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(Plenary)

11:50 - 12:15 New Genetic Technologies - Are They Relevant for Primary Care?

Clinical Genetics Group
*Te Rōpū Haumanu Iraka Takata*

# New Genetic Technologies – Are They Relevant for Primary Care?

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# New Genetic Technologies

Pushing themselves into primary care

- Disease Susceptibility and Resilience
  - direct to consumer tests
- Pharmacogenetics
- Non invasive prenatal screening
- Predictive risk scores
- Epigenetics

# 1. Individual genomic profiling for multiple health-related traits

## Direct marketing to the public and Primary Health Care Practitioners

Health

Relationships

Ancestry


Sporting ability

Pharmacogenetics

Nutrigenetics

"Genomic wellness"

Many tests offered online: "direct-to-consumer"

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# Direct to Consumer Testing

## Categories of Genomic Test

### Health related traits

- Penetrant Mendelian Diseases (includes carrier status)
- Common morbidities
- Pharmacogenetics
- Non invasive prenatal screening

### Lifestyle related factors

- Diet and food preferences
- Exercise regimens

(Traits exhibit complicated interactions between genes and environmental factors; Evidence is lagging behind provision of such testing)

### Ancestry

(Accuracy contingent on size and breadth of population databases)

# Direct to Consumer Testing

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# Direct to Consumer Testing

## The ground rules

- Patient initiates the test
- Patient controls and manages the data
- Patient often chooses a third party to interpret the data
- Information interpreters may not be accredited
- Test quality may be unregulated
- Multiple questions being asked by the customer
- Data may be sold for secondary use.

# Direct to Consumer Testing
# Categories of Genomic Test

## Health related traits

### 1. Penetrant Mendelian Diseases (includes carrier status)

BRCA1/2, haemochromatosis, α1-antitrypsin deficiency
carriers for cystic fibrosis….dozens of recessive diseases,

### 2. Common morbidities

Dementia, Parkinsons disease, type 2 diabetes, coronary artery disease

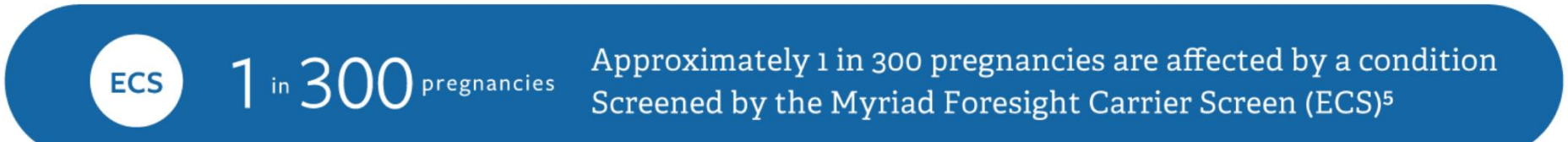
### 3. Pharmacogenetics

antithrombotics, anti-depressants, statins……

# Genetic testing

## Pre-conception genetic screening for mendelian disorders

- A burgeoning area facilitated by new genetic sequencing technologies
- Bewildering array of 7000 disorders - most being recessive
- All of us are carriers of some of these disease alleles - therefore individual screening problematic
- Couple screening being trialed in Australia for 1300 disorders
- Similar panels available via USA by commercial companies



