Otago Spotlight Series
Cancer Research

Molecularly-informed treatment strategies in breast and ovarian cancer

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Cancer. What are the Challenges?

Prevention

Understanding (and modulation of) cancer risk factors to decrease incidence

Early Detection

Many cancers are far more treatable in their early stages than in their more advanced stages

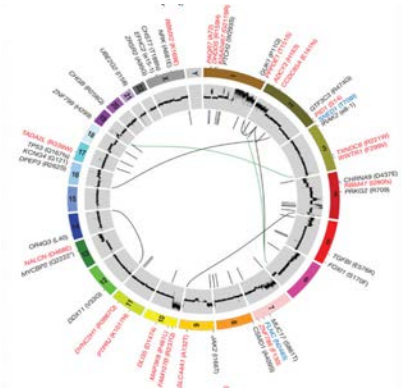
Understanding risk factors (including genetic) to promote targeted disease surveillance

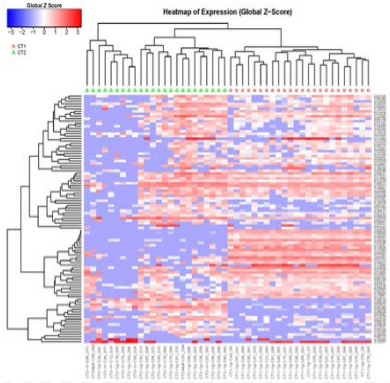
Personalized / Targeted Therapy

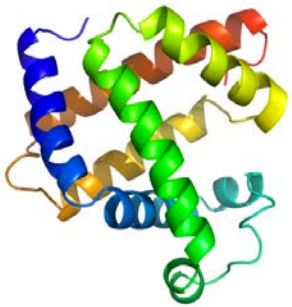
How can you define what therapy a patient will respond to?

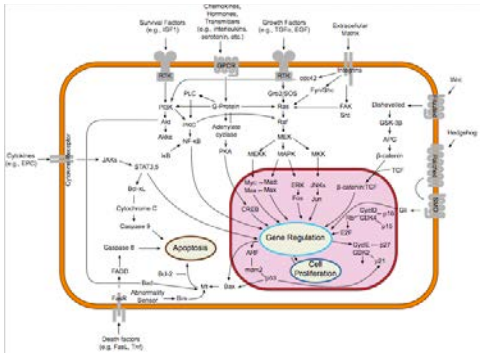
‘omic’ technologies: revolutionizing today’s medical advances

