Genetics for GPs:

Pathology, Genetic Counselling & Genomic Equity

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Deadly Doctors FORUM 2026

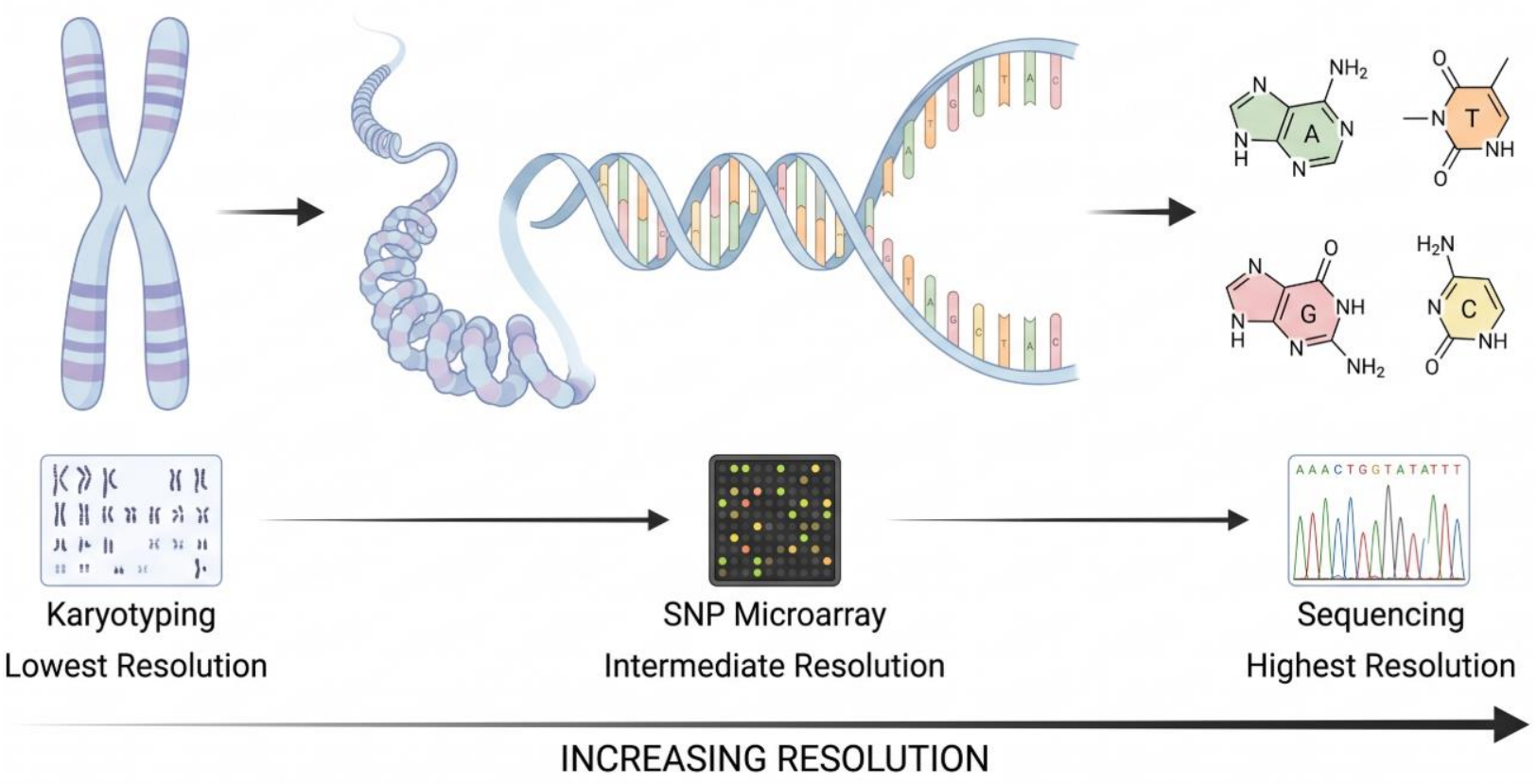
I acknowledge the Traditional Custodians of the land on which we meet today, the Gweagal, Bidjigal and Gadigal People, and pay respect to the people, the culture, and Elders past and present.

Overview

- **Common types of genetic testing**
  1. Karyotype
  2. Chromosomal microarray
  3. Sequencing
     - Targeted sequencing
     - Whole exome sequencing (WES)/Whole genome sequencing (WGS)

- **Genetics and precision medicine**
  1. Somatic testing
  2. Pharmacogenomics (PGx)

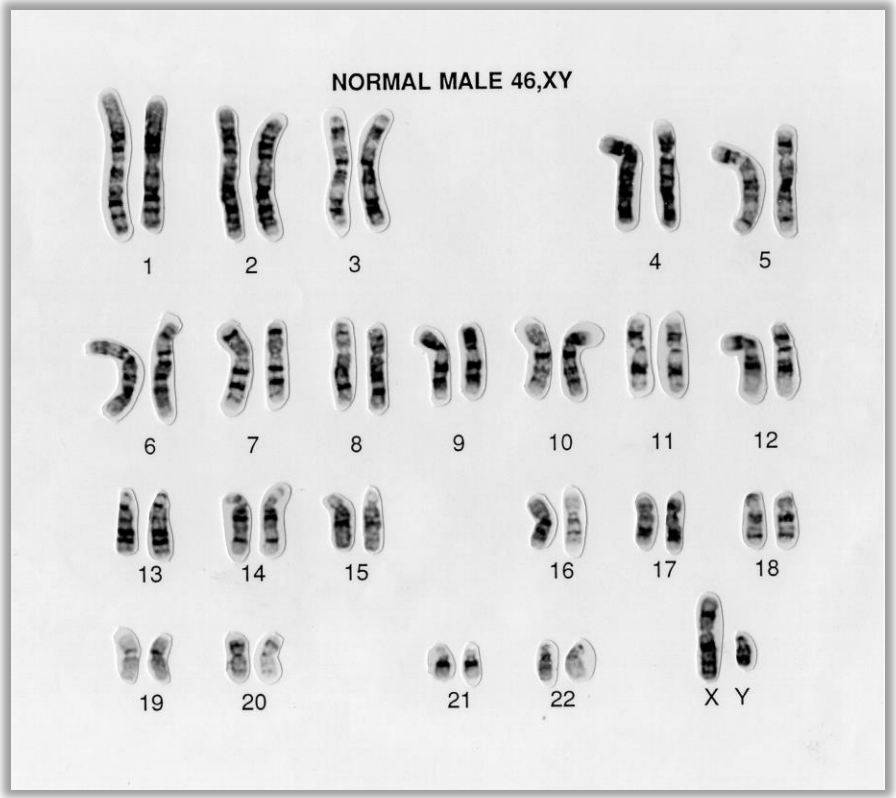
Common Types of Genetic Testing


A
T
G
C
AAACTGGTATATTT
Karyotyping
Lowest Resolution
SNP Microarray
Intermediate Resolution
Sequencing
Highest Resolution
INCREASING RESOLUTION