# Preconceptual genetic screening

- The key issue is that residual risk remains

myriad WOMEN'S HEALTH

*Myriad Foresight® Carrier Screen Residual Risk Table*

| Disease (*gene*) | Carrier Frequency | Detection Rate | Residual Carrier Risk |
|---|---|---|---|
| **11-beta-hydroxylase-deficient Congenital Adrenal Hyperplasia (*CYP11B1*)**<br>NM_000497:1-9<br>Inheritance: Autosomal Recessive | Northwestern Europe: 1 in 220<br>Southern Europe: 1 in 220<br>Other Populations: 1 in 190 | Northwestern Europe: 94%<br>Southern Europe: 94%<br>Other Populations: 94% | Northwestern Europe: < 1 in 3,800<br>Southern Europe: < 1 in 3,800<br>Other Populations: < 1 in 3,300 |
| **21-hydroxylase-deficient Congenital Adrenal Hyperplasia (*CYP21A2*)**<br>I173N, V282L, R357W, P31L, c.293-13C>G, G111VfsX21, Q319*, L308FfsX6, CYP21A2 deletion, CYP21A2 duplication, Q319*+CYP21A2dup, [I237N;V238E;M240K], CYP21A2 triplication<br>Inheritance: Autosomal Recessive | African American: 1 in 120<br>Ashkenazi Jewish: 1 in 58<br>Eastern Asia: 1 in 72<br>Finland: 1 in 58<br>French Canadian/Cajun: 1 in 58<br>Hispanic: 1 in 56<br>Middle East: 1 in 42<br>Native American: 1 in 56<br>Northwestern Europe: 1 in 58<br>South Asia: 1 in 42<br>Southeast Asia: 1 in 59<br>Southern Europe: 1 in 58 | African American: 92%<br>Ashkenazi Jewish: 99%<br>Eastern Asia: 88%<br>Finland: 89%<br>French Canadian/Cajun: 96%<br>Hispanic: 95%<br>Middle East: 97%<br>Native American: 90%<br>Northwestern Europe: 96%<br>South Asia: 89%<br>Southeast Asia: 88%<br>Southern Europe: 96% | African American: < 1 in 1,400<br>Ashkenazi Jewish: < 1 in 5,700<br>Eastern Asia: < 1 in 590<br>Finland: < 1 in 530<br>French Canadian/Cajun: < 1 in 1,400<br>Hispanic: < 1 in 1,100<br>Middle East: < 1 in 1,200<br>Native American: < 1 in 550<br>Northwestern Europe: < 1 in 1,400<br>South Asia: 1 in 360<br>Southeast Asia: 1 in 480<br>Southern Europe: < 1 in 1,300 |
| **6-pyruvoyl-tetrahydropterin Synthase Deficiency (*PTS*)**<br>NM_000317:1-6<br>Inheritance: Autosomal Recessive | Eastern Asia: 1 in 350<br>Middle East: 1 in 45<br>Other Populations: < 1 in 500 | Eastern Asia: 99%<br>Middle East: 99%<br>Other Populations: 99% | Eastern Asia: < 1 in 35,000<br>Middle East: < 1 in 4,400<br>Other Populations: < 1 in 50,000 |
| **ABCC8-related Familial Hyperinsulinism (*ABCC8*)**<br>NM_000352:1-39<br>Inheritance: Autosomal Recessive | Ashkenazi Jewish: 1 in 45<br>Eastern Asia: 1 in 140<br>Finland: 1 in 100<br>Middle East: 1 in 140<br>Other Populations: 1 in 170 | Ashkenazi Jewish: 99%<br>Eastern Asia: 99%<br>Finland: 99%<br>Middle East: 99%<br>Other Populations: 99% | Ashkenazi Jewish: < 1 in 4,400<br>Eastern Asia: < 1 in 14,000<br>Finland: < 1 in 10,000<br>Middle East: < 1 in 14,000<br>Other Populations: < 1 in 17,000 |
| **AMT-related Glycine Encephalopathy (*AMT*)** | | | |

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# Preconception screening for mendelian disorders - is there a middle ground?

- "Prepair" test - Melbourne-based Victorian Clinical Genetics Services
- Tests for three of the more common (but still rare) genetic disorders:

| | Number of people who are carriers | Number of people with the condition |
|---|---|---|
| Cystic fibrosis | 1 in 25 | 1 in 2500 |
| Fragile X syndrome | 1 in 250 | 1 in 4000 |
| Spinal muscular atrophy | 1 in 40 | 1 in 6000 - 1 in 10,000 |

- Blood or saliva - requires physician ordering

https://www.vcgs.org.au/tests/prepair

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# Non Invasive Prenatal Screening (NIPS)

- Cell-free placental (= fetal) DNA fragments in maternal plasma
  - Present from around 5/40
  - Short half life, clears within an hour of birth
  - Will replace current prenatal screening for trisomies 13, 18 and 21
  - c.$600 currently