Genomics | Transcriptomics | Proteomics | Metabalomics







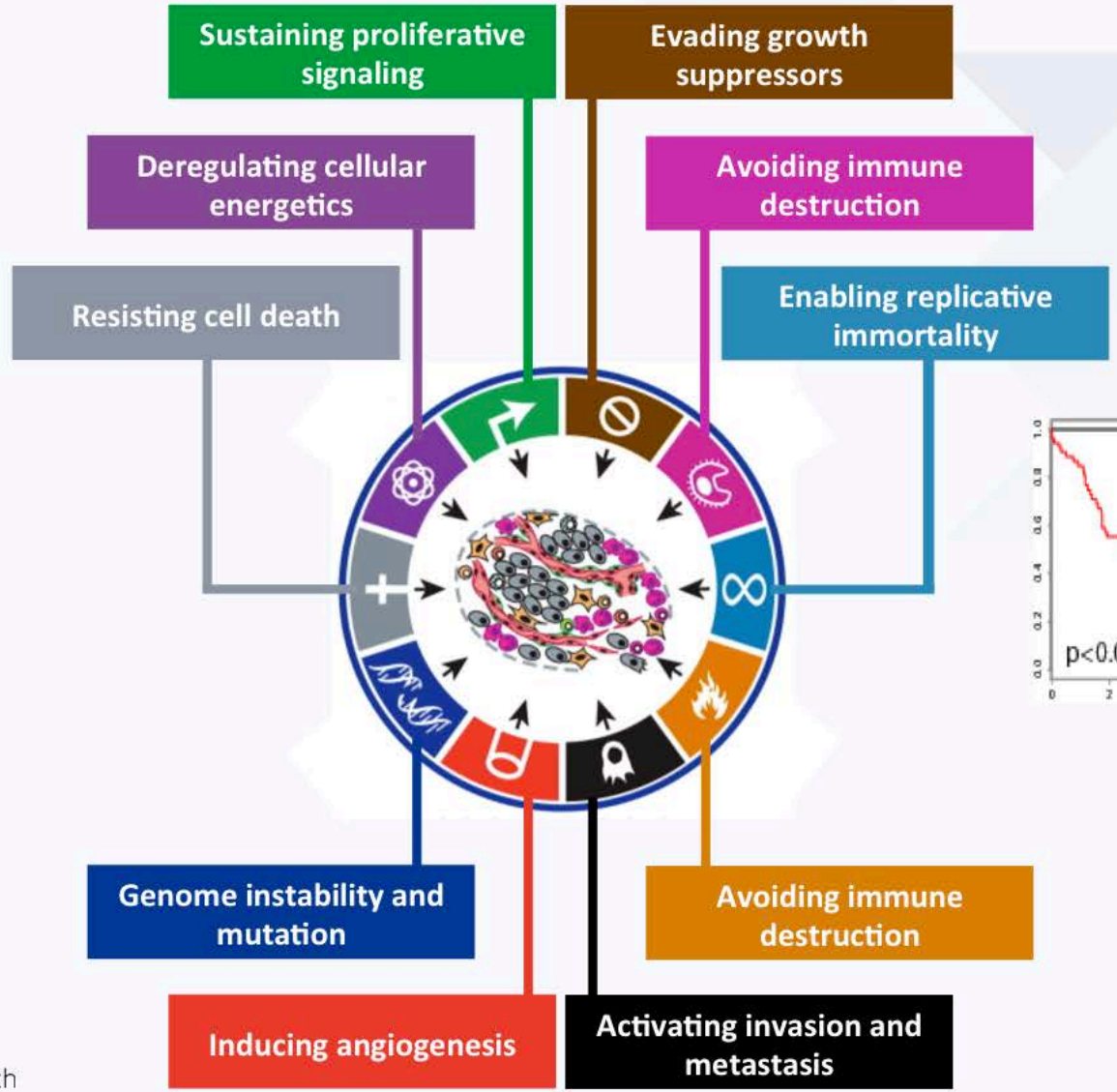


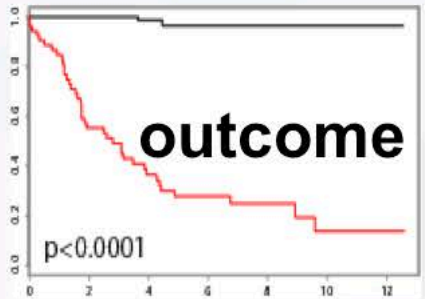
Tumor classification into distinct molecular subtypes exposes:

- Shared biologic features
- Shared clinical progression features
- More predictable responses to targeted therapies

Objective classification adds significant prognostic information independent of standard clinical parameters, and is a new guide for clinical decision making.

Acquired capabilities for tumor growth and progression





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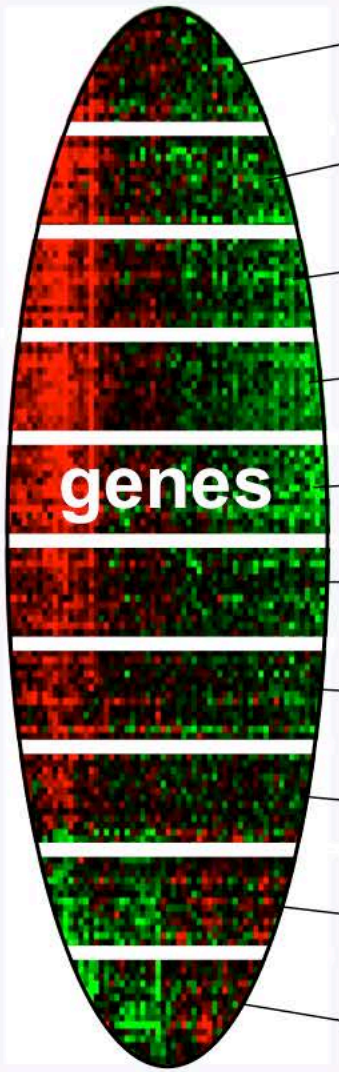
Adapted from: The hallmarks of cancer: The next generation. Hanahan and Weinberg, 2011 *Cell*

