	Genomics, 2014 (REF. 1)	National	Clinic	Adult	Provide criteria for return of results, consent and confidentiality versus communication to family members
United Kingdom (UK10K)	Ethical governance, 2010 (REF. 12)	National	Research	Adult and paediatric	Provide criteria for return of results, consent and confidentiality versus communication to family members
United States (ACMG)	Incidental findings, 2012 (REF. 44); 2013 (REF. 36); 2013 (REF. 45); 2013 (REF. 46); 2015 (REF. 9)	National	Clinic	Adult and paediatric	Provide criteria for return of results, consent, counselling and confidentiality versus communication to family members
United States (Presidential Commission for the Study of Bioethical Issues)	WGS and privacy, 2012 (REF. 47)	National	Research and clinic	Adult and paediatric	Consent, counselling and confidentiality versus communication to family members
United States (Presidential Commission for the Study of Bioethical Issues)	Incidental findings, 2013 (REF. 25)	National	Research and clinic	Adult and paediatric	Provide criteria for return of results, consent, counselling and confidentiality versus communication to family members
United States (ASHG)	Genetic testing in children and adolescents, 2015 (REF. 37)	National	Research and clinic	Paediatric	Provide criteria for return of secondary findings, consent, counselling and confidentiality versus communication to family members

ACMG, American College of Medical Genetics; ASHG, American Society of Human Genetics; CCMG, Canadian College of Medical Geneticists; ESHG, European Society of Human Genetics; HUGO, Human Genome Organisation; MRC, Medical Research Council; PHG Foundation, Foundation for Genomics and Population Health; WGS, whole-genome sequencing.

Policies governing the return of results from WGS-based testing: National and International (multijurisdictional) bodies.

Table 3 | **Policies for the return of results from WGS-based genetic testing**

Jurisdiction	Policies	Approaches	Refs
Canada (CCMG)	Clinical application in monogenic diseases, 2015	• Opt-out from receiving IFs (medically actionable IFs) • No opt-out from receiving IFs (if ACA during childhood) • ACA criteria	10
Denmark (Danish Council of Ethics)	Genome testing: ethical dilemmas (clinic and research), 2012	• Opt-out from receiving IFs • ACA criteria • No individual return ("do not have the right to information about individual results")	13
Europe (ESHG)	WGS in health care, 2013	• Opt-out from receiving IFs ("right not to know") • No opt-out from receiving IFs (if ACA during childhood)	38
Germany (German National Ethics Council)	Genetic diagnostics (research and clinic), 2013	• Opt-out from receiving IFs ("right not to know") • No opt-out from receiving IFs (if ACA during childhood)	27
Multijurisdictional (P^3G)	Population biobanks, 2013	• Return of general research results, ongoing • Opt-out from receiving IFs (other data) • ACA criteria	43
Multijurisdictional (P^3G)	WGS in paediatric research, 2014	• No opt-out from receiving IFs (if ACA during childhood) • ACA criteria • Case-by-case determination by research team (in rare situations, return if potential benefit to family)	11
Multijurisdictional (P^3G, ESHG, HUGO and PHG Foundation)	WGS in newborn screening, 2015	• Return all (results and IFs) (targeted only) • ACA criteria	41
United Kingdom (MRC and Wellcome Trust)	Health IFs (research), 2014	• Opt-out from receiving IFs (health-related findings) • ACA criteria • Case-by-case determination by research team	17
United Kingdom (PHG Foundation)	Genomics (clinic), 2014	• Opt-out from receiving IFs	1
United Kingdom (UK10K)	Ethical governance (research), 2010	• Opt-out from receiving IFs • ACA criteria • No individual return ("will not feedback to participants their genome sequence data")	12
United States (ACMG)	IFs (clinic), 2015	• Opt-out from receiving IFs	9
United States (Presidential Commission for the Study of Bioethical Issues)	WGS and privacy, 2012	• Opt-out from receiving IFs	47
United States (Presidential Commission for the Study of Bioethical Issues)	IFs (clinic and research), 2013	• Opt-out from receiving IFs • Case-by-case determination by research team ("assess [IFs] significance, consulting with experts as appropriate")	25
United States (ASHG)	Genetic testing in children and adolescents, 2015	• In general, parents can opt-out from receiving IFs • Case-by-case determination by clinicians (communicate to parents when "there is strong evidence that a secondary finding has urgent and serious implications for a child's health or welfare, and effective action can be taken to mitigate that threat")	37

ACA, analytical validity, clinical significance and actionability; ACMG, American College of Medical Genetics; ASHG, American Society of Human Genetics; CCMG, Canadian College of Medical Geneticists; ESHG, European Society of Human Genetics; HUGO, Human Genome Organisation; IFs, incidental findings; MRC, Medical Research Council; PHG Foundation, Foundation for Genomics and Population Health; WGS, whole-genome sequencing.

