

# Clinical Genetics in Healthcare

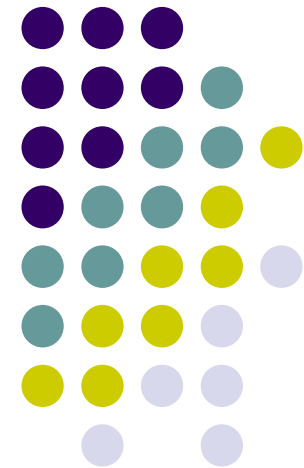


Brisbane South PHN

12<sup>th</sup> Feb 2019

Dr Chirag Patel

Clinical Geneticists  
Genetic Health Queensland  
Brisbane



Genetic Health Queensland

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Queensland  
Government



# Overview – General Genetics

- **Basic principles**
  - Genetics 101
- **Genetics in primary care**
  - Roles, pedigree taking, referrals
- **Clinical genetics service**
  - Referral pathway, patient pathway in service
- **Genetic testing**
  - Indications, types, limitations, costs, interpretation
- **Reproductive genetics**
  - Preconception carrier screening, NIPT, prenatal genetic tests, PGD
- **Ethical, social, and legal issues**
  - Predictive/presymptomatic testing, consent, insurance

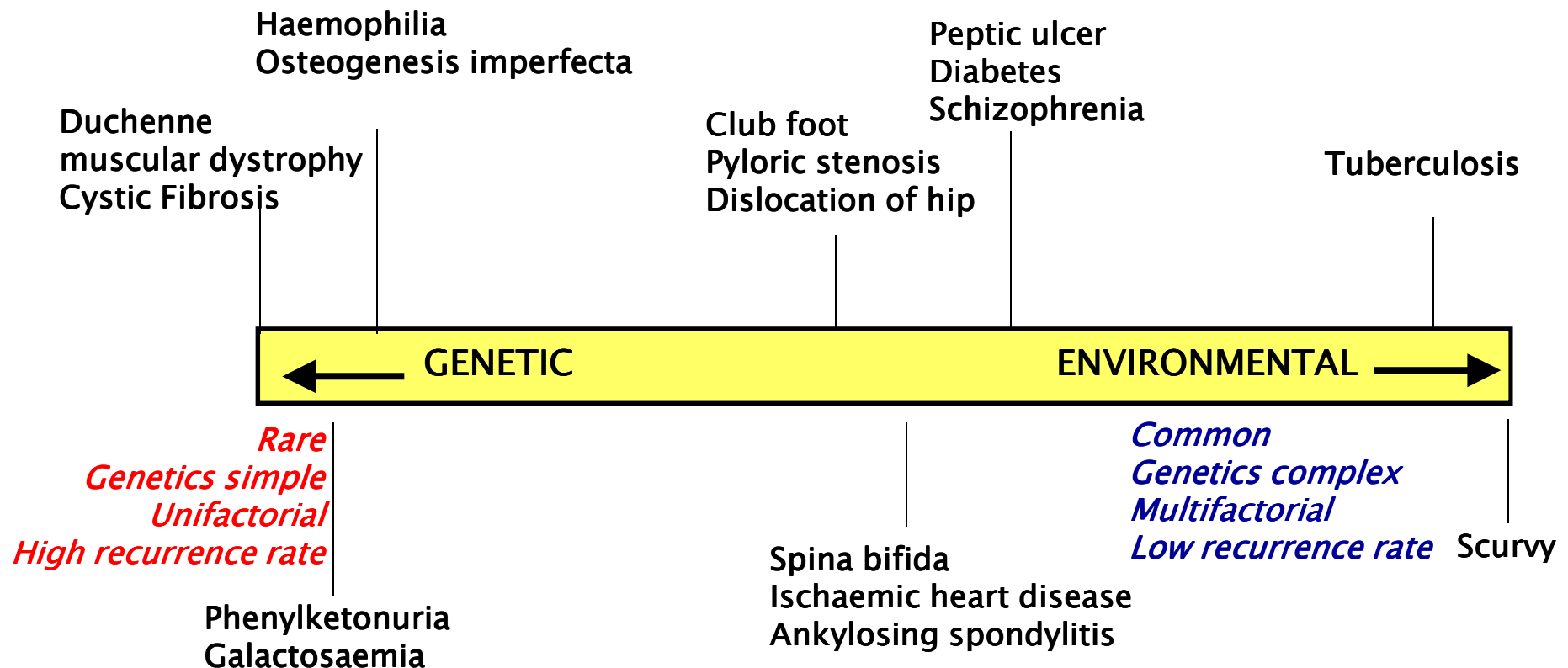


# Basic Principles



# Spectrum of genetic diseases

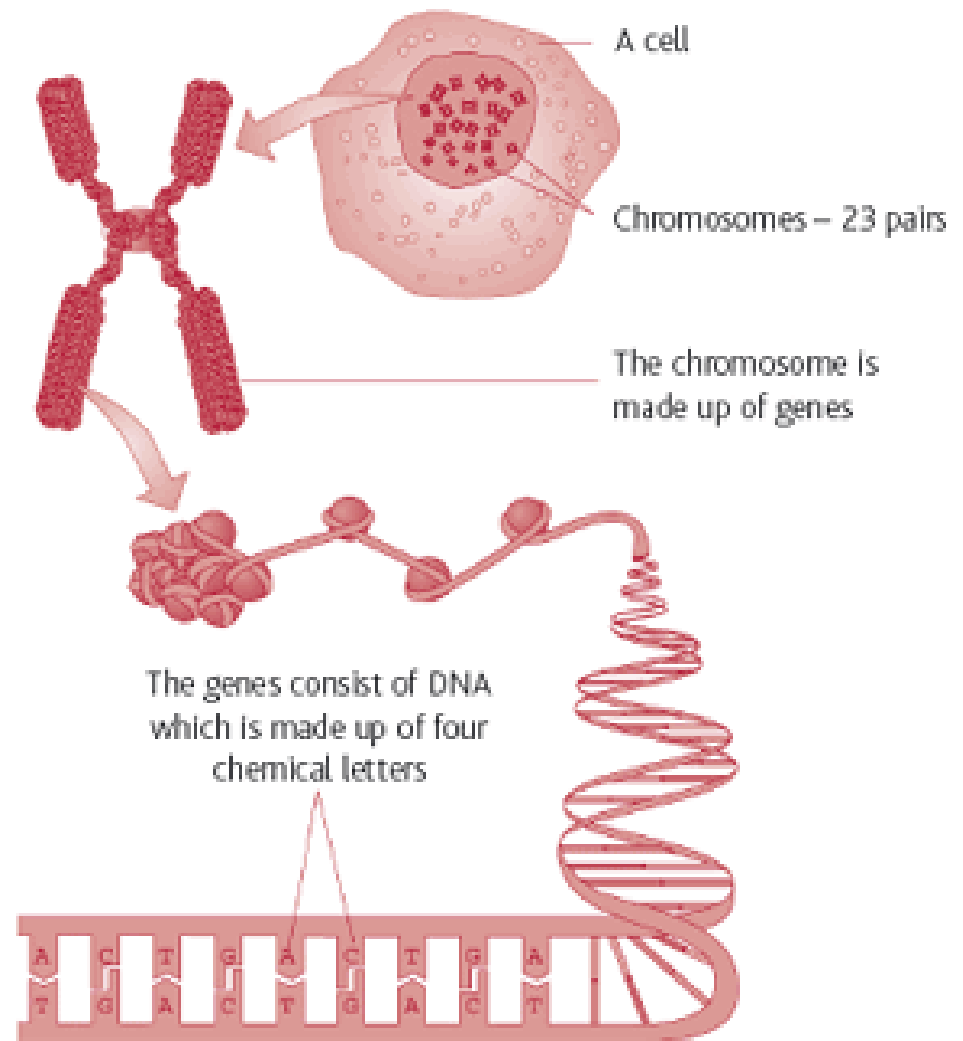
- *Genetic disease and congenital malformations - 4-5% live births*
- *Chronic disease with a major genetic component - 10% adults*





# Genetics 101

- Cells (*library*)
  - Body composed of millions
- Chromosomes (*bookshelves*)
  - Located within nucleus of cells
  - Come in 23 pairs
  - Inherit 23 from each parent
  - Made up of genes
- Mitochondria (*batteries*)
- Genes (*books*)
  - ~24000 genes
  - consist of DNA





# Classification of genetic disorders

- **Chromosomal**

- Numerical (monosomy/trisomy), mosaicism
- Structural (deletions/duplications/translocations)

- **Single gene**

- Autosomal dominant
- Autosomal recessive
- X-linked

- **Mitochondrial**

- **Imprinting/epigenetic**

- **Multifactorial** (e.g. genetic variant + environment)

- **Acquired somatic** (e.g. cancer)

- **[Non-genetic]** (e.g. teratogen, infective, mechanical in utero)]

# Chromosomes disorders



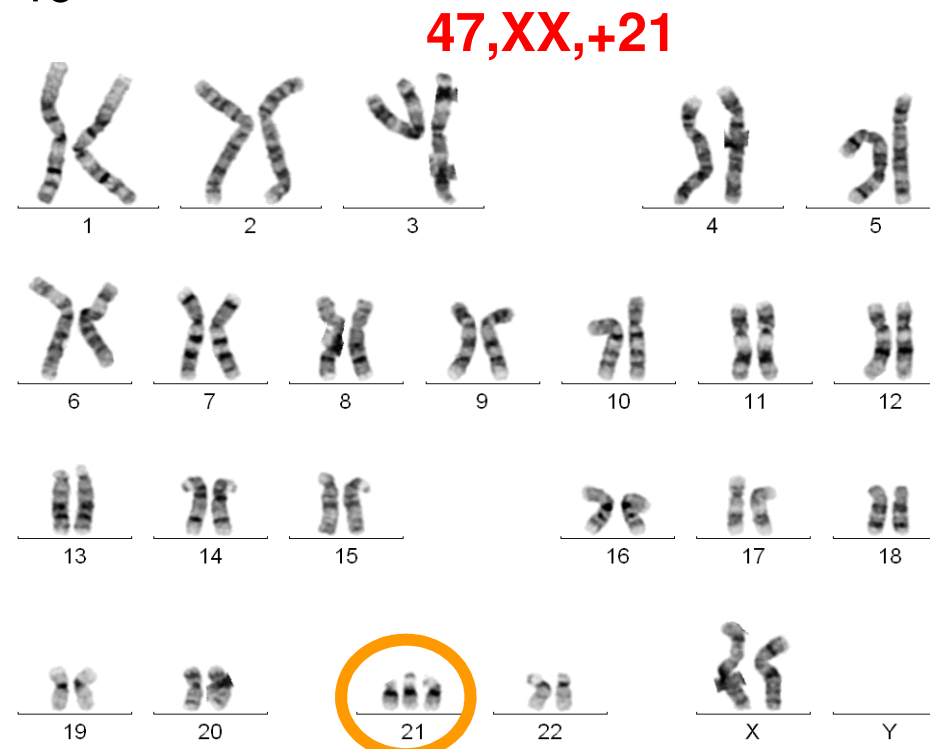
## Numerical

- More or fewer chromosomes than 46
- One extra = Trisomy
- One fewer = Monosomy

e.g.