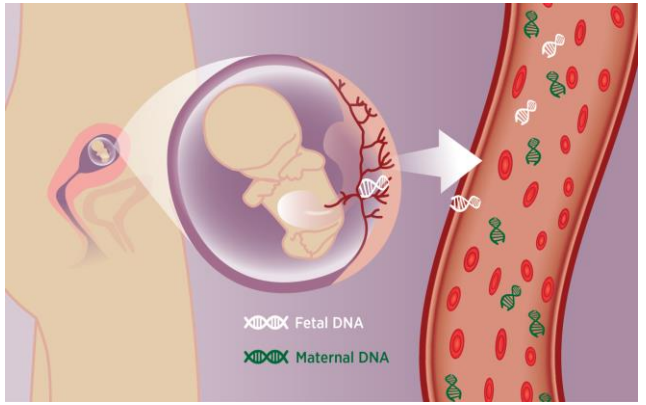


Figure courtesy of Gendia, Belgium

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# With access to the fetal genome what can be tested for?

- Aneuploidy - Down syndrome (and other rare aneuploidies), sex chromosome anomalies
- Fetal sex
- Microdeletions and duplications
- (rhesus status)
- (*de novo* dominant disorders/paternally inherited dominant disorders)

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# Providers of NIPT offer all these as options

NIPT performs differently for different indications - choose carefully

1. Down syndrome (similar for trisomy 13/18)
   - Excellent for excluding the disorder
   - Invasive testing still needed for positive screen results
2. Sex chromosome anomalies (Turner syndrome, Klinefelter syndrome)
   - Pre-test counselling is key re. these phenotypes
   - Does your consultand really want to test for them?
   - Severity can't be predicted for many/most instances.
3. Private chromosomal anomalies
   - Rare, interpretation/prognostication often difficult

