DELAYED DIAGNOSIS OF GUT DISEASE & DELAY-REDUCTION INTERVENTIONS

A Literature Review

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Introduction

It is well documented that delays in diagnosis and treatment of gut disease result in more serious illness with increased morbidity and mortality. Early diagnosis and treatment is likely to lead to better outcomes (Heyhoe et al., 2020; Mounce et al., 2017). It is therefore important to understand the pathway between the time that symptoms first appear for an individual and a diagnosis being made and treatment begun. This pathway is influenced by patient factors, disease factors, health care provider, and health system factors (Brousselle et al., 2017; Korsgaard et al., 2008) and delay may occur at any or all of the following stages:

- Patient-attributed delay: the time from an individual first noticing a symptom until they first consult a medical provider;
- Doctor-attributed delay: the time from the first consultation to the ordering of tests targeted at diagnosis;
- Diagnostic delay: the time taken for the tests to be carried out and a diagnosis made;
- Intervention delay: the time from diagnosis to treatment;
- Overall delay: the combination of all the above delays (Cerdan-Santacruz et al., 2011).

While this list is taken from a study on colorectal cancer, the delays it notes are generalisable to the other gut diseases under consideration here. This report is divided into three sections that investigate patient-attributed delay, health care provider and system delays and interventions designed to reduce delays.

PART ONE - Patient delay

Symptom awareness, appraisal and help seeking

A considerable literature has examined the many factors that contribute to patient delays in seeking help for gastrointestinal symptoms. Studies of colorectal cancer dominate this literature (Brousselle et al., 2017; Courtney et al., 2012a; Courtney et al., 2012b; Esteva et al., 2013; Hall et al., 2015; Jones et al., 2007; Macdonald et al., 2019; McCutchan et al., 2015; Molassiotis, Wilson, et al., 2010; Ramos et al., 2010; Whitaker et al., 2015; Whitaker et al., 2016). There have also been investigations of patient consulting behavior in other cancers of the gastrointestinal tract and in non-cancer diagnoses including inflammatory bowel diseases, irritable bowel syndrome, coeliac disease and gastroesophageal reflux (Jones & Ballard, 2008; Jones et al., 2009; Lewis et al., 2018; Molinder et al., 2015; Nobrega et al., 2018; Oberoi et al., 2015a; Ringström et al., 2007).

A characteristic of gastrointestinal diseases is that they have a "broad symptom signature" (Koo et al., 2018, p. 168); the symptoms are widely varied in type, duration, and severity. They range from unexplained abdominal pain, gastrointestinal discomfort or cramps, changes in bowel habits (diarrhoea or constipation), unintended weight loss, loss of appetite, fatigue, anaemia, nausea, vomiting, blood noticed on toilet paper or in the stools, rectal bleeding, bloating, dysphagia, gastro-oesophageal reflux, and a general feeling of being unwell (Esteva et al., 2013; Hall et al., 2015; Jones et al., 2007; Ramos et al., 2010; Ristvedt et al., 2014; Whitaker et al., 2015).

One of the key difficulties in patient delay is that initial symptoms are often mild, vague, and sporadic. Many of them are non-specific and may be present in any gastrointestinal condition, whether serious, or not. Symptoms may resolve and then return or gradually get worse over time. As MacDonald et al (2019) point out, it is reasonable to ignore symptoms if they come and go and do not interfere with normal daily activities. Recall of when they first started may be poor because of the longstanding nature of the symptoms so that estimating the extent of patient delay is often difficult. Calendar landmarking techniques based on events of personal, local, or international significance have sometimes been used to assist patient recall (Emery et al., 2013a). Moreover, people are widely different in how they interpret and respond to symptoms, with their reaction depending on "…a range of interacting and often competing biopsychosocial, contextual and cultural influences" (Hall et al., 2015, p. 1). One Danish study of 733 patients who had been diagnosed with colorectal cancer (Korsgaard et al., 2008) demonstrated how widely people varied in the length of time they waited to consult a doctor about their symptoms. While the median delay of 18 days for colon and 44 days for rectal cancer appeared moderate, 25% of patients delayed between 90 and 489 days for colon, and 115-366 days for rectal cancer.

One reason for delay appears to be a general lack of knowledge about the significance of such symptoms and therefore a low perception of the risk they present (Christou & Thompson, 2012; Dawson et al., 2016; Javanparast et al., 2012; Jones & Johnson, 2012; Koo et al., 2010; Oberoi et al., 2016a). Gastrointestinal cancers, for example, are less prominent in public discourse in Australia and New Zealand than breast and skin cancers, where more attention has been paid to promoting awareness among the public (Bong & McCool, 2011). However, this lack of knowledge has also been found across a broad range of international studies that have covered general, minority and underserved populations (Bong & McCool, 2011; Bradley et al., 2015; Green et al., 2017; Ivey et al., 2018; Robb et al., 2008). People may interpret their symptoms as being part of existing health conditions, arising from a medication change, or a passing gastrointestinal infection that will clear up spontaneously (Ramos et al., 2010). Other individuals may not consider the possibility they could have a serious illness because they believe they have too healthy a lifestyle with regular exercise and a good diet (Molassiotis, Wilson, et al., 2010). Competing demands from business or family affairs may also mean that people do not see their health as a priority and put off seeing a doctor until symptoms reach an advanced stage (Emery et al., 2013a).

Certain personality characteristics are also associated with delays in seeking help for symptoms. People who are optimistic, stoic, or self-reliant may decide to wait and see if their symptoms worsen; they may self-treat, or minimise their symptoms in the expectation that they will eventually pass (Leal et al., 2018; Rogers et al., 2017; Whitaker et al., 2016). These qualities were found to be strongly present among 66 rural Australians diagnosed with colorectal cancer and were an important reason for delay especially when combined with the perceived and actual problems with access to GP care for people who lived far away from main centres (Emery et al., 2013a). Individuals who tend to be fearful, fatalistic or assume a worst-case scenario may also delay seeking help for their symptoms (Lyratzopoulos, Liu, et al., 2015). Public narratives about the meaning of cancer – its "randomness, unpredictability, fear, severity and tragedy" (Macdonald et al., 2019, p. 32) influence perceptions that nothing can be done (Brown et al., 2017) or that a diagnosis leads only to painful and life limiting treatments and will inevitably end in death.

Many studies have examined gender differences in delay but results are inconsistent and appear to be linked to the specific societal context rather than being universally applicable. Male stoicism and machismo has been highlighted in several Australian studies as a predictor of delay (Emery et al., 2013a; Oberoi et al., 2015b; Oberoi et al., 2016b) yet two Spanish studies found women would encourage male family members to see a doctor while delaying over their own symptoms (Esteva et al., 2013; Ramos et al., 2010). Korsgaard et al (2008) recorded longer delays in women with colon cancer, but in men with rectal cancer. Yet another study found no association by gender for any of the gastrointestinal cancers (Macleod et al., 2009).

The awkwardness and embarrassment of talking about and being examined for symptoms like rectal bleeding and incontinence may also deter people from seeking help until their symptoms can no longer be ignored (Haigh et al., 2016; Leal et al., 2018; Siminoff et al., 2014; Smith et al., 2005). Multiple, persistent, or increasingly severe symptoms, especially pain and bleeding, however, tend to alert most people that something is wrong (Courtney et al., 2012b; Deng et al., 2012; Whitaker et al., 2015). In a New Zealand survey, rectal bleeding was one of the most common triggers for consulting a doctor, whereas anaemia and low energy were the least likely (Windner et al., 2018). Yet not everyone takes action even then. Non-recognition of rectal bleeding as a warning sign for cancer has been examined in several population-based studies across different countries. The Hunter Community study in Australia reported that 31% of the participants aged between 56 and 88 years of age reported ever experiencing rectal bleeding yet 18% of those had not consulted a doctor (Courtney et al., 2012a; Courtney et al., 2012b). Those who recognised that the bleeding may be a sign of something serious were more likely to have sought help. A similar finding was reported in the United Kingdom (UK) by Quaife et al (2014); those who did not appreciate that rectal bleeding may be serious were likely to delay for more than two weeks before seeing a doctor. A nationwide Danish survey of alarm symptoms for colorectal cancer (Jarbol et al., 2018) found that 69.8% of those who had experienced rectal bleeding had not consulted a doctor, mostly citing being too busy or afraid they would be seen as wasting the doctor's time. Another UK study that surveyed almost 10,000 adults over the age of 50 found that over a third of people who reported at least one cancer 'alarm' symptom in the previous three months had not consulted a doctor (Whitaker et al., 2015). None of these studies, however, indicated the proportion of people who were subsequently diagnosed with serious illness.

Health system factors are also influential in delay; long waits for an appointment, language difficulties, transport needs, distance, cost, and previous negative experiences with health professionals have all been associated with delay in help seeking. Lack of trust in the health system is particularly important for people in marginalised and minority groups (Clarke et al., 2016; Lesnovska et al., 2017; MacArtney et al., 2017; Schoenberg et al., 2016; Ward, Coffey, Javanparast, et al., 2015; Ward, Coffey, & Meyer, 2015; Whitaker et al., 2016). Additionally, studies from the UK and Scandinavian countries consistently report that pressure from authorities not to overburden their fully publicly funded health systems also deters people from consulting in case they are accused of wasting the doctor's time on trivial matters (Cromme et al., 2016; Hall et al., 2015; Jarbol et al., 2018; MacArtney et al., 2017; Macdonald et al., 2019; Power & Wardle, 2015; Whitaker et al., 2015). On the other hand, some individuals who have seen a doctor may delay going back because they have previously been reassured that their symptoms are due to a benign condition and they do not need to be worried (Macleod et al., 2009).

Confirmation of these reasons for delay comes from the related area which has investigated reasons for declining bowel screening (Bradley et al., 2015; Dharni et al., 2017; Filippi et al., 2016; Frerichs et al., 2018; Honein-AbouHaidar et al., 2016; Martens et al., 2016). These studies have found generally poor public knowledge about the risk of bowel cancer so that screening is viewed as unimportant. They also highlight the avoidance of screening by those who have experienced access and/or cultural barriers in the past and do not trust the health system. Fear of what the screening test might find has also been shown to be influential. In contrast with the literature above, there does, however, appear to be a consistent association between male gender and declining bowel screening. This is attributed to concepts of masculinity that deny the possibility of disease, whereas women are already familiar with breast and cervical screening and so more readily accept the concept of screening (Clarke et al., 2016; Getrich et al., 2012; Reeder, 2011; Ritvo et al., 2013; Thompson et al., 2012; Winterich et al., 2011; Wong et al., 2013).

Although the patient delay literature is dominated by colorectal cancer, there are nevertheless some studies that have focused solely on patient appraisal and help seeking in oesophageal, gastric or pancreatic cancers (Evans et al., 2014; Humphrys et al., 2020; Keane et al., 2014; Lewis et al., 2018; Macdonald et al., 2006). Late-stage diagnosis in all these cancers is common largely for the same reasons as have been outlined above. A systematic review that examined 19 studies on patient delay factors in upper gastrointestinal cancer found that lack of awareness of symptoms and interpreting their significance was a key issue (Macdonald et al., 2006). Delays in presenting could extend many months, with people attributing their symptoms to benign causes and self-treating. As with colorectal cancer, increasing severity of symptoms, usually pain and bleeding, or the presence of multiple symptoms was likely to trigger consultation, though fear of cancer could also cause delays even when symptoms were recognised as serious. Two studies published more than a decade after this older review found that little had changed in the intervening years (Humphrys et al., 2020; Lewis et al., 2018). A qualitative study by Lewis (2018) of 14 patients with oesophageal cancer found that early symptoms were normalised by these patients; they were largely unaware that they may be a warning of serious disease and therefore did not cause any alarm or provide a reason to visit a doctor. Only when they were persistent, became worse, or began to interfere with daily life did people seek help. Most were unprepared for the diagnosis and were shocked and distressed at having an unfamiliar disease.

Similar findings were recently published from an investigation of 127 patients in England who had been newly diagnosed with oesophageal or gastric cancer who participated in a survey about their symptom experience prior to diagnosis (Humphrys et al., 2020). Patients' and clinicians' different understandings of the meaning of heartburn, indigestion and reflux made communicating their symptoms challenging for patients and interpreting them difficult for doctors. In this study, symptoms initially represented to a GP ranged across a wide spectrum from indeterminate conditions such as fatigue to highly alarming symptoms such as vomiting blood. This study, too, reported limited awareness of upper gastrointestinal cancers, with the usual response being to normalise and self-manage until symptoms became severe and persistent. The median patient interval reported in this study was 79.5 days but with the same wide variability between patients (range 1-712 days).

Pancreatic and biliary tract cancers tend to have a low life expectancy because they are often diagnosed at an advanced, inoperable stage (Mangge et al., 2017). Three UK studies specifically examined the symptoms that led up to the diagnosis of these cancers (Evans et al., 2018; Keane et al., 2014; Mills et al., 2017). Keane et al (2014) examined thousands of records drawn from a repository for 562 GP practices, extracting the records of patients diagnosed with pancreatic and biliary tract cancers and matching each one with six controls, then reviewing the patient histories over the previous two years before diagnosis. The same pattern of intermittent nausea, indigestion, bowel changes, fatigue and varying types of abdominal pain were present, but these patients showed some symptoms more specific to pancreatic and biliary tract cancers including back and shoulder pain, new onset diabetes and jaundice, the latter being a sign of advanced disease. Patients had similarly self-managed until their symptoms became severe and persistent. A qualitative study of 40 patients diagnosed with pancreatic cancer (Evans et al., 2014) identified four clear triggers that were the tipping point between self-management and deciding to consult a doctor: a pattern of symptoms becoming apparent; increased frequency of symptoms; a change in the nature of symptoms; and the occurrence of additional symptoms.

A more recent study (Mills et al., 2017) took a different approach that avoided the retrospective nature of most others by recruiting patients newly referred to hospital with symptoms suggestive of pancreatic cancer – i.e. not diagnosed - and therefore in an earlier stage in the patient journey. Twenty-six patients were interviewed; 13 were ultimately diagnosed with cancers (nine with pancreatic cancer). The other 13 diagnoses included pancreatitis, hernia and gallstones. The patient interval to presentation was a median 21 days (range 1-270 days). The investigators were unable to find any clear differences in symptom appraisal and help seeking between the cancer and non-cancer diagnoses. A similar cycle of bodily changes, symptom attribution, self-management and triggers to seeking help were identified as in previous studies and were not different between the cancer and non-cancer groups. All three studies also commented on the number of visits to GPs that were often needed before being referred. This issue is further discussed in Part 2 of the literature review.