Tumor behavior and prognosis can be measured by gene behavior



Sustaining proliferative signaling

Evading growth suppressors

Avoiding immune destruction

Deregulating cellular energetics

Enabling replicative immortality

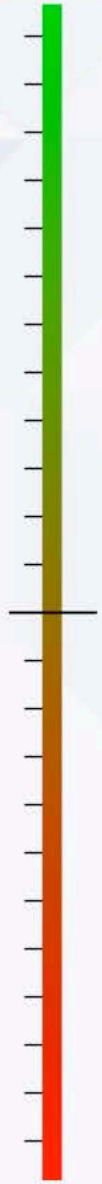
Resisting cell death

Avoiding immune destruction

Genome instability and mutation

Activating invasion and metastasis

Inducing angiogenesis



Good Prognosis

Poor Prognosis

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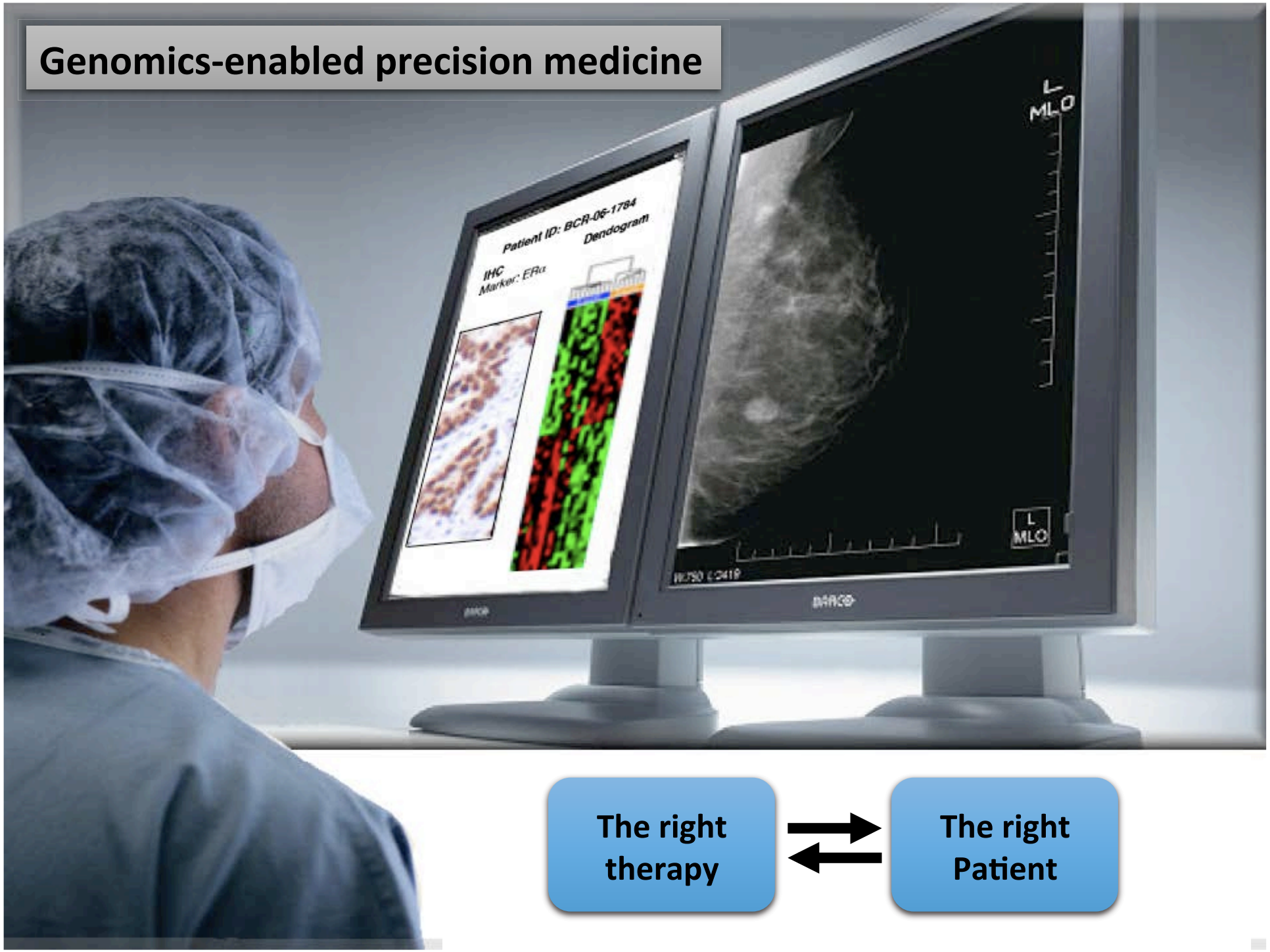
Adapted from: The hallmarks of cancer: The next generation. Hanahan and Weinberg, 2011 *Cell*

Genomics-enabled precision medicine



The right therapy ⇄ The right Patient

Molecular insights to targeted therapeutics:

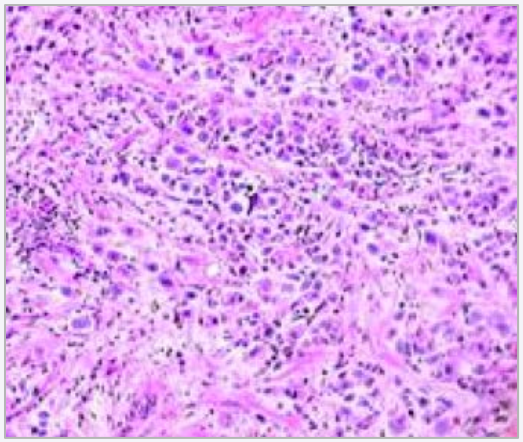
Developing precision power tools for oncologists

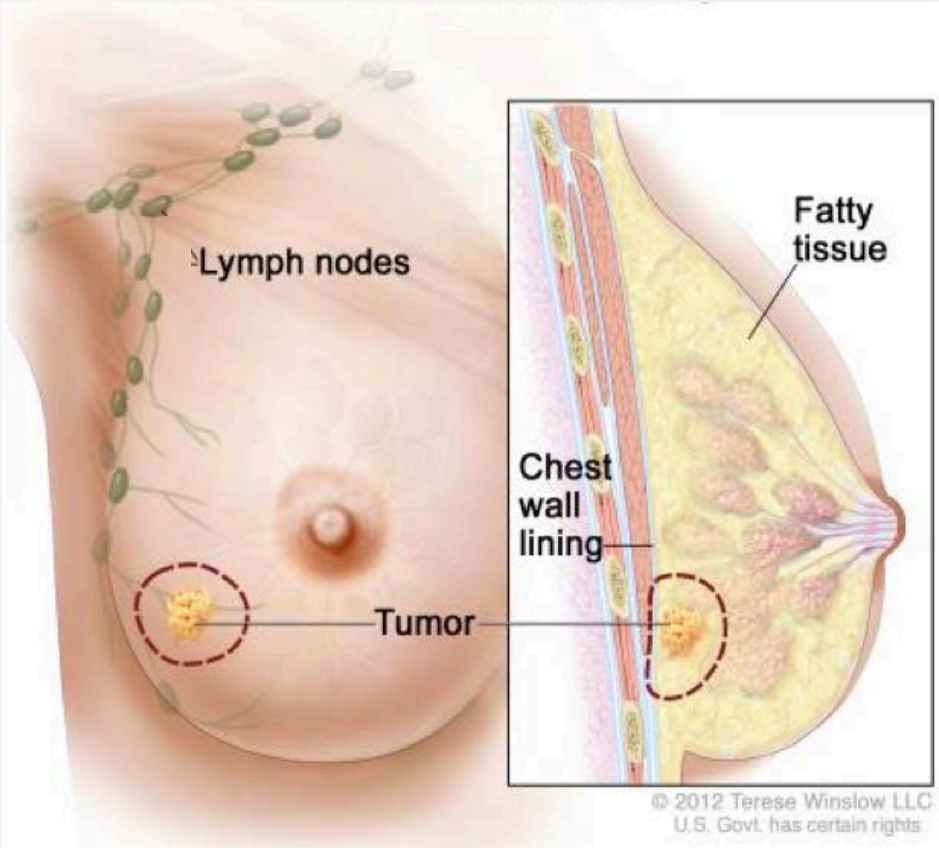
Recent advances to characterize and target the molecular pathology operating in aggressive subtypes of breast cancer and ovarian cancer.