Karyotype: overview

- Used to visualise chromosomes
- Time intensive process that requires cell culture

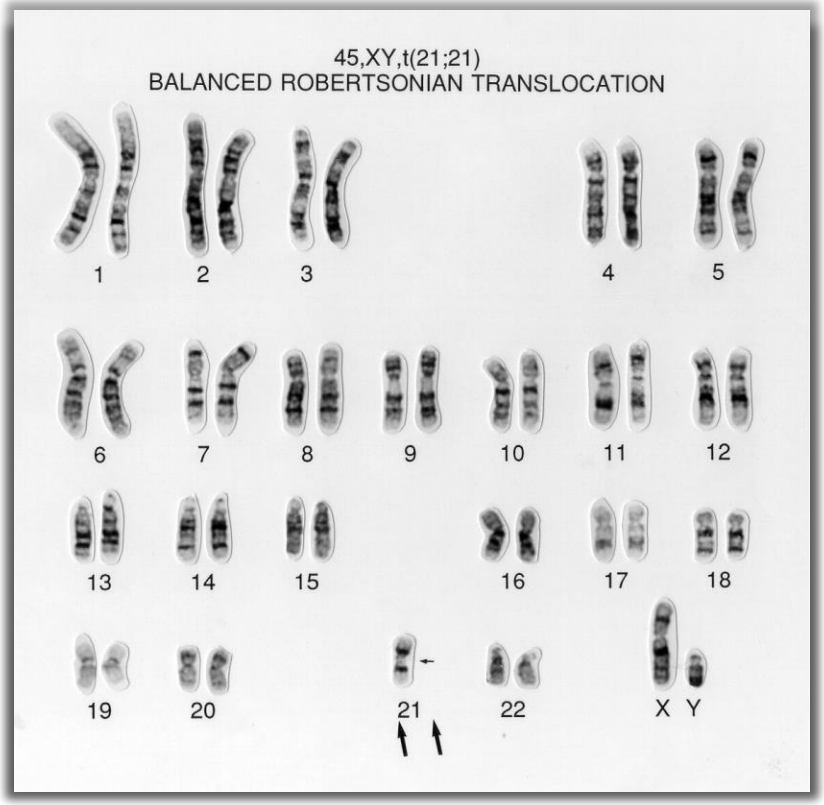
- Can be performed in multiple contexts using a variety of sample types:
  - Constitutional testing (blood, skin)
  - Prenatal testing (chorionic villi, amniotic fluid)
  - Oncological testing (bone marrow)



Karyotype: what can it detect?

1. Useful for identifying **whole chromosome changes**
   - Trisomy/monosomy
   - Sex chromosome aneuploidy - X0, XXY, XYY, etc.

2. Can also identify **structural chromosomal rearrangements**
   - Translocations, inversions, ring chromosomes, etc.
   - Balanced carriers are usually unaffected



Karyotype: limitations

- Cannot detect:
  - Small chromosomal deletions/duplications (e.g. microdeletion, microduplication syndromes)
  - Sequence changes (single nucleotide variants)

Karyotype: when to order



Recurrent miscarriage and/or infertility

?balanced translocation, inversion, extra chromosomal material, etc.



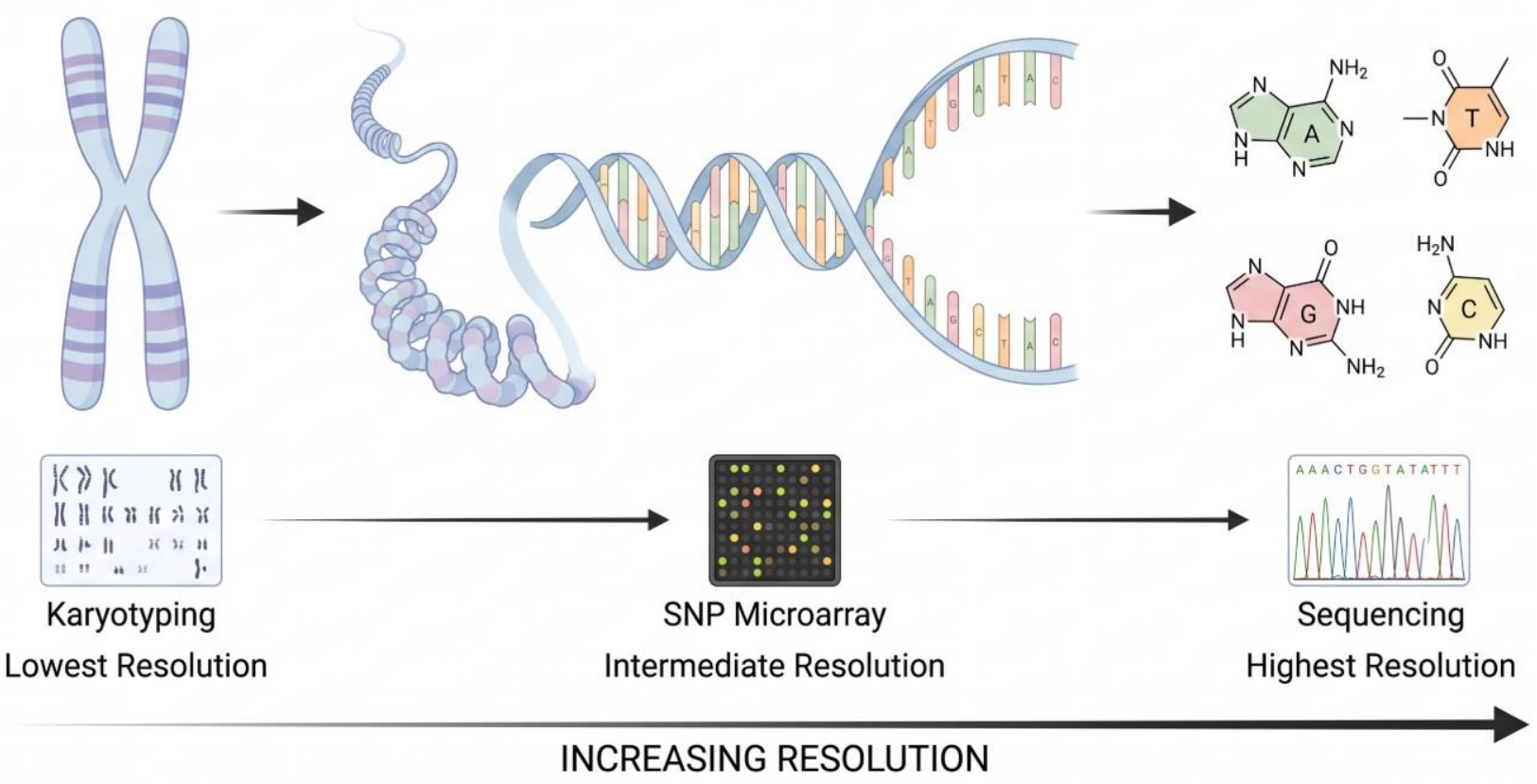
Previous pregnancy with **T13**, T14, T15, **T21** or T22 in fetus