Endnotes

1. B Knoppers, M Zawati, K Senecal "Return of Genetic Testing Results in the Era of Whole-Genome Sequencing" (2015) 16 Nature Reviews Genetics 553 at 555.
2. Id.
3. [2015] EWHC 1394 (QB).
4. *Caparo v Dickman* [1990] 2 AC 605.
5. However, the defendants claimed that the final criterion of *Caparo's* tripartite test was not satisfied in the circumstances, i.e. that it was not fair, just or reasonable to impose a duty of care on the defendants. The defendants argued that although the law of confidence conferred a discretion on doctors to disclose confidential information in limited circumstances when the public interests in disclosure outweighed the public interest in preserving confidence, [*Attorney-General v Guardian Newspapers* (No.2) [1990] 2 AC 109; in addition, *W v Egdell* [1990] Ch 359] this fell short of a duty to do so.
6. Cf *Safer v Estate of Pack* 291 N.J. Super. 619 (1996).
7. For a critique of the case, see Roy Gilbar and Charles Foster, "Doctors' Liability to the Patient's Relatives in Genetic Medicine " (2015) 24 Medical Law Review 112.
8. *ABC v St George's Healthcare NHS Trust & Ors* [2017] EWCA Civ 336.
9. [2016] EWHC 817 9QB).
10. The claimants alleged that the delay in diagnosing the patients adrenomyeloneuropathy (AMN) which causes deterioration in the white matter of the brain caused a delay in diagnosing the condition in the patient's relatives with childhood versions of the disorder.
11. M Otlowski, "Australian reforms enabling disclosure of genetic information to genetic relatives by health practitioners" (2013) 21 *Journal of Law and Medicine* 217-234.
12. Privacy Amendment (Enhancing Privacy Protection) Act 2012. The Privacy Act now includes a set of privacy principles (the Australian Privacy Principles) that regulate the use and disclosure of personal information by Government agencies and some private organisations.
13. Privacy Commissioner, Health Information Privacy Code 1994 s 95AA: Amendment No. 6 (April 2007).
14. *The Use and Disclosure of Genetic Information to a Patient's Genetic Relative under Section 95AA of the Privacy Act: Guidelines for Health Practitioners in the Private Sector* (2009).
15. However, this only provides protection under the Privacy Act, and a clinician is not immune from a claim of breach of the duty of confidentiality at common law—according to which disclosure must be within the public interest exception for it to be lawful.
16. NHMRC *Use and Disclosure of Genetic Information to a Patient's Genetic Relatives Under s 95AA of the Privacy Act 1988* (CTh) (National Health and Medical Research Council 2014).
17. Ibid at 31.
18. However, this legislation only applies to persons/agencies who hold health information, such as clinicians, clinics, and hospitals.
19. As amended by the Privacy Act Amendment Bill 2013.
20. Bartha Knoppers, Ma'n H Zawati, and K Senecal "Return of Genetic Testing Results in the Era of Whole-Genome Sequencing" (2015) 16 Nature Reviews Genetics 553.
21. Bartha Knoppers, Ma'n H Zawati, and K Senecal "Return of Genetic Testing Results in the Era of Whole-Genome Sequencing" (2015) 16 Nature Reviews Genetics 553 at 554.
22. At 556

Appendix Four

References summary of empirical evidence regarding psychosocial effects of newborn screening (chapter 2)

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d. J Beucher, E Leray, E Deneuville et al "Psychological effects of false-positive results in cystic fibrosis newborn screening: a two-year follow-up" (2010) 156 J Pediatr 771.

e. G Bodegard, K Fyro, A Larsson "Psychological reactions in 102 families with a newborn who has a falsely positive screening test for congenital hypothyroidism" (1983) 304 Acta Paediatr Scand Suppl 1;

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p. R Grob "Is my sick child healthy?: changing parental experiences of cystic fibrosis in the age of expanded newborn screening" (2008) 67 Soc Sci Med 1056;

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Appendix Five

A summary of guidelines on incidental findings

Author/ institutional affiliation	Definition of incidental finding	Return of results policy	Reference to filtering or masking of results	Duty to disclose discussed
Green et al[1] (2013) USA American College of Medical Genetics and Genomics (ACMG) recommendations	Results of a deliberate search for pathogenic alterations in genes that are not apparently relevant to a diagnostic indication for which the sequencing test was ordered.	Laboratories performing clinical sequencing should seek and report mutations of the specified classes or types in the 56 recommended genes, irrespective of age of person.	Recommends restricting the variants to be reported as IF to two categories: 1) sequence variation previously reported and recognised as causal (KP); and 2) sequence variation previously unreported and of the type expected to cause the disorder (EP).	Default position is mandatory reporting, but subsequent recommendations allow patients to opt-out of receiving all results – cannot choose to receive some.
Botkin et al[2] (2015) USA American Society of Human Genetics (ASHG) Position statement on genetic testing in children and adolescents	"Secondary Finding" is clinically relevant information unrelated to the condition for which the sequencing was originally ordered.	Clinicians may offer to disclose secondary findings for a child to the child's parents or guardians only when the information has clear clinical utility (validated in an approved facility) for the child and/or family members. Wherever genomic testing is likely to return IFs, there needs to be a robust informed-consent process. In general, parents should be able to decline to receive secondary findings in advance of genetic testing. It is ethically acceptable, but not required, to search for secondary findings not relevant to clinical or research indications for sequencing. Reporting consanguinity is only mandated in cases of suspected sexual abuse of a minor.	Unless there is clinical intervention appropriate in childhood, predictive or pre-dispositional testing for adult-onset conditions should be deferred until adulthood or adolescence when the child can participate in decision-making in a relatively mature manner. When clinically indicated, the scope of genetic testing should be limited to single-gene analysis or targeted gene panels.	When there is strong evidence that a secondary finding has urgent and serious implications for a child's health or welfare, and effective action can be taken to mitigate that threat, clinicians should communicate those findings regardless of parental preference. Testing for carrier status in adolescents where there is a positive family history may be done in the presence of adolescent assent and parental consent. Genetic testing in children should include a long-term communication plan for all results, including consideration of who should be involved in the communication of