- **Triple negative breast cancer**
- **Small cell ovarian cancer**

Therapeutic decisions in breast cancer

Primarily a clinical judgment, based on classical pathology, surgical staging and a limited number of molecular markers

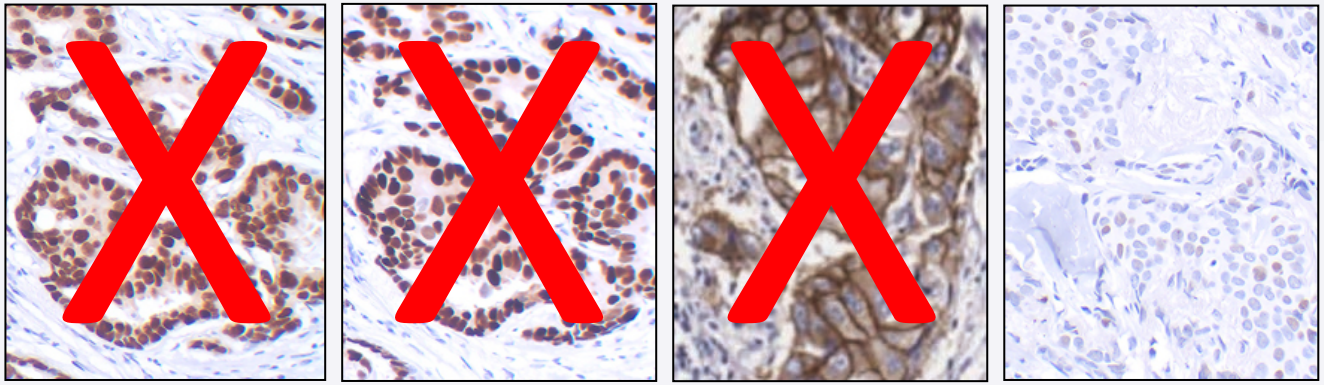




Markers for prognosis and treatment selection

Despite decades of research, there are few molecular markers that currently impact prognosis prediction and therapeutic decision making in breast cancer

ER PgR HER2 Ki67



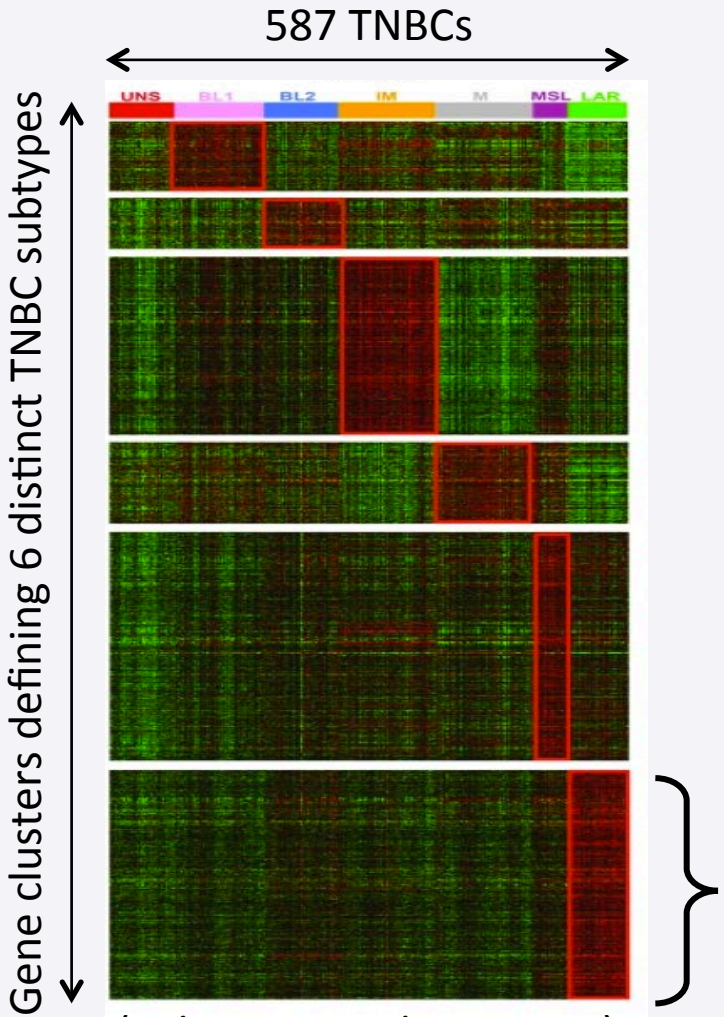
Gene Aberrations: BRCA1, BRCA2, CHEK2, PTEN, PIK3CA, EGFR…

10-25% of invasive breast cancers are “triple negative”

Triple Negative Breast Cancer (TNBC)