# Outcomes and Results - common scenarios - 1
# Common Disorders

**Products that screen for variants statistically associated with disease states**

**Tens, if not hundreds of variants for each disease; each individually weak**

**Tests only measure a few**

**Estimates of risk that they confer vary wildly between providers**

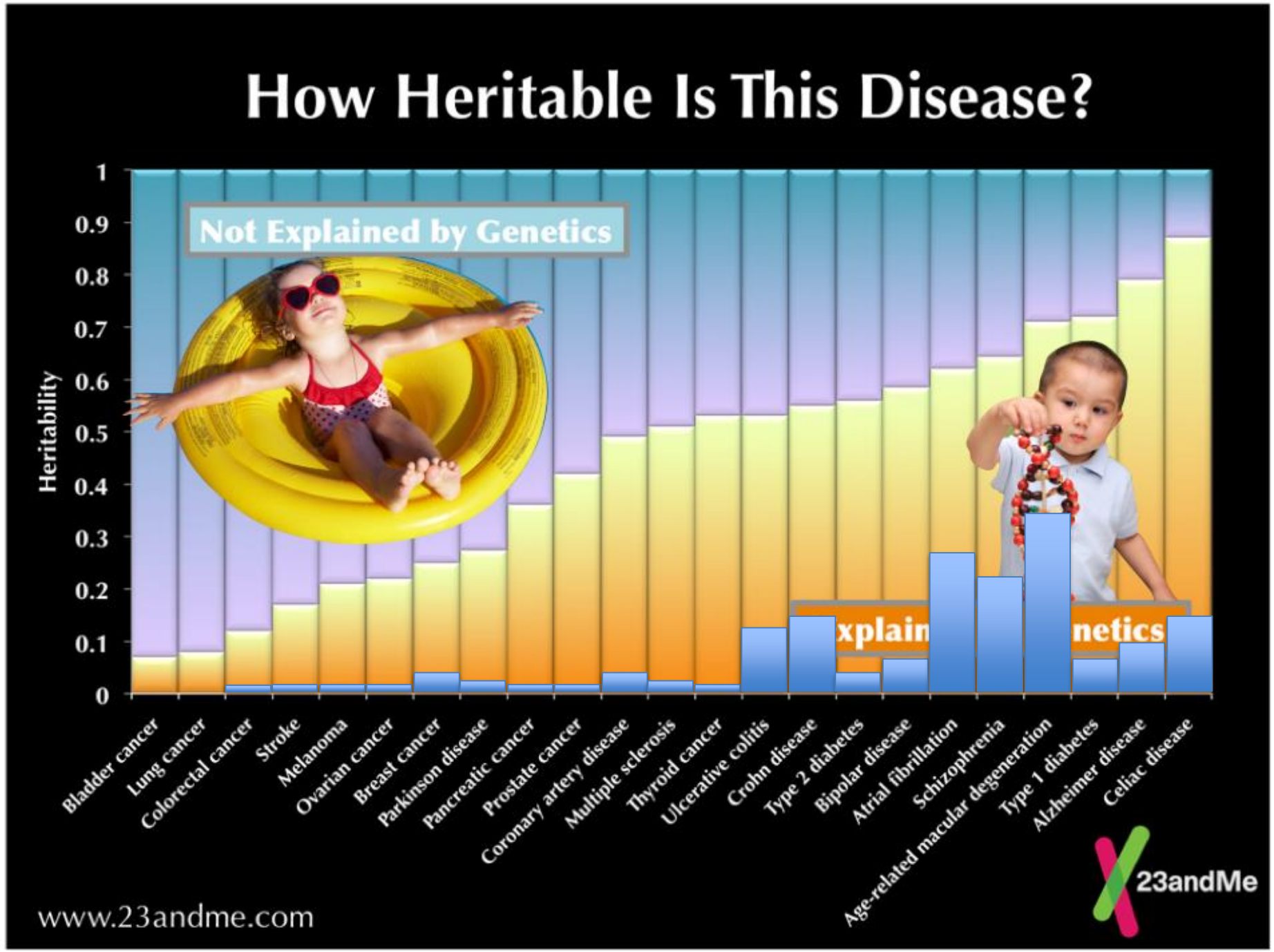
**Traits:**

- Diabetes
- Heart disease
- Cancer susceptibility
- ……..

**A few tests are useful:**

- Coeliac disease (for exclusionary purposes)
- Macular degeneration (especially if family history)

# How Heritable Is This Disease?



# Common Morbidities

## Patients seeking a "genetic warrant of fitness" for the big killers

(typical examples: Parkinsons, Alzheimer)

- Summed genetic contributions to these diseases **are large**
- Named explanatory genetic factors **are few**
- Tests measure a very small number of these factors
- Each genetic variant typically has a weak effect
- These results report **very small increases in absolute risk**
- Some tests have little evidence for clinical validity (e.g. *MTHFR* variants for miscarriage, vascular disease, thrombophilia).

