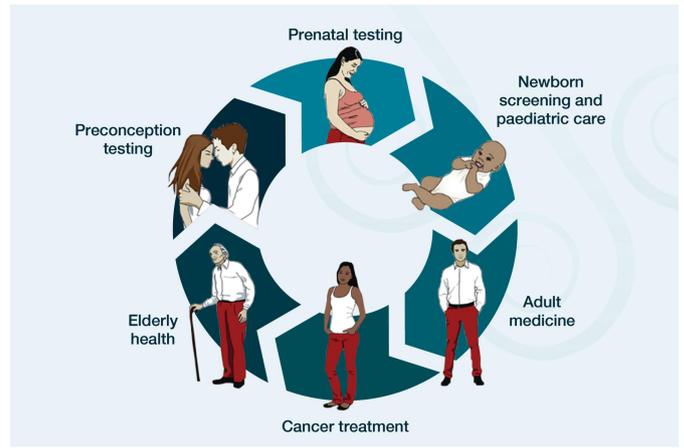
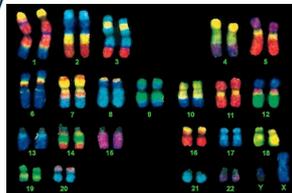


GENETICS AND BREAST CANCER

Dr. Erica Whineray Kelly



- Testing for genetic predisposition; Including partner selection
- Testing for cancer prognosis;
- Testing for cancer responsiveness to Rx;
- Using genetic technology to 'fix' mutations;
- Using genetic technology to treat.

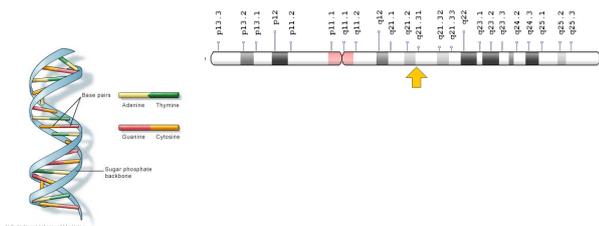


Testing for HBOC Risk

- BRCA1/2, PT53, PTEN
Highest risk of developing breast cancer (and other cancers)
Act for 25% of inherited breast cancers
- 1/800 BRCA carrier in population
1/40 Ashkenazi Jews
- Testing in unaffected member in a +ve family-risk/follow up/possible exclusion from high risk.

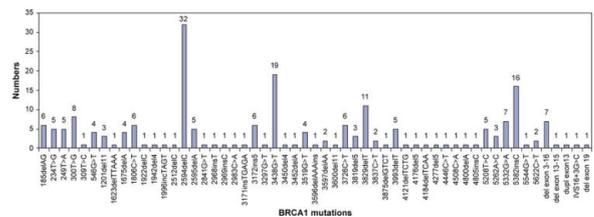
What does gene testing look like?

- e.g. BRCA 1 gene



- base pairs 43,044,295 to 43,125,483

Danish HBOC Families



Ashkenazi Jewish Testing

Table 3

Frequency of Recurrent Mutations in Ashkenazi Jewish Families

Gene [reference]	Mutation	Exon	Frequency in Jewish Population (%)
BRCA1[18]	185delAG	2	1.05%
	5382insC	20	0.11%
BRCA2[24]	6174delT	11	1.36%

- The 10 million AJ now are thought to descend from 350 individuals approximately 600- 800 years ago.

Other Founder Mutations

- Icelandic: BRCA1 G5193A BRCA2 999delE5
- Finnish: BRCA1 IVS1-2A=>G
- Dutch: BRCA1 large deletions
- Norwegian: BRCA1 1675delA and 1135insA
- Scottish/Irish: BRCA1 2800delIAA

HBOC Gene Testing

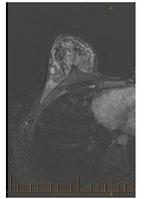
- Results: +ve or -ve on non-informative VUS- variation of unknown significance

- Often still rely on the FHx for basis of advice.