?Robertsonian translocation



To investigate for a constitutional genetic condition

Microarray used more commonly than karyotype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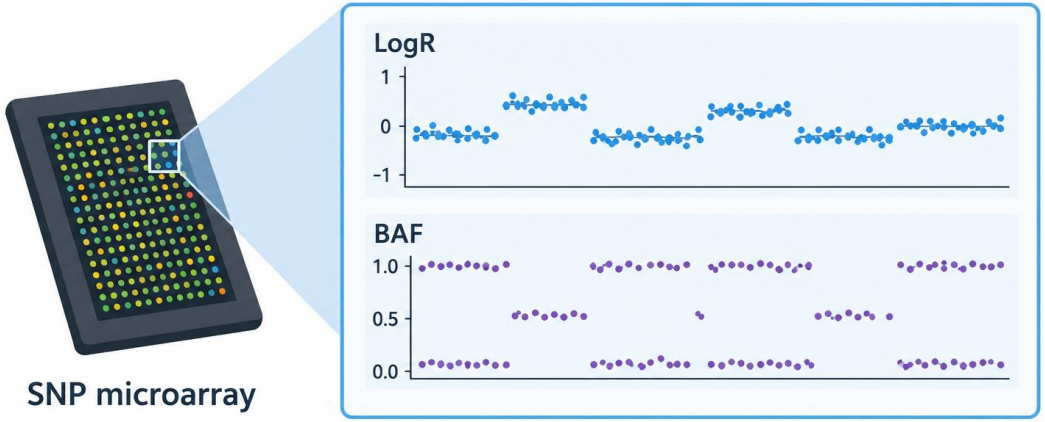
Microarray: overview

Also known as CMA, SNP array, array, and (previously) CGH array

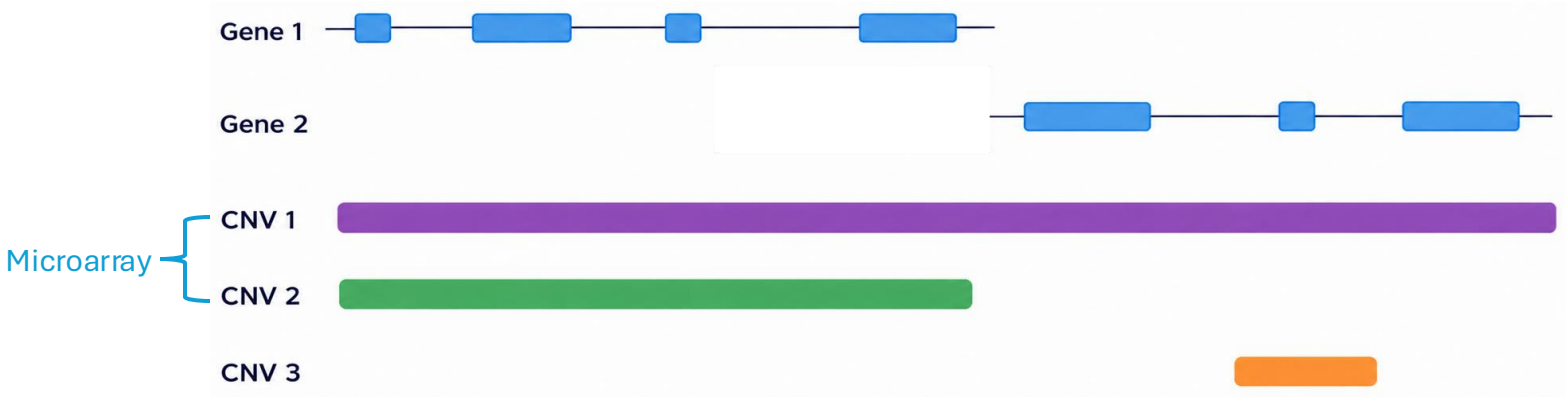
- Genomic technique for visualisation of chromosomes
  - Computer based visualisation
  - Genome-wide assessment of copy number with thousands of probes
- Can be used in many contexts similar to karyotyping
  - May replace karyotyping in some settings



SNP microarray

Microarray: what can it detect?

- Can detect chromosomal gains and losses, including **whole chromosome events** and copy number variants (CNVs)



- Much better resolution than karyotype
  - Can detect microdeletion or microduplication syndromes, e.g. 22q11.2 deletion/duplication syndrome

Microarray: limitations

- Cannot detect:
  - Balanced changes
  - Structural chromosome changes – but usually indicative → proceed to karyotype
  - Sequence changes