Symptom appraisal and help seeking in non-cancer gastrointestinal diseases

Overall, there appears to have been less interest in patient symptom appraisal and help seeking in non-cancerous conditions of the gastrointestinal tract, than there has been in relation to the gastrointestinal cancers. Much of the literature is focused on treatment rather than attempting to encourage people to seek help at an early stage. However, the symptoms are largely similar, the diagnosis not always straightforward, and there are the same difficulties that deter people from seeking help and compromise understanding between patients and health care professionals. While there are a few general studies of help seeking for symptoms, most of the literature tends to be focused on particular conditions.

A study of 100 people seeking help in gastrintestinal clinics or pharmacies (Dhaliwal et al., 2018) found the component stages of being able to communicate symptoms required being able to recognise, characterise, and describe them. In this study the lack of standard terms was a barrier to communicating in a healthcare setting; more than three quarters of participants reported difficulty describing their symptoms and being uncertain whether their descriptions had been understood by the health provider they consulted. Three Australian studies on men's help seeking for bowel symptoms (Oberoi et al., 2015a, 2015b; Oberoi et al., 2016b) also found widespread unawareness and/or misinterpretation of symptoms, fear of cancer diagnosis, low confidence in medical consultations, and access barriers including the cost of health care. In the United States, a focus group study of 39 women with accidental bowel leakage (Brown et al., 2017) identified 12 separate barriers to help seeking. These included lack of recognition of their condition and its significance, fear, stigma and shame about bowel leakage, not knowing that treatments were available, and access barriers to obtaining health care.

Gastro-oesophageal reflux disease

A study of healthcare seeking in gastro-oesophageal reflux disease (GORD) (Jones & Ballard, 2008) recruited 164 people in four countries (UK, US, France and Germany). There were equal numbers of participants with a GORD diagnosis and members of the public who reported the same symptoms but had not been diagnosed. Twelve focus groups and 66 personal interviews with participants aimed to discover what kind of symptoms people experienced and how they dealt with them. Symptoms reported included burning and pain in the upper digestive tract, back pain, regurgitation, bad breath, stomach noises, choking sensations, sleep interruption, bloating and difficulty breathing. Minor symptoms were mostly addressed with lifestyle or dietary changes and worsening symptoms with help from a pharmacist or use of over the counter products. Severe symptoms that could not be controlled in these ways and were restricting or preventing participation in usual work or leisure activities were the most usual trigger for consulting a doctor. Participants who had confidence that prescribed medicines could help and already had a positive relationship with a health professional were also more likely to seek help promptly. Consistent with studies highlighted earlier, suspecting their symptoms might be cancer could either trigger medical consultation or, in some people, deter them for fear of what they might find out. Overall, four key factors were identified with health care seeking: the intensity and amount of control over symptoms; perceived seriousness; degree of interference with daily life; and views about medicines and the medical profession.

Inflammatory bowel disease

A number of different studies have all reported similar behavior around seeking help for the awkward symptoms of inflammatory bowel disease. A British study (Norton & Dibley, 2013) analysed 617 free text responses to questions about help seeking for faecal incontinence extracted from a survey of members of an inflammatory bowel disease charity. A minority of these reported actively seeking help (84/617), among whom 36 had found the response from medical or nursing services was helpful, 29 unhelpful, and 10 had sought help from complementary therapies such as acupuncture, herbalism, and hypnotherapy. Reasons for not seeking help were believing that nothing could be done, not knowing who to ask for help or being aware of available services, and feeling embarrassed or ashamed. Difficulty accessing services and the wish to avoid intrusive tests deterred some respondents while others felt their problem was too insignificant to warrant asking for help, or that health professionals would lack interest, sympathy and understanding.

A detailed Brazilian study of the symptoms of inflammatory bowel disease (Nobrega et al., 2018) aimed to alert clinicians to the clinical manifestations and reduce diagnosis delay. The study included 306 participants, 141 diagnosed with Crohn's disease and 165 with ulcerative colitis who were asked about their experience of 22 different symptoms. The main clinical manifestations were weight loss, followed by diarrhoea, abdominal pain, faecal urgency, asthenia and bloody stools. The Crohn's patients had a higher frequency of systemic manifestations including more weight loss, anaemia, insomnia, fever, nausea and vomiting, whereas the ulcerative colitis patients had a higher frequency of intestinal symptoms (blood and mucus in the stool, urgency, faecal incontinence and tenesmus). There were long delays in diagnosis, ranging from 18-37 months for Crohn's disease and 12-52 months for ulcerative colitis patients. This study did not ask about the reasons for patient delay.

Coeliac disease

Coeliac disease (CD) is an autoimmune disorder that occurs in genetically predisposed individuals who develop an immune reaction to gluten and according to a recent review in the Lancet has a worldwide prevalence of around 1% a (Lebwohl et al., 2018). Coeliac disease is notable for the large age range at which the onset can occur. It has considerable symptom crossover with all the conditions described above but also a number of important differences. It was initially believed to affect only the gastrointestinal tract, but it is now recognised that it can affect other bodily systems and gastrointestinal manifestations may be absent altogether. Symptoms include most of the symptoms of other gastrointestinal conditions but in addition there may be headaches, chronic fatigue, infertility, anaemia, vitamin and mineral deficiencies, dental enamel defects, failure to thrive and others. Copleton and Valle (2009) list 36 symptoms which they term only a 'partial' list. Lebwohl et al (2018) list chronic diarrhoea, weight loss and failure to thrive, along with iron deficiency, bloating, constipation, chronic fatigue, headache, abdominal pain, and osteoporosis. Treatment is by removal of gluten from the diet, which stops the autoimmune reaction that causes the symptoms. Therefore, many individuals are able to manage the condition themselves. Coeliac disease is considered by many to be only part of the spectrum of gluten related disorders, including non-coeliac gluten sensitivity, gluten intolerance, or wheat allergy. These other gluten related disorders are a contested area between individuals who have self-diagnosed and follow a gluten free diet and medical and scientific studies which are still debating whether these conditions exist and how to categorise them (Moore, 2014). People who believe they have one of these conditions and have already changed their diet accordingly tend to reject the biomedical tests that diagnose coeliac disease because of the need to go back to consuming gluten over a relatively long period – and suffer the symptoms of the disorder - so as to show damaged villi (Copelton & Valle, 2009).

The relationship between diagnosis and bowel symptoms in CD, however, is not entirely straight forward. The Lancet review (Lebwohl et al., 2018) noted that in spite of adhering to a gluten free diet, some individuals have persistent or recurrent symptoms which are likely to be related to additional conditions. They also noted that CD is associated with an increased risk of lymphomas, and adenocarcinoma of other sites in the gastrointestinal tract. In another study by Hauser et al (2007) certain individuals with medically diagnosed CD continued to experience bowel symptoms and to seek healthcare for them. Twenty three percent of the 412 patients with biopsy confirmed CD reported ongoing bowel symptoms and for most of them, their symptoms led to them seeking health care. It was concluded that continuing symptoms arose from both clinical (occasional non-adherence to the gluten free diet) and non-clinical reasons, and particularly affected people with mental health conditions and/or low health-related quality of life. The investigators noted however, that the non-clinical symptoms could be the consequence as well as the cause of gastrointestinal symptoms and there was no clear cause and effect relationship. Another study (Ciacci et al., 2013), also found that stress may play a role in triggering the propensity to develop CD. The study compared a group of adults recently diagnosed with CD to a control group with recently diagnosed gastro esophageal reflux disease (GERD). While there was no significant difference between the two groups in length of symptoms prior to diagnosis, those with recently diagnosed CD were significantly more likely to have had more frequent stressful events, particularly in the year preceding diagnosis.

Irritable bowel syndrome

The issues around symptom recognition and health care seeking for irritable bowel syndrome (IBS) are complex and make IBS somewhat different from the conditions reviewed above. Firstly, the diagnosis of IBS is based on symptom reports, with tests being able only to rule out other illness rather than being able to provide a specific diagnosis. Secondly, the reported prevalence of IBS differs markedly according to geographical area and the criteria used for diagnosis. In a systematic review and meta-analysis conducted by Lovell et al (2012) the pooled global prevalence from 80 separate population studies was 11.2%. However, prevalence ranged widely from 1.1% to 45.0% depending on the country where the study was carried out and the criteria used to define IBS. The greatest prevalence was reported when three or more of the Manning criteria (1978)[1] were used, whereas using the Rome II criteria (Thompson et al., 1999),[2] the prevalence was 8.8%. In general, prevalence was consistently higher for women than men and lower for people older than 50 compared to those younger. The review was unable to comment on socioeconomic effect because of the dearth of studies on this aspect.

In the absence of a specific diagnostic test for IBS, the discrepancy between the terms used by lay people to describe their symptoms and the terms listed in the diagnostic criteria appear to be of particular relevance. In a study by Molinder et al (2015) Swedish gastroenterologists randomly sampled 1,244 individuals from the general population, asking them to describe any gastrointestinal complaints in their own words without any further prompting or follow up questions. The 601 participants who reported at least one gastrointestinal symptom then completed the Rome II questionnaire used for diagnosing IBS.   The 128 who filled the criteria were further examined, and after excluding those who had already been diagnosed or had other gastrointestinal conditions, 81 participants were assessed as having IBS. However, only five of them had given an initial description that would have suggested IBS without further prompting. The study concluded that the standard terminology used for diagnosis should be modified to reflect the language used by the lay public.

A key feature of IBS is the considerable number of people with symptoms which meet the criteria for diagnosis but who are ‘non-consulters’ – that is, people who never seek help for their symptoms and manage alone. Three studies of widely different populations have all resulted in similar findings in this respect (Fan et al., 2017; Katsinelos et al., 2009; Ringström et al., 2007). A Swedish study (Ringström et al., 2007) compared health care seeking behavior across 95 patients seen in secondary/tertiary care, 53 seen in primary care with IBS, and 70 people who met the Rome II criteria for IBS but had not sought care for their symptoms. Participants in the first two groups were recruited through the relevant medical services. Non-consulters were recruited through newspaper advertisements. All participants completed eight different self-administered questionnaires and scales covering relevant aspects of IBS, coping and quality of life. Factors that independently predicted being a consulter were poor social functioning and low emotional, mental health and physical

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[1] Manning criteria: a questionnaire used to diagnose irritable bowel syndrome

[2] Rome II criteria: an updated system used to diagnose irritable bowel syndrome

functioning on standard scales used to measure quality of life (QOL). Non-consulters generally had better QOL, less severe psychological symptoms and better coping resources than consulters. Consulters seen in primary care tended to have less severe gastrointestinal symptoms than those seen in secondary care as well as better QOL and lower anxiety. Of the 70 non-consulters, some stated they did not seek help because they had mild symptoms they could control themselves and believed they were nothing to worry about. A few did not seek help because they feared what might be found or were afraid of invasive tests, and others attributed their symptoms to stress rather than gastrointestinal disease. Some had consulted alternative practitioners, pharmacists, or psychologists or found it easy to discuss their symptoms with friends and relatives and receive advice and reassurance, while others had not consulted anyone and gave no reason why. The study concluded that psychological symptoms and poor QOL predict health care seeking in IBS so that health care practitioners might reduce the need for consultation by listening to patient concerns and helping them to better cope with their symptoms in daily life.

A similar study in Northern Greece (Katsinelos et al., 2009) recruited 3112 adult participants who visited participating hospital centres but were not seeking consultation for themselves (i.e. patients' escorts, family and friends) and responded to an advertisement at the information desk. They answered a detailed questionnaire and had a complete physical examination by a primary care or internal medicine specialist. After excluding 715 who did not meet the inclusion criteria, 737 (15.7%) of the remaining 2397 participants reported gastrintestinal symptoms compatible with IBS; 151 consulters and 220 non-consulters. Consulters were significantly more likely to be female, unemployed or engaged in household duties, and to have more anxiety than non-consulters, but there was no difference between the groups in depression or sleeping disorders. This study did not ask non-consulters why they did not seek help, but suggested that the greater representation of women compared to men who were consulters suggested that women were generally more comfortable seeking health care than men.

A Chinese study (Fan et al., 2017) also analysed predictors of health seeking behavior in 516 participants who had been diagnosed with IBS from a university gastroenterology clinic. The median disease course was 6.5 years, however, more than 30% had a disease course of more than 10 years, and 12%, more than 20 years. Excluding their current consultation, 55.2% of participants had sought healthcare at least once for IBS symptoms. This group was termed the 'consulters' and compared with the remaining participants who were the 'non-consulters'. Among the consulters, there were 190 frequent consulters with an average of 4.5 visits during the past year. Consulters were more likely than non-consulters to present with more severe abdominal pain, persistent symptoms, anxiety and depression, loose stools and weight loss, to have a longer disease course and to have had multiple colonoscopies and take long term and/or multiple medications. Most treatments were only partially effective and patients reported low satisfaction rates, particularly patients with co-existing anxiety. Common to all three of these studies that examined non-consulter groups was the finding that consulters had more severe symptoms, were more likely to have psychological symptoms, especially anxiety, and were more likely to be female than male.

Summary: Factors related to Patient Delay

- Symptoms of bowel and gut disease are very broad and vary widely between individuals;
- There is considerable crossover between the symptoms of cancer, other serious gastrointestinal illnesses and benign conditions;
- 'Red flag' symptoms identified in the literature are pain, bleeding, and dysphagia but not everyone with serious disease will experience these;
- Serious symptoms appear to be poorly known and recognised by the general public;
- The threshold for consulting differs markedly between individuals; those who value self-sufficiency and stoicism are more likely to delay; others may delay because they fear invasive tests and what the tests may find;
- Most individuals will consult on experiencing increasing severity of symptoms, multiple symptoms, or when symptoms begin to restrict work or leisure activities;
- Health system factors also influence decisions about seeing a doctor, including travel and the distance from services, cost, availability of appointments, and pressure to avoid unnecessary consulting over what may seem to be trivial concerns;
- Previous negative experiences with health services or unwarranted reassurance through an incorrect diagnosis are also associated with delays;

- Psychological symptoms, especially anxiety, are associated with the chronic bowel and gut diseases but the relationship is complex, not one of cause and effect;
- Poor outcomes from delayed consultation are most relevant for cancer. However, consultation is likely to expedite treatment, reduce morbidity and improve quality of life in all gastrointestinal conditions if it results in prompt and accurate diagnosis and treatment.

PART TWO - Practitioner and system attributed delays

The second phase of the pathway to diagnosing gut disease begins at the point when an individual first presents to a health professional - usually a general practitioner – seeking advice about symptoms that concern them. What happens next determines the extent of delay in diagnosis and treatment (Emery et al., 2013b). Symptoms of gastrointestinal distress are common in general practice and it is clearly unrealistic for doctors to refer every patient with any of the symptoms of gut disease for specialist investigation or they would overwhelm health systems by "filling outpatient services with mild pathologies" (Esteva et al., 2013, p. 11). Most symptoms have low predictive value and "overwhelmingly have causes that are more benign" (Siminoff et al., 2014, p. 355) than life-threatening illnesses such as cancer. The individual general practitioner is faced with:

> … the often difficult task of separating the minority of patients whose symptoms could indicate serious disease and who require urgent diagnostic attention from the majority with less serious, self-limiting illness, in whom time can often be used both as a diagnostic and therapeutic tool (Jones et al., 2009, p. 1).