47,XY+21 = **Down** syndrome

45,X = **Turner** syndrome



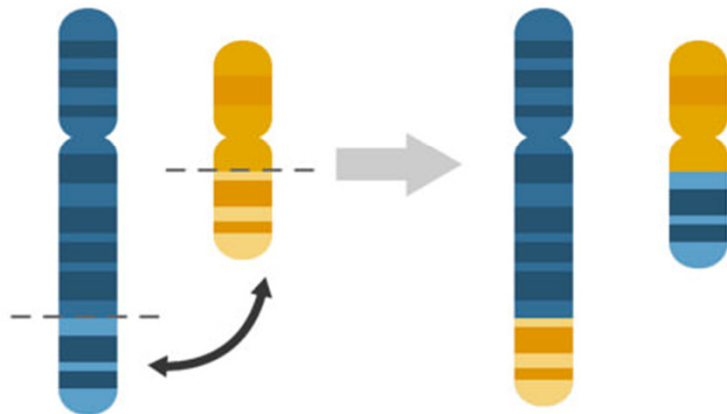


# Chromosomes disorders

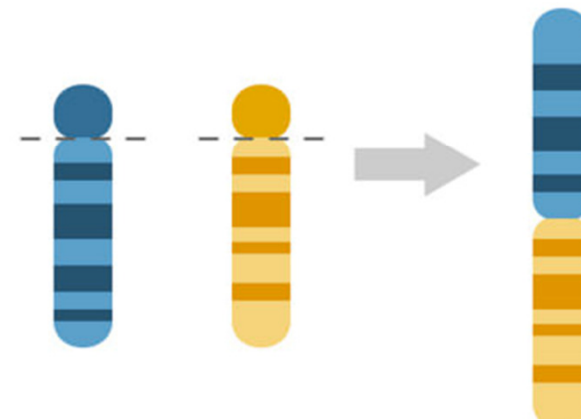
## Structural

- Translocations
  - **Balanced** = no net loss of genetic material
  - **Unbalanced** = net loss or gain of genetic material
    - *miscarriage, stillbirth, liveborn with congenital anomalies*

**Reciprocal translocation**  
(1 in 500)



**Robertsonian translocation**  
(1 in 1000)

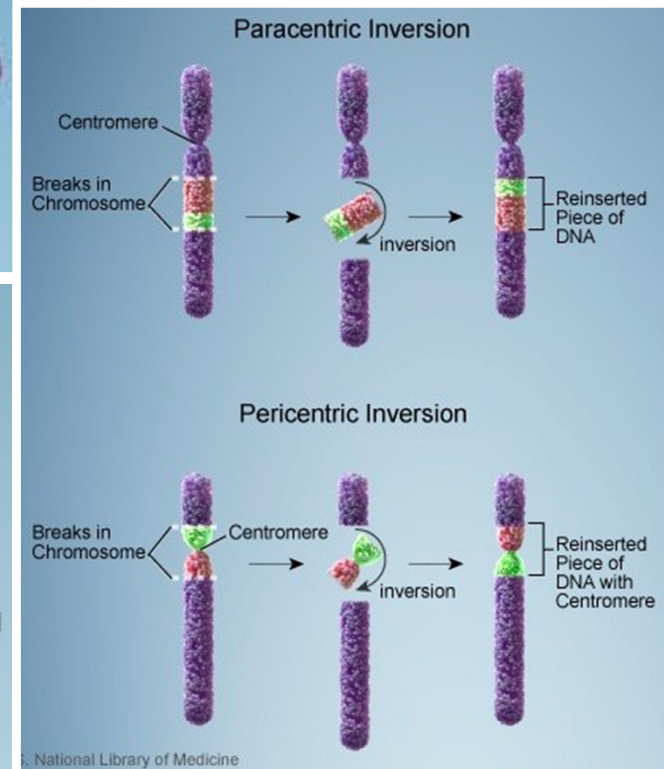
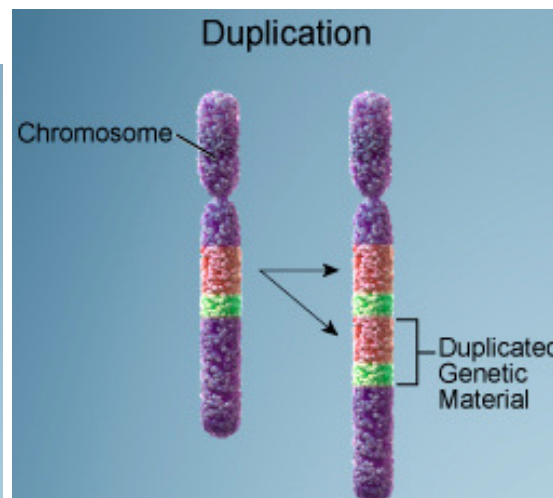
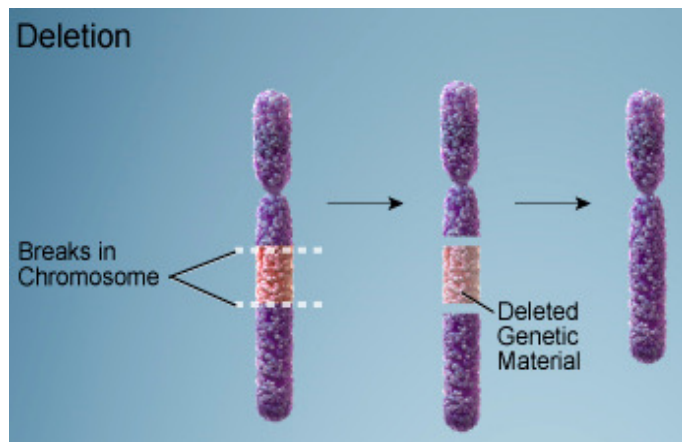
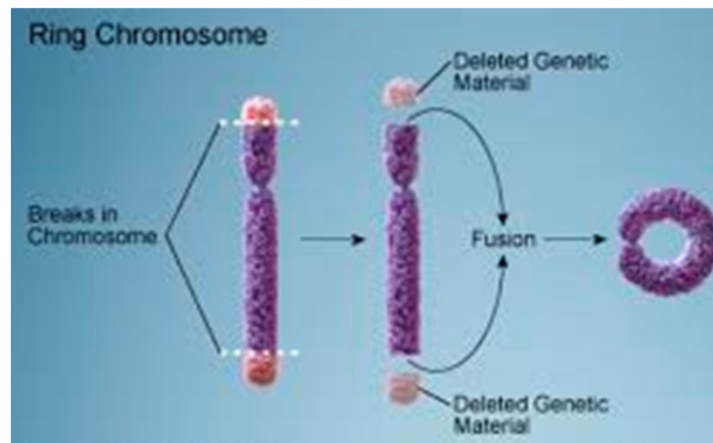


# Chromosomes disorders



## Structural

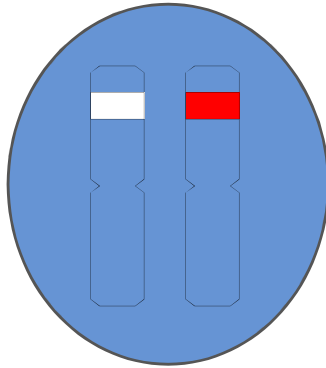
- Deletions
- Duplications
- Ring
- Inversions





# Single gene disorders

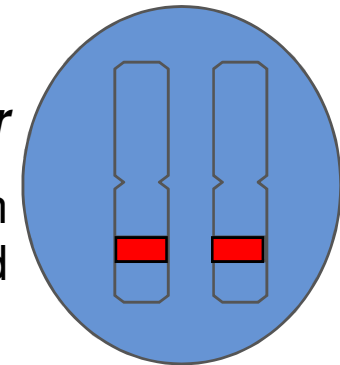
## *Dominant disorder*



Heterozygotes with **one copy** of the mutated gene are affected

## *Recessive disorder*

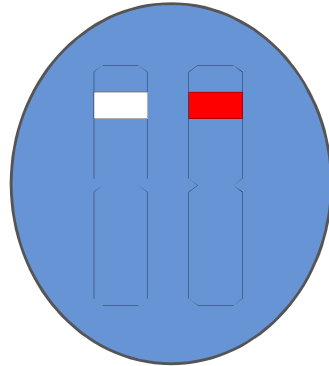
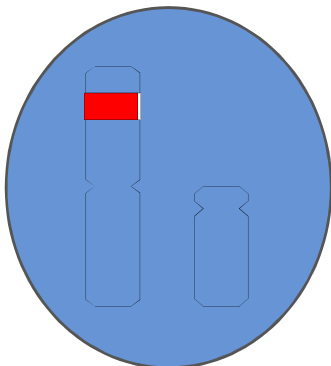
Homozygotes / compound heterozygotes with **two copies** of the mutated gene are affected



## *X-linked recessive disorder*

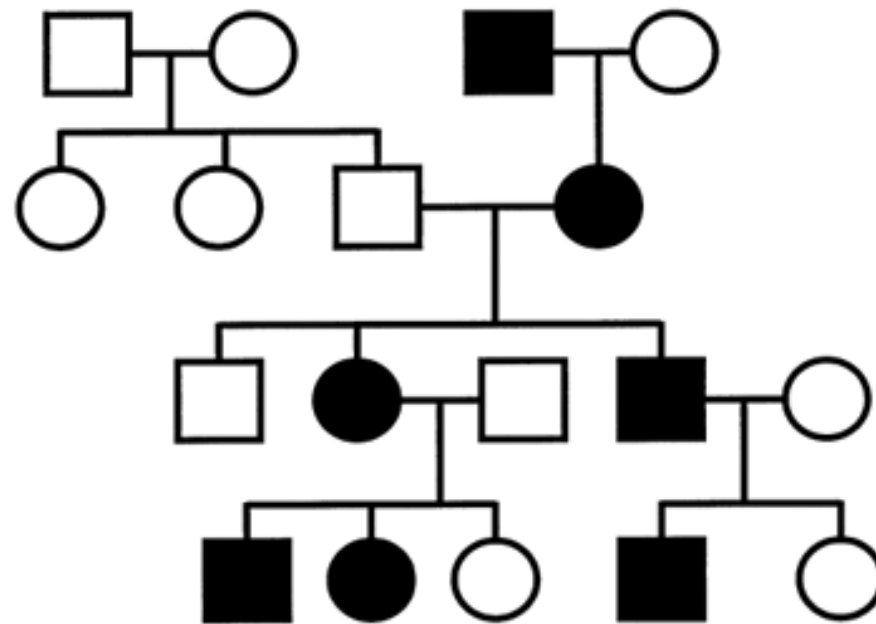
Males with **one copy** of the mutated gene on X-chromosome are affected

Females with **one copy** of the mutated gene on X-chromosome are 'carriers'





# Autosomal dominant inheritance



- Multiple generations affected – no skipped generations
- Transmitted by affected males and females
- Males and females can be affected
- For affected parent the offspring risk = 1 in 2 (50%)



# Penetrance & Expressivity

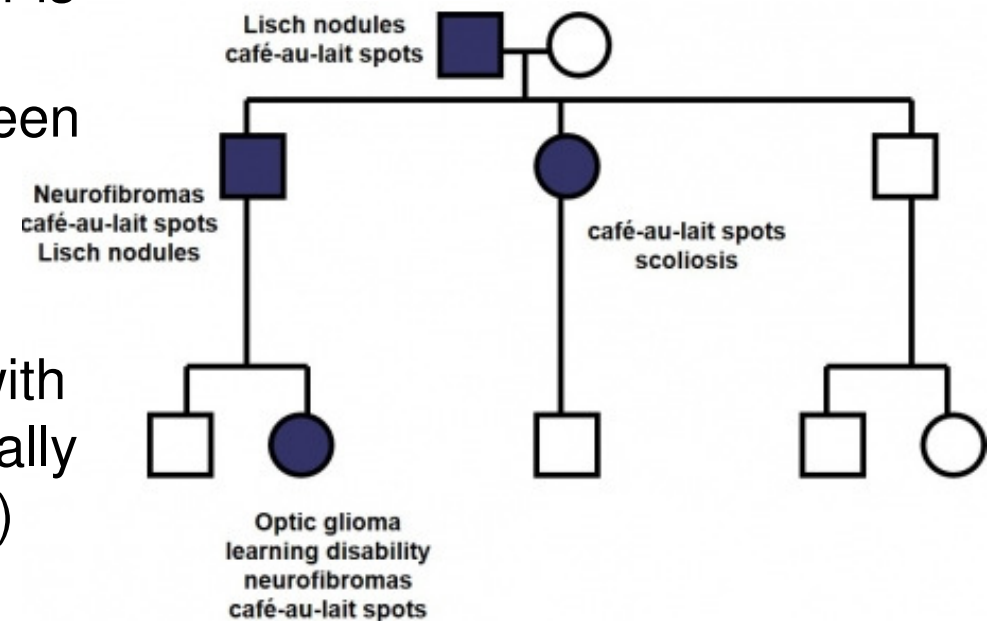
## *Autosomal dominant disorders*

### **Expression:**

- 'The degree to which a disorder is expressed in an individual'
- This can differ within and between families

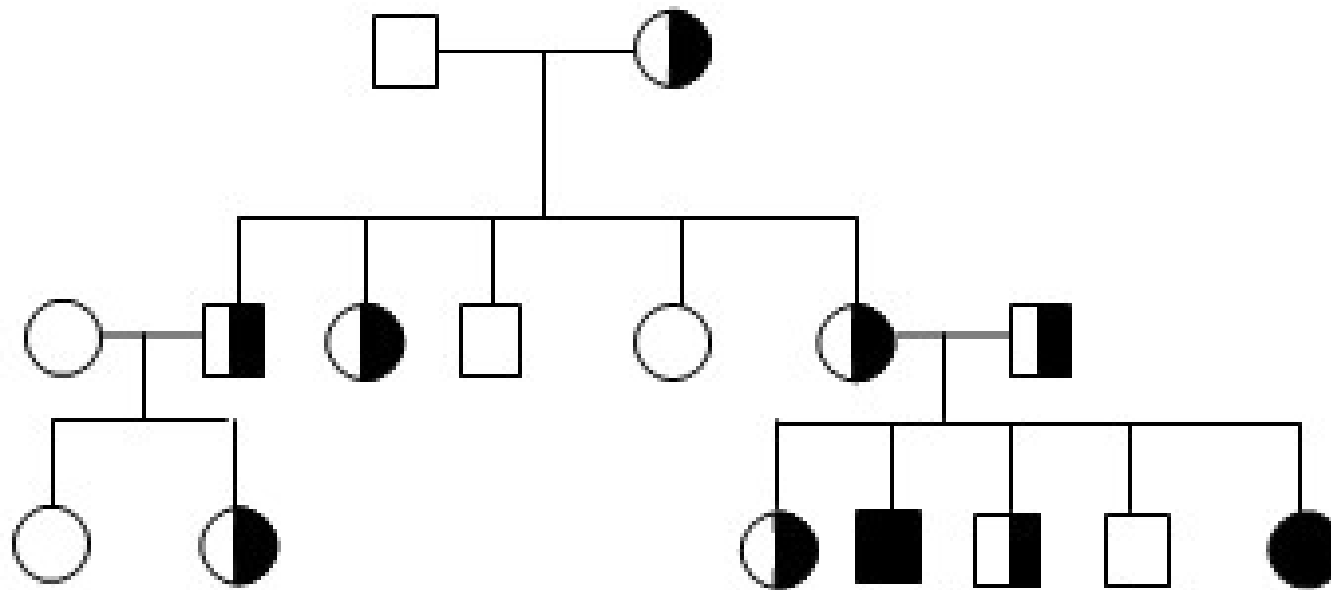
### **Penetrance:**

- 'The proportion of individuals with the gene mutation who are clinically *affected*' (e.g. reduced, 60% etc)