Author/ institutional affiliation	Definition of incidental finding	Return of results policy	Reference to filtering or masking of results	Duty to disclose discussed
		Recommend that health-care providers avoid disclosure of misattributed parentage unless there is a clear medical benefit that outweighs the potential harms. **Research:** When secondary findings are likely to be generated in the conduct of paediatric research, ASHG recommends that investigators develop and follow an IRB-approved plan to manage such findings.		information and the staging of information sharing on the basis of age, maturity, and capacity to understand.
American Medical Association[3] **(2009) USA** AMA	No specific definition given	Results of testing should not be disclosed to third parties without explicit informed consent. Genetic testing of children should only be offered or required if the condition has paediatric onset and or which there are therapeutic or preventative measures available. When a child's genetic status is determined incidentally, the information should be retained by the clinician and entered into the patient record. Discussion of the existence of the finding should be taken up when the child reaches maturity or needs to make reproductive decisions.		Physicians have a professional duty to protect confidentiality of patients' information. They should clearly explain when results have implications for biological relatives that should be disclosed to such relatives, and can help the patient with such communication, as appropriate.

Author/ institutional affiliation	Definition of incidental finding	Return of results policy	Reference to filtering or masking of results	Duty to disclose discussed
Fabsitz et al[4] (**2010**) **USA** National Heart, Lung, and Blood Institute Working Group	No specific definition given	Genetic findings **should be** returned in the research context if: 1. they have important health implications for the participant, and the associated risks are stablished and substantial; 2. the finding is actionable; the test is analytically valid; and 3. prior informed consent to receive such information has been obtained Genetic findings **may be** returned when 1. the investigator concludes benefit of return outweighs risks from the participant's perspective; 2. IRB approval has been granted; 3. test is analytically valid and disclosure plan complies with all applicable laws; 4. the participant has opted to receive results		When a participant has opted-in or opted -out of receiving results, investigators should honour the decision, regardless of potential magnitude of harm. When the informed consent is silent as to return, consultation with the IRB on possible options is recommended. A researcher's obligation to return individual research results to a study participant should not extend beyond study funding.

Author/ institutional affiliation	Definition of incidental finding	Return of results policy	Reference to filtering or masking of results	Duty to disclose discussed
Hegde et al[5] (2015) USA Association of Molecular Pathology	IF includes all findings that are clearly or expected to be pathogenic but do not address the clinical question that motivated the testing. Distinguishes between IFs from WGS and other areas of medicine in that additional findings, beyond the genes analysed to answer the clinical question that prompted testing, require extra effort to detect, and therefore are not unavoidable, but require additional analysis and interpretation.	Laboratories should clearly describe on their consent form what type of variants are possible and what will be reported and should base their policy on their ability to provide this information with sufficient accuracy.	If a patient has opted out of receiving IFs, it requires a modified analysis to reveal or mask specific genes.	It is not permitted to report IF if the laboratory has not established that the performance specifications of this aspect of testing meets CLIA or equivalent accreditation standards
Van El et al[6] (2013) Europe European Society for Human Genetics (ESHG) recommendations	Unsolicited findings" " – data that are) generated that are not related to the initial diagnostic question.	If an IF is indicative of serious health problems (either in person tested or close relatives) and can be treated or prevented, in principle it should be reported. Guidelines for informed consent need to be developed. "In the case of testing minors, guidelines need to be established as to what unsolicited information should be disclosed in order to balance the autonomy and interests of the child and the parental rights and needs (not) to receive information that may be in the interest of their (future) family."	In the clinical setting, targeted sequencing should be used first. Filtering should limit the analysis to specific sets of genes. Known genetic variants with limited or no clinical utility should be filtered out and not reported.	Patient's right 'not-to-know' is not absolute and can be overridden. A general duty to recontact cannot be maintained given the impossibility to delimit its scope. However, balancing pros and cons may require recontacting when findings have a potentially high information value, for example, therapeutic options might emerge for some disorders (581)