It is within this complex context that practitioner and system delays are discussed below.

Cancer diagnoses

The broad symptom signatures of colorectal, pancreatic and oesophageal cancer, as discussed in the review by Koo et al (2018), contribute to diagnostic difficulty. Rectal bleeding was considered to be the alarm symptom most likely to predict colorectal cancer; jaundice and abdominal pain for pancreatic cancer; and dysphagia for oesophageal and gastric cancers. A study by Jones et al (2007) using seven years of data from a large general practice database, analysed records of first presentations of 'alarm' symptoms, including dysphagia (5,999 records) and rectal bleeding (12,289 records) to determine how many of these ultimately resulted in a cancer diagnosis. From the 5,999 new presentations of dysphagia listed in the database, 150 diagnoses of oesophageal cancer were made in men and 81 in women. From the new presentations of rectal bleeding, 184 diagnoses (positive predictive value 2.4%) were made in men and 154 (2.0%) in women. The authors noted new onset of these symptoms was associated with an increased likelihood of a cancer diagnosis within the first three to six months. They recommended monitoring progress over a fairly narrow time frame for both dysphagia and rectal bleeding particularly in people over 65 years and in men of any age, taking into account the clinical presentation and the results of a physical examination.

Identifying the minority who are developing serious disease is a challenge in the absence of overtly alarming symptoms. ‘Red flags’ are not necessarily present in all patients, and there may be a broad spectrum of other symptoms of much lower predictive value. Because of the vague nature of symptoms, their gradual onset, and their similarity in both serious and non-serious conditions, general practitioners are likely to reassure the patient that their symptoms are minor or temporary and prescribe medicines or advice on lifestyle and diet. If symptoms do not resolve after the first doctor visit, there may be a cycle of repeat visits resulting in further delays (Macleod et al., 2009). A study of 75 cancer patients in the UK (Molassiotis, Wildon, et al., 2010) found they had made an average of 5.1 GP visits before their cancer was diagnosed. Brousselle et al (2017) similarly reported multiple GP and/or specialist visits and long wait times for specialist investigation following referral for patients subsequently diagnosed with colon cancer. A detailed history of the patients from their first symptoms to their diagnosis of colon cancer in this study showed delays ranging from one week to many years, mostly caused by the symptoms being attributed to other diagnoses including haemorrhoids, hormonal symptoms causing fatigue, and psychiatric symptoms.

A systematic review (Macdonald et al., 2006) concluded that there were three main influences on practitioner delay in diagnosis of gastrointestinal cancers: not making a diagnosis at the initial encounter with the patient; an initial misdiagnosis of a common symptom; and attributing the symptoms to a benign condition the patient was already being treated for. The review found that patients with oesophageal cancer had longer delays than those with stomach cancer and patients with any upper gastrointestinal cancers had longer delays than those with colorectal or any other cancer. The authors noted the challenges for doctors assessing symptoms such as dyspepsia particularly in the context of acid suppression therapy. Ordering inappropriate tests, inaccurate test results, and having had a previous negative test result all had important implications for delay. A subsequent review by Renzi et al (2016) confirmed that an ‘all clear’ message from a negative test result could result in over-reassurance that could lead to months or even years of delay. Negative results could also mean that the doctor was dismissive of further concerns so that patients were left unsure what to do next if they continued to experience symptoms but were “concerned about appearing hypochondriacal or foolish” (Renzi et al., 2016, p. 5).

A wide range of factors were identified as being associated with referral delay in colorectal and upper gastrointestinal cancers in a review by MacLeod et al (2009). This review noted that older people (> 70 years) presenting with symptoms suggestive of bowel disease were more likely to be referred promptly whereas younger people were more likely to experience delays (Emery et al., 2013b; Korsgaard et al., 2008; Macleod et al., 2009; Windner et al., 2018). Pain and bleeding were associated with a shorter time to referral, particularly in upper gastrointestinal cancer. Men were less likely to have delayed referral than women for upper gastrointestinal cancers, but there was inconclusive evidence on gender for colorectal cancer. Patients with low socio-economic status were more readily referred for upper gastrointestinal cancer, but better off patients were more speedily referred for colorectal cancer. Consistent with other studies, misdiagnosis, either by treating patients symptomatically, for example prescribing acid suppression medication, or relating symptoms to another non-cancer condition resulted in delays for both upper gastrointestinal and colorectal cancer. Failure to adequately examine the patient, use of inappropriate tests and failing to follow up on inconclusive, or negative test results were also implicated in delays. A Danish study (Korsgaard et al., 2008) also found that failure of GPs to routinely perform rectal examination of patients before referral appeared to be an important contributor to GP delay in rectal cancer.

Poor communication between doctor and patient proved to be an important contributor to delayed diagnosis in a study of 242 patients in the US with colorectal cancer (Siminoff et al., 2014). Dismissing symptoms as unimportant, giving an alternative diagnosis, providing lifestyle advice, or telling the patient to return if their symptoms did not improve created a longer delay. However, making a plan for ‘next steps’ and communicating it clearly, referring to a specialist, ordering investigations, or sending the patient to urgent care all shortened the interval to diagnosis. For their part, patients were more likely to be taken seriously and to have a shorter time to diagnosis when they took a proactive approach, highlighted their belief that their symptoms were serious, asked for tests or referral, or mentioned cancer. Those who downplayed symptoms, mentioned them during a consultation for other matters or had difficulty describing them had a respectively longer path. Overall, clear communication and follow up by both doctors and patients facilitated swifter diagnosis.

Non-cancer diagnoses

Cancer is not the only condition for which delayed diagnosis is important when patients present with gastrointestinal symptoms. Jones et al (2009) in an examination of primary care records of patients who presented with the 'red flag' alarm symptoms of rectal bleeding (15,289) or dysphagia (5,999) found that one diagnosis (either of cancer or another condition) would be made for every four to seven patients within the following three months. In those with dysphagia, 22.6% of men and 17.2% of women were diagnosed with conditions including oesophagitis, hiatus hernia, oesophageal stricture and disorders of the stomach and duodenum as well as oesophageal and gastric cancers. For rectal bleeding, 16.7% of men and 14.5% of women had diagnoses of diverticulitis, Crohn's disease and ulcerative colitis in addition to the colorectal cancers found. The study concluded that these two alarm symptoms were not only red flags that could indicate cancer but also 'yellow flags' that should alert clinicians to "conduct investigations or intervene therapeutically in these benign but potentially serious disorders" (Jones et al., 2009, p. 8).

The literature shows that diminishing numbers of serious conditions are identified from specialist investigation in patients with no alarm symptoms. In one example, 2,471 patients with dyspepsia without 'red flags' were recruited from 190 primary care centres in 17 countries (Vakil et al., 2009). All participants underwent endoscopy and 635 (23%) were found to have abnormalities; six were malignancies and the remainder were gastric, oesophageal, or duodenal ulcers or erosions. Of the six cancers, only one was in a patient aged <50. The authors concluded that "performing early endoscopy in all patients presenting with dyspepsia offers the greatest chance that a silent malignancy will not be missed" (Vakil et al., 2009, p. 759), but the cost for every one detected is high. They noted, however, that their findings were not generalizable to countries with widespread Helicobacter pylori infections.

Helicobacter pylori is an organism that causes chronic inflammation of the stomach, which is a risk factor for developing gastric cancer (Correa & Piazuelo, 2008; Huang et al., 1998). In countries where untreated Helicobacter pylori infections are common, the likelihood of identifying serious disease in patients with dyspepsia is increased (Graham, 2015). In an example from Africa, investigators in a teaching hospital in Ghana (Dakubo et al., 2011) reported on the final diagnosis of 1,643 patients who were referred for gastroscopy. Patients were interviewed, and their clinical data and endoscopic findings examined to determine the appropriateness of the referral based on the clinical information. Dyspepsia was the most common presenting complaint, and 372 patients had ‘alarm symptoms’ including bleeding, significant weight loss, dysphagia, vomiting, and anaemia. Patients both with and without alarm symptoms were diagnosed with organic disease, though bleeding, suspicion of malignancy and older age were significantly associated with positive findings on endoscopy. Overall, 681 (41.4%) had negative endoscopies, while 522 (31.8%) patients had organic disease, 26.8% of which were inflammatory conditions such as gastritis. The authors noted that their findings showed a higher rate of inflammatory conditions in younger people compared to studies in high income countries. The following sections examine delays associated with irritable bowel syndrome, inflammatory disorders and coeliac disease.

Irritable bowel syndrome

IBS is characterised as a functional rather than an organic disorder, that is, there is “no demonstrable structural abnormality to explain the symptoms” (Lovell & Ford, 2012, p. 712). Currently no investigative tests provide a definite diagnosis. Instead, diagnosis is based on symptom criteria that have been progressively revised over the past decades, beginning with the Manning criteria (Manning et al., 1978) and followed by the Rome I criteria, its updates II and III (Olafsdottir et al., 2012, p. 3717) and most recently the Rome IV criteria (Linedale & Andrews, 2017).

A major issue around the diagnosis of IBS appears to be that it has often being treated as a ‘diagnosis of exclusion’, that is, the ‘fall back’ option that remains when tests prove negative and no organic disease can be found. This approach has been described as the cause of “frustration and dissatisfaction in patients and doctors alike” (Linedale & Andrews, 2017, p. 309); both parties may feel they are left without a satisfactory diagnosis, as the symptoms that generated the investigation have not disappeared. This may lead to a cycle of repeat visits by patients, instigating further investigations with similarly negative results, as well as putting unnecessary strain on health resources.

Several studies have reported limited awareness among primary care doctors about the recommendations to use the Rome criteria for a positive diagnosis of IBS and avoid unnecessary investigations in patients with no alarm symptoms (Olafsdottir et al., 2012; Quigley et al., 2006; Spiegel et al., 2010). Spiegel et al (2010) found a 'disconnect' between guidelines and community practice in a survey of primary care providers, gastroenterologists and IBS experts which was driving use of unnecessary resources for no benefit. At that time, only 8% of the 117 experts considered IBS to be a diagnosis of exclusion, compared to 72% of the community providers. More recent work in this area has suggested that some progress has been made in combinations of non-invasive serological tests that are able to discriminate between both IBS and inflammatory bowel disease on the one hand (Menees et al., 2015) and between IBS and healthy controls on the other (Mujagic et al., 2016).

Linedale and Andrews (2017) contend that part of the responsibility for fruitless investigation lies in the language used by specialists to communicate the findings from investigations. In a previous paper these authors report on their study of 207 letters from gastroenterology specialists sent to referring GPs (Linedale et al., 2016). They note the uncertain diagnostic language was more often used by specialists in patients with functional gastrointestinal diseases compared to patients with conditions such as reflux, Crohn's disease or peptic ulcers. The specialist might write, for example, "it is possible that this patient might have" rather than the more definite "this patient is diagnosed with" (Linedale et al., 2016, p. 1735). The hesitancy of this language then flowed through to the referring GPs who, in turn, lacked confidence to make a positive diagnosis and initiate appropriate treatment. Instead, the uncertainty of the doctor and the intermittent symptoms of IBS in the patient were likely to generate the continuing search for something more definite, and which was often compounded by the psychological distress, which is known to be common among people with IBS (Bowers et al., 2020; Harvey et al., 2018; Sweeney et al., 2018).

Psychosocial factors, especially anxiety, depression and somatisation are known to be associated with functional gastrointestinal symptoms (Dainty et al., 2014; Dibaise et al., 2016; Enck et al., 2017; Levy et al., 2006; Sayuk & Gyawali, 2020; Van Oudenhove & Aziz, 2013; Wauters et al., 2020). Poor mental health and social and emotional functioning have been associated with continued health seeking behavior, generating further investigations that fail to reassure patients, consume health resources and add to the burden on the overall health system (Fan et al., 2017; Linedale & Andrews, 2017; Patel et al., 2015; Quigley et al., 2006). On the other hand, as discussed in Part One of this report, there is also ample evidence that many individuals who meet the criteria for irritable bowel syndrome never seek medical attention (non-consulters) (Fan et al., 2017; Katsinelos et al., 2009; Ringström et al., 2007). Optimism, social support and coping skills have been investigated for their mediating effect (Dindo & Lackner, 2017; Khaledian et al., 2019; Knowles et al., 2017; Wilpart et al., 2017). More recently, Bowers et al (2020) examined 'psychological flexibility' and acceptance of illness as moderating factors in IBS. Positive diagnosis along with the tests recommended that differentiate between IBS and inflammatory bowel disease (Crohns and Colitis Australia, 2013; Linedale & Andrews, 2017) therefore would seem to be the most sensible approach along with dietary and psychological support.

Nevertheless, there appears to be a very blurred area between functional and organic gastrointestinal disease, making it virtually impossible to draw an absolute dividing line between them. Psychosocial factors are not limited to IBS alone but also play a considerable role in pain experienced by individuals with inflammatory bowel disease (Fuller-Thomson et al., 2015; Gobbo et al., 2018; Neuendorf et al., 2016; Odes et al., 2017; Rakovec-Felser, 2011; Sweeney et al., 2018). Optimism, self-sufficiency and coping skills may positively benefit individuals with functional disease. They can, however, increase the patient interval before seeking health care, and therefore contribute to late diagnosis of cancer as described in Part One of this report (Emery et al., 2013b; Leal et al., 2018; Rogers et al., 2017; Whitaker et al., 2015; Whitaker et al., 2016).

Having IBS symptoms has been implicated in diagnostic delay of both inflammatory bowel disease and coeliac disease. Barratt et al (2011) looked at the interval from the start of symptoms to the time of diagnosis in 683 biopsy confirmed patients with ulcerative colitis (228 patients), Crohn's disease (230 patients) and coeliac disease (225 patients). This study found that having symptoms consistent with the IBS Rome II criteria was responsible for longer diagnostic delays in both Crohn's and coeliac disease, (though not in ulcerative colitis) and suggested that there is an 'overlap' between the conditions which is not well understood.