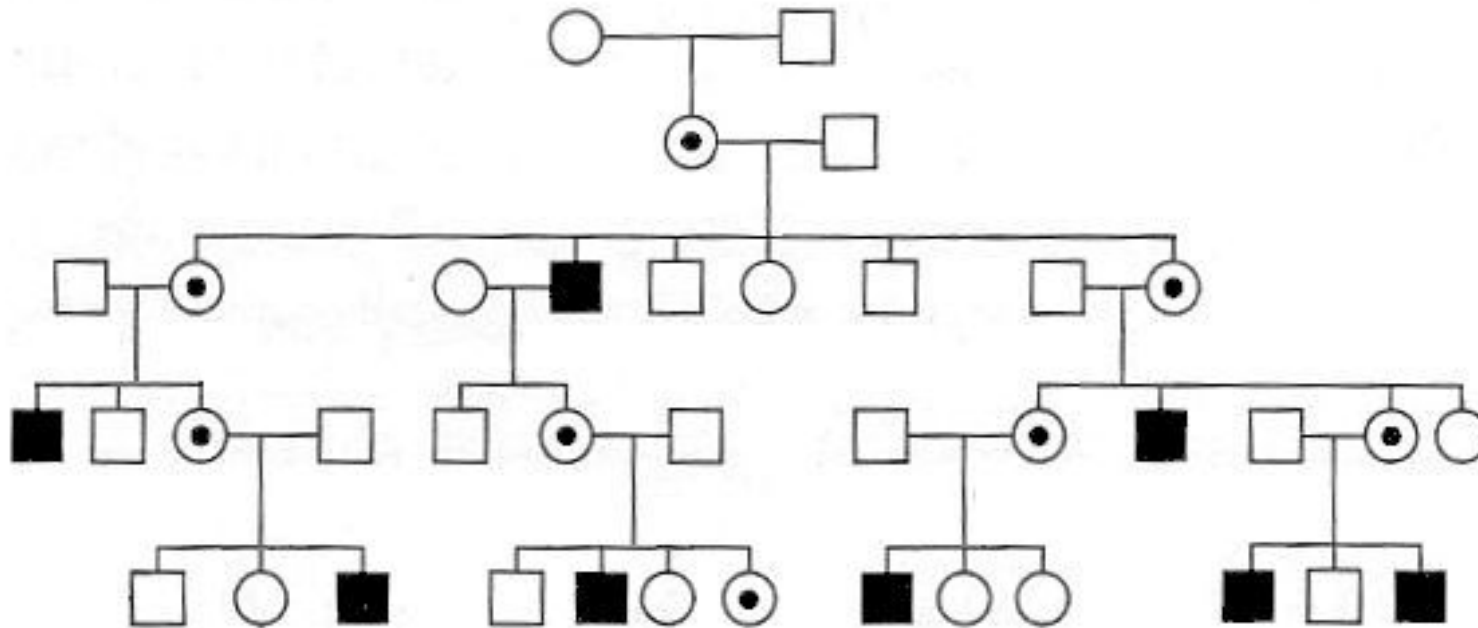


# Autosomal recessive inheritance



- Usually individuals affected in a single generation
- Both parents are carriers and unaffected
- Males and females can be affected
- For two carrier parents the offspring risk = 1 in 4 (25%)

# X-linked recessive inheritance



- Males affected mostly
- Female carriers usually unaffected but can be affected
- Affected males cannot transmit disorder to their sons



# Genetics in Primary Care

# Typical questions patients ask:



- “My aunt and grandmother died of breast cancer. My Mum’s just been told she’s got cancer. Am I going to get it too?”
- My sister has just been told her son has cystic fibrosis. I’m pregnant. Could my baby get cystic fibrosis too?”
- “My uncle had Huntington’s disease. Should I have the test? I’m just in the process of buying a new house.”
- “My 23 yrs old son died suddenly recently of a cardiomyopathy. I’m finding it hard to cope, and I’m worried about my other children.”
- “Lots of people on my Dad’s side of the family have polycystic kidney disease and had dialysis or transplants. What is my risk?”



# Genetics and primary care



*Identifying patients and families with, or at risk of, genetic conditions*

*Knowing indications for referral to specialist*

*Making diagnosis*

*Ordering and understanding genetic test results*

*Recommending treatments*

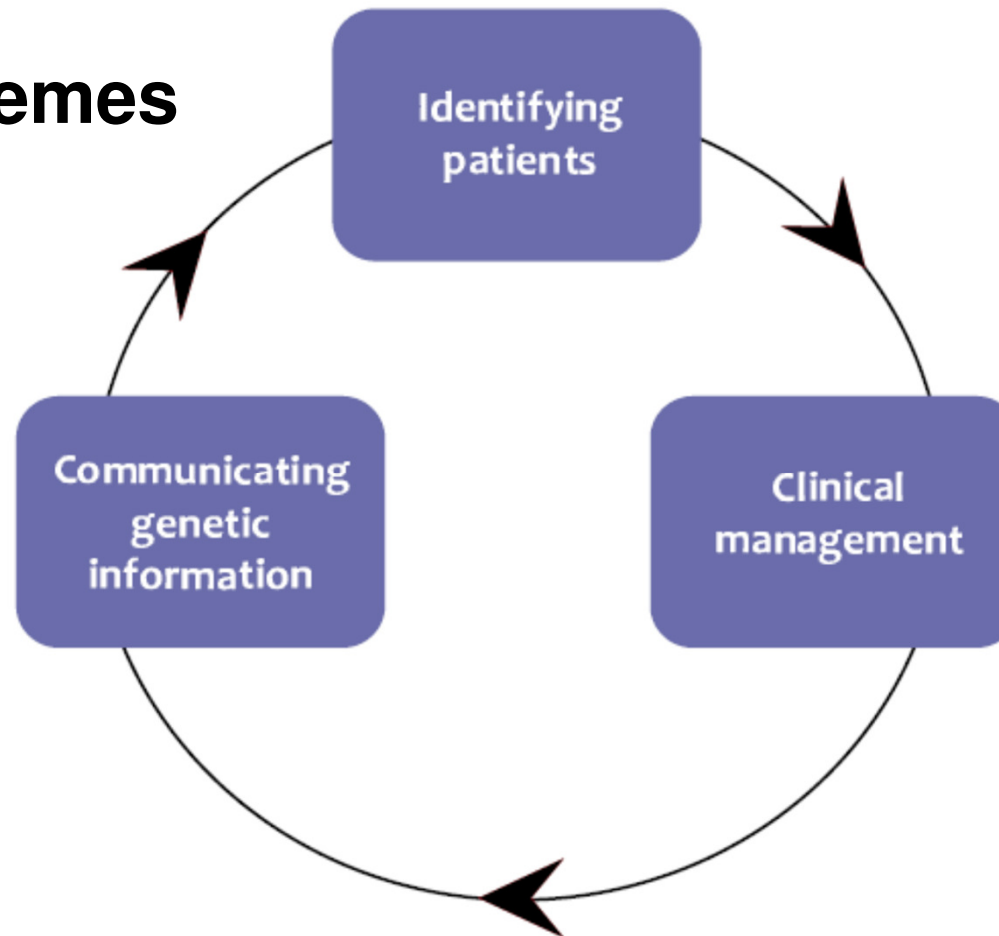
*Treating/ managing condition*

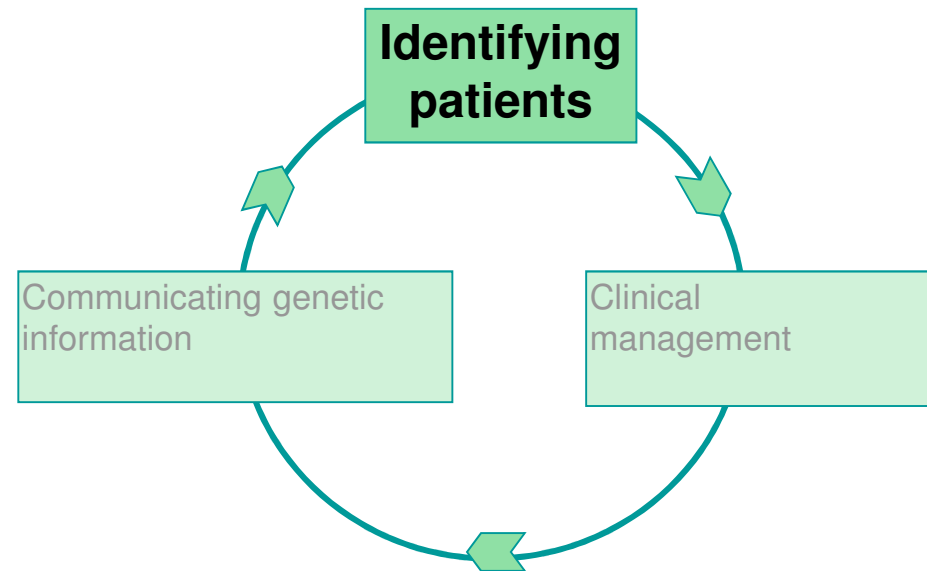
*Implications for patient with condition and for other family members*



# Genetics and primary care

- **3 main themes**





### ***How do I recognise patients with or at risk of genetic conditions?***

- From a known genetic diagnosis or by recognising signs and symptoms of common genetic conditions
- From interpreting a family history
- From the results of screening programmes



## ***What does clinical management for people with genetic conditions involve?***

### **Accessing information**

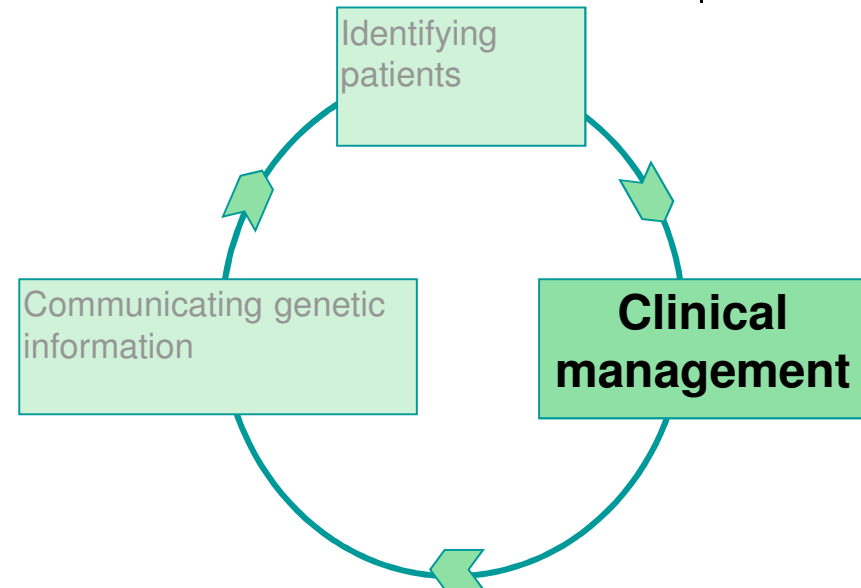
- Information about genetic conditions
- Referral and management guidelines

### **Management in primary care**

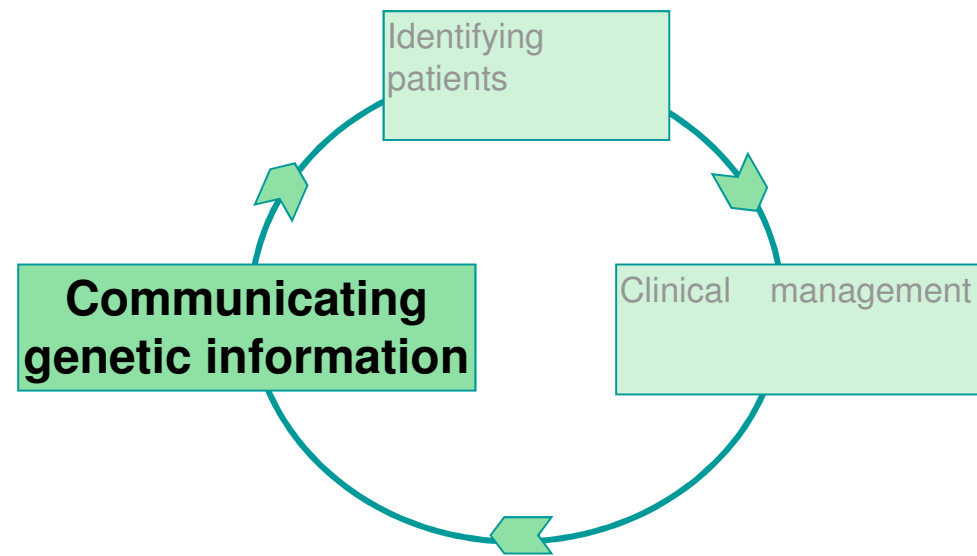
- Reassurance, preventive measures, surveillance, treatment, reproductive options, genetic testing
- Patient-centred, co-ordinated care and support

### **Referring to specialist services**

- How are services for patients with or at risk of genetic conditions organised?
- Where is your local genetics service located?
- How do you refer patients to specialist services for genetic conditions:
  - to your Regional Genetics Centre for investigation, information or diagnosis?
  - to other specialist services for investigation, diagnosis or treatment?