Microarray: when to order



Prenatal testing

High probability NIPT/cFTS, atypical ultrasound findings



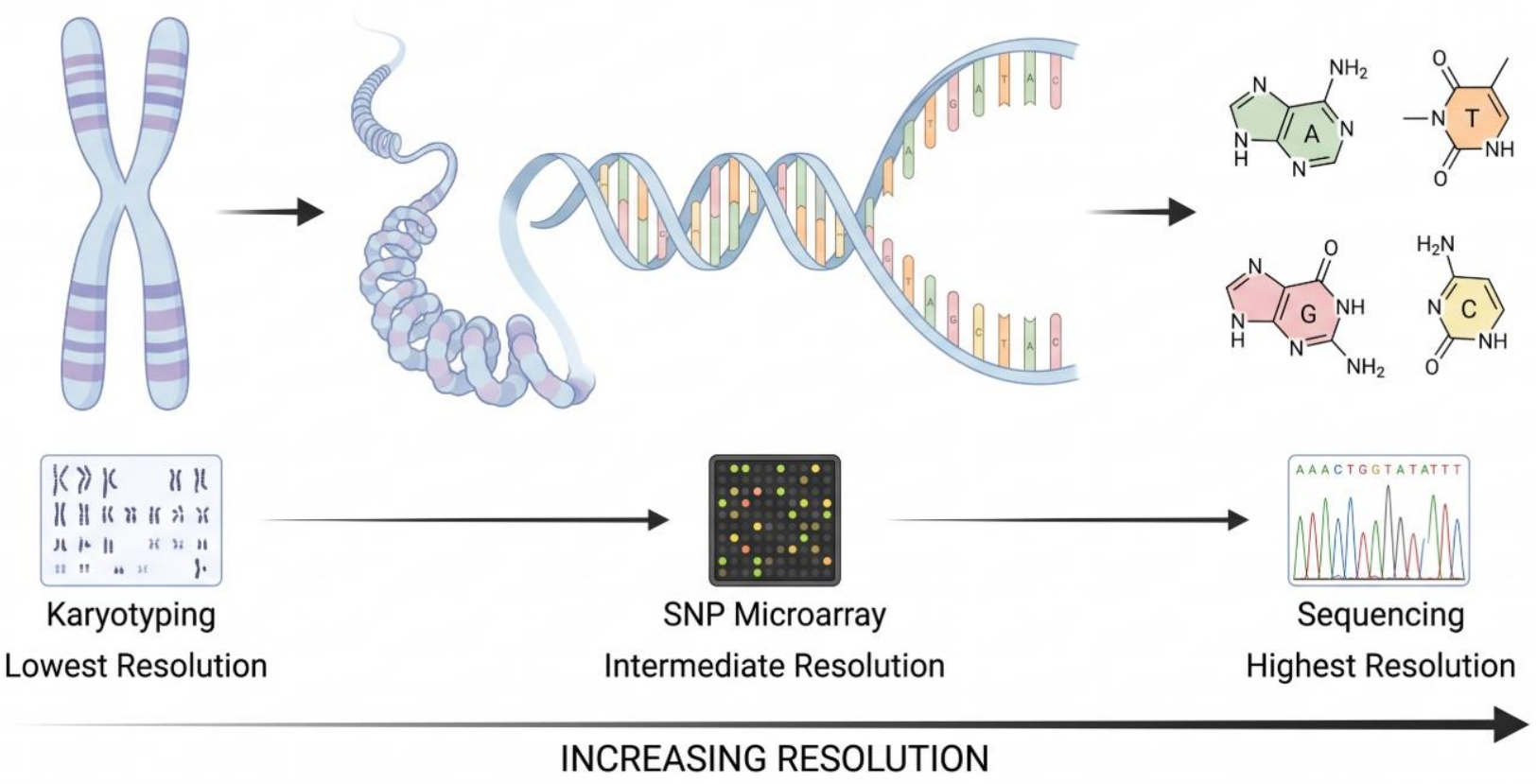
Paediatric testing

Developmental delay, intellectual disability, or autism



Constitutional testing

Presence of congenital anomalies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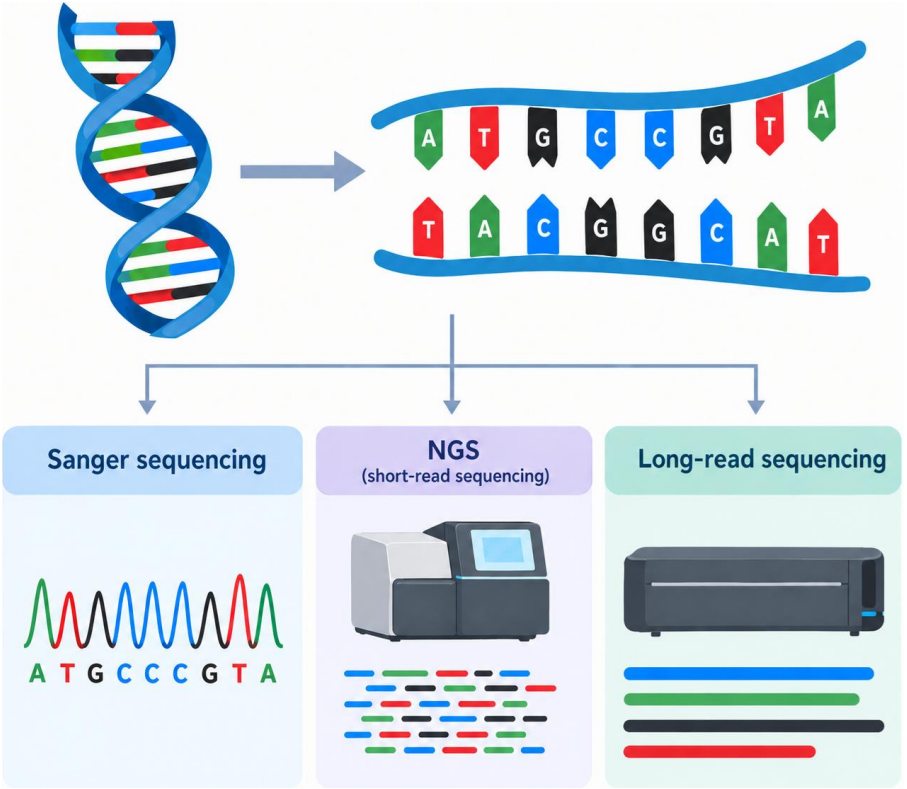
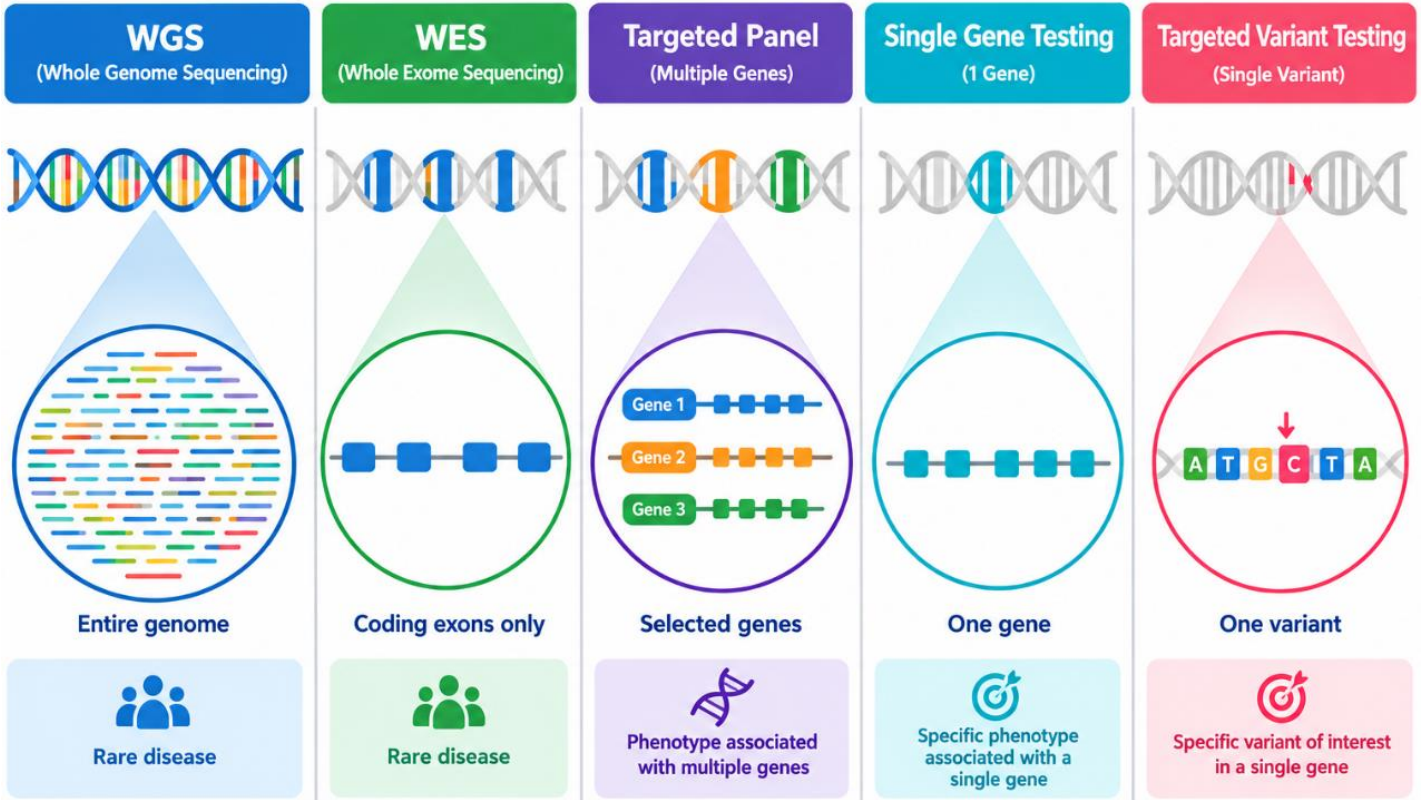
Sequencing: overview