- TNBCs do not express clinically significant levels of ER, PR and HER2; targeted therapies to these receptors are ineffective
- 10-25% of invasive breast cancers are TNBC, depending on biomarker scoring criteria and population demographics
- No established options for systemic therapy other than chemotherapy
- Initially respond to chemotherapy, but have a high frequency of early relapse with distant metastases (typically visceral and CNS) and poor overall survival

Androgen Receptor positive (AR+) TNBC



(*Lehmann et al, JCI, 2011*)

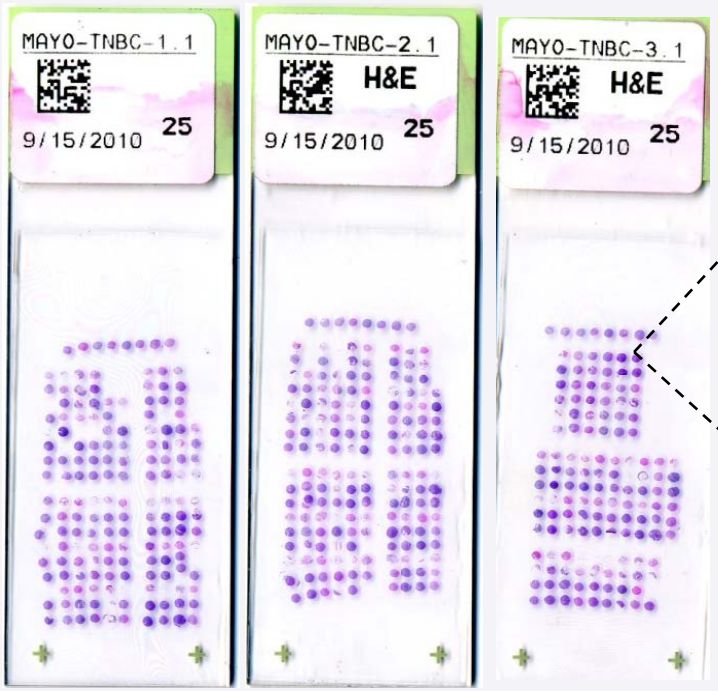
Luminal AR subtype identified by characterization of 587 TNBC transcriptomes
(Lehmann et al, 2011)

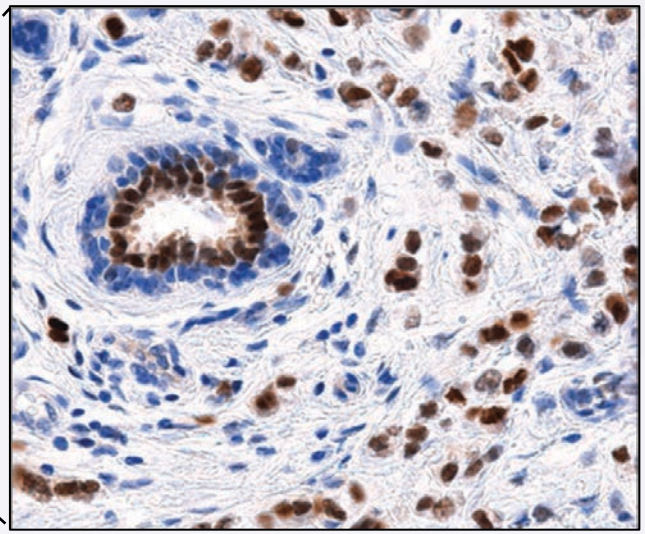
Prominent gene expression:
Androgen receptor, steroid biosynthesis genes, androgen and estrogen metabolism

Lehmann et al (2011) *J Clin Invest*. **121**(7):2750-67

Androgen Receptor positive (AR+) TNBC

We report nuclear staining of AR in 22/94 (23%) of TNBC by IHC



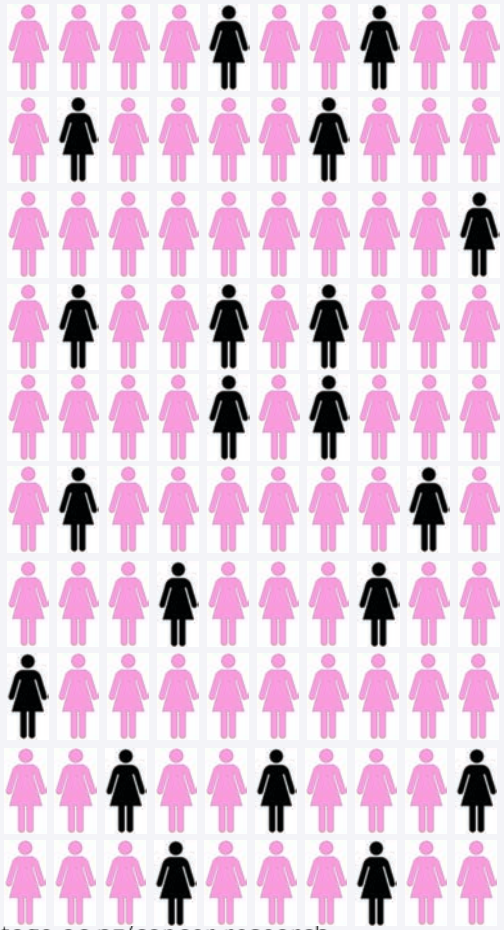


AR+ TNBC was statistically significantly more common in older patients and had a higher propensity for LN metastasis. No difference in survival. The data suggests AR+ TNBC has a unique clinical behavior.