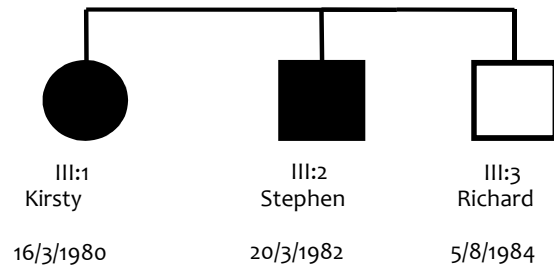




### ***What does communicating genetic information involve?***

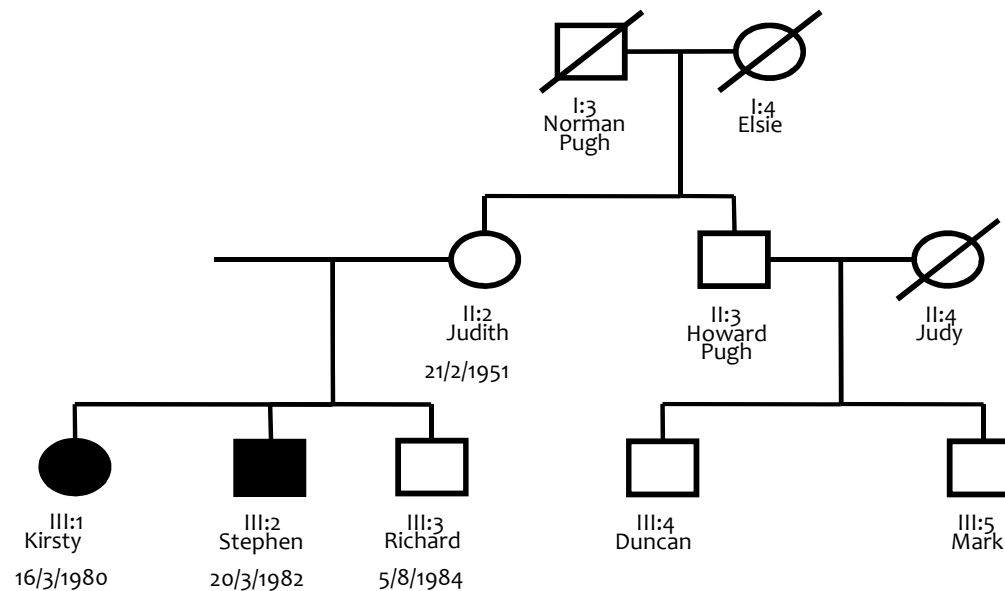
- Communicating genetic information in an understandable way
- Being non-directive and supporting informed decision making
- Understanding consent and confidentiality issues
- Appreciating the emotional, ethical, legal and social impact of genetic information for a patient and their family

# Drawing a family pedigree



Build up the tree from the "bottom" starting with affected child and siblings. Record names, dates of birth.

Choose one parent.  
Ask about sibs and their children, then parents.



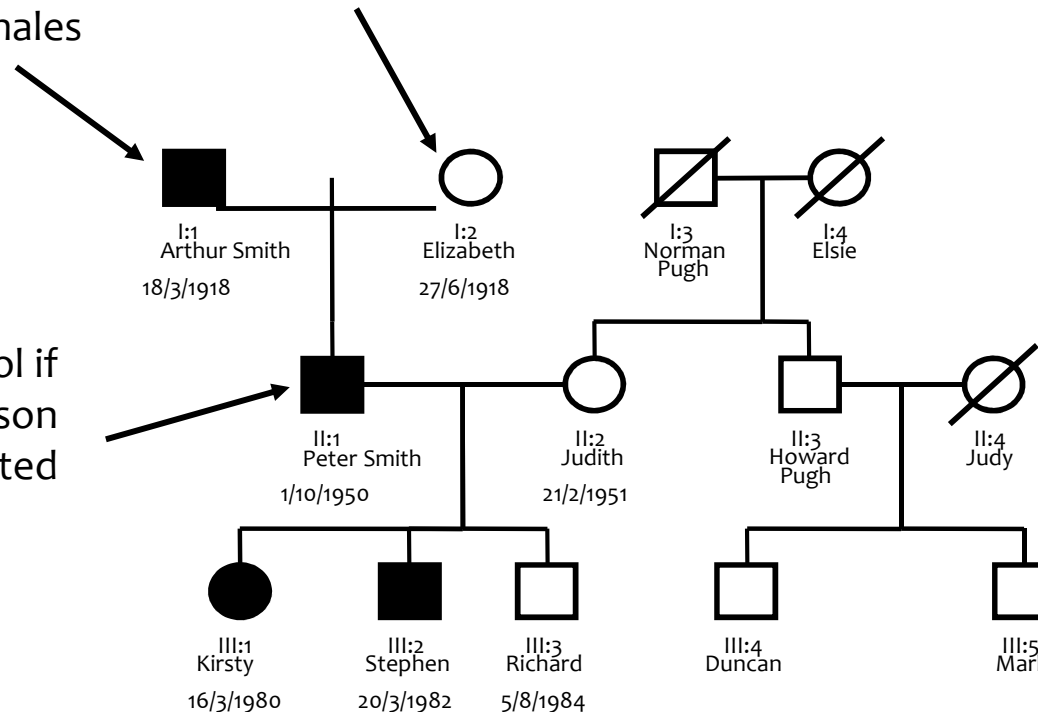
# Drawing a family pedigree



Use clear symbols: circles for females  
squares for males

Put a sloping line  
through the symbol  
(from the bottom  
left hand corner) if  
the person has died

Colour in the symbol if  
the person  
is affected

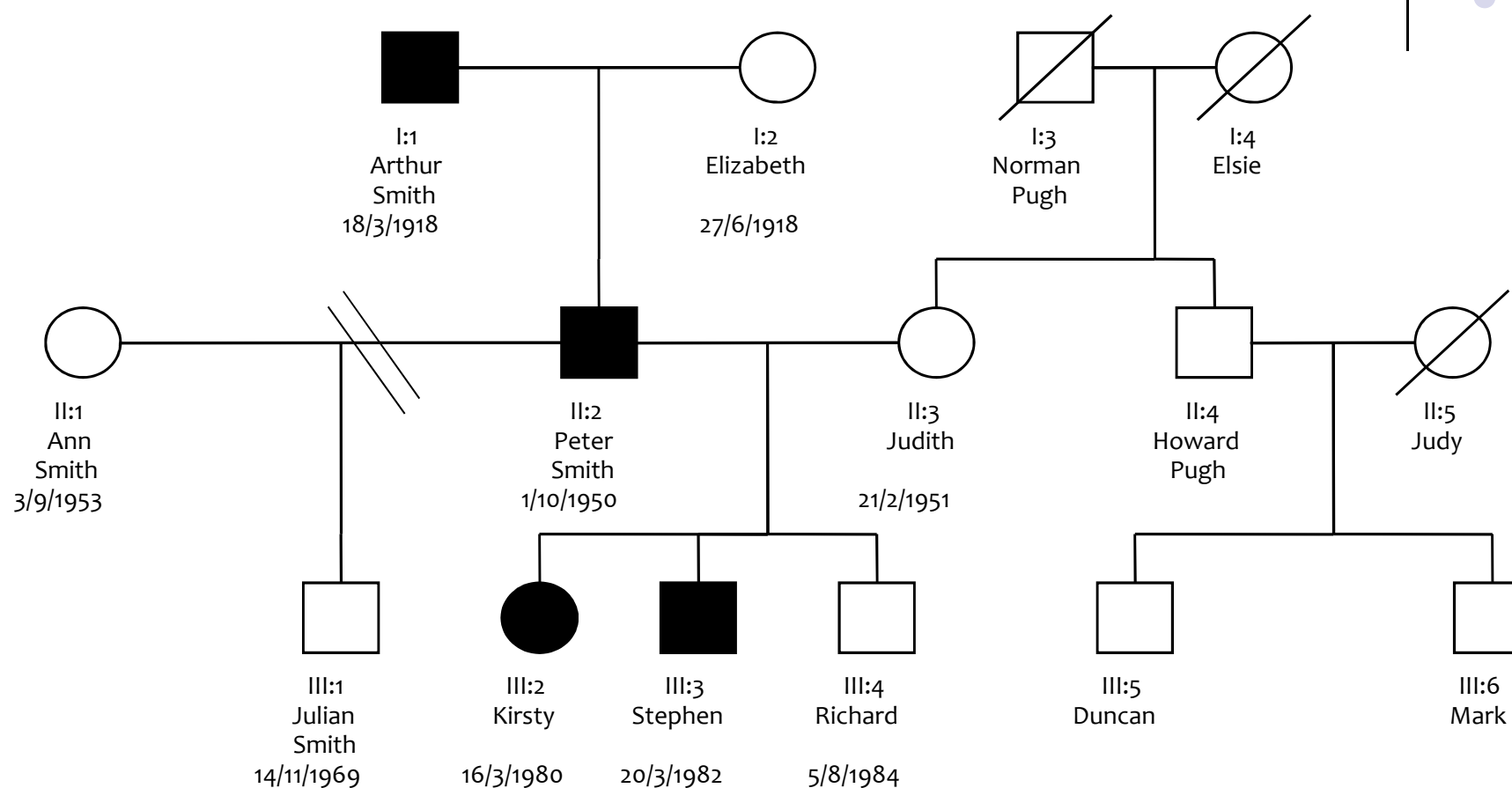


Record names, dates of birth and maiden names

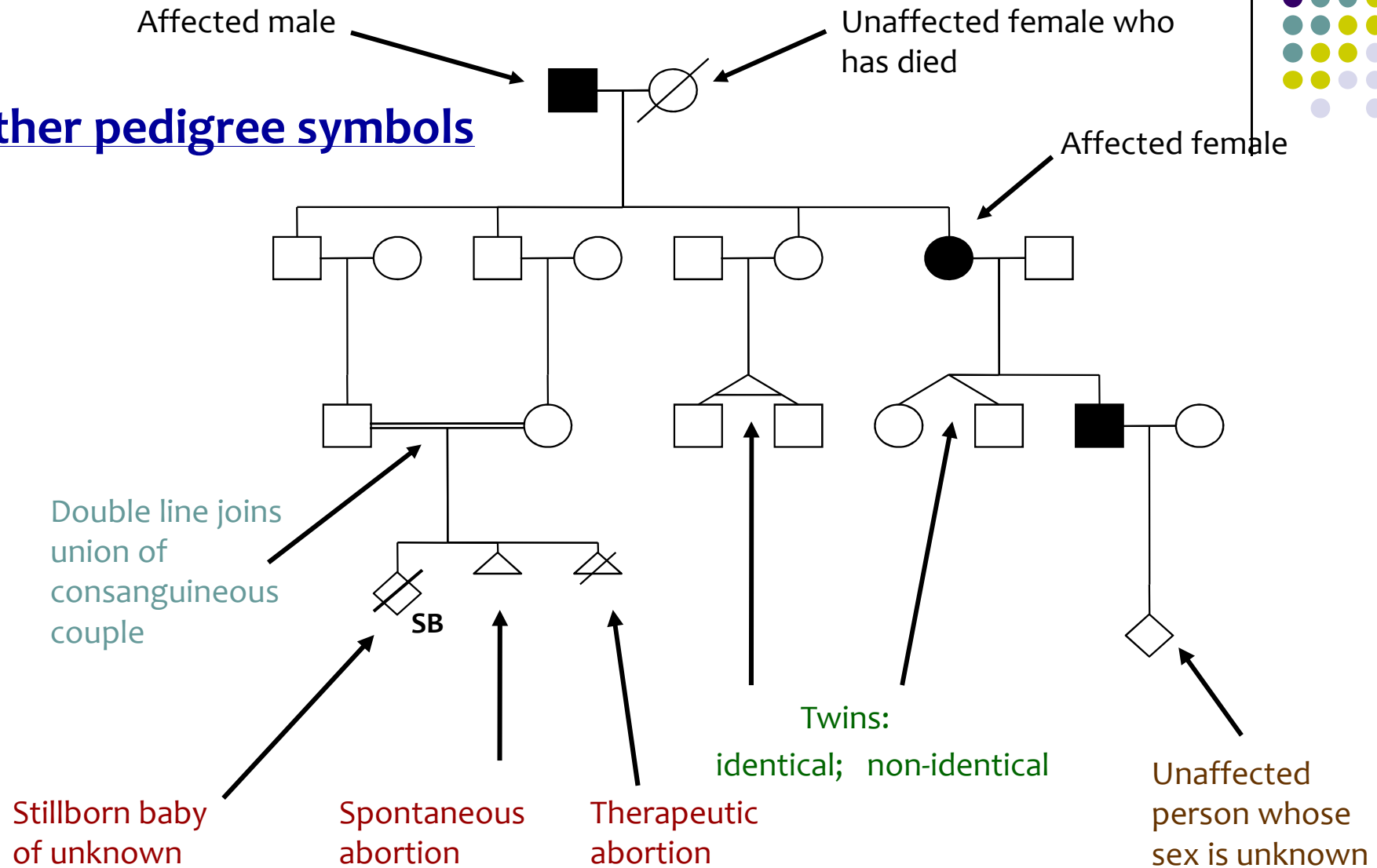
Ask for miscarriages, stillbirths or deaths in each partnership



“May I ask: have you had any children with other partners?”