Author/ institutional affiliation	Definition of incidental finding	Return of results policy	Reference to filtering or masking of results	Duty to disclose discussed
Claustres et al[7] (2014) **Europe** ESHG guidelines for reporting results of diagnostic genetic testing	Distinguish between: **normal** (within the range of physiological variation for the given individual); **non-specific findings without clinical relevance** (outside of physiological variation but not associated with a known disease); **incidental findings with possible clinical relevance** (indicating a clinically relevant issue, but unrelated to the clinical question being investigated; **findings of uncertain significance** (outside of the physiological variation but with possible relevance to the clinical question being asked)	Reporting is to the referring clinician. Non-specific findings should only be reported if they may be relevant to the result (for example, if the sample quality could be the problem). Return of IFs "will depend on local policy and on how the patient has been counselled about this possibility. A clear policy on reporting incidental findings should be in place in all institutions offering genetic testing". Findings of uncertain significance should be included in reports, as their significance may become clear at a later date.		Laboratory reports should specifically state if a diagnosis may have "potentially important implications for other family members". Depending on the context, it may be appropriate to explicitly mention the recommendation to test the partner, or the possibility of cascade screening tests in relatives, and the possibility of prenatal diagnosis or PGD.
Health Council of the Netherlands[8] (2015) **Europe** recommendations for neonatal screening	Unintended findings that raise questions and may be clinically meaningful, of unclear meaning or not clinically meaningful	IFs that indicate a condition that cannot or can barely be influenced should not be reported, unless there is the possibility that a disease should manifest very early and reporting would spare the child a 'diagnostic odyssey'. Conditions that only manifest in adulthood and/or carrier status should not be reported.	Conditions should be included in neonatal screening programme if they prevent significant, irreversible damage and/or yield substantial health gains for the child or where tests are available that can yield health gains.	Actionable conditions must always be reported to parents and the parents' right not to know may not be called upon, even if the IF in question may affect the parents or their other or future children.

Author/ institutional affiliation	Definition of incidental finding	Return of results policy	Reference to filtering or masking of results	Duty to disclose discussed
Hehir-Kwa et al[9] (2015) **Europe** ESHG consensus meeting	"Unexpected positive findings" which are "clinically or socially relevant for the individual or his/her family members, … but not relevant to the diagnostic question". "A major concern with the term 'incidental finding' is that this implies that the finding was either an incident or not expected, whilst the discovery of such variants is intrinsic to genome-wide screening technologies"	"It is not the role of the clinical lab to disclose an IF to a patient, but the role of the medical professional requesting the test…The impact of the IF determines how the finding should be disclosed to a patient. If it has minor consequences or a clinical possible, then the variant should be reported ... If the variant results in a late onset disorder or has major consequences, counselling and consent will determine if and when the variant can and should be disclosed to the patient"	Testing should be targeted rather than a broad screening approach to detect IF. Tests should be designed to minimise IFs.	Reporting a variant to a clinician does not mean that it will be disclosed to the patient; clinicians will use a contextual approach in deciding what to report. IF in neonates regarding late-onset conditions might not be reported. Clinicians may also "postpone" reporting IF *"when the parents or patients are given a diagnosis related to the clinical question that entail a poor prognosis"*. When reporting NGS results the clinical lab should consider the extent of the data and information needed to be included in the patient report as patients have a legal right to view their own medical records as well as the results of a lab investigation.
Hallowell et al[10] (2015) **UK** PHG Foundation (charitable foundation)	Distinguishes 'pertinent' findings that are intentionally sought as part of the diagnostic process from other clinically significant findings that are generated in the course of the WES and WGS but have not been deliberately sought. "These incidental findings emerge because WGS and WES screening techniques are less finely targeted than more classical genetic tests" (317).	In the clinical context: Individualised - additional findings should be disclosed if the **clinician** assesses that the benefits of disclosure outweigh the harm, and "this will need to be informed by their knowledge of the patient and the clinical context"	Analytical approach for clinical interrogation should be clinically directed, so only variants of relevance to the specific condition are analysed and shared with patients. Filtering should be used based on criteria for predicting likely pathogenicity[11]	Clinical context: physician to ascertain whether it is in the patient's **best interests** by balancing the professional obligations of **beneficence and non-maleficence,** which could override patient's **autonomy** where, for example, the IFs reveal a life-threatening condition that is easily treatable.

Author/ institutional affiliation	Definition of incidental finding	Return of results policy	Reference to filtering or masking of results	Duty to disclose discussed
		In the research context: each research project should have a rule-based framework in place, with a feedback continuum informed by the significance of the finding, its actionability and disease severity, balanced against patient autonomy		Onus on physician to be able to justify disclosure or retention of information. Research context: contractual obligation to be determined uring the informed consent process.
Middleton et al[12] (2014) UK and Ireland Association of Genetic Nurses and Counsellors (AGNC)	Additional findings unrelated to the original medical question	Following appropriate genetic counselling, patients should be allowed to consent to or opt out of opportunistic genomic screening. Children should not be routinely tested for adult-onset conditions	Laboratory should only test for/analyse conditions that the patients have consented to. Any list of predetermined variants should be consensus-driven and should only include variants for serious or life-threatening conditions for which there are treatments, interventions or preventative strategies available.	If true IFs are discovered, genetic test results should be shared with the patient or family following the guidelines from the Joint Committee on Medical Genetics (2010)
Lucassen et al[13] (2010) UK British Society for Human Genetics (BSHG)	No specific definition given	Presymptomatic or predictive genetic testing of children for late onset disorders is only appropriate when there is a best-interests benefit such as a preventative therapeutic intervention that outweighs the need for caution in early testing	Routine disclosure of carrier test results which carry no medical implications for the child is not recommended	