Patel et al (2015) examined colonoscopy findings from 559 patients in the UK who met the criteria for IBS, 432 of whom reported at least one alarm symptom and 136 who had no alarm symptoms. While organic disease was more often identified among those with alarm symptoms (117/432, [27.7%]), 21 of the 136 (15.4%) without alarm symptoms were also found to have organic disease, including Crohn's disease, coeliac disease and microscopic colitis. The authors of this study acknowledged that current advice was to make a positive diagnosis of IBS based on the criteria and avoid extensive investigation. However, they concluded that their findings added to "the growing body of evidence that suggest that organic gastrointestinal disease can be mistaken for IBS" (Patel et al., 2015, p. 822). These complexities may affect only a minority of cases. But, these studies, together with others reviewed in the following sections (Card et al., 2013; Irvine et al., 2017; Maconi et al., 2015; Porter et al., 2012; Vavricka et al., 2012; Vavricka et al., 2016) strongly suggest that there is more to be discovered about the interconnection between IBS and other bowel disease.

Inflammatory bowel disease

Long delays in diagnosing inflammatory bowel disease – primarily ulcerative colitis and Crohn's disease - are well documented across many studies (Banerjee et al., 2018; Lee et al., 2017; Nguyen et al., 2014; Schoepfer et al., 2019; Szanto et al., 2018; Vavricka et al., 2012). While they may not be as life threatening as cancer, delayed diagnosis means that opportunities for early treatment to modify disease are missed and patients are more likely to have bowel damage and other complications requiring surgery and a lower quality of life (Novacek et al., 2019; Vavricka et al., 2012).

A systematic evaluation of risk factors associated with both patient and physician-attributed delay in diagnosis of inflammatory bowel disease was carried out in Switzerland by Vavricka et al (2012). This study found shorter delays for people with ulcerative colitis, for whom 50% were diagnosed within four months and 75% within a year. However, it took 10 months for 50% and 24 months before 75% of Crohn's patients had been diagnosed. Younger age (<40) was also associated with longer delay between first doctor visit and specialist referral. The authors noted that the more frequent bleeding seen in ulcerative colitis was more alarming for the physician and led to speedier referral compared to the less dramatic presentation with pain, fatigue, weight loss and diarrhoea in Crohn's disease. They also pointed to the overlap with symptoms of irritable bowel syndrome which appeared to potentially result in "an underestimation of underlying Crohn's disease by the treating physician" (Vavricka et al., 2012, p. 504).

Another study (Nguyen et al., 2017) similarly found that among a cohort of 177 patients in the United States (110 with Crohn's and 67 with ulcerative colitis) the interval from first seeing a doctor to evaluation by a gastroenterologist was an average of 7 months for patients with Crohn's disease compared to 3 months for those with ulcerative colitis. This was in addition to the longer history of symptoms (> two years) that 25% of patients with Crohn's disease reported. As with the Swiss study, any patients with Crohn's disease with bleeding had shorter delays than those without (11.4 vs 31 months overall). Longer time to diagnosis was associated with more Emergency Department visits per patient and increased the odds of developing complications that required surgery. Patients with delay exceeding 26 months had almost nine times the odds of developing complications. The authors of this study too commented that the alarm created by bleeding was likely to "trigger expedited work up and referral" (Nguyen et al., 2017, p. 1828). The investigation concluded that there was considerable physician related delay, especially in primary care providers, a need to increase awareness among them and develop a better "diagnostic paradigm" (Nguyen et al., 2017, p. 1830). The same longer delay in diagnosing Crohn's disease compared to ulcerative colitis has been reported in studies from a range of different countries (Lee et al., 2017; Novacek et al., 2019; Walker et al., 2020; Zaharie et al., 2016). All of these similarly commented on the lack of awareness amongst primary care doctors and the absence of bleeding as reasons for the comparative delay in the diagnosis of Crohn's disease.

Another complexity around diagnosis of inflammatory bowel disease is distinguishing symptoms from those of IBS. IBS is widely estimated to affect between 10 and 15% of Western populations at any one time and up to 40% of people at some time during their life (Barratt et al., 2011; Lovell & Ford, 2012; Marugan-Miguelsanz et al., 2013; Quigley et al., 2006) in contrast to the much lower rates of inflammatory bowel disease (Barratt et al., 2011, p. 3273). An Italian study (Maconi et al., 2015) found a significant increase in diagnostic delay of Crohn's disease in patients who complained of abdominal bloating, a typical symptom of IBS, and a lack of awareness among GPs about the need for prompt referral. While incorrectly attributing symptoms of inflammatory bowel disease to IBS has been shown to be associated with delay in referral for specialist investigation (Blackwell et al., 2020), a number of studies have shown that the relationship is not simply a case of misdiagnosis; Vavricka et al (2012), for example, described the symptoms as overlapping, rather than being distinct.

Porter et al (2012) directly investigated the interconnection between having IBS and a subsequent diagnosis of inflammatory bowel disease in later years using 10 years of data from the US military health services database. The study located 9,341 individuals with IBS and compared them to a reference cohort of 18,678 subjects with non-IBS conditions. Subjects were representative of the active duty military population and had an average age of 30 for the IBS cohort vs 28.5 for the non-IBS reference group. The study found the incidence of IBD in the group with a prior diagnosis of IBS was approximately 9 times that of the comparator group, and even greater in those individuals who had episodes of acute infectious gastroenteritis recorded. They suggested that IBS may present a subclinical expression of inflammation that progresses in severity to IBD; or alternatively, that there are potential misdiagnoses even after negative colonoscopies which do not detect small intestinal abnormalities. They noted that their study highlighted the complex inter-relationship between functional and inflammatory bowel disease and suggested that there was likely to be a “common pathogenesis” (Porter et al., 2012, p. 9) which was not yet understood.

Coeliac disease

Late diagnosis of coeliac disease continues to be widely reported; years-long delays have been documented, with doctor-attributed delays often longer than the interval that patients waited before seeking help (Card et al., 2013; Cichewicz et al., 2019; Evans & Sanders, 2011; Fuchs et al., 2014; Irvine et al., 2017; Vavricka et al., 2012; Violato & Gray, 2019). Norstrom et al (2011) reported a total mean delay of 9.7 years in their study of a group of Swedish people with coeliac disease, of which 5.8 years were between the first doctor visit and eventual diagnosis. A Canadian survey of 2,681 adults with biopsy confirmed coeliac disease (Cranney et al., 2007) reported a mean delay in diagnosis of 11.7 years. Ten Australian participants with coeliac disease in an in-depth qualitative study by Taylor et al (2013) reported delays ranging from three months to over 25 years and that their diagnosis was usually made only after consulting multiple doctors. A recent review of literature on the current state of coeliac disease diagnosis and treatment (Cichewicz et al., 2019) also noted long delays in diagnosis, ranging from 4-12 years, especially in patients with non-gastrointestinal symptoms. Barriers to under- and delayed diagnosis identified in the review were atypical presentation, lack of awareness by primary care physicians, as well as failure to interpret tests accurately, follow guidelines and refer to a gastroenterologist for investigation and follow up.

A Finnish study (Fuchs et al., 2014) set out to investigate factors associated with long diagnostic delay in coeliac disease. By nationwide advertising they recruited 825 adult participants (76% female) with coeliac disease. Sixty eight percent of patients had reported symptoms including abdominal pain, diarrhoea and malabsorption before being diagnosed. Almost a third of all participants had a diagnostic delay of more than 10 years, with those diagnosed before the year 2000, when national guidelines were established, more likely to have extended delay. Being male or having a family history of coeliac disease, however, was likely to shorten the time.

Vavricka et al (2016) in a survey of 1,689 Swiss patients with coeliac disease found a total mean delay of 87 months with the proportion of doctor delay being longer in women. They noted that the distribution of delay values was very uneven; a large proportion of patients had delays of 12-24 months but a small number had extremely long delays. The authors concluded that under-diagnosis of coeliac disease is a problem, leading to risk of nutritional deficiencies and a more severe course of disease. They highlighted doctor-attributed delay as the greatest underlying factor, particularly in women, suggesting a “gender-dependent reduced awareness” of coeliac disease in some physicians (Vavricka et al., 2016, p. 1153). This study identified a pre-existing diagnosis of irritable bowel syndrome (IBS) as a risk factor for delayed diagnosis of coeliac disease. Individuals who had been diagnosed previously with IBS had a mean delay of 141.8 months compared to 74.5 months for those with no previous diagnosis; within this overall delay, the mean doctor-attributed delay was 71.3 vs 30.6 months respectively.

Several other recent studies have also focused on the relationship between a diagnosis of IBS and a subsequent diagnosis of coeliac disease. Maconi et al (2015), for example, also found the presence of IBS had delayed the diagnosis of coeliac disease among the 83 patients in their study. They suggested that this finding could be interpreted either to indicate a lack of attention and awareness of IBS in general practice, or that a different coeliac disease phenotype may be present in some patients who experience a long period where signs and symptoms cannot yet be definitively linked to coeliac disease.

Another study used records from the British general practice research database, in the time period 1987-2010, to carry a matched case-control study (Card et al., 2013). It aimed to investigate how commonly people diagnosed with coeliac disease had previously been diagnosed with IBS. Records of 6,826 adults newly diagnosed with coeliac disease (the cases) were matched to 61,850 controls. A prior diagnosis of IBS (based on the diagnostic code) was found to be three times as common among the cases as the controls (16% vs 4.9%) with many of these diagnoses made in the year before coeliac disease was diagnosed. The authors concluded that there was a “clear excess of IBS diagnoses and/or treatments in patients who had gone on to be diagnosed with coeliac disease compared to the general population” (Card et al., 2013, p. 805). They recommended that serologic testing to exclude coeliac disease should be offered to anyone in primary care who met the IBS diagnostic criteria.

A systematic review and meta-analysis of the literature by Irvine et al (2017) of screening for coeliac disease by serological testing in people diagnosed with IBS similarly found that the odds of having a positive serological test for coeliac disease was three times higher in people meeting the criteria for IBS. They suggested that given the effective treatment available for coeliac disease and the important long-term consequences of leaving it untreated, that “clinicians should continue to pursue the diagnosis of CD aggressively in patients with suspected IBS” (Irvine et al., 2017, p. 72). They suggest this even though around 30 people would need to be tested to diagnose one biopsy-confirmed new case of coeliac disease.

Health system attributed delay

Practitioner-attributed delay does not happen in isolation but interacts with and is dependent on the health system within which practitioners work. A key factor in the total diagnostic delay in bowel disease is the capacity of the wider health system to accept referrals from primary care for specialist investigation and action them promptly. While the particular factors differ between countries and jurisdictions, there is a general theme in the literature that demand tends to exceed capacity but that referring every patient who presents with gastrointestinal symptoms is neither wise nor even possible in most health systems.

A Danish study (Korsgaard et al., 2008) examined delay using data generated from questionnaire interviews with 743 patients in a colorectal cancer hospital department. Median GP delay was relatively modest but the range was extremely wide (0-1900 days for colon cancer and 0-1541 days for rectal cancer); 25% of patients with colon cancer had a delay of 60 days or more before referral, and 25% of rectal cancer patients waited 53 days or more. Fewer than 50% of patients in the study group were referred to the hospital at their first visit. Only twenty six percent of patients with colon cancer and 18% with rectal cancer had total delays of 60 days or less. The authors noted that, other than the patient delay, lack of resources in finance or manpower in the wider system were largely responsible for long waiting periods for investigations, mistakes in booking systems, and letters not sent to patients.

System factors were also responsible for preventable delays in diagnosis of colorectal cancer for 104 cases identified from a records analysis in the US Veterans Affairs (VA) health system (Singh et al., 2012). The majority were because of delays in being given an appointment, but there were also cases where the consultation was refused or patients were ineligible for the service. A small minority were from patients not following through with the appointment. The median time between first referral and completion of the diagnostic colonoscopy was 123 days (range 62-938 days). This study also interviewed 11 primary care providers for their experiences of delay. While some delays could be attributed to patient factors, the major reasons were referral and scheduling inefficiencies and procedural bottlenecks caused by inadequate capacity. Primary care providers attempted to reduce delays by contacting gastroenterologists directly, making multiple referrals, or admitting patients under urgency. They called for a dedicated service for colorectal cancer diagnosis, modelled on a successful breast cancer programme in the VA that had been set up to facilitate access and minimise delays.

Thinly stretched rural health services contributed to delay in two Australian studies that highlighted the disadvantages for rural GPs and their patients (Emery et al., 2013b; Harris et al., 2011). In a small focus group study Harris et al (2011) examined the views of 19 GPs from Queensland, New South Wales and South Australia on the referral pathway for colorectal cancer. The participants perceived the public system as having longer delays and poor communication so preferred to refer patients to private health services. They reported that developing personal relationships with specialists and cultivating them over time was the most effective way they could advocate for their patients and get the best care. The study of GP/diagnosis delay (Emery et al., 2013b), a companion study to the one on patient factors (Emery et al., 2013a) found that the absence of alarm symptoms was linked to longer delay and the need for more appointments both with GPs and specialists before a diagnosis was made. Other factors that increased delay were the time taken to order and follow up on blood tests, extended delays from negative or uncertain test results, and long waits for specialist appointments and radiological investigations. Referring to private specialists decreased the delay except during the December-January holiday period when it lengthened delay. Going to private specialists or presenting to the emergency department have also been noted as ways of 'sidestepping' the system barriers that incur long waits for investigations (Ramos et al., 2010). However, it appears that even specialists may find it difficult to access investigations in some regions of New Zealand (Steyl, 2020). Recently the Southern District Health Board acknowledged "lapses and inadequacies" over a number of years in colonoscopy services that had led to delays and loss of trust from those in the region (Southern District Health Board, 2020).

Other studies have retrospectively examined the records of those diagnosed with colorectal cancer to quantify the overall delay across patient, doctor and health system factors. Among 795 cases of colorectal cancer in Spain, the median interval between symptoms appearing and diagnosis was 128 days, with 155 days between symptom appearance and treatment (Esteva et al., 2013). Abdominal pain, vomiting and patient perception of seriousness of their symptoms were all associated with a shorter interval to diagnosis as was GP suspicion and prompt referral for investigation. Intervals were lengthened when GPs failed to physically examine patients, misinterpreted symptoms, and ordered tests to rule out other diagnoses. Poor investigations by outpatient and emergency doctors were found to be more serious for delay because they lacked the continuity of care that patients had with their GP and the greater likelihood that the patients would return if they were still concerned. In another Spanish study of 152 patients with colorectal cancer (Cerdan-Santacruz et al., 2011), the overall delay added up to a mean 7.28 months, attributable respectively to patient delay of 2.75 months, 1.89 months of physician delay, and 2.64 months waiting for testing. A similar retrospective study of 364 patients with colorectal cancer diagnosis in China (Deng et al., 2012) reported a mean interval across all patients of 156.07 days from symptom onset to diagnosis. In this study treatment was usually swift post diagnosis (mean 8.17 days) but only in centres with adequate health care facilities.