## Other pedigree symbols





# Why interpretation is important?

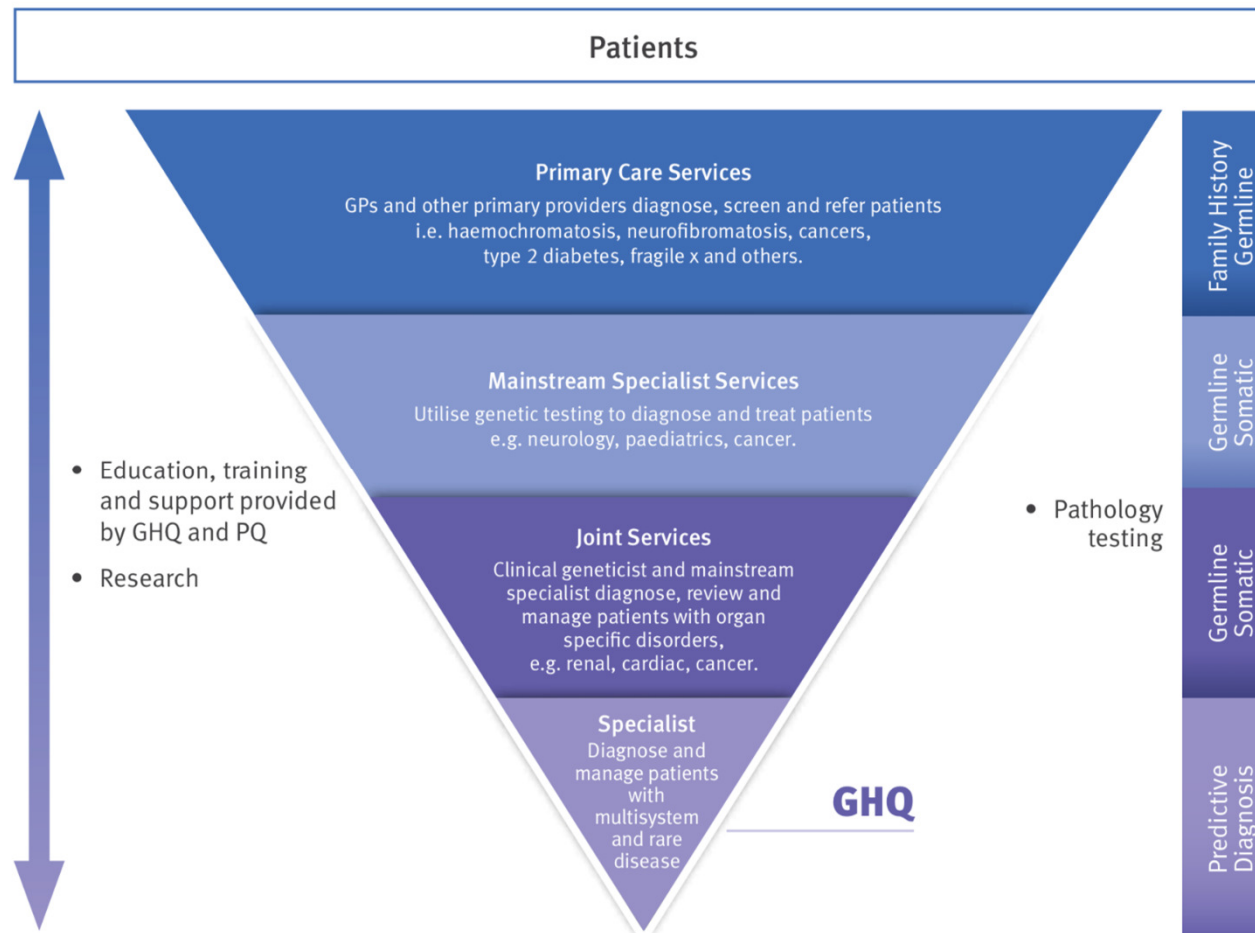
- Help to make/refine a diagnosis
- Reveal patterns of inheritance
- Assess likelihood of genetic disease in relatives
- Affect testing, treatment, and management strategies
- Highlight need for specialist referral
- Correct any family misconceptions



# Clinical Genetics Services



# Genetics Service Model



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# Clinical genetics services

- Public services are available in every state
- Departments are located in one major hospital
  - provide outreach clinics in various hospitals/HHS
- Consist of clinical geneticists and genetic counsellors



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# Clinical Genomics / Genomic Medicine



## Definition:

- *"an emerging medical discipline that involves using genomic information about an individual as part of their clinical care (e.g. for diagnostic or therapeutic decision-making) and the health outcomes and policy implications of that clinical use".*
- **NOT research genomics**

## Genetic counselling:

- *An education process that seeks to assist affected (and/or 'at risk') individuals to understand the:*
  - nature of the genetic disorder and its management/surveillance
  - genetic basis, inheritance pattern, and risk to family members
  - options for family planning
  - role/option/availability/outcome of genetic testing



# Reasons for referral

- **Adult:**
  - Known diagnosis (information) or diagnostic
  - Family history (including cancer)
  - Genetic test results
  - Predictive /carrier testing
  - Reproductive planning
- **Child:**
  - Known diagnosis (information) or diagnostic
  - Birth anomalies, dysmorphic features
  - Developmental delay, learning difficulties
  - Genetic test results
- **Pregnancy:**
  - Known genetic disorder (prenatal testing)
  - Abnormality detected on screening/invasive testing
  - Previous fetal loss/abnormalities

# Referral process

- [www.health.qld.gov.au/ghq](http://www.health.qld.gov.au/ghq)



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## Welcome to Genetic Health Queensland

Genetic Health Queensland (GHQ) is a statewide service that provides clinical genetic services across Queensland by a team of specialist health-care professionals. We see individuals and their families with a suspected or known inherited or genetic health condition.

A team of medical specialists (clinical geneticists) and genetic counsellors work together at GHQ to look after patients and families all over Queensland. Regular clinics are held in Brisbane, Gold Coast, Toowoomba, Nambour, Bundaberg, Rockhampton, Mackay, Townsville and Cairns. Telehealth consultations are also available for suitable patients. The Queensland Familial Cancer Registry (QFCR), Queensland Cardiac Genetics Clinic, and RBWH Renal Genetics Clinic are also based within GHQ.

Patients  
and Families

Health  
Professionals

Queensland  
Cardiac  
Genetics Clinic

Queensland  
Familial  
Cancer  
Registry



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# Referral form

- Discuss the option of a referral with the patient.
- **Ensure that the patient consents to the referral and is aware of how the service is set up.**
- Send in a completed referral with all relevant information
- If you are unsure if referral is appropriate, or if urgent, then telephone your regional genetics centre for further advice.

**Queensland Government**  
**Royal Brisbane & Women's Hospital**  
**GENETIC HEALTH QUEENSLAND (GHQ) REFERRAL FORM**

URN: \_\_\_\_\_  
 Family Name: \_\_\_\_\_  
 Given Names: \_\_\_\_\_  
 Address: \_\_\_\_\_  
 Address: \_\_\_\_\_  
 Contact number: \_\_\_\_\_  
 Date of Birth: \_\_\_\_\_ Sex: ☐ M ☐ F ☐ I

Please tick: ☐ Dr Julie McGaughran (Director)

**Complete all sections, sign and fax to:**  
**1300 364 952**  
**(Metro North Central Patient Intake Unit)**

**For urgent referrals or clinical queries please contact the on-call team: 07 3646 1686**

☐ Patient / family aware of referral ☐ Translator required Language: \_\_\_\_\_

☐ Urgent (indication): \_\_\_\_\_  
☐ Non-urgent  
☐ Ward review - Location: \_\_\_\_\_  
☐ Pregnant (please also refer the partner) Gravity/parity: \_\_\_\_\_ EDD: \_\_\_\_\_

Specialty: \_\_\_\_\_  
 Consultant / GP name: \_\_\_\_\_  
 Consultant / GP Provider number: \_\_\_\_\_  
 Contact number: \_\_\_\_\_  
 Address: \_\_\_\_\_

**Clinical information (please attach all relevant investigations)**  
**Diagnosis and relevant family history:**

**Reason for referral:**

Doctor's name: \_\_\_\_\_ Designation: \_\_\_\_\_  
 Signature: \_\_\_\_\_ Date: \_\_\_\_\_

DO NOT WRITE IN THIS BINDING MARGIN  
 Do not reproduce by photocopying  
 All clinical form sections and amendments must be completed through Health Information Services


MR 60380  
 V3.0 - 09/2017  
 Locally Printed

GENETIC HEALTH QUEENSLAND REFERRAL FORM

# Clinical Prioritisation Criteria

Completed and live from January 2019



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General Paediatrics

General Surgery

**Genetics Cancer**

Genetics General

Gynaecology

Hepatology

Nephrology

Neurology

Neurosurgery

Oncology and Malignant Haematology

Ophthalmology

Orthopaedics

Paediatric Surgery

Persistent Pain Management

**Clinical Prioritisation Criteria (CPC)** are clinical decision support tools that will help ensure patients referred for public specialist outpatient services in Queensland are assessed in order of clinical urgency.

CPC will be used by both **referring practitioners** when referring into the Queensland public hospital system and **Queensland public specialist outpatient services** when determining how quickly the patient should be seen (urgency category).

CPC have been developed to improve patients' specialist outpatient experience. They aim to ensure:

- Equitable assessment of patients regardless of where they live
- Specialist outpatient appointments that are delivered in order of clinical urgency
- Patients are ready for care at their first specialist outpatient appointment
- Improved referral and communication processes between referrers and specialist outpatient services

**Developed by clinicians**

A Clinical Advisory Group (CAG) was established for each medical specialty and a medical specialist appointed as the Clinical Lead. CPC are developed by a multi-disciplinary team of clinicians to ensure that the criteria are clinically relevant. Clinical Excellence Division would like to acknowledge the valuable contribution of Queensland Health staff and primary care clinicians during the development of Clinical Prioritisation Criteria. We would also like to recognise the utilisation of reference material from state, interstate and international sources throughout the development of CPC.

Please note this is not an exhaustive list of all conditions considered for outpatient services

☒ All conditions ☐ Adult only ☐ Paediatric only

[A](#) | [B](#) | [C](#) | [D](#) | [E](#) | [F](#) | [G](#) | [H](#) | [I](#) | [J](#) | [K](#) | [L](#) | [M](#) | [N](#) | [O](#) | [P](#) | [Q](#) | [R](#) | [S](#) | [T](#) | [U](#) | [V](#) | [W](#) | [X](#) | [Y](#) | [Z](#)

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# Clinical Prioritisation Criteria



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## Genetic General

### Conditions

Please note this is not an exhaustive list of all conditions for outpatient services and does not exclude consideration for referral unless specifically stipulated in the CPC exclusions section. *Condition category legend: (AO) – Adults Only Conditions, (A/P-AFF) – Adult and Paediatric Conditions in AFFECTED Patients, (A/P-UN) – Adult and Paediatric Conditions in UNAFFECTED Patients, (PO) – Paediatric Only Conditions.*

- Cardiac genetics (A/P-AFF)
- Endocrine genetics (A/P-AFF)
- Gastroenterology / hepatology genetics (A/P-AFF)
- Haematology genetics - excluding cancers (A/P-AFF)
- Metabolic genetics (A/P-AFF)
- Neurology genetics (A/P-AFF)
- Ophthalmic genetics (A/P-AFF)
- Other adult genetic conditions (AO)
- Paediatric genetics
- Renal genetics (A/P-AFF)
- Reproductive genetics (AO)
- Respiratory genetics (A/P-AFF)
- Untested and AFFECTED blood relative of a person with an identified gene mutation/chromosomal anomaly (predictive/presymptomatic testing) (A/P-UN)
- Untested and UNAFFECTED blood relative of a person with an identified gene mutation/chromosomal anomaly (confirmatory testing) (A/P-AFF)

### Emergency referrals

- No referrals to emergency relating to clinical genetics

### GP Genetics referral advice line

For advice regarding referrals and clinical questions regarding patients that may require referral to Genetics Health Qld please **phone** (07) 36461686

### Send referral

**Hotline: 1300 364 938**

**Fax: 1300 364 952**

**Electronic:** eReferral system

**Mail:** Metro North Central Patient Intake  
Aspley Community Centre  
776 Zillmere Road  
ASPLEY QLD 4034

### Health pathways ?

Access to Health Pathways is free for clinicians in Metro North Brisbane.