Author/ institutional affiliation	Definition of incidental finding	Return of results policy	Reference to filtering or masking of results	Duty to disclose discussed
Zawati et al[14] (2014) Canada Canadian College of Medical Geneticists (CCMG)	Unsolicited, unanticipated and pertinent findings. Recommendations include **all** results as "the distinction between solicited and unsolicited results may become increasingly untenable" as WGS becomes cheaper and more widespread.	Competent adults should be able to make informed choices over whether to receive any/all results. Return of results for incompetent adults should be guided by the person's best interests. Results revealing clinically significant and actionable (in childhood) conditions in minors should be reported to the parents. Adult-onset conditions should not be communicated unless disclosure to the parents could prevent serious harm to their health or that of family members as determined on a case-by-case basis.	WGS/WES "should be used in a judicious and cost-efficient manner".	Any clinically significant and actionable results for an adult incapable of informed consent should be reported to the legal representative who cannot refuse to receive such results. Parents of minors cannot refuse to receive results of clinically significant and immediately actionable conditions. Physician's must maintain patient confidentiality; if results reveal significant and actionable results for identifiable family members, they can encourage the patient to communicate such results, and can facilitate such return with consent.
Boycott et al[15] (2015) Canada CCMG	Genetic variant(s) identified by genome-wide sequencing unrelated to the primary indication for testing	Cautious approach – CCMG does not endorse the intentional clinical analysis of disease genes unrelated to the primary indication, even if the results might be medically actionable. If a broader assessment is taken, then competent adults should be given the option prior to testing to receive (or not) IF, based on informed consent. For minors, IFs should only be reported to the parents if results reveal risk for a highly penetrant condition that is medically actionable during childhood.	Bioinformatic analysis of GWS should be performed using selective filtering (in silico gene panels) that are highly specific to the primary indication	Legal representatives of incompetent adults cannot refuse to receive clinically pertinent and medically actionable results, unless the incompetent adult concerned expressed wishes to the contrary while still competent. For minors, late-onset conditions will only be communicated if (a) the parents request such disclosure **and** (b) disclosure of such information could prevent serious harm to the health of a parent or family member.

Author/ institutional affiliation	Definition of incidental finding	Return of results policy	Reference to filtering or masking of results	Duty to disclose discussed
National Health and Medical Research Council[16] (2010) Australia	Findings unrelated to the clinical presentation that "may be of potential health or reproductive significance, either for the person being tested or for other family members, and may vary from copy number variations known to be benign or of unknown significance to those known to be pathogenic including segmental loss of heterozygosity" (p 62)	Genetic counselling should be recommended for decision-making about tests likely to provide uncertain results. Lab professionals interpret analytical results and report this to the requesting health professional who then decides the extent to which the test result is shared with the patient.		Individuals can refuse to pass on genetic information to genetic relatives without a breach of law. In exceptional circumstances, health professionals can release information to genetic relatives without consent under the Privacy Act.
Pathwiki[17] (2013) Australia Royal College of Pathologists of Australasia (RCPA)	No specific definition given	Patients should receive a clear written record of the policy regarding reporting of IF – currently dictated by standard practice (clinical reasoning, advice of peers and local ethics committees). Results should be conveyed to the patient during post-test face-to-face counselling.	Testing should be targeted so that only genes relevant to the specific disease phenotype are analysed, if feasible, and results from a broader analysis should be 'binned'.	Under the Federal Privacy Act, the health service provider in the private sector is responsible for the security and privacy of a patient's health information, and there are provisions which allow medical practitioners to divulge a patient's genetic information without their consent to a relative if there is a serious threat to life, health, safety of the relative and the use or disclosure is necessary to lessen or prevent that threat.

Author/ institutional affiliation	Definition of incidental finding	Return of results policy	Reference to filtering or masking of results	Duty to disclose discussed
Presidential Commission for the Study of Bioethical Issues[18] **(2013) USA** Bioethics commission report	Divides IF into two categories: **anticipatable** (finding known to be associated with a test or procedure (eg misattributed paternity) and **unanticipatable** (findings that could not have been anticipated given the state of current scientific knowledge). They further categorise findings as *secondary* (those actively sought by a practitioner even though not the primary target – specifically referring to the ACMG guidelines) and discovery (results of a broad or wide-ranging test or screen.	In both clinical and research (and DTC) potential recipients of IFs should be informed about the likelihood of such findings arising from a particular test or procedure as part of the informed consent process. Researchers should develop a plan for the management of IFs with the IRB, but there is no duty to look for secondary findings.		Clinicians should respect patient's autonomy in returning results, but should consider whether the risk of harm of pursuing an incidental finding is greater than the risk that the finding presents (60).