- Highest resolution of genetic testing
  - Interrogation of the DNA sequence itself – C, G, A, T

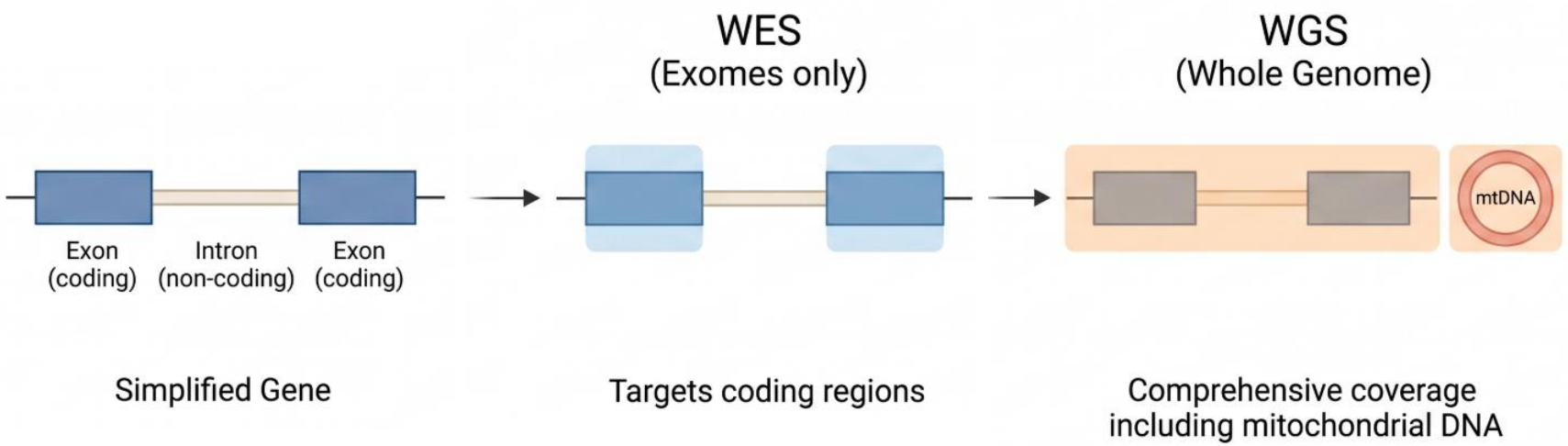
- Multiple different technologies can be used, e.g. Sanger sequencing, NGS, etc.