For login details email:  
[healthpathways@brisbanenorthphn.org.au](mailto:healthpathways@brisbanenorthphn.org.au)

Login to Brisbane North Health Pathways:  
[brisbanenorth.healthpathwayscommunity.org](http://brisbanenorth.healthpathwayscommunity.org)

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# Clinical Genetics Patient Pathway



## Referrals triaged:

- Cancer vs. General
- Face to face clinic
- Telehealth clinic
- Conjoint MDT clinic  
e.g. cardiac, renal



## Prior to clinic:

- Pedigree taking
- Clinical information  
(letters, investigations)
- Relatives' info/consent
- Literature review



## Clinic Appointment:

- History review
- Family history review
- Clinical examination
- Diagnosis/differential
  - Management issues
  - Genetics/inheritance
  - Risk to relatives
- Genetic testing
  - Indication, type
  - Outcomes, caveats
- Reproductive options
- Psychosocial support



## Post clinic:

- Case discussion
- Expert opinions
- Dx formulation
- Genetic test results  
(interpretation)



## Further appointment:

- Result disclosure
- Same points as blue





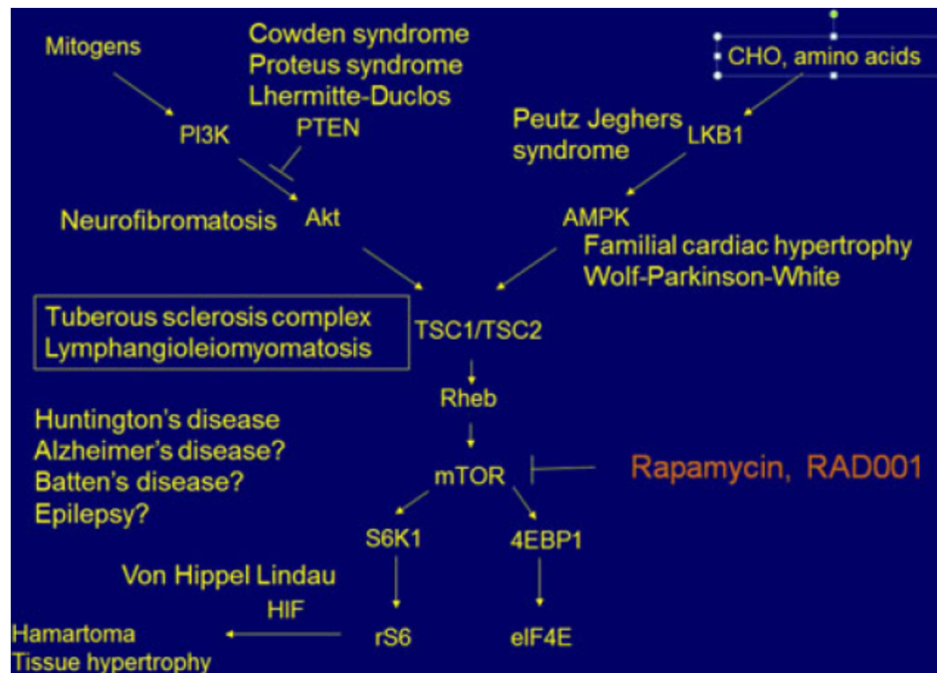
# Genetic diagnosis

## Benefits:

- End to the diagnostic odyssey (doctor and patient)
- Limitation of other invasive and costly investigations
- Potential targeted medical therapies
- Initiation of medical surveillance pathway
- Prognostication information
- Psychosocial benefits to patient/families
- Clarification/early identification of at-risk relatives
- Reproductive options



# Current - Therapeutics



## Molecular Therapies for Tuberous Sclerosis and Neurofibromatosis

David Neal Franz • Brian D. Weiss

## Tolvaptan in Patients with Autosomal Dominant Polycystic Kidney Disease

Vicente E. Torres, M.D., Ph.D., Arlene B. Chapman, M.D.,  
Olivier Devuyst, M.D., Ph.D., Ron T. Gansevoort, M.D., Ph.D.,  
Jared J. Grantham, M.D., Eiji Higashihara, M.D., Ph.D., Ronald D. Perrone, M.D.,  
Holly B. Krasa, M.S., John Ouyang, Ph.D., and Frank S. Czerwiec, M.D., Ph.D.,  
for the TEMPO 3:4 Trial Investigators\*

## Usefulness of Losartan on the Size of the Ascending Aorta in an Unselected Cohort of Children, Adolescents, and Young Adults With Marfan Syndrome

Christiane Pees, MD<sup>a,\*</sup>, Franco Laccone, MD<sup>b</sup>, Marion Hagl<sup>b</sup>, Veerle DeBrauwere, MD<sup>c</sup>,  
Elisabeth Moser, MD<sup>d</sup>, and Ina Michel-Behnke, PhD<sup>a</sup>

# Current - Therapeutics



STUDY RESULTS

SAFETY

TAKING SPINRAZA

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Clinical Overview

Infantile-onset

Later-onset

Presymptomatic

## UNLOCK THE POTENTIAL BENEFITS OF SPINRAZA

The SPINRAZA clinical study program is the largest in spinal muscular atrophy (SMA) to date



**Claire**  
age 19

Later-onset (Type 2) SMA  
treated with SPINRAZA

Individual results may vary based on several factors, including severity of disease, initiation of treatment, and duration of therapy.

The effectiveness of SPINRAZA was established in the pivotal ENDEAR study and supported by multiple clinical studies. Results were measured differently based on factors such as the age and physical ability of individuals in the clinical studies.

For individuals with infantile-onset (Type 1) and presymptomatic SMA in the ENDEAR and NURTURE studies, results included the achievement of developmental motor milestones.

The CS2/CS12 studies focused on individuals with later-onset (Types 2 and 3) SMA, evaluating improvements and maintenance of motor function over time, as well as specific motor skills—for example, walking and upper limb function.

Australian Government listed **nusinersen**:

- on PBS
- from 1 June 2018
- for treatment of SMA types 1, 2, and 3a

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# Future/Current - Therapeutics



## HUNTINGTON'S DISEASE

### HUNTINGTON'S DISEASE

What Is Huntington's Disease?

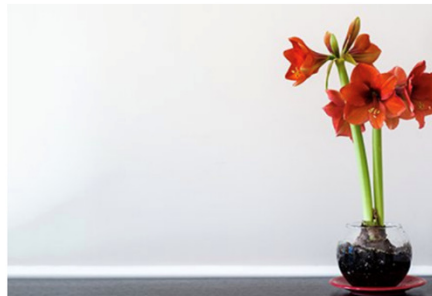
Genetic Testing & Terminology

Symptoms

What To Expect & Requirements

Treatment for HD

### TREATMENT FOR HD



## DRUG TRIALS

In December 2017, Huntington's disease made global headlines for a great reason: scientists had made a breakthrough in the hunt for a treatment. The drug has been developed by researchers and it is hoped the drug will be able to lower the amount of huntingtin protein in a person with HD and that this may possibly slow down, stop or even reverse some of the symptoms of HD. **DRUG X** was tested for safety on 40 volunteers over a 27-month period. The trial results were published in a media release on December 11, 2017, with two important announcements:

1. The drug proved entirely safe for humans, allowing researchers to plan for the next phase of testing – outcomes.
2. Early indications are that the drug is effective in reducing the amount of huntingtin protein.

What researchers do not yet know is whether or not this reduction will have any effect on people's symptoms. There is hope that by 'silencing' the protein, symptoms may be reduced, stopped or even reversed, but this is not yet known. The next phase of the trial, hopefully starting late in 2018, will investigate this.

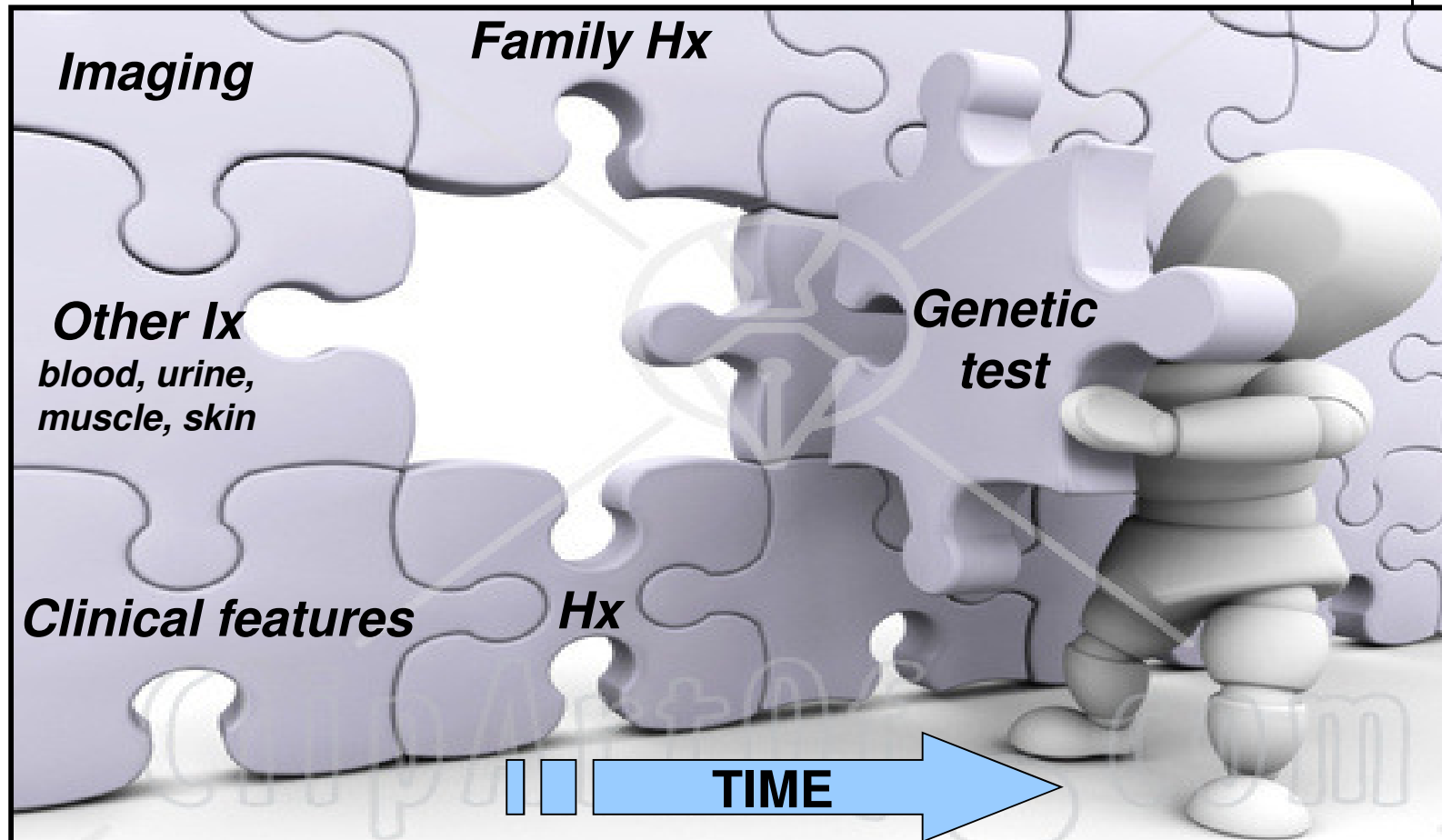
Many people are hoping to get involved with the trial, but at this point there is no indication that the trial will be available in Australia. The best course of action for those located in Australia is to get involved with Enroll-HD, as any trial information or opportunities will come through there. To read the news articles about this new drug, visit our page of news about the drug trial.

Genetic Health Queensland

Great state. Great opportunity.