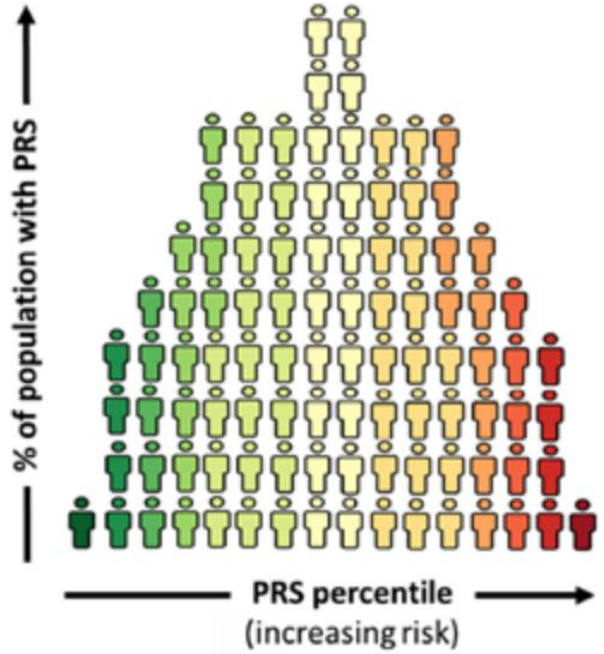
# Polygenic risk scores

## The ultimate answer?

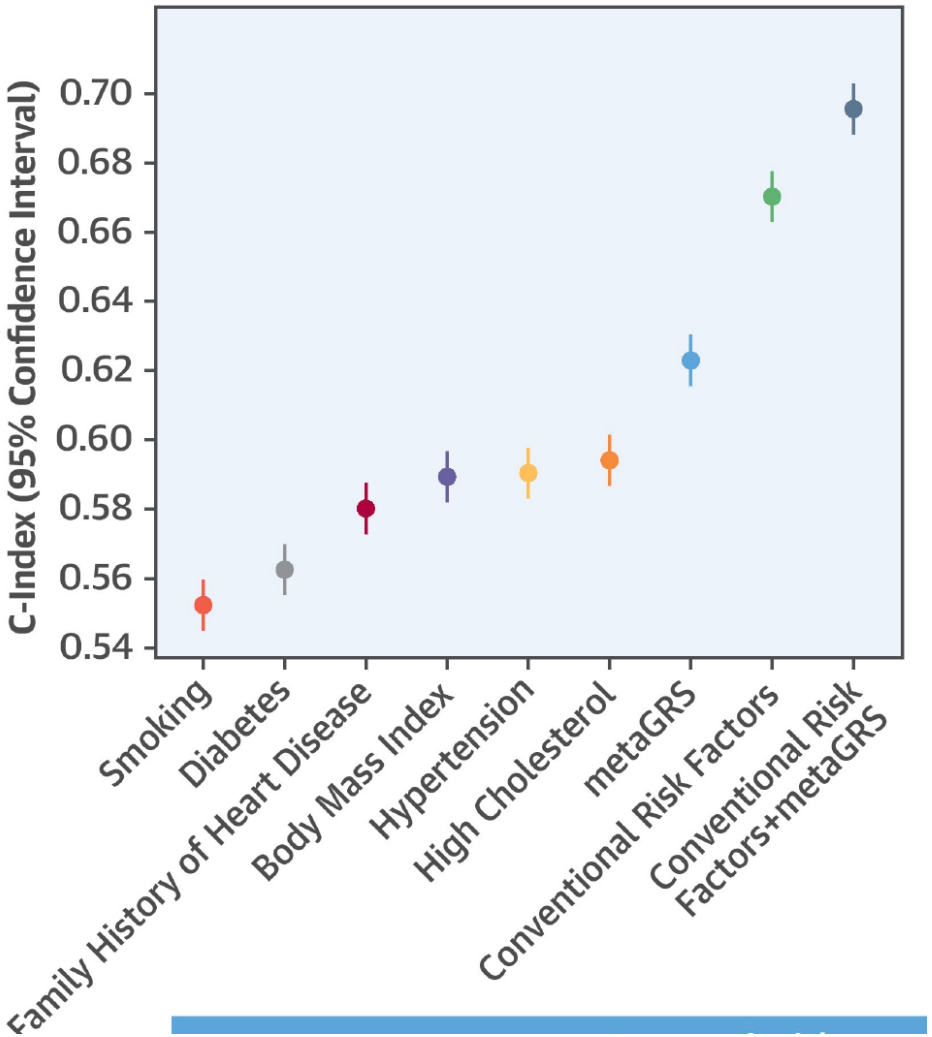
Figure 2 - Polygenetic

| PRS percentile | Risk of disease vs. reference group |
|---|---|
| 0-1 | Lowest |
| 1-5 | |
| 5-10 | |
| 10-20 | |
| 20-40 | |
| **40-60 (reference)** | **1** |
| 60-80 | |
| 80-90 | |
| 90-95 | |
| 95-99 | |
| 99-100 | Highest |

*Source: RGA*



# Polygenic risk scores - Performance




Inouye et al 2018

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# Pharmacogenetics

**Table 1**

Actionable germline genetic variation and associated medications

| Genetic Variation | Medication |
|---|---|
| *TPMT* | mercaptopurine, thioguanine, azathioprine |
| *CYP2D6* | codeine, tramadol, tricyclic antidepressants |
| *CYP2C19* | tricyclic antidepressants, clopidogrel, voriconazole |
| *VKORC1* | Warfarin |
| *CYP2C9* | warfarin, phenytoin |
| *HLA-B* | allopurinol, carbamazepine, abacavir, phenytoin |
| *CFTR* | Ivacaftor |
| *DPYD* | fluorouracil, capecitabine, tegafur |
| *G6PD* | rasburicase |
| *UGT1A1* | irinotecan, atazanavir |

Relling and Evans (2015)