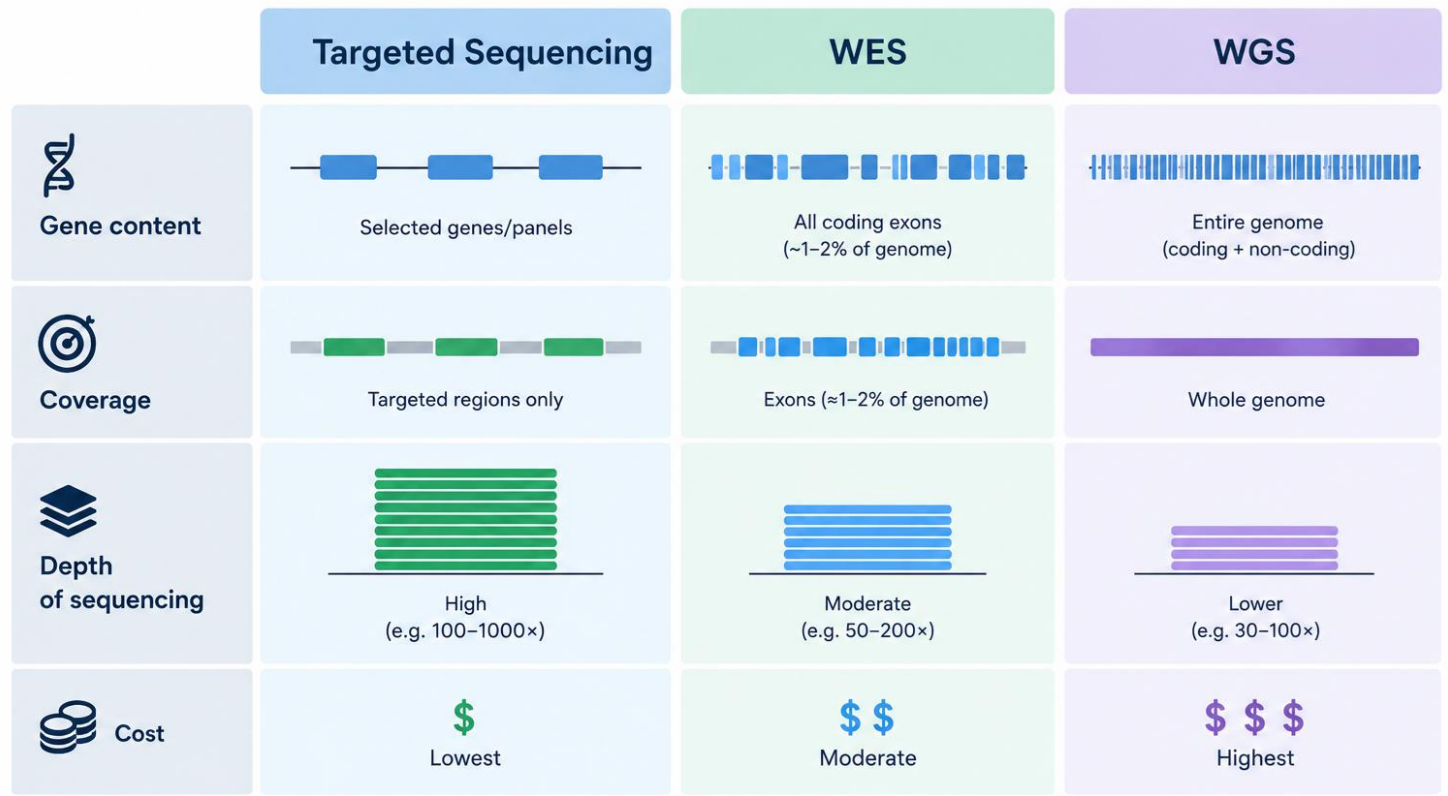
Sequencing: approach



Sequencing: approach (WES vs WGS)



Sequencing: approach



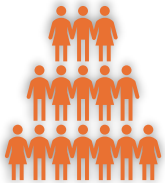
Sequencing: limitations

- Panels
  - Will not detect variants in genes outside the panel
- Whole exome sequencing
  - Will not detect variants outside of the coding regions

- Other types of genetic mechanisms may not be detected
  - Structural variants
  - Repeat expansions
  - CNVs

} Dependent on technology used

Sequencing: when to order



Predictive testing

Family history of a genetic condition

MBS rebate available for some indications



Prenatal testing

Atypical ultrasound findings

No MBS rebate (MSAC application pending)



Paediatric testing

Rare disease, ID

MBS rebate available for some indications

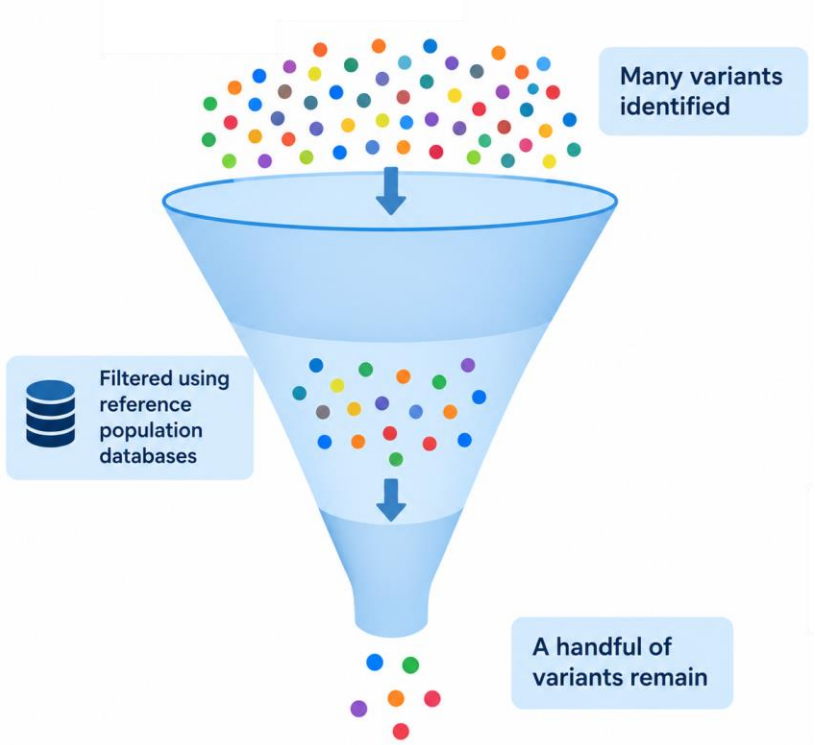


Constitutional testing

Various indications depending on phenotype

MBS rebate available for some indications

Indigenous genomics and NGS



- Each ancestral ethnic group has unique genomic variation including Aboriginal and Torres Strait Islander peoples
- Underrepresented in reference population databases and genomic studies
- This has significant implications for both rare disease genetics and cancer genetics

Indigenous genomics and NGS

	gnomAD v4*	
	Sample count	%
Admixed American	30,019	3.72%
African/African American	37,545	4.65%
Ashkenazi Jewish	14,804	1.83%
East Asian	22,448	2.78%
European^	622,057	77.07%
Middle Eastern	3,031	0.38%
Remaining^	31,712	3.93%
South Asian	45,546	5.64%
Total	**807,162**	-

Summary

- Numerous types of genetic tests exist beyond karyotyping, microarray and NGS
- Many of the specialised tests are currently ordered by clinical geneticists or relevant specialists
  - This will change over time with mainstreaming
- Choosing the right test for the clinical indication is important
- If in any doubt about what to order or what the correct test is, please ask the testing laboratory!