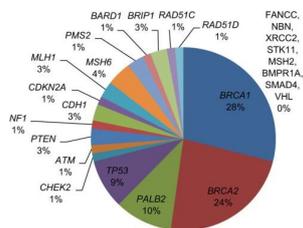
32 yrs Multifocal IDC

- Unilateral Grade 3 EP (-/+) but Her 2 +ve
- Father Polish Jew, No Fhx
- PreRx SNB & Portacath insertion
- Neoadjuvant chemotherapy
- BRCA founder mutations negative
- Bilateral NSMx, implant reconstruction
- pCR on EP- Her 2+
- Residual EP+ Her 2 +
- Completion Herceptin/ Tamoxifen

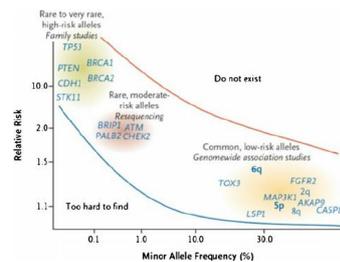


Multigene Assays

- Additional testing- 2.8%
- Similar cost? Driven by Pharma?
- Provides information for which there are no guidelines
- Causes anxiety with possible increase in over Tx and Rx.



Multigene Assays



Personal Genome Service™
Get to know your DNA. All it takes is a little bit of spit.

Here's what you do:

1. Order a kit from our online store.
2. Register your kit, spit into the tube, and send it to the lab.
3. Our CLIA-certified lab analyzes your DNA in 6-8 weeks.
4. Log in and start exploring your genome.

PATHWAY GENOMICS

There's DNA. And then there's what you do with it.

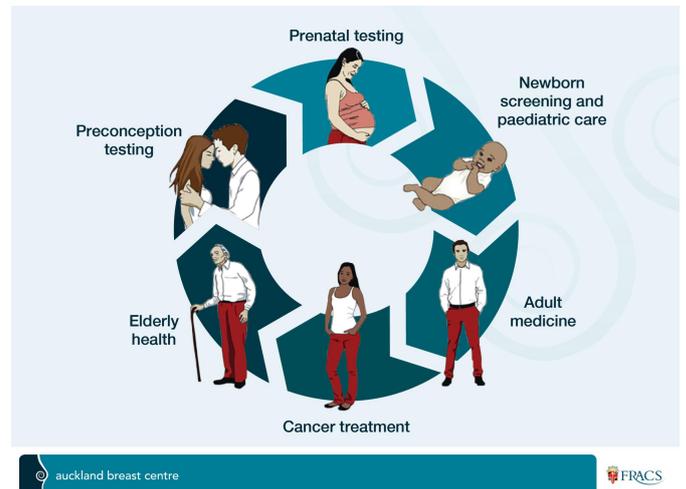
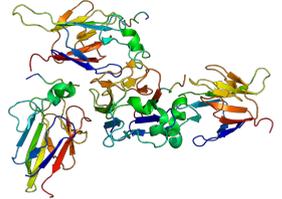
What your DNA says about you.
Find out things like if your body metabolizes caffeine quickly, or if you're at a higher risk for diabetes. The more you know about your DNA, the more you know about yourself.

- Carrier status**
Find out if your children are at risk for these conditions, so you can plan for the health of your family.
- Health risks**
Understand your genetic health risks. Change what you can, manage what you can't.
- Drug response**
Ask your doctor with information on how you might respond to certain medications.

23 Pairs of chromosomes. One unique you.

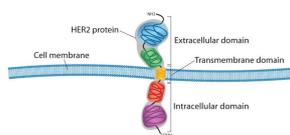
CHEK 2 Gene

- 32 year old Female living in NZ Polish grandmother
Incidental gene testing when admitted for a CVA
- CHEK2 mutation- family all alerted and scared!
- NO FAMILY HISTORY
- Rec: Routine screening from 40.