Endnotes

1. RC Green, JS Berg, WW Grody et al "ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing" (2013) 15 Genet Med 565 at 566
2. JR Botkin, JW Belmont, JS Berg et al "Points to Consider: Ethical, Legal and Psychosocial Implications of Genetic Testing in Children and Adolescents" (2015) 97 Amer J Hum Genet 6.
3. American Medical Association *"AMA Code of Medical Ethics' Opinions on Genetic Testing"* (2009) 11 AMA J Ethic Virtual Mentor 683 (www.virtualmentor.org)
4. RR Fabsitz, A McGuire, RR Sharp et al "Ethical and Practical Guidelines for Reporting Genetic Research Results to Study Participants" (2010) Circ Cardiovasc Genet 574.
5. M Hegde, S Bale, P Bayrak-Toydemir et al "Reporting Incidental Findings in Genomic Scale Clinical Sequencing – A Clinical Laboratory Perspective" (2015) 17 J Molec Diagnostics 107.
6. CG van El, MC Cornel, P Borry et al "Whole-genome sequencing in health care: Recommendations of the European Society of Human Genetics" (2013) 21 Eur J Hum Genet 580.
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8. Health Council of the Netherlands *Neonatal screening: new recommendations Executive Summary* (Health Council of the Netherlands, The Hague, 2015) publication no 2015/08
9. JY Hehir-Kwa, M Claustres, RJ Hastings et al "Towards a European consensus for reporting incidental findings during clinical NGS testing" (2015) Eur J Hum Genet 1.
10. N Hallowell, A Hall, C Alberg, R Zimmerman "Revealing the results of whole-genome sequencing and whole-exome sequencing in research and clinical investigations: some ethical issues" (2015) 41 J Med Ethics 317 at 317. See also A Hall, N Hallowell, R Zimmern *Managing incidental and pertinent findings from WGS in the 100,000 Genomes Project: A discussion paper from the PHG Foundation* [PHG Foundation, Cambridge, 2013].
11. PHG Foundation *Next steps in the sequence: The implications of whole genome sequencing for health in the UK* [PHG Foundation, Cambridge, 2011] at 155.
12. A Middleton, C Patch, J Wiggins et al "Position statement on opportunistic genomic screening from the Association of Genetic Nurses and Counsellors (UK and Ireland)" (2014) 22 Eur J Hum Genet 955.
13. A Lucassen, T Clancy, J Montgomery et al *Report on the Genetic Testing of Children* (British Society for Human Genetics, Birmingham, 2010).
14. MH Zawati, D Parry, A Thorogood et al "Reporting results from whole-genome and whole-exome sequencing in clinical practice: a proposal for Canada?" (2014) 51 J Med Genet 68.
15. K Boycott, T Hartley, S Adam et al "The clinical application of genome-wide sequencing for monogenic diseases in Canada: Position Statement of the Canadian College of Medical Geneticists" (2015) 52 J Med Genet 431.
16. National Health and Medical Research Council (NHMRC) *Medical Genetic Testing: Information for health professionals* (NHMRC E99, Canberra, 2010).
17. Royal College of Pathologists of Australasia (RCPA) "Implementation of Massively Parallel Sequencing in Diagnostic Medical Genetic Testing" http://pathwiki.rcpaqap.com.au/pathwiki/index.php/introduction [accessed 18/08/2015].
18. Presidential Commission for the Study of Bioethical Issues *Anticipate and Communicate: Ethical Management of Incidental and Secondary Findings in the Clinical, Research and Direct-to-Consumer Contexts* (Bioethics Commission, Washington DC, 2013).

Appendix Six

Screening and prenatal diagnostic procedures/tests

Figure[1]

Table 1
Testing modalities available in making reproductive decisions after genetic counselling.

Testing modality	Timing and advantages	Risk to fetus	Limitations
Parental carrier screening	Preferably preconceptually	None.	Not all mutations in genes analysed.
First-trimester screening for aneuploidy	10–13 wks; high detection rate.	None.	False-positive rate; false-negative rate.
Second-trimester screening for aneuploidy and open neural-tube defects	From 15 weeks onwards.	None.	High false-positive rate; later in pregnancy.
Chorionic villus sampling	10–13.6 weeks; early diagnosis.	Depends on operator skill.	Confined placental mosaicism.
Amniocentesis	From 15 weeks onward; detects open neural-tube defects.	Depends on operator skill.	Results available late in gestation.
Preimplantation genetic diagnosis	Transfer of only unaffected embryos.	None.	Pregnancy rates less than 30%; accuracy of genetic analyses not established.
Array comparative genome hybridisation	Anytime; higher detection rate of copy-number variations.	None.	May identify copy-number variations of unknown clinical significance.
Ultrasound fetal anatomic survey	18–22 weeks; minimal risk.	None.	Skill of ultrasonographer; anxiety caused by presence of 'soft' signs.
Non-invasive prenatal diagnosis	10 weeks onwards.	None.	Limited to aneuploidy; false negative rate; false positive rate.

1 Pergament, E and Pergament, D "Reproductive Decisions after Fetal Genetic Counselling" (2012) 26 Best Practice and Research Clinical Obstetrics and Gynaecology 517, 520.