# Genetic Diagnosis







# Genetic testing *(diagnostic)*



# Genetic testing - indications

<u>Indication</u>	<u>Person</u>	<u>Purpose</u>	<u>Example</u>
<b>Diagnostic</b>	Symptomatic	Diagnose a specific disease	FBN1 gene testing in person with Marfan syndrome
<b>Carrier</b>	Asymptomatic with known high risk for being a carrier (AR, XL)	Determine genetic carrier status for reproductive risks	Cystic fibrosis carrier testing
<b>Predictive</b>	Asymptomatic with a known high risk of genetic condition (AD, AR, XL)	Determine genetic status/risk before onset of symptoms	Huntington disease gene testing in adult offspring of affected person
<b>Prenatal</b>	Pregnant woman	Diagnose/determine risk of a specific disease before birth	Prenatal test for Duchenne muscular dystrophy
<b>Pharmacogenetic</b>	Patient with disease using a medication	Identify variants that impact drug metabolism and dosing	CYP2C9 and VKORC1 variants for warfarin use
<b>Direct-to-consumer</b>	Healthy person or clinical disease	Determine relative (not absolute) risk of a multifactorial condition	Multiple variants that confer a risk to diabetes

# Genetic testing - type/method

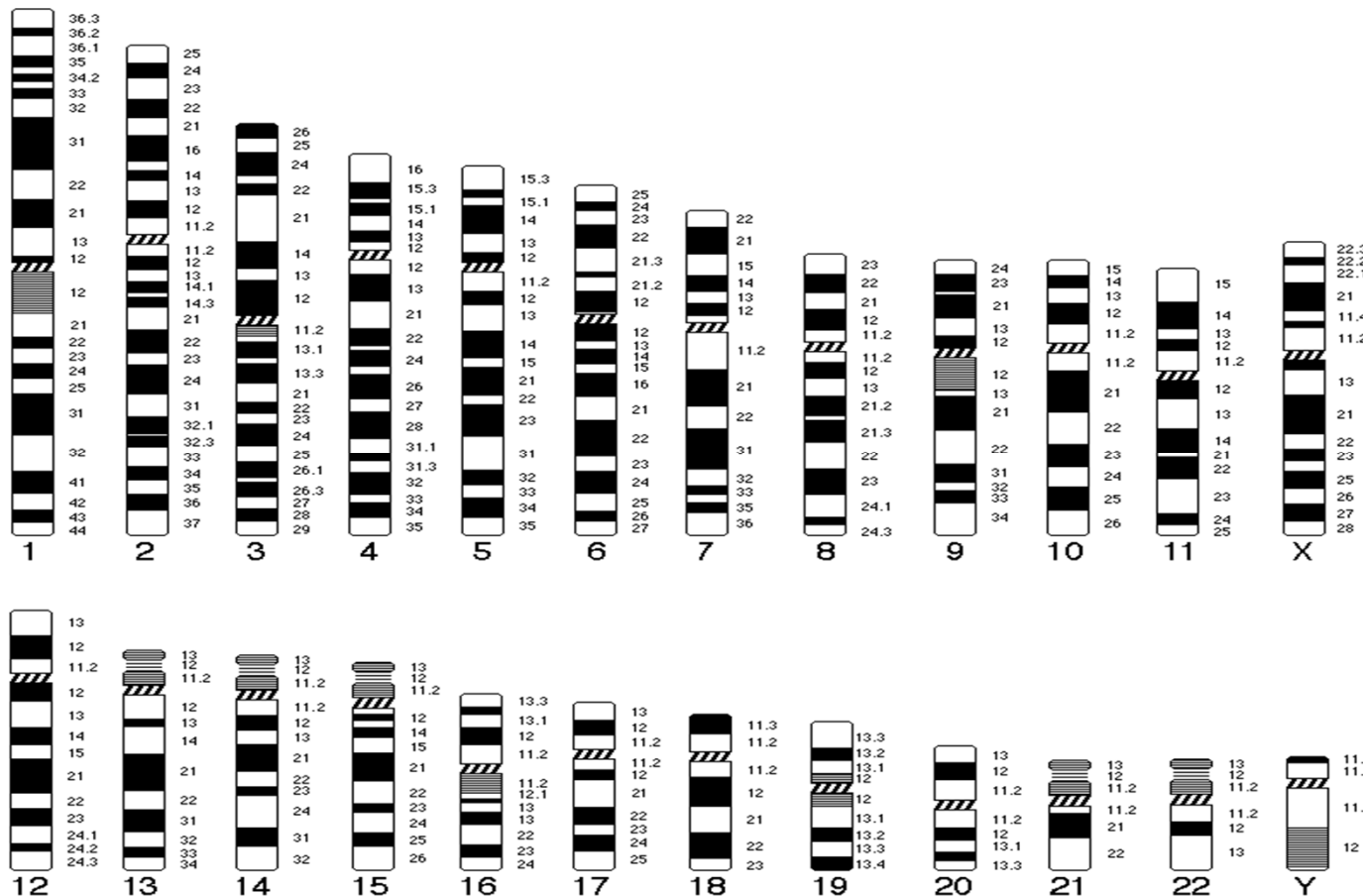


## Test type depends on:

- Suspicion of aetiology/mechanism
  - Chromosomal, single gene, mitochondrial, imprinting
- Limitations of test
  - Resolution, interpretation, Incidental findings
- Cost of test
  - Medicare rebate (Arrays, FRAX), Public (medical dept), Private
- Availability
  - State, Interstate, International
- Time
  - 4 weeks, 3 months, 6+ months



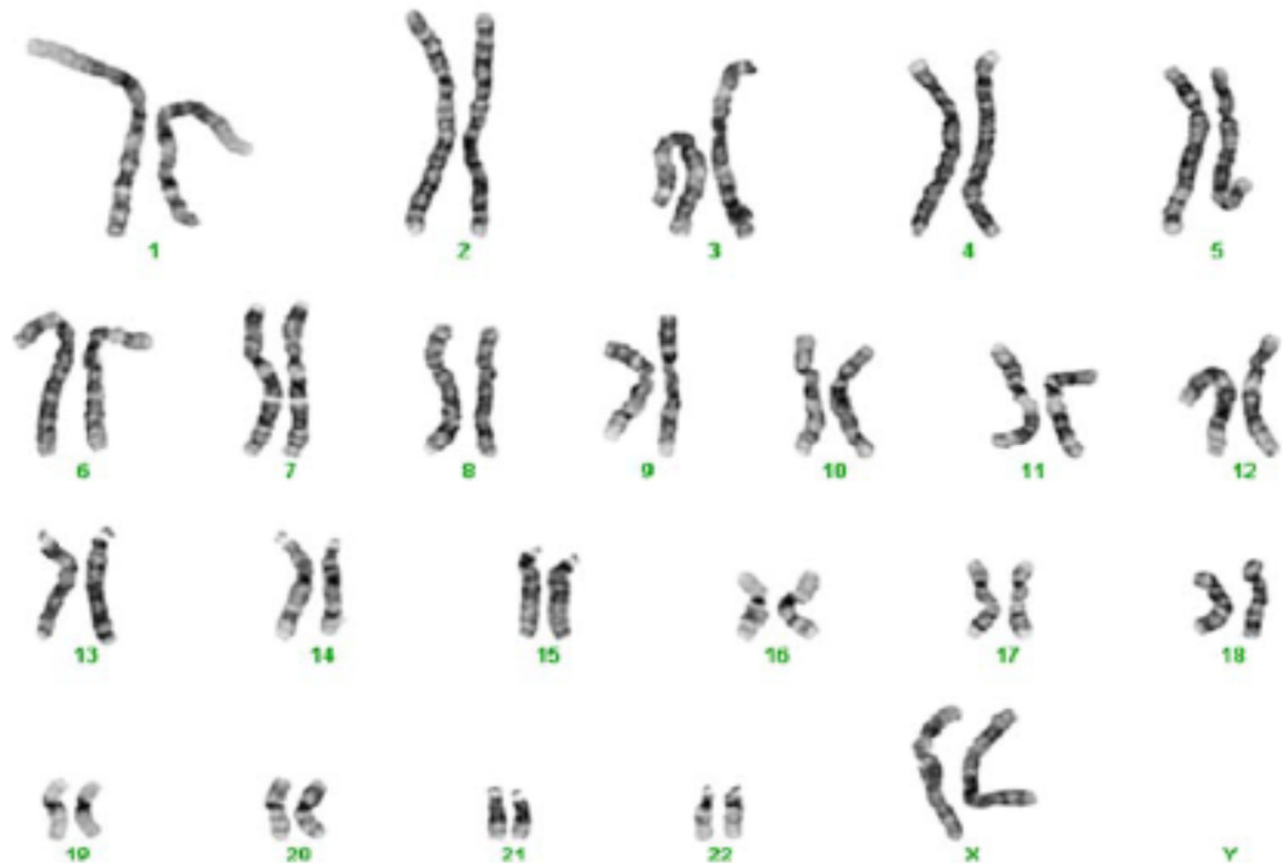
# Genetic testing - Chromosomes



# Genetic testing - Chromosomes



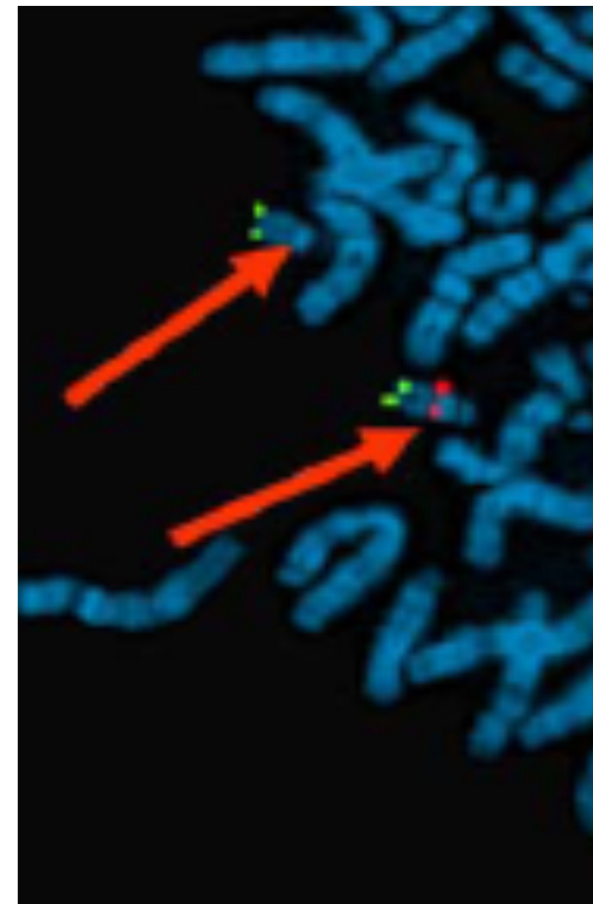
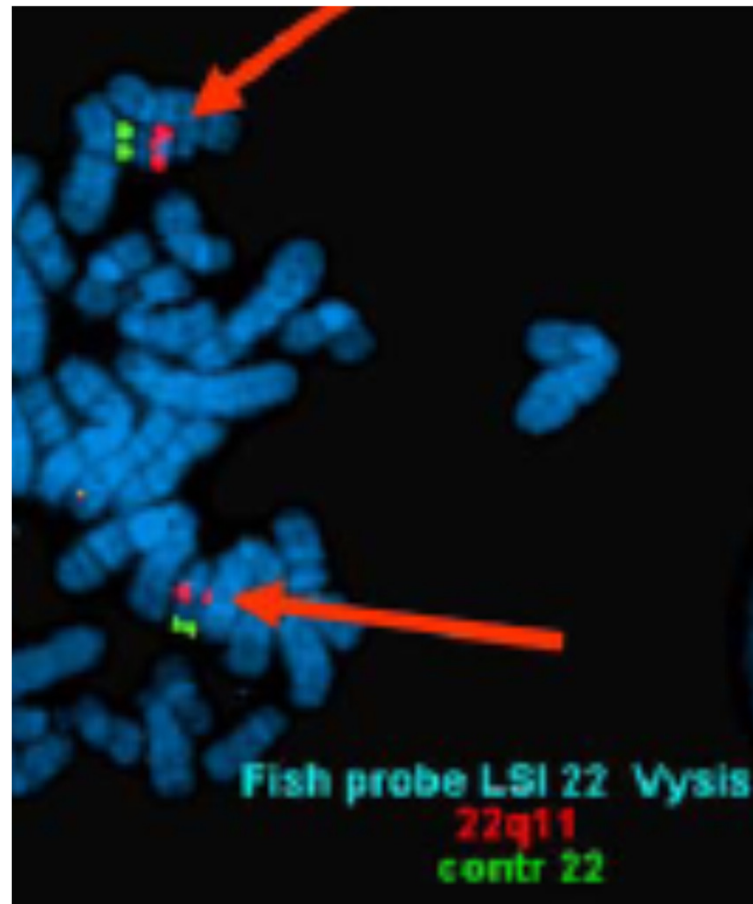
- Karyotype