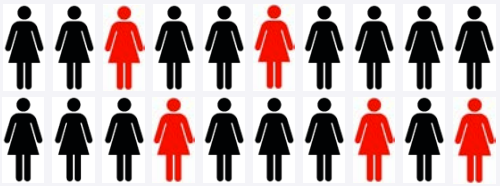
McGhan et al. *Ann Surg Oncol* (2014) **21**:361-67

Elevated AR in TNBC creates a potentially molecularly informed treatment strategy

For every 100 patients with invasive breast cancer



10-25% of invasive breast cancers are **TNBC**. There are no effective targeted therapeutic strategies for these women



Of these cases, 10-43% are **AR Positive**
Drugs: Bicalutamide, Enzalutamide

Clinical trial feasible for AR+ TNBC with combination targeted therapy

Goal: develop robust preclinical data to support a clinical trial

Literature consistency: reporting 10-43% of TNBCs are AR+.
Potential clinical significance of AR+TNBC in NZ is under investigation

www.impactjournals.com/oncotarget/ Oncotarget, Vol. 6, No. 28

Genomic amplification of 9p24.1 targeting *JAK2*, *PD-L1*, and *PD-L2* is enriched in high-risk triple negative breast cancer

Barrett et al, July 03, 2015

- Using comparative genomic hybridization, we recently identified high level amplification of *PD-L1*, *PD-L2*, and *JAK2* (PDJ amplicon) at 9p24.1 in 12/41 (29%) of TNBC
- PDJ amplification was not observed in ER+ and HER2+ tumors
- Amplification correlated with PDL1 and JAK2 overexpression
- TNBC patients with the PDJ amplicon had a significantly worse prognosis (5 year disease-free survival, $p = 0.005$; overall survival, $p = 0.004$)

JAK2, *PD-L1*, and *PD-L2* is enriched in high-risk TNBC

- Our findings demonstrate that the PDJ amplicon is enriched in TNBC, targets signaling pathways that activate the PD-1 mediated immune checkpoint, and identifies patients with a poor prognosis.

- We propose that the PDJ amplicon provides a candidate biomarker for identifying high-risk patients and for advancing emerging immunotherapies in TNBC.

Barrett et al, Oncotarget, July 2015

Molecular insights to targeted therapeutics:

Developing precision power tools for oncologists

Recent advances to characterize and target the molecular pathology operating in aggressive subtypes of breast cancer and ovarian cancer.

- **Triple negative breast cancer**
- **Small cell ovarian cancer**

Small Cell Carcinoma of the Ovary of Hypercalcemic type (SCCOHT)

- Rare undifferentiated ovarian tumor affecting young women and girls (median age at diagnosis 23 years, youngest reported 14 months).
- 70% of cases have associated paraneoplastic hypercalcemia
- Highly aggressive extremely proliferative tumors typically diagnosed at an advanced stage
- All patients fail standard of care chemotherapy (platinum + taxane). Current treatment includes surgical debulking followed by multi-agent chemotherapy with or without radiation. Most have a transient response then rapid progression. No robust molecular evidence to direct targeted therapy.
- Prognosis is very poor, with 2-year survival rate < 35%
- The infrequency of SCCOHT has hindered empirical study of it's biology and clinical management.

Loss of SMARCA4 in SCCOHT

Inactivating mutations in the SWI/SNF chromatin remodeling gene *SMARCA4* with concomitant loss of SMARCA4 protein have recently been identified in SCCOHT. This breakthrough discovery is the first significant insight into the pathogenesis of this disease, and firmly establishes SMARCA4 as a tumour suppressor.

nature genetics

May 2014, Volume 46(5)

otago.ac.nz

Ramos *et al.*
Jeff Trent, David Huntsman, Heather Cunliffe
TGen, Phoenix AZ
University of British Columbia, Canada

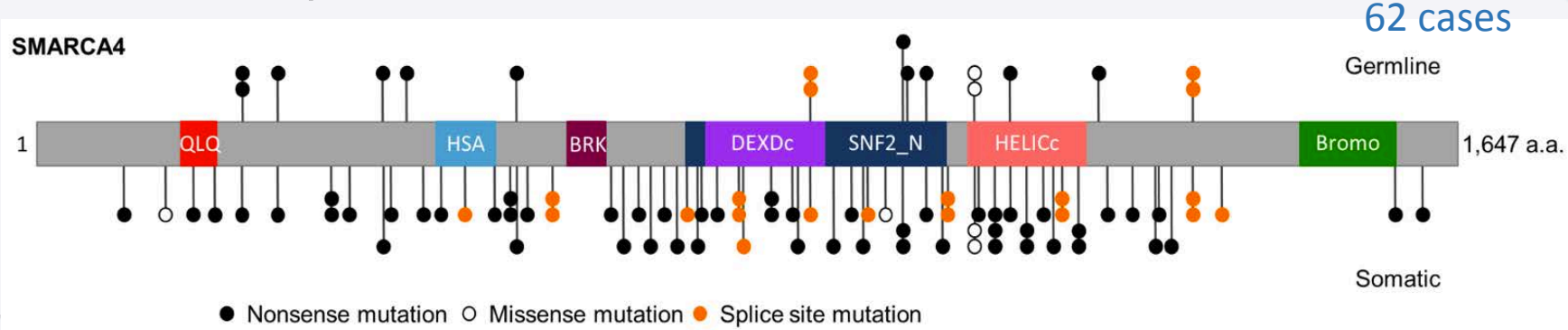
Jelinic *et al.*
Douglas Levine
Memorial Sloan-Kettering Cancer Center, New York, NY