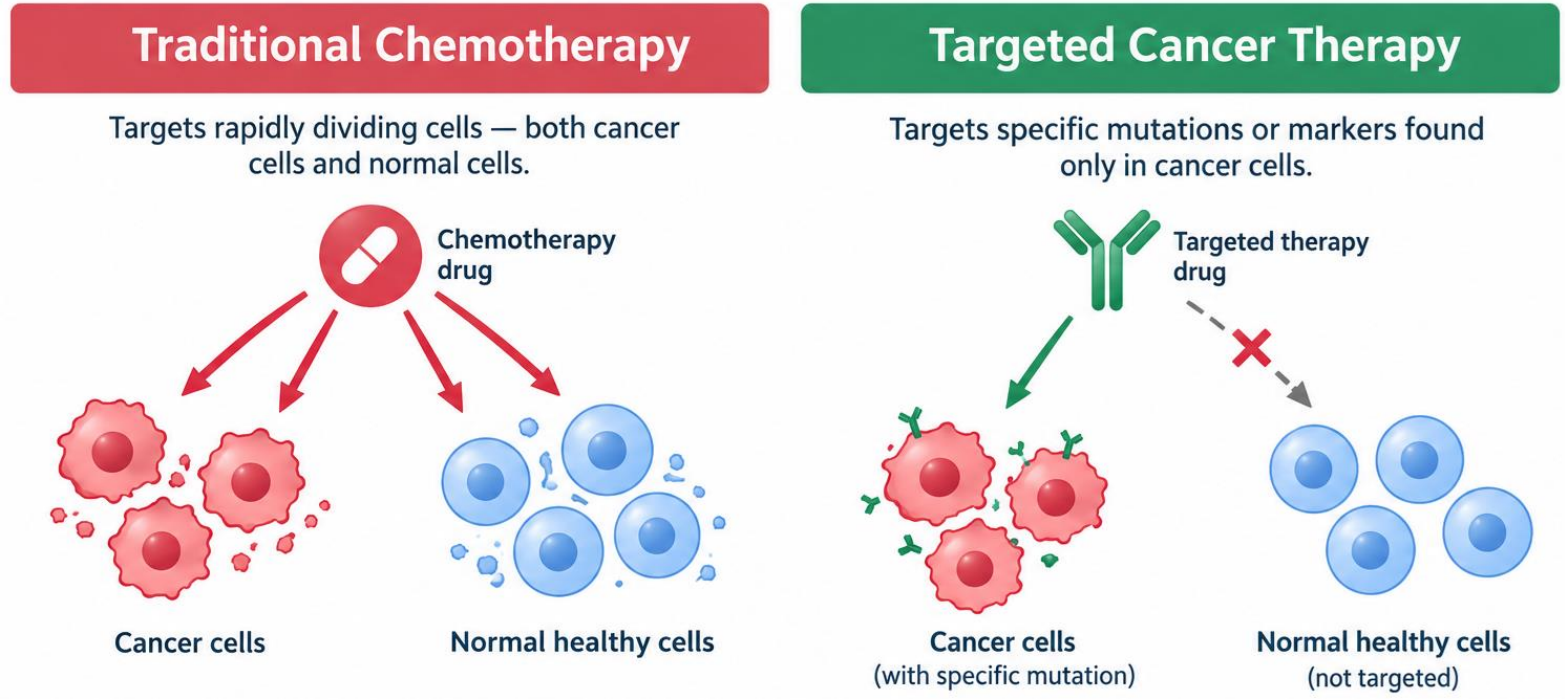
Genetics and Precision Medicine

Precision medicine: overview

- Individualised or personalised medicine
- Treatments are specifically tailored for the patient based on their genetic makeup
  - Traditional methods take a one size fits all approach

- Genetics:
  1. Targeted cancer therapies
  2. Pharmacogenomics (PGx)

Targeted cancer therapies



Targeted cancer therapies



BRCA+ breast Ca → treatment with PARP inhibitors, e.g. Olaparib



KRAS G12C+ CRC→ treatment with specific mutation inhibitor, e.g. Sotorasib



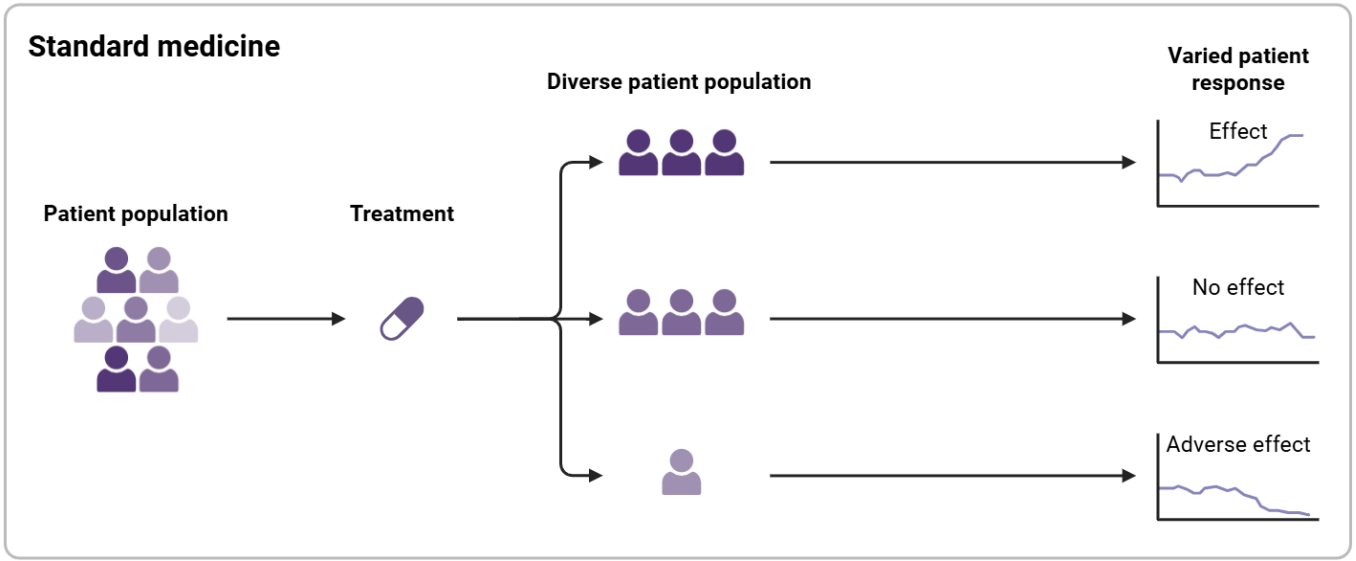
EGFR L858R+ NSCLC → treatment with a TKI, e.g. Osimertinib