# The evidence behind actionability

- **Warfarin** – conflicting studies of clinical utility
  - *CYP2C9, VKORC1*

  Ancestry specific effects clear
- **Carbamazepine** - hypersensitivity (risk ~10%)
  - *HLA-A*31:01 (*NNT caucasian 47)
  - *HLA-B*15:02* Toxic epidermal necrolysis in SE Asians
- **Clopridogel**
  - variants that confer loss and gain of function
  - LoF alleles common ++ in Maori and Pacific Islanders ➔ clinical in-efficacy (as judged by in vitro platelet assays)
  - a priori case for pharmacogenomics in clinical practice
  - Still requires systematic clinical evaluation

# Pharmacogenetics

## What is just around the corner?

Statins

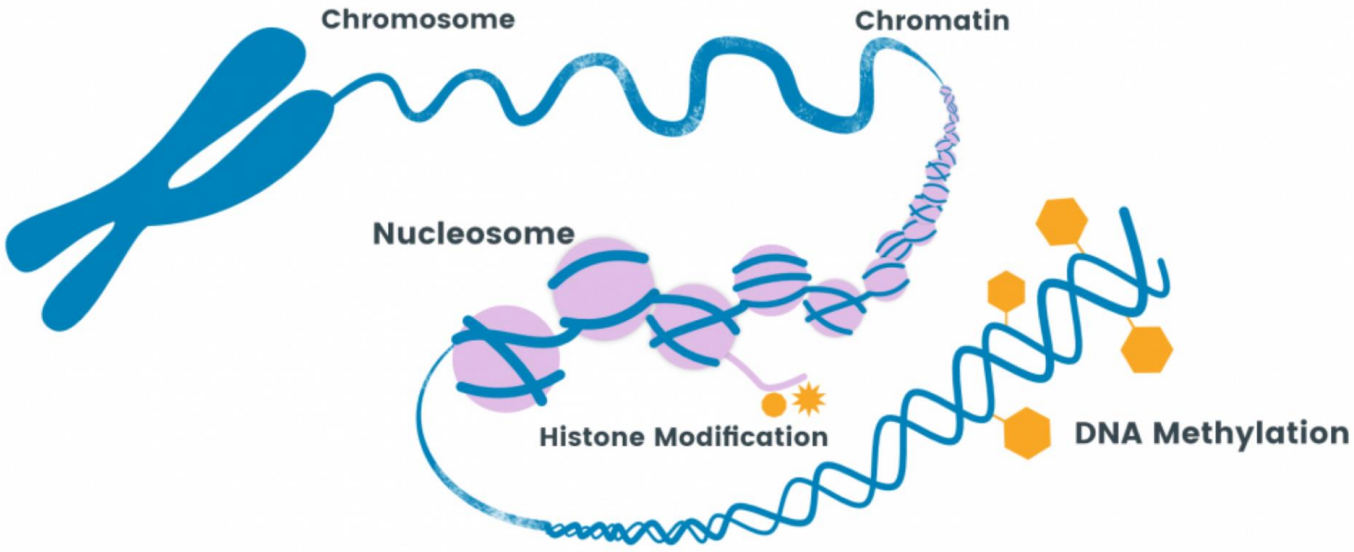
Antidepressants

Psychotropics

The Caveats for NZ Practitioners: Applicability to Māori

# Epigenetics - the great promise?

The chemical modification of DNA
Alters/regulates gene function
A readout of gene x environmental exposures




**The problems**

Many epigenetic marks are tissue specific
It is a continuous readout, not a binary one
Expensive to measure

# Will the market improve?

Consumer driven testing with health professional involvement

A litmus test question to ask:

Is the genetic test I am interested in available through any mainstream health system globally for someone in my clinical situation?

If so, is cost the barrier? - good wrap-around options are available

If not: Does the offering fail on validity and utility grounds?

# State of play - genetic technologies in primary care

- DTC genetic factors conferring disease susceptibility and resilience

Most explain very little evidential risk but can act as a motivating tool, enhance self awareness etc

- Pharmacogenetics

The dawn is here. Some practice ahead of the evidence. Risk of inequity in NZ

- Non invasive prenatal screening

Requires more wrap around support and counseling than is on offer. Tests perform very well; patient comprehension key

- Predictive risk scores

For some traits, some promise. Add marginal benefit to susceptibility prediction

- Epigenetics

Technical practicalities inhibit clinical use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