Appendix Seven

UK prenatal CMA recommendations

Copy number variants (CNVs) Susceptibility CNVs to report[1]

CNV	Size	Gene	OMIM	Penetrance* %	De novo* %	Ultrasound findings	Phenotype
Distal 1q21.1 del	1.35 Mb	GJA5	612474	36.9 (23–55)	18–20	CHD, eye, microcephaly	ID, ASD, E
Distal 1q21.1 dup	1.35 Mb	GJA5	612475	29.1 (16.9–46.8)		CHD, eye, macrocephaly	ID, ASD, SCZ
15q13.3 del	1.5–2 Mb	CHRNA7	612001	80.5		(CHD)	ID, ASD, E, SCZ
Distal 16p11.2 del	220 kb	SH2B1	613444	62.4 (26.8–94.4)	30–33.3		ID
Prox 16p11.2 del	550 kb	TBX6	611913	46.8 (31.5–64.2)	65–70.2	(CHD)	ID, ASD, E
17q12 del	1.4Mb	HNF1B	614527	34 (13.7–70)	55.6–62	Renal and urogenital	ID, ASD, (SCZ)

Susceptibility CNVs not to report

CNV	Size	Gene	OMIM	Penetrance* %	De novo* %	Ultrasound findings	Phenotype
15q11.2 BP1-BP2 del	450 kb	NIPA1	615656	10.4 (8.45–12.7)	0		ID, ASD
15q11.2 BP1-BP2 dup	450 kb	NIPA1	608636				ASD
16p13.11 del	1.5 Mb	MYH11		13.1 (7.91–21.3)	21.7		

1 Carol Gardiner, Diana Wellesley, Mark D Kilby and Bronwyn Kerr on behalf of the Joint Committee on Genomics in Medicine, Recommendations for the use of chromosome microarray in pregnancy (2015). http://www.bsgm.org.uk

16p13.11 dup	1.5 Mb	MYH11					
Proximal 1q21.1 dup	0.5 Mb	RBM8A	612475	17.3			ID
16p12.2 deletion	0.5 Mb	CDR2	136570	12.3			
Xp22.31 dup	1.5Mb	STS					ID
Xp22.33 del	Varies	SHOX					

Consider detailed scan looking for associated anomalies or reporting in a clinical context

CNV	Size	Gene	OMIM	Penetrance* %	De novo* %	Ultrasound findings	Phenotype
22q11.2 dup	1.5/3 Mb	TBX1	608363	21.9 (14.7–31.8)	7–25.5	Bladder exstrophy, (CHD), (CP)	ID
Proximal 1q21.1 del	200 kb	RBM8A	274000	17.3 (10.8–27.4)	0	Absent radius	TAR syndrome
17q12 dup	1.4 Mb	HNF1B	614526	21.1 (10.6–39.5)	22.2	Renal (OA & TOF),	ID, E, ASD (SCZ)

Key

OA = oesophageal atresia, SCZ = schizophrenia, TAR = thrombocytopaenia absent radius
ASD = autistic spectrum disorder, CHD = congenital heart disease, CP = cleft palate syndrome E = epilepsy
TOF = trachea-oesophageal fistula, ID = intellectual disability ( ) = association less clear
*reference 1 Rosenfeld et al, 2013.

Appendix Eight

Conditions that may be tested for by NIPT

Gene/ Chromo-some	Common name	Estimated prevalence live births	Sex affected	Presentation
Trisomy 9	Dandy-Walker malformation	1:10,000 to 1:30,000	both	(Can also be caused by trisomies 18, 13 and 21) – a malformation of the brain resulting in problems with movement, coordination, intellect, mood and other neurological functions. Variable presentation – up to half of affected individuals have an intellectual disability ranging from mild to severe.
Trisomy 13	Patau syndrome	1:100,000	both	Most affected fetuses die in utero. Complex and multiple organ and limb defects and severe intellectual disability. Only 5-10% of affected children live beyond the first year.
Trisomy 16		n/a	both	Full trisomy 16 is not compatible with life. Mosaic 16 has wide variation of presentation and can include intrauterine growth retardation, delayed development and heart defects.
Trisomy 18	Edwards syndrome	1:6000	both	Most affected fetuses die in utero. Major heart, kidney and other malformations. Most children die before the age of 1; surviving children often have severe intellectual disability.
Trisomy 21	Down syndrome	1:800	both	Variable presentation with cognitive delay. Mild to moderate intellectual disability. Heart defects common; may have digestive abnormalities, celiac (gluten allergy), underactive thyroid, increased risk of hearing and vision problems. Behavioural issues may include obsessive/compulsive behaviour and stubbornness or tantrums. Increased risk of early-onset Alzheimer's disease.
Trisomy 22	Emmanuel syndrome Cat-eye syndrome	n/a	both	Emmanuel syndrome is caused by the presence of extra genetic material from both chromosome 22 and 11 in each cell. It occurs when a balanced translocation becomes unbalanced when passed to the next generation and leads to intellectual disability and birth defects. Partial trisomy 22 can cause intellectual disability, delayed development, delayed or absent speech, distinctive facial features and behavioural problems. Inverted duplicated 22 can cause cat-eye syndrome, which presents with iris colomba (split in lens of eye), unusually formed ears, heart defects, kidney problems, malformations of the anus, and in some cases, delayed development.