A New Zealand study examined the pathway to diagnosis for 98 people with colorectal cancer recruited through a national charity (Windner et al., 2018). Participants completed a questionnaire covering demographics, symptoms, help seeking and diagnostic pathways. A key issue found in this study was the delay between being referred by a GP and being investigated by a specialist. While 71% of participants had been diagnosed within 12 months, younger age, less formal education, negative health care experiences, a higher number of visits in primary care before being referred and diagnosis in the public system were all associated with longer symptom to diagnosis interval. Although the design of the study meant that results were not representative of the New Zealand patient population with colorectal cancer, the authors noted their concern that a large proportion of those who responded were below the age for inclusion in the bowel-screening programme. They suggested that “care is needed to ensure timely diagnosis for this screening ineligible younger group” (Windner et al., 2018, p. 36). This study also highlighted the perverse effect noted by Bagshaw and Cox (2020) of instituting a screening programme if the health system is insufficiently resourced to cope with the load generated by screening, as well as patients who are referred with symptoms.

Pressure on fully publicly funded health systems that discourage referrals outside guidelines has also been associated with delays. Cases continue to be highlighted in the popular media, for example, where individuals were considered ‘too young’ to be investigated and were finally diagnosed with late stage cancers (Broughton, 2019; Jamieson, 2020; Mutton, 2019). Lack of continuity of care across primary care providers has continued across the years to be acknowledged as another system reason for delay (Esteva et al., 2013; Heyhoe et al., 2020; Macleod et al., 2009). Having multiple providers in primary care or attending the emergency department has been noted as preventing an ongoing patient-provider relationship developing, reducing patient motivation and engagement and fragmenting record keeping and diagnostic information.

While most studies focus on delays in cancer diagnosis, the purpose of referring patients for investigation is not solely to rule cancer in or out but is just as relevant in diagnosing other gastrointestinal conditions. As outlined in the sections above, there are often long delays in diagnosing non-cancerous conditions in which health system factors play a role. Maconi et al (2015, p. 650), for example, state the long delay between referral and being investigated by a specialist was due to a "burdened" health care system'" that was responsible for late diagnosis of Crohn's disease. Similarly, a recent study by Blackwell et al (2020) found that only 5.6% of the individuals in their study with suspected inflammatory bowel disease had received specialist review within the set standard of four weeks, calling for enhanced pathways to accelerate specialist referral and timely diagnosis (Blackwell et al., 2020, p. 210).

Summary: Factors related to practitioner and system-level delay

- Bleeding, pain and difficulty swallowing are 'alarm symptoms' that signal to a health practitioner that an individual may have a serious gastrointestinal disease that needs specialist investigation;
- Serious disease may also present initially with indeterminate, common or mild symptoms which occur in benign conditions and are difficult to distinguish apart from them;
- Delay occurs when symptoms are attributed to a non-serious condition, or considered as part of other illnesses that patients are already being treated for;
- Other reasons for delay include inadequate physical examination of the patient, use of inappropriate tests, providing reassurance without following up on test results and not telling patients what to do next if their symptoms persist;
- Delay in diagnosing cancer is the most life-limiting but long delays in identifying inflammatory bowel disease and coeliac disease can also lead to bowel damage, surgery and other complications as well as lower quality of life.
- Diagnosis of irritable bowel syndrome and functional dyspepsia, in contrast to organic disease, cannot be definitely established by endoscopic or serological investigations. A positive diagnosis based on international criteria is preferable to diagnosis by exclusion;

- There is no sharp dividing line between functional and organic diseases of the gastrointestinal system. The way they interact biomedically appears to have complexities which are not yet fully understood. The role of psychosocial factors in pain perception and coping with disease also appears to be important in some cases;
- Health system factors interact with practitioner delay to affect the overall time to diagnosis of disease. Gastrointestinal services may be under-resourced for the capacity needed;
- Lack of specialist staff, long waiting times to be seen, criteria that exclude certain patients, poor referral details that mean referrals are refused all contribute to delays;
- Lack of continuity of care that occurs through seeing multiple providers in the same primary care practice or attending the emergency department are also associated with delayed diagnosis.

PART THREE - Reducing delay in the diagnosis of serious gut disease

Introduction

This section provides an overview of the literature on approaches to improving early and accurate detection of gut disease with the ultimate aim of improving health outcomes (Abdel-Rahman et al., 2009; Tørring et al., 2013). There are three major sections that examine interventions and developments at the individual, health practitioner, and health system levels respectively.

Section One: Reducing patient delay

National awareness campaigns

National public awareness campaigns are a starting point for encouraging individuals to be aware of symptoms of disease and to seek medical help early in the disease process. The advantage of large public campaigns is that they can disseminate messages repeatedly over time to large audiences through a wide range of media at a very low cost per head (Wakefield et al., 2010). The UK 'Be Clear on Cancer' (BCOC) campaign was a key example of a sustained campaign to raise public awareness of the symptoms of eleven different cancers. It was designed to encourage people with those symptoms to see a doctor, with the ultimate aim being to increase diagnosis of cancer early in the disease process and so to improve cancer survival across the population (Lai et al., 2021). Be Clear on Bowel Cancer was one of these eleven campaigns. It ran between 2011 and 2013 on television, radio, print media and face-to-face events and encouraged people with bowel symptoms for three weeks or more to see their general practitioner (Bethune et al., 2013; Moffat et al., 2015; Peacock et al., 2013). Simple messages aimed at people over 55 from low socioeconomic groups (Moffat et al., 2015) focused on two key symptoms: 'if you have blood in poo or loose poo for 3 weeks your doctor wants to know.'

Six papers that analysed the impact of the BCOC bowel campaign on awareness and referrals from primary care were examined for this report (Bethune et al., 2013; Hall et al., 2016; Moffat et al., 2015; Pande et al., 2014; Peacock et al., 2013; Power & Wardle, 2015). Two of these took a national approach while the others examined the impact in a particular region. Moffat et al (2015) investigated the impact of the campaign on symptom awareness and GP attendances using data from face-to-face surveys across England with respondents 55 years and over. Surveys were carried out pre-and post-campaign with different samples of participants and weighted to be representative of the population. The survey also examined GP attendances for the pre- and post-campaign periods from 355 GP practices and analysed them according to age, gender and socioeconomic status. Results showed significant increases in unprompted awareness of the bowel symptoms featured in the campaign (14% increase in blood in stools and 13% in looser stools compared to the pre-campaign survey), with the highest increase (18%) in the oldest age group. Awareness of looser stools as a warning sign increased among men and lower socioeconomic groups by 12%. During the weeks of the campaign, there were significant increases in GP attendances, particularly by men, across all age groups for symptoms directly related to the campaign messages in comparison with the same period the previous year. The highest percentage increase in attendances was in people over 50 in the most deprived quintile - 72% in comparison to 18% for practices in the least deprived quintile. The authors concluded from these results that the campaign had reached the broad target audience, and had shown particularly encouraging results for men and for those in low socio-economic groups.

Another study of the BCOC bowel campaign (Power & Wardle, 2015) used data from the ‘cancer awareness measure’ included in the Opinions and Lifestyle Survey run by the UK Office of National Statistics to assess impact. This survey recruited participants using random probability sampling and was administered face-to-face in respondents’ homes. Awareness of symptoms (including but not limited to gastrointestinal cancer) and perception of barriers to seeing a doctor were assessed using both unprompted and prompted methods. Results showed that unprompted recall of ‘change in bowel or bladder habits’ doubled from 21% to 43% of respondents between 2010 and 2012, and recognition (from a list of symptoms) rose from 87-91%. Improvements occurred in both men and women, across all levels of occupation and education and across ethnic groups. In contrast, the two barriers targeted in the campaign, being worried about wasting the doctor’s time or finding the doctor difficult to talk to showed almost no change between the two surveys. However, the authors cited the Moffat study (reviewed above) to show that GP attendances were up, suggesting that recognising the potential seriousness of symptoms had been effective in prompting action even in the face of these barriers. This study concluded that the campaigns appeared to have improved public awareness of the targeted symptoms across all population groups but that a different approach may be needed to change perceptions about GP approachability, including interventions targeted at general practices themselves.

The first of the regional studies, Bethune et al (2013), examined the impact of a seven-week pilot 'Be Clear on Bowel Cancer' campaign that ran across the Peninsula Cancer Network in southeast England starting in early January 2011. Data from the five hospitals in the network were analysed for the period between July 2010 (i.e. 6 months before the start of the pilot) to July 2011 to assess the number of urgent 'two-week' referrals (the details of this strategy will be discussed later in the review) received, the number of new cancers diagnosed and the number of endoscopies performed. Results showed a statistically significant increase in the number of referrals following the campaign but the effect stopped after three months. Endoscopies also increased slightly but only for a short time and the number of new cancers detected did not increase. The researchers concluded that the increase in referrals had been a result of the campaign encouraging more people with symptoms to present to their GP, however, it had not achieved the aim of earlier diagnosis and reduction of cancer mortality in the area under study.

Another regional study by Peacock et al (2013) compared the number and outcome of referrals to the Royal Derby Hospital in the three months before and three months following the start of the nine-week national bowel cancer awareness campaign in early 2012. Results showed a 59% increase in gastrointestinal referrals in the period after the campaign began, and a fall in appointment non-attendances (10% to 1%). These results suggested an impact of the campaign in raising public awareness of symptoms and their potential link to disease. However, while the raw number of diagnoses of colorectal cancer increased after the campaign compared to the previous period (32 vs 27), diagnoses as a proportion of referrals fell slightly (6% vs 8%). Moreover, only a small number of referrals were for the symptoms highlighted by the campaign; bleeding as a reason for referral rose from 13 to 15% while a change in bowel habits fell from 41 to 34% of total referrals. Other results showed that slightly more people under 55 and from ethnic minorities were referred compared to the pre-campaign period.

A subsequent study (Hall et al., 2016) at the Royal Derby Hospital compared data from three periods; the three months prior to the campaign (November 2011- January 2012); the three months after the first campaign (February-April 2012); and three months following the reminder campaign (May-July 2012). It looked at the impact on hospital services and diagnosis and also at the socioeconomic background of the patients referred before and after the campaign. The authors noted a significant increase in the monthly referral rate compared with the baseline but found that the referrals were not evenly spread across the socioeconomic groups in the area, with more people from the professional and skilled grades being referred than from the more disadvantaged unskilled/unemployed groups. The study found the campaigns were resource intensive because of the number of diagnostic tests being carried out yet the number of cancers diagnosed was not significantly different across the pre-campaign (27), post campaign (32), and post reminder campaign (27) periods. Moreover, 56%, 71% and 42% respectively across the pre- post- and post-reminder campaigns had no abnormality detected from investigation. Other diagnoses of gut disease were noted, but dismissed as being irrelevant to the purpose of the campaign.

In contrast, a study from the University Hospitals of Coventry and Warwickshire (Pande et al., 2014) found a positive impact of the campaign on referrals and detection of cancers and adenomas. Data from the immediate post-campaign period (February-July 2012) were compared to the same period the previous year. All patients referred from any source were included, with results showing a 47.1% increase in referrals between the two time periods (1297 compared to 882 the previous year) with the largest increase being GP referrals under the two-week rule. Significantly more cancers (20.3%) and adenomas (13.2%) were detected compared to the pre-campaign period. The BCOC aim of detecting cancers at an earlier stage was not realised as the largest increase was in stage 3 cancers. It was suggested, however, that this may have been balanced by the significant number of adenomas detected and polyps removed. The authors commented on the workload generated through the two-week rule, noting that they needed to recruit two additional surgeons and introduce evening and weekend sessions to cope with demand. All studies from the UK BCOC campaigns commented on the extra workload from referrals and investigations. This was not unexpected; providers had been advised to plan for a 50% increase in referrals and a “sustained increase in colonoscopy demand over the next five years” (Snowball et al., 2012, p. 335).

The British Be Clear on Cancer bowel campaign was culturally adapted as a Be Cancer Alert campaign for the multi-ethnic population of Malaysia. It ran for five weeks (April-May 2018) on television and radio, and via billboards, banners, posters and brochures, and the Facebook page of the National Cancer Society Malaysia. An evaluation (Schliemann et al., 2018) aimed to assess the campaign's reach, its impact, and effect on health service use, both overall, and by ethnic group. Randomly selected households from an ethnically diverse area were interviewed at home during a period 1-12 weeks before and again 1-12 weeks after the campaign. In the first period 954 participants from 710 households were interviewed. Of these 75.5% completed the follow up (730 from 559 households). Those who completed the study were 65.1% Malay, 28.1% Indian, 10% Chinese and 5.8% other, being an over-representation of Indian and under-representation of Chinese ethnic groups (respectively 6.9% and 23% of the overall population).

Results showed that around 71% of Malays reported seeing at least one of the campaign materials, followed by 68% of Indians and 34% of Chinese participants. Malay participants were more likely to see the television advertisement than others, whereas radio messages reached more Indians. Print displays were also more effective at reaching Malay and Indian participants than Chinese. Only 2.3% of participants felt the messages were not culturally acceptable. Almost a fifth of participants (19.7%) reported that they or someone they knew had seen a doctor as a result of the campaign messages. Older people, particularly those over 70 years and those without formal education were less likely to have seen the campaign. The Facebook posts attracted Malay participants but had very little reach among other ethnicities. All measures of unprompted and prompted awareness of symptoms rose post-campaign, with higher scores among those who recognised the campaign materials than in those who did not. The campaign did not appear to have an impact on health service use; the number of colonoscopies remained steady throughout the seven months of the study period and data on the number of cancers diagnosed was not available. The evaluation concluded that a culturally adapted mass media intervention using different modes of communication had a positive impact on improving symptom awareness among an Asian population. A particular strength was that the campaign had managed to reach people of low income, however further work was needed to ensure men, older people, and the Chinese population could be better targeted.

One positive aspect of the public awareness campaigns noted widely in these studies was that they reduced the fear of feeling foolish or being criticised for 'bothering' the doctor over symptoms that appeared mild, intermittent, or had been previously dismissed as unimportant (Hall et al., 2015; Jarbol et al., 2018; Morris et al., 2016; Whitaker et al., 2016). This was particularly relevant in health systems such as the UK and Scandinavia where GP visits are free, there is pressure on services and long waits for an appointment (Dahl et al., 2017; MacArtney et al., 2017). The campaigns were able to reduce the tension between the 'rhetoric' that 'responsible' people should avoid over-burdening the 'scarce' resources of the NHS for minor illnesses, yet "simultaneously urging appropriate and timely help seeking for bodily changes" (Macdonald et al., 2019, p. 37). They were also useful in providing vocabulary to discuss symptoms and make them less awkward to discuss with an individual's family, friends and doctor (Hall et al., 2015; Whitaker et al., 2015). A Danish study proposed that these aspects of public campaigns should be emphasised further so as to give the public increased confidence in approaching their doctor with symptoms (Jarbol et al., 2018).