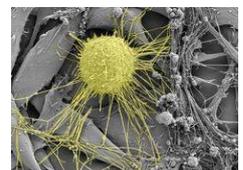
Cancer Assessment & Treatment

- Identify Targets e.g. Her 2 FISH test
- Decision on surgery
Breast conservation?
Contralateral Mx
- Molecular Genetic Assays
- Prognosis
- Response to treatment



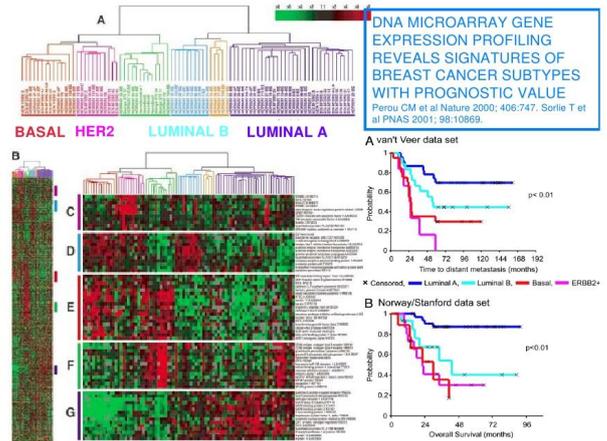
Molecular Assays

- Approximately 5,000 genes coding within a breast cancer
- 80-120 unique mutations
- 20 are prognostic

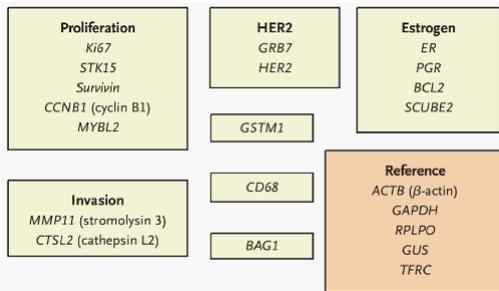


Molecular Assays

- Standard determination of prognosis: Type, Grade, Size, LN, E/P/Her 2, LVI
- Wrong in 20-30%
- Because it is more than ductal vs lobular...
- Aim: Prognosis
Treatment Response

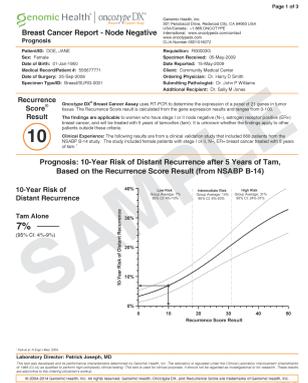


Molecular Assays

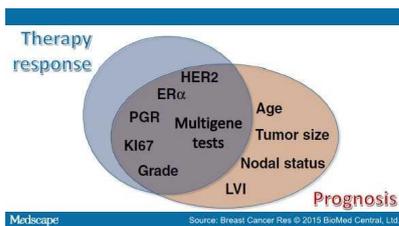


Oncotype Dx Report

- Varying LN status
- Useful in a small group of cases
- NICE UK



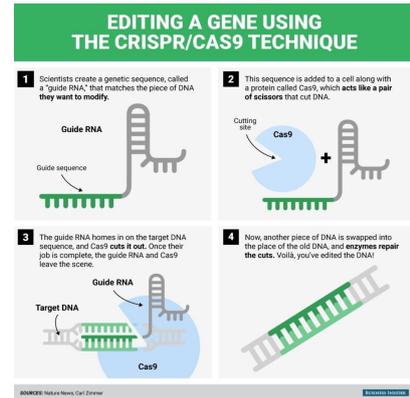
Molecular Assays



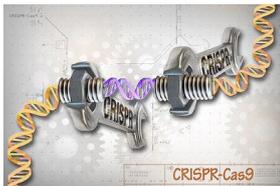
The Future

- CRISPR
-improve defence
-delete mutations
- Pre-gestational diagnosis

CRISPR

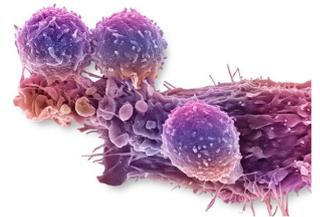


Back in Patent Court...



China Lung Cancer Trial 2016

- Took out T cells
- Removed PD-1 Gene which keeps immune response in check
- Re-insert 'supercharged' t-cell



The Future

- CRISPR on embryos?
- CRISPR on 'driving' genes within a cancer?
- Designer humans??



“ Recombinant DNA technology [genetic engineering] faces our society with problems unprecedented not only in the history of science, but of life on the Earth. It places in human hands the capacity to redesign living organisms, the products of some three billion years of evolution...It presents probably the largest ethical problem that science has ever had to face.”

*George Wald (1976)
Nobel Prize Biologist, Harvard*