Gene/ Chromo-some	Common name live births	Estimated prevalence	Sex affected	Presentation
45,X	Turner syndrome	1:2500	female	Short stature, early loss of ovarian function with most affected females infertile. May be accompanied by heart-defects that can be life-threatening. Most affected individuals have normal intelligence.
47,XXY	Klinefelter syndrome	1:500 to 1:1000	male	Taller than average stature. Variable presentation. Typically small testes or testicular abnormalities. Reduced testosterone production, often infertile. Increased risk of breast cancer and lupus. May have learning disabilities and delayed speech or language development.
47,XXX	Trisomy X	1:1000	female	Taller than average. Most have normal sexual development. Associated with increased risk of learning disabilities and delayed development of language and speech. May be accompanied by seizures or kidney abnormalities.
47,XYY		1:1000	male	Taller than average. Normal sexual development. Increased risk of learning disabilities and delayed development of language and speech. Small percentage of XYY males diagnosed with autistic spectrum disorder.
48,XXYY		1:18,000 to 1:50,000	male	Causes medical and behavioural problems. Smaller testes with reduced testosterone production; often infertile. Physical effects: taller than average, dental problems, and may develop peripheral vascular disease with age. Learning disabilities in language and reading are common, but these males are often better than average in math and visual-spatial skills. Associated with ADHD, mood disorders and/or autistic spectrum disorders.
1p36		1:5000 to 1:10,000	both	Microcephaly and severe intellectual disability. Structural abnormalities of the brain, weak muscle tone and swallowing difficulties. Often presents with seizures. Individuals may have vision or hearing problems, skeletal or organ abnormalities.
2q33.1		n/a	both	Variable presentation. ALS2 gene location – mutations of which can cause amyotrophic lateral sclerosis, infantile-onset ascending hereditary spastic paralysis; juvenile primary lateral sclerosis. HSPD1 gene location – mutations of which can cause autosomal recessive spastic paraplegia. MARS2 gene location – mutations of which are associated with the autosomal recessive neuro-degenerative disease spastic ataxia; or a mitochondrial disorder (COXPD25) that results in developmental delay, growth failure and hearing loss. SF3B1 gene location – mutation of which may be associated with myelodysplastic syndrome.

Gene/ Chromo-some	Common name	Estimated prevalence live births	Sex affected	Presentation
4p	Wolf-Hirschorn syndrome	1:50,000	2:1 female to male	Affects many parts of the body with a distinctive "Greek warrior helmet" facial structure, delayed growth and development, weak muscle tone. Intellectual disability ranges from mild to severe. Good socialisation skills. Seizure that tend to disappear with age. Skin changes and curvature of the spine, dental problems and cleft palate are common.
5p	Cri-du-chat syndrome	1:20,000 to 1:50,000	both	Infants make sound like a crying cat. Microcephaly and intellectual disability. Low birth weight, weak muscle tone. May have a heart defect.
8q		n/a	both	Variable presentation. Disorders on chromosome 8 can cause problems with health and development, including leukaemias; Langer-Giedon syndrome which causes benign bone tumours; recombinant 8 syndrome, which involves heart and urinary tract abnormalities, moderate to severe intellectual disabilities and a distinctive facial appearance.
11q	Jacobsen syndrome	1:100,000	both	Variable presentation. Most have delayed development including speech and motor skills. Most also have cognitive impairment and learning difficulties. Some behavioural issues, including compulsive behaviour and ADHD. Increased likelihood of autistic spectrum disorders. Distinctive facial features, often with microcephaly. High likelihood of a bleeding disorder called Paris-Trousseau syndrome (abnormal platelet production). May have heart or skeletal defects.
15q11-q13	Angelman's syndrome (deletion of maternal copy); Prader-Willi syndrome (deletion of paternal copy)	1:12,000 to 20,000 1:10,000 to 30,000	both	Angelman's: severe speech impediment, moderate to severe intellectual disability. Problems with movement and balance. Frequent smiles and outbursts of laughter are common, with happy, excitable personalities. Hyperactive, short attention span, difficulty with sleeping. short attention span, difficulty with sleeping. Seizures common. Often have unusually fair skin and light hair and curvature of the spine. Prader-Willi: mild to moderate intellectual disability. Insatiable appetite leading to chronic overeating and obesity. Behavioural problems are common. Distinctive facial features. Underdeveloped genitalia and most individuals are infertile.

Gene/ Chromo-some	Common name	Estimated prevalence live births	Sex affected	Presentation
22q11.2	Used to be known as DiGeorge syndrome	1:4000 (may be more common)	both	Extremely variable presentation. May include cleft palate and heart abnormalities. Can cause issues with the immune system. Sometimes presents with developmental delays and learning disabilities. Believed to be an increased risk for mental illness, ADHD and autistic spectrum disorders.
Vanishing Twin				Syndrome where a fetus in a multiple pregnancy can be reabsorbed by the viable twin, a fetus papyraceous (mummified) may form, or development of a subtle abnormality on the placenta such as a cyst. Often may be due to the presence of chromosomal abnormalities which are not present in the viable twin.

Source: National Institutes of Health: Genetics Home Reference: US National Library of Medicine at www.ghr.nlm.nih.g