Witkowski *et al.*
William Foulkes
McGill University, Montreal, Quebec, Canada

Loss of SMARCA4 in SCCOHT

- Across all published studies to date, mutations in *SMARCA4* have been identified in 64 of 69 cases including 2 cell lines (93%). Protein loss in 54 of 61 (89%) cases by IHC
- SMARCA4 protein loss was observed in only 2/485 (0.4%) of other primary ovarian tumors
- Loss of SMARCA4 is thus an important marker to aid in differential diagnosis of SCCOHT
- The majority of *SMARCA4* mutations are truncating, frameshift, deletion or splice-site mutations

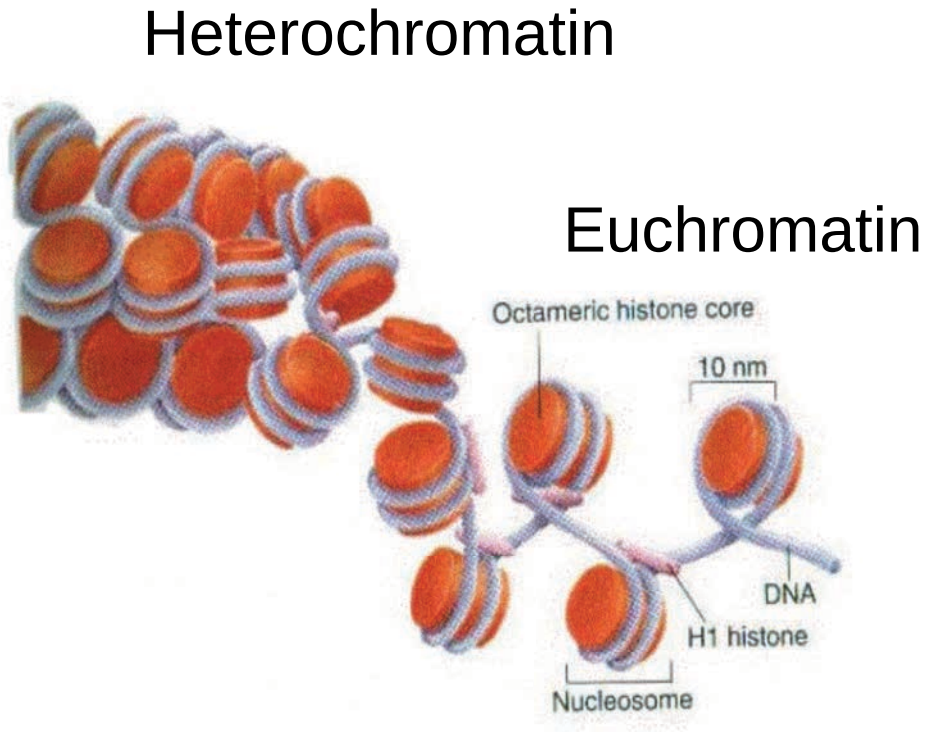
62 cases

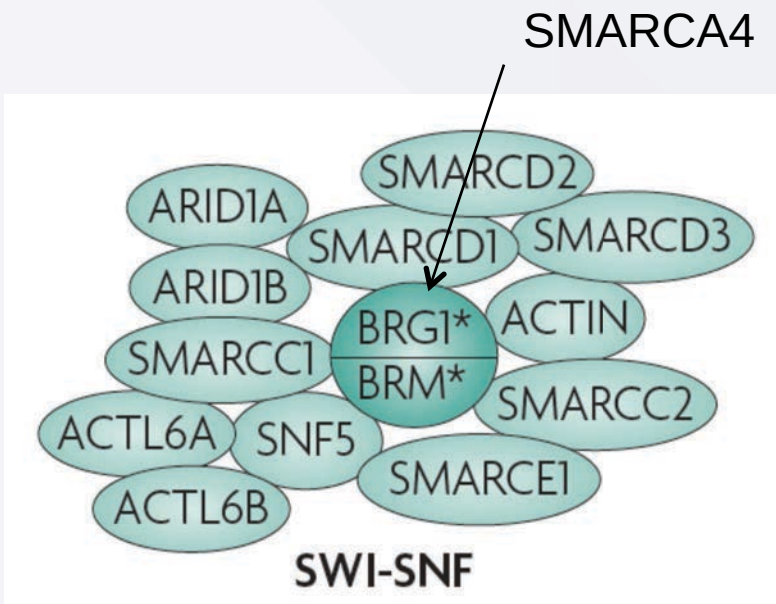


Ramos *et al*. (2014) OJRD. Nov 2014 Vol 2(1)

SMARCA4 and The SWI/SNF Complex

- SMARCA4 (BRG1) is a transcription factor with helicase and ATP activity.
- Part of the of the ATP-dependent chromatin remodeling complex SNF/SWI that remodel nucleosome structure. Allows dymanic access to packaged DNA, and transcriptional activation of genes normally repressed by chromatin.