Lai et al (2021) carried out an overview and synthesis of the short-term impact of all 11 national BCOC public awareness campaigns from 2012-2016. Impact was assessed by comparing primary care attendances and number of urgent referrals for suspected cancer between an analysis period around the campaign and a 'reference period' (usually the same period in a previous year). For the bowel campaign, the percentage change in the average number of GP attendances increased 29%, and the number of referrals increased 39.6%. For the oesophageal-gastric campaign, the increases were 33.9% and 84%. This was consistent with Lewis et al (2018) who noted the effectiveness of the campaign in changing the perceived seriousness of difficulty swallowing as an alarm symptom that should trigger consulting a doctor. Campaigns that ran multiple times had a smaller impact each time, though the extent varied across cancer sites targeted. The authors noted that the campaigns ran against a background of other awareness and early diagnosis initiatives and therefore a direct link between the campaigns and change could not be established. Cancer diagnoses resulting from urgent referrals rose 11.5% for bowel cancers and 20.4% for oesophageal cancers compared to the reference period. However, the study found that there were fewer than 5 weeks in the analysis period when the proportion of cancers diagnosed at an early state was higher than the comparison reference period. The overall conclusion of the study was that the BCOC campaigns on awareness had most impact on patient help-seeking and GP referral behaviour with 'less evidence on impact of stage at diagnosis and no measureable impact on survival' (Lai et al., 2021, p. 1179). Further analysis from a wider systems point of view is covered in Section Three..

Awareness raising activities of support organisations

Loosely related to large national campaigns such as BCOC in the UK, are the activities undertaken by independent organisations to raise awareness of gut diseases and advance the public policy agenda for services and support. In New Zealand, for example, the Gut Foundation has worked over the last almost thirty years to promote research and education about gut diseases and disorders (Gut Foundation, Undated). Bowel Cancer New Zealand provides support for people with the disease and promotes awareness through the "Move your Butt" campaign to encourage exercise during Bowel Cancer Awareness Month in June each year (Bowel Cancer New Zealand, undated). Crohn's and Colitis New Zealand, and Coeliac New Zealand work in their specific areas in the same way (Coeliac New Zealand, undated ; Crohns and Colitis NZ, Undated). Many other countries have agencies that work in a similar way to raise awareness and support people who have been diagnosed with disease. A frequently used strategy is to designate a particular day, week or month during each year to draw special attention to the particular disease(s) of interest.

The effectiveness of these activities is unclear, primarily because the measures that would provide a meaningful assessment of the impact are limited. A review by Martini et al (2016) found that mass media promotions, special events, health fairs and awareness days could encourage GP visits, referrals and screening but only in the short term. Purtle and Roman (2015) examined the phenomenon of awareness days/weeks/months in the United States. They acknowledged that such campaigns have the potential to increase knowledge while also generating media coverage about a health issue. However, they warned that simply aiming to increase awareness without a counterbalancing effort to promote healthy contexts may "reinforce ideologies of individual responsibility and the false notion that health outcomes are simply the product of misinformed behaviours" (Purtle & Roman, 2015, p. 1065). Referring to the concerns raised by this commentary, Vernon et al (2021) conducted a systematic review of literature that examined outcomes from awareness campaigns across any kind of health issue. In general, the review found that most awareness days, weeks or months did increase online activity and many improved knowledge about the condition in question (Vernon et al., 2021, p. 10). The authors pointed out some potentially perverse effects of too much publicity about one cancer (particularly breast cancer) at the expense of others that present a larger population burden. They also noted the plethora of awareness campaigns may confuse individuals who would donate to campaigns and potentially deter them from donating at all because of the excess of choice.

Only eight studies from the Vernon review had any relevance to gut disease. Five that dealt with online activities found a positive relationship between awareness weeks and relevant online activity related to colorectal cancer (Cooper et al., 2005; Huang et al., 2017; Mukhija et al., 2017; Phillips et al., 2018; Schootman et al., 2015), while one (Lee et al., 2016) did not. The remaining two small studies (Pullyblank, Cawthorn, et al., 2002; Pullyblank, Dixon, et al., 2002) found an association between awareness of Bowel Cancer Awareness Week (BCAW) and increased knowledge of colorectal cancer symptoms among patients attending a general practice in one study, and patients attending 'one stop' breast and rectal bleeding clinic in the other. While knowledge of BCAW week was low in both studies, those patients who were aware of it were almost five times more likely to be able to name some symptoms. These studies concluded that the awareness week had the potential to increase knowledge of symptoms but too few people were aware of it.

As the widespread use of social media has grown, it has been seen as a potentially powerful tool in the dissemination of public health messages (Vos et al., 2019; Xu et al., 2016). A review by Plackett et al (2020) found that social media appeared to be most often used for national or regional 'cancer awareness months' to promote breast or prostate cancer awareness and/or screening, with Twitter the most commonly used platform, followed by Facebook. Colorectal cancer was infrequently highlighted and appeared to have a far lower profile on social media than breast, lung or prostate cancer (Vos et al., 2019; Xu et al., 2016).   A Twitter campaign by the Korean Society of Coloproctology to increase awareness of colorectal cancer also had disappointing results; almost all the onward tweets were commercial spam, forcing the evaluators of this campaign to conclude that "the transmissibility of the awareness campaign among Twitter users was questionable at best" (Lee et al., 2016, p. 184).

Digestive Cancers Europe (2019) appeared to have more success with a promotion of colorectal cancer awareness through videos on Facebook, Youtube and Instagram across Finland, Slovakia, Spain, Italy, Portugal and France during colon cancer awareness month in March 2019. Impact was measured by the number of 10 second views, the number of people watching videos through to completion, and the number of clicks on the onward links. Facebook was the most successful channel, generating over 500,000 views at a relatively small cost. The study concluded that there was a major opportunity to improve the uptake of screening in this way, however, there was no evidence given or comment made as to whether screening rates had improved following the campaign. This was consistent across the studies covered in the review by Plackett et al (2020). While they concluded that there was some evidence that social media campaigns may improve cancer awareness and intention to be screened or consult a doctor, and may potentially influence social norms around help-seeking and screening uptake, most studies had not incorporated evaluation frameworks nor measured actual increases in screening or consultation.

Insights from bowel screening campaigns

This review is focused on reducing delay in symptomatic people, but aspects of the screening literature provide additional insights into successful public health awareness campaigns. Two Australian studies (Durkin et al., 2020; Durkin et al., 2019) describe intensive mass media campaigns in Victoria and Queensland respectively to promote the uptake of bowel screening. The 2017 campaign in Victoria (Durkin et al., 2020) consisted of seven weeks of 30 second advertisements shown on television, in health centre waiting rooms, advertorials in light entertainment television, social media posts, radio advertisements and online advertising. There were five simple messages emphasising the importance of early detection. A high intensity 8-week campaign in Queensland used a similar range of media to disseminate messages encouraging return of bowel screening kits from eligible individuals. Impact was measured by the number of bowel screening kits returned and compared to the number returned in comparison states in which no campaign, or a low-key campaign, was run (South Australia and West Australia respectively). In Victoria, there was a significant increase (1.31, p=<0.01) in the rate of kits returned for analysis during the campaign weeks compared to non-campaign weeks. There was no significant increase in the comparison state. Moreover, in a telephone survey of 1700 eligible individuals, 80% of those in Victoria were aware of the campaign compared to only 24% in the comparison state. In Queensland, the rate of screening kits returned for analysis increased by 20% during the campaign and for the following two months. Both studies commented on the importance of such campaigns being well funded and intensive (Broun & Harper, 2018). They also noted that a particular strength of the work was being able to measure the number of screening kits returned, described as "an objective behavioural health outcome rare in public health campaign evaluations" (Durkin et al., 2020, p. 23). Commentary on these two campaigns (Worthington et al., 2020) suggested that further benefits in terms of early cancers detected and lives saved could be realised if they were run more regularly as the effect faded fairly quickly after the campaign finished. Moreover, it was necessary to keep repeating the messages as new cohorts of people 'aged into' eligibility for screening.

It has been suggested that campaigns would be more effective in increasing screening uptake if they were linked to clinical settings to "increase [their] legitimacy and importance" (Martini et al., 2016, p. 1553). Three different studies across different health care systems support this view. An Australian survey of non-participants in the bowel screening programme (Goodwin et al., 2019), for example, found that GP endorsement through a letter or text message would encourage more than half of them to participate in future, particularly if they already had a trusted relationship with a GP. Similar findings came from a study by Hewitson et al (2011) that tested the effect of a letter from a person's GP accompanying the invitation to participate in the UK bowel screening programme. A trial in an inner-city primary care practice in the United States where patients were personally contacted through letters, personal phone calls or point of care prompts (Fiscella et al., 2011) resulted in higher rates of screening in the intervention group (28.8% vs 10 %) across ethnicity, socioeconomic and insurance status.

Celebrity endorsement of promotions for screening has also been used, particularly in the United States. For example, in the Centers for Disease Control 'Screen for Life' messages, the African American actor Terence Howard speaking about his mother's premature death from colon cancer was found to have higher recall among African Americans than other groups (Cooper et al., 2015). Endorsement appears to be effective in increasing intention to screen and screening rates but only where the celebrity is relevant to the targeted groups (Martini et al., 2016).

Community participation in co-designing campaigns that target populations with low screening uptake has been another approach in the United States (Campo et al., 2008; Croager et al., 2018; Katz et al., 2011; Katz et al., 2007; Katz et al., 2017; Krok-Schoen et al., 2015; Zittleman et al., 2009). Studies of campaigns in Iowa, Colorado, and Appalachian Ohio to encourage participation in bowel screening featured radio and print messages using images of 'real' rural people taken at local community events and distributed wherever people gathered, including farm auctions, coffee shops, pharmacies, farm supplies shops, libraries, equipment and feed stores and liquor outlets, as well as social service providers and health clinics. Community talks, personal stories, advertisements and articles by local health professionals in local papers were also used in some of the campaigns. All the studies cited above assessed the reach of the campaign through telephone surveys of the local populations. Results showed that the community focus was a key strength and that all had succeeded in raising awareness and increasing knowledge about bowel cancer as well as increasing intention to talk to a doctor about being screened. These positive results, however, did not translate into increased screening rates; in one time period of the Appalachian study, screening was actually slightly lower in the intervention than in the comparison counties. The investigators concluded that personal contacts from lay health advisors and patient navigators was likely to be needed to facilitate access to screening in these population groups (Krok-Schoen et al., 2015).

Other US campaigns have used a similar community engagement approach to promote bowel screening among disadvantaged urban African American and Latino populations (Blumenthal et al., 2005; Blumenthal et al., 2010; Cole et al., 2017; Holt et al., 2011; Leone et al., 2016). They worked through churches, senior centres, health centres and community programmes where health workers, peer counsellors or medical students provide free advice and education about bowel symptoms, encouragement to be screened, navigation services and financial assistance. Barbershops have been another setting for culturally based interventions to reduce 'masculinity barriers' to help seeking for colorectal cancer symptoms and to encourage screening among African American men (Cole et al., 2017; Rogers et al., 2019). Results of these studies have tended to be modest, concluding mostly that they were 'promising' or 'had the potential' to increase screening rates among these groups. As with the promotions in rural populations, it was not clear whether cost and access barriers were limiting factors rather than willingness to be screened.

Other gut diseases

Efforts to reduce the patient delay in the diagnosis of gut disease are overwhelmingly focused on cancer, mostly bowel cancer, and to a lesser extent oesophageal and gastric cancer. This is understandable because of the morbidity and mortality caused by cancer, and the capacity for improved outcomes due to early diagnosis (Hamilton et al., 2016; Neal et al., 2015). While other gut diseases receive less attention, the symptoms people experience are often similar, so that encouraging investigation for symptoms that raise suspicion of cancer, even if none is detected, is likely to lead to other clinically relevant diagnoses (Jones et al., 2009).

Beyond awareness: reducing barriers to seeing a doctor

While public awareness campaigns clearly have a positive impact on awareness and help seeking, they tend to assume that once a person decides they ought to see a doctor about symptoms, actually doing so is unproblematic. In systems where GP care is not free some may be unable to afford to go. In New Zealand, while bowel screening (where it is available) and any follow up is free, seeing a GP for gut symptoms is not. The most recent New Zealand Health Survey showed that 15.9% of all women, 10.5% of all men, and 20.5% of Māori had not visited a GP during the past year because of cost. Māori adults were 1.5 times more likely to not visit a GP because of the cost than all other adults after adjusting for age and gender (Ministry of Health, 2020a) Moreover, 6% of the overall population was not enrolled with a GP in 2019, with Māori enrolment (91%) lower than non-Māori (94%) (Irurzun-Lopez et al., 2021). The only other alternative for people with symptoms they are worried about is to present to the Emergency Department, where advanced bowel cancer continues to be diagnosed, particularly in Māori and Pasifika people (Health Quality and Safety Commission, 2017).

Rogers et al (2020, p. 18) drew attention to those “individuals who did not seek routine medical care, did not have a regular healthcare provider, or lived with lower socioeconomic status” and who were effectively excluded, including from research which was frequently carried out in clinical settings. To make any progress with these groups, these authors stated, it was important to move promotional campaigns to community-based locations with programmes that had sustainable funding and an adequately trained workforce to deliver the promoted service.

There may also be access problems for those who are distant from services as well as the deterrent effect of fear of what may be found and, in some groups, a distrust of the health system from previous negative experiences (Koo et al., 2018; MacArtney et al., 2017; Rogers et al., 2020; Shahid et al., 2016; Whitaker et al., 2015). Shahid et al (2016, p. 8) noted the "tyranny of distance and lack of transport" that affected indigenous Australians and called for services to be brought closer to where they lived and to work within a culturally sensitive context that engendered trust among the disadvantaged Aboriginal communities. The disadvantage created by distance from services was also highlighted in other work in West Australia (Emery et al., 2013a; Emery et al., 2013b). McCutchan et al (2015, p. 21) urged that campaigns should also work to break down "unhelpful myths surrounding cancer survival and treatment options."

Campaigns generally fail to address these other barriers that influence help seeking (Koo et al., 2018; Whitaker et al., 2015) and reports of interventions to tackle them appear to be few. One recent initiative - the Māori Cancer Pathway - implemented by the Nelson-Marlborough District Health Board (2020) was designed to increase awareness of cancer symptoms and understanding of cancer pathways and processes among Māori, as well as improving the cultural appropriateness of services. A review by Campbell et al (2018) supports the contribution that Aboriginal community-controlled services are making to improving Aboriginal health in Australia, by increasing their access and acceptability. Other initiatives are more likely to be part of general improvements for access to care rather than linked to campaigns, which urge people to see their doctor about gut symptoms. The very low-cost practices that exist across New Zealand in high needs areas (Ministry of Health, 2020b), for example, have a reduced fee per visit, and low cost GP clinics run by health providers with a kaupapa Māori focus (He Waka Tapu, 2021) are becoming available with even lower cost to the patient.