Targeted cancer therapies

- Many different tests for different genes are available depending on the tumour type
- Specific MBS item numbers exist for somatic (tumour) testing
  - Generally requested by medical oncology

- *Future direction - comprehensive genomic profiling of tumours*
  - Sequencing hundreds of known tumour-related genes to identify variants that might:
    1. Be a target for therapy
    2. Aid in tumour diagnosis
    3. Provide prognostic information
    4. Allow enrolment in a clinical trial

Pharmacogenomics (PGx)



- **Genetic variations** can influence the way our bodies respond to certain medications.
- PGx uses genetic data to predict the response

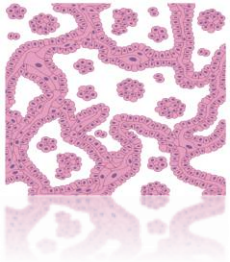
PGx: overview

Two broad approaches offered by laboratories:

1. Targeted pharmacogenetic testing for a particular indication, e.g. testing prior to starting chemotherapy

2. Comprehensive panel testing approach, e.g. testing for multiple medications

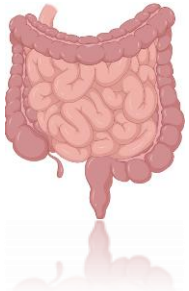
PGx: targeted testing



DPYD, UGT1A1

Toxicity to 5-FU (DPYD) and Irinotecan (UGT1A1)

MBS rebate available



TPMT/NUDT15

Risk of toxicity with thiopurines

MBS rebate available



HLA-A*31:01, HLA-B*15:02

Risk of SJS/TEN with Carbamazepine/ Oxcarbazepine

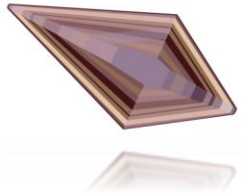
MBS rebate available



HLA-B*57:01

Risk of hypersensitivity reaction with Abacavir

No MBS rebate



HLA-B*58:01

Risk of SCAR to Allopurinol

No MBS rebate

PGx: comprehensive panel

- Testing of multiple genes that are involved in drug metabolism pathways, e.g. CYP genes

- Comprehensive information about multiple common medications:
  - **Antidepressants**, e.g. Fluoxetine, Desvenlafaxine, Sertraline, etc.
  - **NSAIDs**, e.g. Ibuprofen, Celecoxib, etc.
  - **Opioids**, e.g. Codeine, Morphine, Tramadol, etc.
  - **Anticoagulants**, e.g. Warfarin
  - **Antiplatelets**, e.g. Clopidogrel
  - **PPIs**, e.g. Pantoprazole, Esomeprazole, etc.
  - **Statins**, e.g. Atorvastatin, Rosuvastatin, etc.
  - Etc.

PGx: comprehensive panel

- Guidance is NOT provided for every possible medication
  - It is only provided where there are published guidelines available
- Each testing laboratory will have their own list of genes and medications
  - NB: no two testing laboratories offer the same panel!
- No MBS item number is available = private testing fee ($200-300)

PGx: how does it work?

CYP2D6



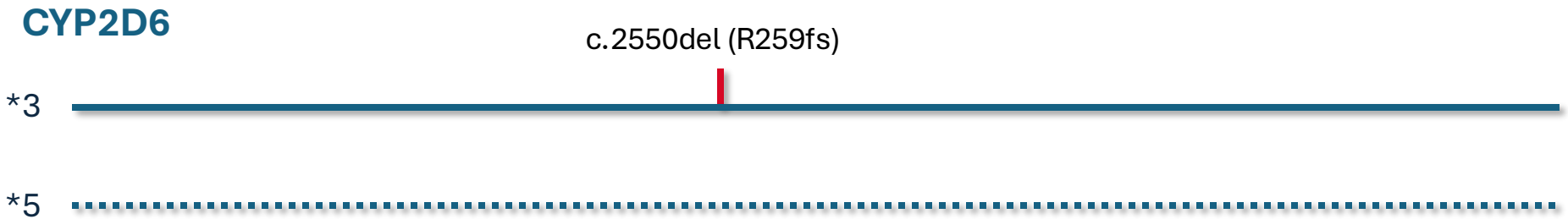
*2 is a known normal function allele

*3 is known NO function allele

In combination the patient will be an *INTERMEDIATE* metaboliser

- No changes to dosing for **codeine**, **metoprolol** or **venlafaxine**

PGx: how does it work?



*3 is known NO function allele

*5 is a known NO function allele (gene deletion)

In combination the patient will be a *POOR* metaboliser

- **Codeine**: diminished analgesia, consider alternative non-tramadol opioid
- **Metoprolol**: decreased metabolism leading to increased concentrations, low starting dose with careful titration upwards
- **Venlafaxine**: increased risk of adverse effects, consider alternative antidepressant not metabolised by *CYP2D6*

Indigenous genomics and PGx

- PGx advice relies on well-established genetic haplotypes that have been extensively studied
  - Identification of variants within the population
  - Functional studies or experimental data
  - Clinical data
  - Publication in relevant guideline/database

- If variants have not been identified or studied they will NOT be included in guidelines/database
- Due to genetic diversity, current testing methodologies may be omitting important variants within the Aboriginal and Torres Strait Islander patient cohort → PGx is less useful

Summary

- PGx is a useful tool to direct therapy
  - Very helpful but must consider other factors as well, e.g. renal/hepatic function, weight, drug-drug interactions
- Ideally performed prior to therapy but can be performed due to onset of adverse symptoms
- Specific tests exist for specific therapies – some are MBS funded
- Further research is needed in this area to investigate relevant ancestral alleles that may impact Aboriginal and Torres Strait Islander peoples

Additional Resources

- RACGP reference – *Genomics in General Practice*
  https://www.racgp.org.au/getattachment/63568f23-e288-4a0e-a23a-39fbd046cc21/Genomics-in-general-practice.aspx
- Patient facing literature:
  - Pathology tests explained
    https://ptex.au/