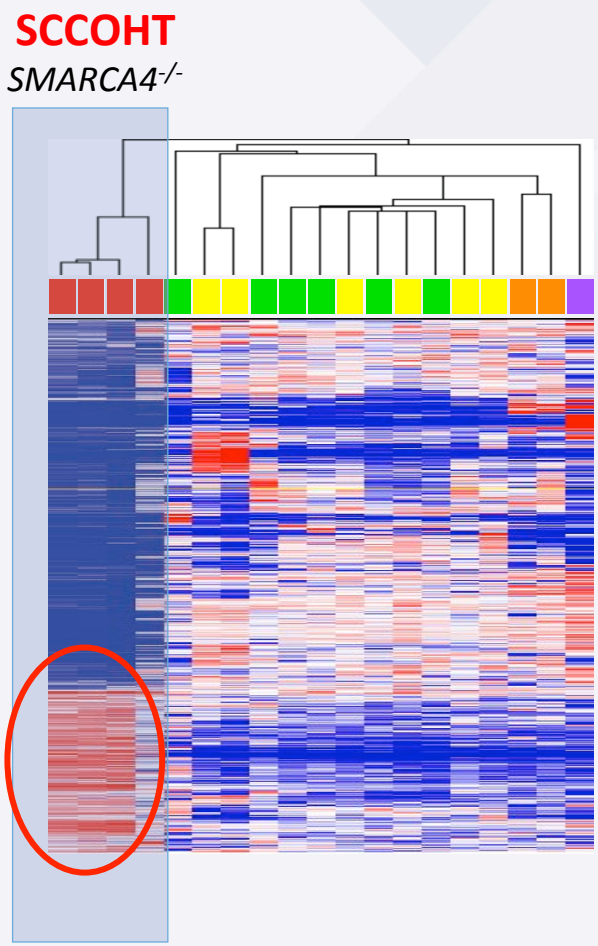




Review: You and Jones (2012), Cancer Cell 22, 9-20

SCCOHT transcriptome profiles reveal candidate tractable drug targets

- SCCO transcriptomes are strikingly distinct from epithelial ovarian cancer. The loss of normal SWI/SNF complex function appears reflected in the global transcriptome reprogramming
- Current studies are to elucidate how loss of SMARCA4 might constitute a key therapeutic vulnerability.



Genes uniquely and highly expressed in SCCOHT.

Why study rare tumors?

- Defining the molecular basis of rare tumours frequently sheds light on effective treatments in other tumour indications found to harbour a similar molecular aberration (converging on the same biology), and improves our fundamental understanding of all cancers.
- Rare tumors tend to have a more simple etiology (for example, retinoblastoma, angiosarcoma), which when understood can provide insight into the etiology of common, more complex cancers.

Genomics-Enabled Medicine

Discovery and knowledge of molecular alterations driving tumor progression → Improved clinical management and patient outcome

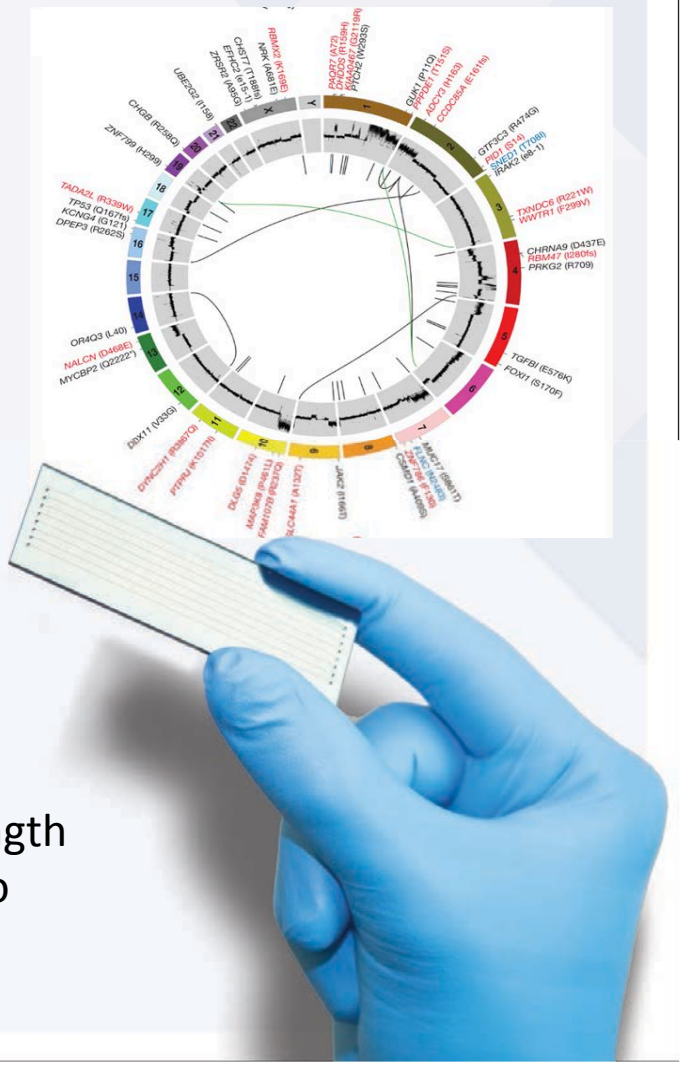
- Discovery of new drug targets
- Clinical trial design - patient stratification
- Knowledge based-therapeutic options

Use of genomic technologies is a rational approach to increase the “options” available to oncologists for treating cancer patients, namely those who fail standard of care with persistent, recurrent, drug-resistant disease.

Successful use of powerful technologies in cancer research requires access to high-quality biospecimens

"The lack of high-quality, clinically annotated human specimens is the #1 limiting factor for translational cancer research worldwide"

Carolyn C. Compton, M.D., Ph.D.
Director, Office of Biorepositories and Biospecimen Research, NCI



A significant area of strength at the University of Otago

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