Section Two: Reducing practitioner delay

As discussed, a difficulty for primary practitioners lies in distinguishing the minority with serious disease from those with self-limiting, mild conditions. Increasing the expertise of primary care doctors in knowledge and awareness of cancer signs and symptoms, therefore, is "of equal, if not greater, importance to raising awareness among the general population (Koo et al., 2021, p. 39).

Upskilling primary care doctors

Supporting GPs to improve their quality of history taking and examination and reducing barriers to optimal clinical assessment and reasoning were suggested by Lyratzopoulos et al

(2015) as key areas where diagnostic delay could be tackled. One example of an intervention in Denmark that attempted to do this (Toftegaard et al., 2016) consisted of a three-hour continuing education package that aimed to increase GPs knowledge about cancer and optimise their referral practices so as to promote earlier diagnosis. Participating GPs were sent a questionnaire focusing on knowledge, attitudes and their response to clinical vignettes, one month before and seven months after the intervention. Additionally they were asked to assess the risk of cancer in a series of patients urgently referred to a fast-track pathway. Results showed that the education improved the GPs assessment of the cancer risk in urgently referred patients and had some, though a limited, effect on the GPs' knowledge about cancer diagnosis and their attitude towards their own role in cancer detection. The study did not assess whether there was any change in the number of patients that they referred for specialist investigation. The study was able to conclude only that such an intervention may be effective in changing GP attitudes and knowledge towards risk assessment and may therefore influence change in clinical practice.

An intervention with GPs in West Australia similarly aimed to improve timely diagnosis of cancer by promoting early recognition of symptoms and clarifying pathways for referral and investigation (Emery et al., 2017). Sixty-nine GP practices received an educational resource card listing the risk assessment tools for the most common cancers, local guidelines and contacts with multidisciplinary hospital teams. They also had four in-practice visits from Cancer Council West Australia officers to discuss the resource card and facilitate discussion of case studies featuring recently diagnosed patients. The remaining 73 practices in the area had no intervention. The primary outcome assessed was the total time to diagnosis for patients with cancer. The intervention ran for two years but was unable to find any evidence of a difference between intervention and control practices, median time to diagnosis being 97 vs 96.5 days. The authors believed that the lack of effect could have been because the campaign had not been intense enough or sustained over a long enough time period. However, they concluded that fast track specialist pathways and improved access to diagnostic tests may be more important than community campaigns in reducing delayed diagnosis.

Safety netting and other strategies

A second focus of reducing practitioner delay centres around proactive strategies that can be adopted routinely in general practice. The best documented of these is the UK ‘safety netting’ strategy designed to “protect against inaccurate working diagnoses” in primary care settings (Evans et al., 2018, p. e505). The aim is to ensure that patients do not ‘drop through the net’ but are followed up until a definite diagnosis is established (Lyratzopoulos, Vedsted, et al., 2015; Nicholson et al., 2016). Safety netting requires clear communication between a doctor and a patient about the diagnostic uncertainty around their symptoms. Recent recommendations developed by Heyhoe et al (2020) from interviews and workshops with both patients and primary care doctors outlined three basic components: a verbal discussion at the initial presentation of the problem and a plan with a specific time frame for re-consulting if symptoms did not resolve; written documentation of the plan for the patient to take away; and a follow-up prompt at an agreed time later to remind the patient to return. This is particularly applicable to people who present with ‘low risk but not no risk’ symptoms (Evans et al., 2018).

While the concept of safety netting appears to be well accepted among primary care professionals in the UK, implementation is known to be variable and there is no evidence on which strategies are practically feasible within the workload of general practice settings (Evans et al., 2018; Heyhoe et al., 2020). Evans et al (2018), for example, in a study of how GPs understood and carried out safety netting, found low levels of concern about serious illness, problems with the extra workload, and wide variability of documentation both within and between practices.

The capacity of the GP to form a clear suspicion of serious disease and refer a patient for investigation is consistently associated with a shorter time to diagnosis but there is no simple formula for doing this in the absence of alarm symptoms (Esteva et al., 2013; Macdonald et al., 2006; Mills et al., 2017; Molassiotis, Wildon, et al., 2010). Beyond a structured programme such as safety netting, advice in the literature, as discussed earlier in this literature review, reiterates that basic principles are the foundation of reducing practitioner delay in diagnosing serious illness; adequate physical examination of the patient and being alert to patients whose symptoms persist for weeks, become more frequent, develop a pattern or have additional symptoms appear (Esteva et al., 2013; Evans et al., 2014; Korsgaard et al., 2008;

Mitchell et al., 2008; Schroeder et al., 2011). Others have pointed to the importance of avoiding "closing out the diagnosis prematurely" (Schroeder et al., 2011, p. 173) and being assiduous in following up patients who have negative or inconclusive test results (Macleod et al., 2009; Molassiotis, Wildon, et al., 2010; Renzi et al., 2015; Renzi et al., 2016). This appears to be particularly important in younger people, who experience longer diagnostic delays (Boldys et al., 2003; Marmo et al., 2005; Portale et al., 2004; Windner et al., 2018). Using the referral pathways and decision support tools that are used in New Zealand and elsewhere may go some way to ensure that all the relevant factors have been considered (Emery et al., 2017; Linedale & Andrews, 2017; Linedale et al., 2016). It has also been suggested that GPs could offer routine advice to people over 50 years about the seriousness of rectal bleeding or a change in bowel habit and that this advice should be targeted at those who are less likely to seek help promptly, largely people who are from disadvantaged and minority groups (Courtney et al., 2012a; Macleod et al., 2009; McCutchan et al., 2015; Oberoi et al., 2016a; Oberoi et al., 2016b).

As discussed earlier, doctors who communicate effectively have been shown to have fewer patients with delayed diagnoses (Siminoff et al., 2011). Establishing a shared vocabulary is important because of the indeterminate nature of the various terms for gastrointestinal discomfort. Humphrys et al (2020) drew attention to the difference that may exist between the patient and the doctor over the lay and professional meaning of terms such as heartburn, indigestion and reflux, and therefore the potential for miscommunication that contributes to delayed diagnosis. This study criticised the BCOC campaign on oesophageal and gastric cancer for their key message **"**Having heartburn, most days, for 3 weeks or more could be a sign of cancer – tell your doctor" (Cancer Research UK, Undated), for its focus around the one term 'heartburn', to the exclusion of other commonly used descriptors such as 'indigestion' or 'reflux'.

Communication across the patient-GP-specialist continuum is also important, particularly in systems where primary and specialist services serving the same patients do not automatically share information. An Australian study (Pascoe et al., 2013) found that there were areas of communication break-down following referral and called for an integrated system of shared information across private specialists, hospitals and primary care services to ensure continuity and improved feedback to GPs after referral. Strategies identified that helped minimise delays in specialist response involved improving the language used in GP letters of referral so that they specifically mentioned cancer and indicated what physical examinations and laboratory investigations have been done already (Esteva et al., 2013; Linedale et al., 2016; Mitchell et al., 2008).

Non-cancer gut disease

It is well documented that the absence of alarm symptoms does not exclude organic disease; Patel et al (2015) found that up to one in six patients without alarm features may have underlying organic gastrointestinal disease. A number of studies that have focused on this failure to identify inflammatory bowel disease have called for GPs to have a greater understanding and alertness to the complex interaction between organic and functional bowel conditions and to pay greater attention to patients who present with ‘an excess’ of gastrointestinal symptoms over a period of years (Blackwell et al., 2020; Maconi et al., 2015; Porter et al., 2012). A similar complex crossover between functional dyspepsia and gastro-oesophageal reflux disease has been raised in a number of recent reviews (de Bortoli et al., 2018; Eusebi et al., 2018; Geeraerts et al., 2020; Quigley & Lacy, 2013). These reviews focus on the frequent co-existence of both conditions within the one individual, noting that “recent observations point toward joint underlying pathophysiological events” (Geeraerts et al., 2020, p. 1168).

On the other hand, over-investigating patients, sometimes with multiple specialist referrals when no organic disease is found creates an unnecessary burden on health system resources and delays both doctor and patient moving forward with positive treatment that may improve the quality of life for patients with functional disease (Harvey et al., 2018). Commentators variously recommend more education and training for doctors about irritable bowel syndrome (Halpert et al., 2010; Lovell & Ford, 2012; Olafsdottir et al., 2012), better use of the Rome diagnostic criteria (Simren et al., 2017), and using diagnostic support tools that help to differentiate between organic and functional bowel disease (Crohns and Colitis Australia, 2013; Linedale & Andrews, 2017). This enables patients who have indications of organic disease to be referred promptly, and those who do not can move forward with treatment for their symptoms (Harvey et al., 2018; Soares, 2014; Spiegel et al., 2010).

Part Two of this literature review highlighted that for coeliac disease, the highest proportion of diagnostic delay was due to practitioner delay. There is a need for improved physician education about the diverse presentation of coeliac disease (Fuchs et al., 2014) and research into its pathogenesis. Recommendations to improve accurate and timely diagnosis include increasing physician awareness of coeliac disease as a common health problem and the intensification of active case finding in at risk groups, especially people with irritable bowel syndrome or those with a family history (Card et al., 2013; Fuchs et al., 2014; Norstrom et al., 2011; Vavricka et al., 2012). The National Institute for Clinical Excellence in the UK (NICE, 2015) has a full guideline on the recognition, assessment and management of coeliac disease including the use of diagnostic tests. It also draws attention to the range of extraintestinal and atypical presentations which may confuse diagnosis and lead to delay (Fuchs et al., 2014). A mass screening of more than 10,000 Swedish 12 year old children was carried out in the ETICS study (Exploring the Iceberg of Celiacs in Sweden) (Rosen, Emmelin, et al., 2011). However, mass screening remains controversial, and two qualitative studies with adolescents who were diagnosed as a result of the screening found some perceived their diagnoses and the required dietary changes negatively, in spite of the potential health impact of not treating the condition (Nordyke et al., 2014; Rosen, Ivarsson, et al., 2011).

Much has been written about the diagnostic dilemmas surrounding the diagnosis of gut disease with non-specific symptoms, but there still appears to be relative uncertainty in how to improve the situation. Studies outlining the delays in diagnosis have called for “an efficient diagnostic paradigm and … raised awareness among primary health care providers” (Nguyen et al., 2017, p. 1830) but have not been able to demonstrate concrete strategies that would achieve this aim.

Section Three: Reducing system delay

Fast track access to investigation

The largest body of literature on system-wide interventions to reduce diagnostic delay comes from the UK, where there have been significant resources and sustained efforts over more than a decade. These have been focused specifically on improving cancer diagnosis, rather than gut disease in general, primarily it appears, out of concern that cancer survival in Britain was lower than in the rest of Europe (Abdel-Rahman et al., 2009). In parallel with the Be Clear on Cancer public campaigns described above, a number of system improvements were instituted. A fast track pathway that enabled rapid access (within two weeks) to specialist investigation or testing for patients referred urgently under the National Institute for Clinical Evidence (NICE) guidelines was established in 2009 (Møller et al., 2015). In the years since, the guidelines for referring through the fast track pathway have been extended so that currently they advise GPs to offer patients ‘urgent direct access’ within two weeks for a wide range of symptoms, including those like unexplained weight loss and anaemia that are much less specific than the classic ‘alarm symptoms’ (NICE, 2021). This liberalisation has been welcomed as an acknowledgement that GPs have the expertise to use their clinical judgement appropriately rather than having to make patients they believe should be investigated ‘fit’ the guidelines (Hamilton, 2015). In another effort at system improvement, the Cancer Networks Supporting Primary Care programme instituted four quality improvement initiatives from 2011-2013 to improve referral practices in primary care: clinical audit of new cancer diagnoses; a significant events analysis; practice cancer plans; and the availability of risk assessment tools (Rubin et al., 2015).

Monitoring change over time as these various initiatives have been implemented has been possible through the availability of large national datasets that allow researchers to link cancer data with primary care practice referrals and individual anonymised NHS identifying numbers (Rubin et al., 2015). Analyses of these data have resulted in published evidence gradually accruing of improvements in early diagnosis and reduced mortality (Hamilton, 2015; Hamilton et al., 2016; Møller et al., 2015; Neal et al., 2014; Round et al., 2020; Rubin et al., 2015). A recent publication by Round et al (2020), who examined data from more than 1.4 million patients diagnosed with cancer in England between 2011 and 2015, found statistically significant reductions in late stage cancers for practices with high referral rates and there was an observed reduction in mortality, considered likely to be explained by earlier stage at diagnosis. A systematic review of 209 studies on the topic also concluded that efforts to expedite diagnosis of symptomatic cancer was likely to have benefits in terms of “improved survival, earlier stage diagnosis and improved quality of life, although these benefits vary between cancers” (Neal et al., 2015, p. S92). An overview paper (Hamilton et al., 2016) that examined the efforts to fast-track diagnosis from four different perspectives likewise found evidence that cancer survival had improved, time to diagnosis had fallen and the proportion of patients presenting with cancer as an emergency had also fallen. This analysis concluded that the improvements were “contemporaneous with major reconfigurations and investment in cancer services and a liberalisation of the criteria for cancer investigation coupled with better identification of the individuals who are most at risk” (Hamilton et al., 2016, p. 747) and were therefore likely to be cause and effect. This paper commented, however, that evidence on the cost effectiveness of the efforts to expedite diagnosis was still unknown.

A similar system improvement effort in Denmark began in 1998 with the introduction of a two-week wait time for investigation of patients suspected of having colorectal cancer (Korsgaard et al., 2008). This was then followed by the Cancer Patient Pathways (CPPs) introduced in Denmark between 2007 and 2009 in an effort to reduce the time to diagnosis and treatment and improve survival. In an analysis of survival and mortality of patients diagnosed before and after the implementation of the pathways, Jensen et al (2017) found that the time to diagnosis and treatment decreased after the CPP implementation along with improved survival and lower excess mortality. Importantly, however, these results were achieved in the wider context of an overall national cancer plan that had established multidisciplinary teams in centralised locations with expertise in pathology, radiology, surgery and oncology and had boosted in-service training (Iversen et al., 2014).

A recent paper (Koo et al., 2021) reinforces the findings of the earlier analyses of the Danish and English fast track pathways (Hamilton et al., 2016; Jensen et al., 2017) finding that practices with high referral rates have better outcomes for their patients, that cancer mortality has decreased over time, and that emergency department diagnosis of cancer, usually indicating a poor prognosis, has also decreased. Taking this into account in their analysis, they conclude overall that “the introduction of fast-track pathways has been associated with improvements in cancer survival” (Koo et al., 2021, p. 37).

The key role of rapid access to specialist investigation is similarly supported in many other studies (Black et al., 2015; Koo et al., 2018; Macdonald et al., 2006). Indeed, Australian studies (Emery et al., 2017; Emery et al., 2013b) suggested that improved access to diagnostic testing was more likely to be effective than community campaigns and GP education, either through one-stop assessment clinics with direct GP referral or via fast track specialist pathways. Another study from the United States similarly suggested dedicated centres were needed to enable speedy referral, concentrated expertise around aspects of pathology and diagnosis, and assigned case workers and patient navigators who ensured that no patients were lost to follow-up (Singh et al., 2012). Lyratzopoulos et al (Lyratzopoulos, Vedsted, et al., 2015) also supported the concept of specialist units like those established in Denmark where everything can be done “within one day under one roof”. These authors noted the complex sequence of blood tests, imaging, endoscopy, tissue sampling and specialist expertise that is needed for diagnosis and pointed to the errors that can potentially occur when investigations are spread across different services. There are, nevertheless, arguments against centralisation in other studies, especially the additional accessibility barriers they create for those in rural or remote locations (Shahid et al., 2016).

Adequate system capacity for investigation

Of key relevance to health system delay is the overall capacity of the health system to receive and act on patient demand from awareness raising efforts on the one hand or referrals from primary care for specialist investigation on the other. Wakefield et al (2010), note that for any campaign to succeed, adequate access to the promoted service should be ensured. Although the English interventions have proven largely successful, it is clear that they strained the capacity of services to respond to the demand generated by the public campaigns and the two-week wait criteria (Bethune et al., 2013; Lai et al., 2021). A 29% overall increase in two week referral rates was reported between 2010 and 2013 (Rubin et al., 2015), with referrals increasing approximately 10% each year in England by 2018 when more than 2 million referrals were made (Round et al., 2020). Even greater increases were reported in regional studies; 59% in the Royal Derby Hospital study (Peacock et al., 2013) and 47% in Coventry and Warwickshire (Pande et al., 2014). Reports of increased pressure on imaging and endoscopy services followed (Hall et al., 2016; Hamilton, 2015; Hamilton et al., 2016; Pande et al., 2014; Peacock et al., 2013). While there had been provision of additional resources to improve access to diagnostic tests (Neal et al., 2014), the extra £136 million that was reported to have been put into Primary Care Trust baseline funding to support the increase was considered a “gross underestimation” by (Hall et al., 2016, p. 198) in view of the “significant sustained negative impact on resources”. Similarly, the overview by Hamilton et al (Hamilton et al., 2016, p. 742) commented that “diagnostic services need to be more responsive than is currently the case.” Moreover, the increase in bowel cancer detection in the Coventry and Warwickshire area required the recruitment of two extra surgeons and the introduction of weekend and evening sessions to deal with the workload (Pande et al., 2014).

The importance of understanding the flow-on effect of improvements in one area that cause a bottleneck elsewhere is highlighted by the pressure on diagnostic capacity caused by the implementation of the bowel screening programme in some parts of New Zealand. The resultant increase in demand for colonoscopies (Bagshaw & Cox, 2020) has had a negative impact on individuals who have been referred with symptoms and either declined or subject to long waits. Even in Denmark, where the Cancer Patient Pathway was just one part of an overall plan to boost capacity, and where patient satisfaction with referral time did increase, patients then became more dissatisfied with the long waiting times to get an initial appointment with their GP to discuss their symptoms (Dahl et al., 2017).

Non-cancer gut diseases

What is not discussed in any of these papers is the extent to which investigations for suspected cancer may also help to reduce diagnostic delay for individuals in whom no cancer is found, but other conditions are identified. Only passing references were made in several of the UK studies to patients with non-malignant conditions (Hamilton et al., 2016; Peacock et al., 2013), with one dismissing any benefit of the increase and noting that “although it may be useful for non-neoplastic disease, that is not what the campaign was designed to do” (Hall et al., 2016, p. 198). Yet it is clear that a considerable number of other serious non-cancer diagnoses are made as a result of investigating individuals for suspected cancer. Jones et al (2009) found that ‘clinically relevant’ diagnoses, including many non-cancer diagnoses, were made in a high proportion of patients presenting with alarm symptoms.

Some progress in other gut disease is, however, being made. The Royal College of General Practitioners (Undated) made inflammatory bowel disease a ‘Spotlight Project’ between 2017 and 2020. Working in partnership with Crohn’s and Colitis UK, it aimed to help primary care health professionals better identify and manage IBD. As part of the project an IBD toolkit and a suite of diagnostic and educational resources for primary care was developed and made freely available, supported by a GP network of regional clinical champions. The project endorsed the use of different cut off values from test results to stratify patients into high, medium and low risk of having IBD (Turvill et al., 2018) but noted that patients with persistent symptoms should be (re)considered for referral for specialist investigation, and that negative test results were not a replacement for clinical judgement.

Diagnosis of coeliac disease also appear to be improving in recent years with access to serological diagnostic methods, more efforts to increase recognition by primary care physicians and guideline recommendations to routinely test people with irritable bowel syndrome for coeliac disease as well (Cichewicz et al., 2019; Fuchs et al., 2014; Linedale & Andrews, 2017). Serological diagnosis is now accepted without biopsy confirmation in some specialist centres (Holmes et al., 2017), avoiding endoscopy and making diagnosis less difficult for those individuals who are already on a self-imposed gluten free diet and find the weeks-long gluten challenge unacceptable.

As discussed, studies continue to show a long delay in diagnosis of inflammatory bowel disease, particularly Crohn's disease, and there have been calls for developing improved "diagnostic paradigms for primary care providers" (Nguyen et al., 2017: 1830) that set out more clearly the characteristics of the onset of symptoms (Nobrega et al., 2018) and "enhanced pathways to accelerate specialist referral and timely IBD diagnosis" (Blackwell et al., 2020: 210). A public campaign to increase knowledge and awareness that would both aid diagnosis and also help those living with IBD has also been proposed (Vernon-Roberts et al., 2020). Attacking system improvements from another angle is the recommendation by Lyratzopoulos, Vedsted et al (2015) that medical consultation norms should be re-engineered, particularly the time allowed, so that the quality of history taking and examination could be more thoughtful and thorough. An increase in the time available would also make the proactive strategies that general practitioners are urged to undertake a more realistic strategy (Evans et al., 2018; Heyhoe et al., 2020).

Bio-medical research in progress

Current literature points to two major areas of bio-medical research in progress related to the diagnosis of gut disease. The first of these is the growing elucidation of the overlap between functional and organic gut disease with a number of studies drawing attention to the possibility of a common pathogenesis between all gut diseases that is not yet understood (Barratt et al., 2011; Patel et al., 2015; Porter et al., 2012). The second area is the ongoing work in refining and expanding the range of diagnostic tests and tools. Fiorino et al (2020) report on a project to validate a 'red flags index' for use as an early diagnosis tool developed by the International Organisation for Inflammatory Bowel Disease. Other recent work too has focused on reducing the risk of missing organic disease (An et al., 2019; Blackwell et al., 2020;

Linedale & Andrews, 2017). Novel biomarkers, point of care tests, and in-vitro gluten challenge techniques for coeliac disease are being trialled and are likely to assist with diagnosing seronegative cases and atypical forms of coeliac disease with symptoms which may potentially not be recognised by primary care doctors (Cichewicz et al., 2019; Fuchs et al., 2014; Lebwohl et al., 2018). Work is also ongoing to find biomedical tests that can positively distinguish people with irritable bowel syndrome from healthy controls, and to identify the specific sub-types of irritable bowel syndrome from each other (Camilleri et al., 2017; Kim et al., 2017; Mujagic et al., 2016). While these developments are noted for the promise they may hold for future improvements, they are as yet not advanced enough to be used in practice or contribute to reducing delays in the diagnosis of gut disease.

Summary

Reducing patient delay

- There is good evidence that national awareness campaigns with simple, clear messages are effective in encouraging people to see a doctor about symptoms that may indicate gut disease. While they increase doctor visits and referrals for specialist investigation, there is less evidence on whether they increase early diagnosis and improve overall outcomes;
- Messages need to be simple and well researched and piloted with the relevant audience(s) and disseminated in a range of different ways. Campaigns can provide a justification for seeing a doctor and also appear to reduce the awkwardness of discussing symptoms;
- Awareness days, weeks or months run by support organisations for a particular condition are also likely to increase knowledge and generate publicity. Gut diseases, including gut cancers, however, tend to receive far less publicity than breast and prostate cancers. Reliable measures to assess the impact of these kind of awareness activities are lacking;
- Bowel screening promotional campaigns also assist in raising awareness of bowel symptoms and increasing participation in screening. Linking a campaign with a letter, message, or personal contact from a person's GP practice appears likely to further increase screening uptake;

- Awareness activities that result in referrals for investigation tend to be primarily focused on cancer but they also result in relevant diagnoses of other gut diseases;
- There is scant evidence of programmes that reduce practical issues and system distrust that may cause patients to delay help seeking such as cost, transport, and access to a primary care practice, particularly in systems where primary care is not free. Very low-cost GP practices and clinics with a kaupapa Māori focus may be the way ahead for New Zealand if they are sufficiently well resourced.

Reducing practitioner delay

- Professional development interventions to upskill GPs in recognising serious gut disease have been trialled in a few studies but results have been modest;
- Patients with 'alarm symptoms' are relatively straight forward to diagnose and are likely to be referred promptly for investigation. There is no easy solution to reducing delayed diagnosis of gut disease when there are no alarm symptoms present;
- Proactive primary care strategies such as the safety netting scheme in the UK are recommended as a method of reducing delayed diagnosis of gut cancers. It is unclear, however, how realistic these strategies are within the workload of a general practice without further resourcing;
- Clear communication between doctor and patient, and between general practice and specialist services is important in reducing unnecessary delays. Clear and consistent documentation within practices is also necessary as is that between general practice and specialist services;
- Some progress is being made in reducing late diagnosis of non-cancerous gut diseases over recent years through the availability of new tests and the updating of guidelines to include them in routine primary care practice.

Reducing system delay

- System wide interventions in the UK and Denmark show that it is possible to improve cancer outcomes by tackling all the areas where delay occurs but it needs a concerted and sustained effort and significant investment of resources across the entire patient pathway;
- National quality improvement initiatives in the UK include the 'fast track' patient pathway that gives urgent access (within two weeks) to specialist investigation and

the liberalisation of guidelines to allow GPs to refer any patient they are concerned about through the fast track pathway;

- Recent analysis of data from England has shown that cancer survival has improved overall, time to diagnosis has fallen and the proportion of patients presenting with cancer as an emergency has also fallen. The ability to track the performance of individual practices has demonstrated that those practices that refer the most patients for specialist investigation have significant reductions in late stage cancers and a reduction in mortality compared to low referring practices;
- In Denmark, a national cancer plan with a fast track patient pathway in conjunction with the establishment of multidisciplinary teams of relevant experts in centralised locations has resulted in a decrease in the time to diagnosis and treatment along with improved survival and lower excess mortality;
- A ‘whole system’ approach is necessary when improvements are implemented so that the demand caused by raising awareness or liberalising criteria for referral does not cause delays elsewhere;
- System improvements in reducing diagnostic delay of non-cancerous gut disease remain little studied. While the record of lengthy diagnostic delay points to the need to investigate symptoms more assiduously, over-investigating patients with indeterminate symptoms clearly places an unnecessary burden on the health system;
- Progress is being made in better understanding the underlying mechanisms of gut disease and in the development of new diagnostic tests. However, these are not yet available for use in day-to-day practice;
- While not wishing to ignore the human cost, there is an acknowledgement across the literature that the overall financial cost effectiveness of reducing diagnostic delay has not been tackled.

Overall Summary

This literature review indicates that the cause of diagnostic delays for gastrointestinal conditions is multifactorial, with roots in all levels of the healthcare system. Poor outcomes from diagnostic delays are most relevant for cancer, however early identification of other gastrointestinal diseases such as coeliac and inflammatory bowel disease is likely to reduce complication rates and improve quality of life via expedition of treatment. Long delays result from a combination of patient-related, practitioner-related and health system related factors. In this review we have explored these factors and potential interventions for reducing overall diagnostic delay.

Patient-related factors include a lack of awareness of the seriousness of systems, due there being considerable crossover between the presentation of serious and benign conditions. The identified ‘red flag’ symptoms of pain, bleeding and dysphagia are not experienced by everyone with severe disease. It also appears that the threshold for consulting is highly individualistic and dependent on personality factors. Health seeking behaviour is also influenced by barriers such as cost and previous negative experiences in the healthcare system. To address patient delay, national awareness campaigns, awareness days/weeks/months are likely to be effective in generating knowledge, increasing publicity and awareness, and providing justification to see a doctor. There is less evidence as to whether these interventions increase early diagnosis and improve outcomes. Bowel screening promotional campaigns have also been shown to raise awareness and increase participation in screening, especially whether the campaign was linked to a personal letter or contact via the person’s GP practice. These programmes do not appear to reduce other access barriers such as cost - very low-cost GP practices and clinics with a kaupapa Māori focus may be the way ahead for New Zealand if they are sufficiently well resourced.

The broad symptom signature of gastrointestinal conditions and extensive overlap in the presentations of benign and serious conditions also presents diagnostic difficulty for practitioners, with delays often arising from misdiagnosis or attribution of symptoms to another illness that the patient is being treated for. Other important reasons for delay highlight in this review are inadequate physical examination, inappropriate testing, false reassurance based on a negative test and poor communication regarding next steps.

Professional development to upskill GPs as an intervention has been studied, yielding modest results. Safety netting has been recommended but it is unclear how realistic this is to implement within the workload of a general practice without further resourcing. Clear communication and documentation are also advised.

Health system factors also impact on time to diagnosis, with lack of specialist staff, long wait times to be seen, criteria excluding certain patients, lack of continuity of care and poor referral details contributing to delay. National quality improvement initiatives such as the 'fast track' patient pathway allows urgent access to specialist investigation and decreases time to diagnosis, emergency department presentations and improves cancer survival. Practices with high referral rates have significant reductions in late-stage cancers and mortality, however it is evident that over-investigation of patients with indeterminate symptoms places unnecessary burden on the health system. Data have shown that a whole system approach is needed when improvements are implemented so that demand from raising awareness does not cause upstream delays. While not wishing to ignore the human cost, there is an acknowledgement across the literature that the overall financial cost effectiveness of reducing diagnostic delay has not been tackled.

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