# Genetic testing - Chromosomes



- FISH

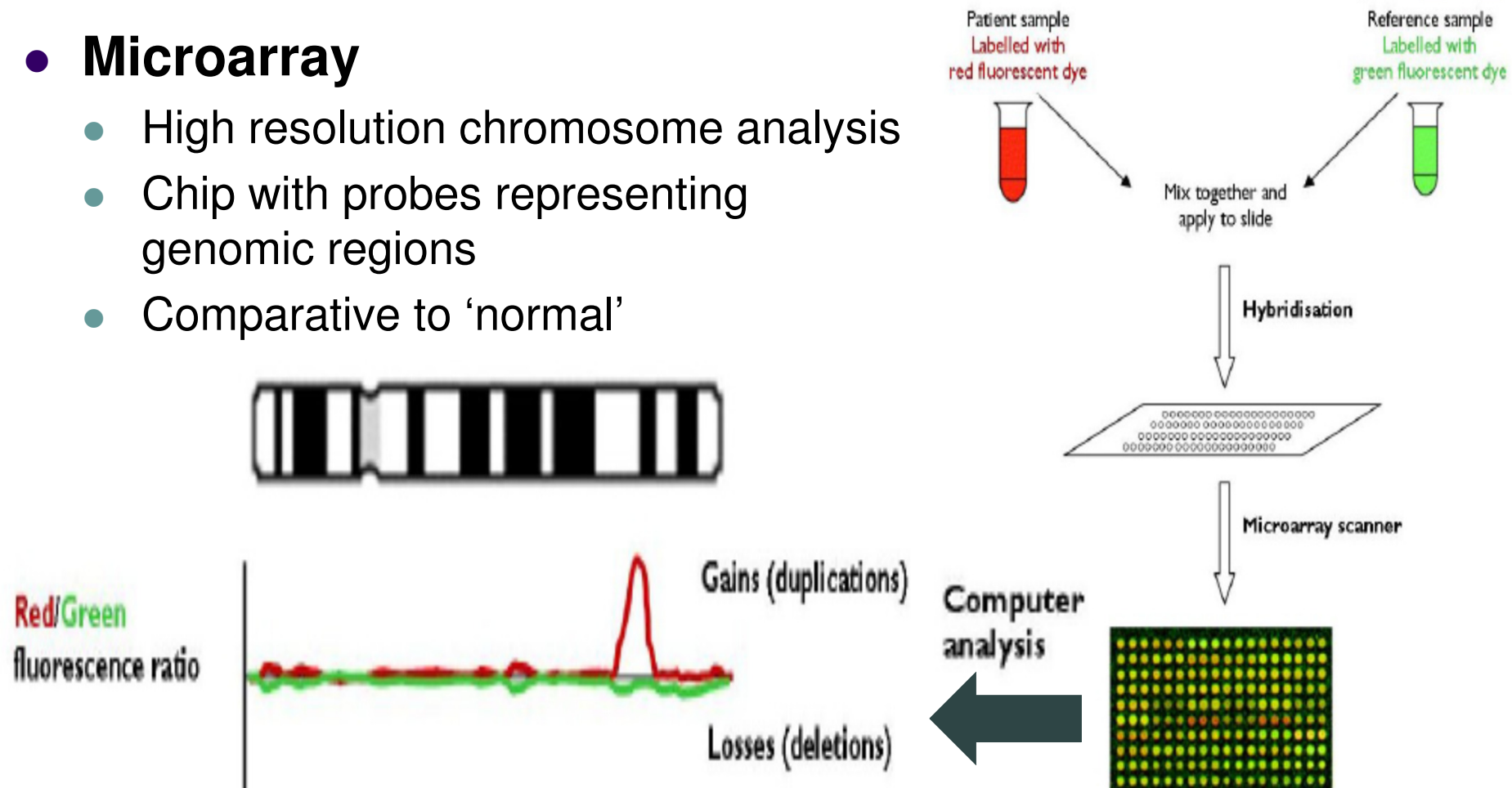


# Genetic testing - Chromosomes



- **Microarray**

- High resolution chromosome analysis
- Chip with probes representing genomic regions
- Comparative to 'normal'



# Genetic testing - Chromosomes



- **Microarray (interpretation)**

- Bioinformatics tools
- Databases
- PubMed
- Gene content of region
- Inheritance

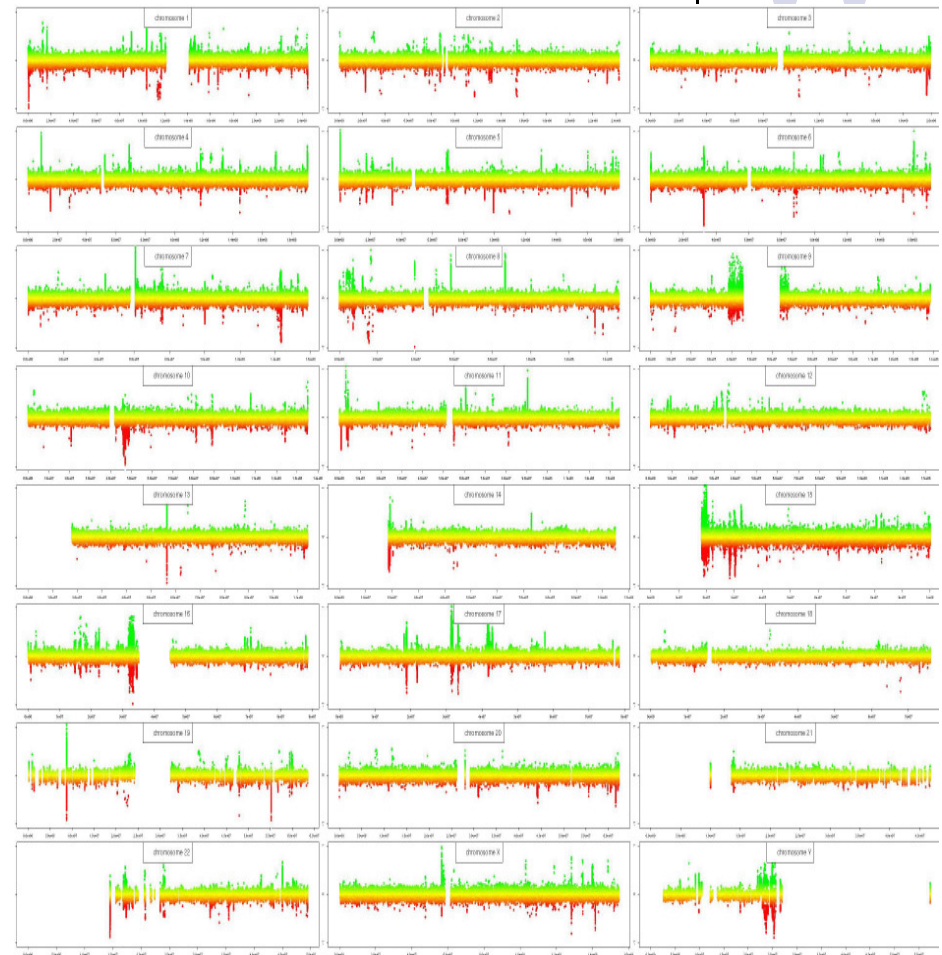
→ Pathogenic

vs.

→ Benign

vs.

→ VOUS (variant of unknown significance)





# Chromosome testing

## • Microarray report

Anomaly detected – del/dup and size

Nomenclature & genomic coordinates

Laboratory interpretation – gene content

Literature review & clinical features

### MOLECULAR KARYOTYPE REPORT

**Summary: ABNORMAL REPORT. Variant of uncertain clinical significance associated with incomplete penetrance and/or variable expressivity DETECTED. Parental samples requested.**

*Clinical information:* Developmental delay, odd posturing, cry sound every 15 seconds.

*Method:* Illumina Whole-Genome Infinium CytoSNP 850K Array v1.1. Results analysed with BlueFuse Multi version 4.2, using genome reference sequence NCBIv37/hg19. Effective resolution 200Kb.

**Result: A 973 Kb deletion was detected at 15q11.2**

*Molecular Karyotype (ISCN 2013):* arr[hg19] 15q11.2(22,299,434-23,272,733)x1

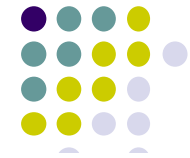
*Interpretation:* Array results show a male molecular karyotype. A heterozygous interstitial deletion of approximately 973 Kb was detected at chromosome 15q11.2, extending from base 22,299,434 to base 23,272,733. The deleted region contains at least 26 known genes between RefSeq genes LOC101927079 and GOLGA8IP, of which one is an OMIM listed disease causing gene [NIPA1; OMIM 608145].

This copy number loss is in a known susceptibility region for developmental delay [Burnside et al., Hum Genet. 2011; 130(4):517-28]. The breakpoints and gene content of the copy number loss seen in this patient corresponds to a "BP1-BP2 deletion" (between breakpoints 1 and 2). Please note that this deletion does not encompass the Prader-Willi/Angelman syndrome critical region, which is between BP2 and BP3.

Common clinical features noted in patients with the BP1-BP2 deletion include developmental delay (including motor and speech delays), congenital heart disease, intellectual disability, autistic features, seizures and behavioural issues [PMID: 25596525]. However, there is phenotypic variability between patients, and the deletion can be inherited from a normal parent. Similar deletions have also been reported in individuals in the normal population.

**Conclusion:** The clinical significance of this copy number change is currently uncertain.

# Genetic testing - Chromosomes



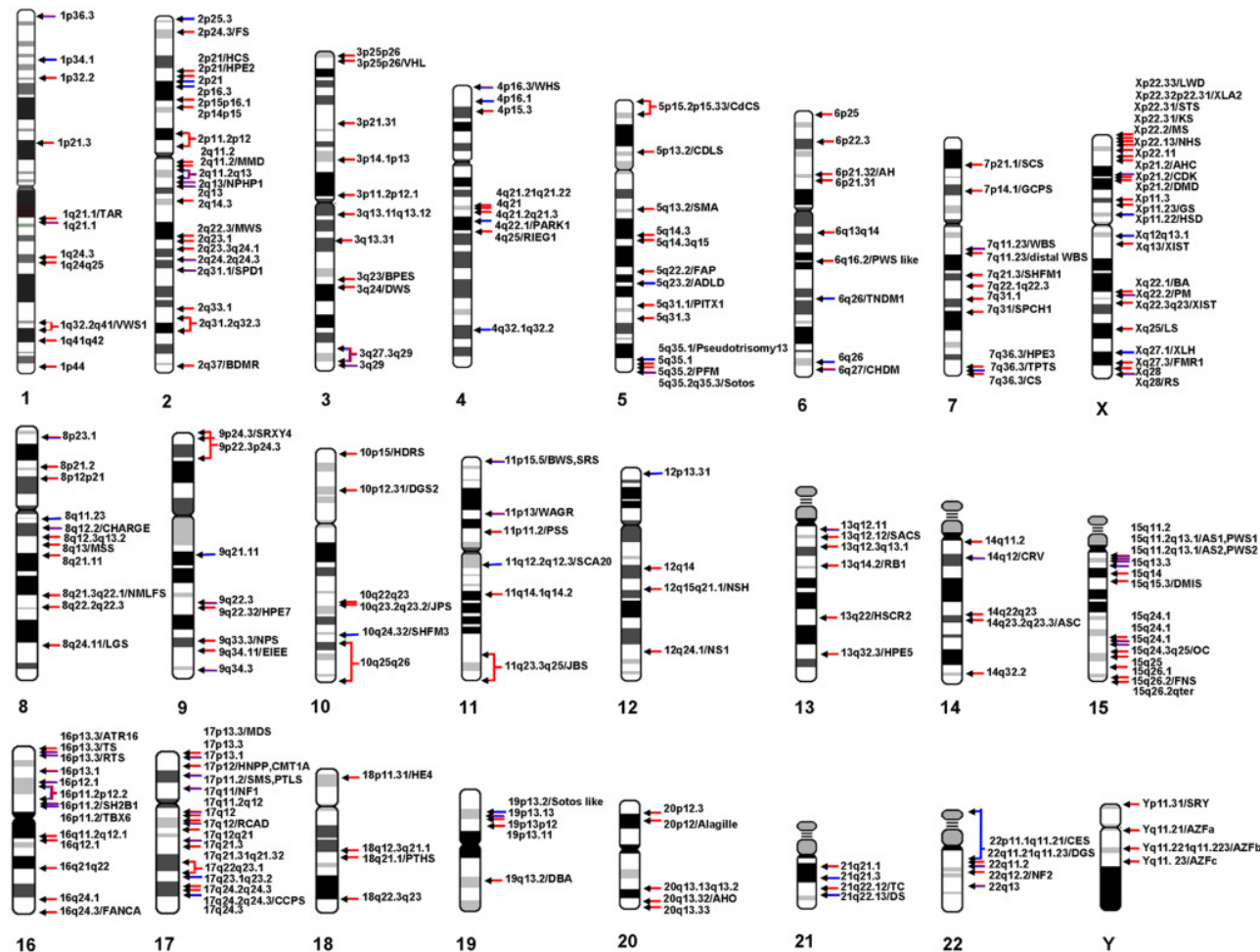
## Chromosome Microarray (CMA) Testing Guide – Children and Adults

Adapted from: Palmer *et al.* Chromosome microarray in Australia: A guide for paediatricians. Journal of Paediatrics and Child Health 48 (2012) E59–E67

1. Patient to undergo CMA testing, a genetic test which checks for DNA copy number variations, not including fragile X
2. Discussion of test process, limitations and counselling about variety of possible outcomes listed below
3. Blood sample collected (5-10ml in EDTA - Confirm sample requirements with local laboratory)
4. Possible laboratory findings include the following:

No abnormality found	Diagnostic of known, expected condition	Variant of unknown significance found	Variant with unexpected implications found
<ul style="list-style-type: none"> <li>• Normal result or known, benign change detected</li> <li>• Consider referral to a genetics clinic if concerns remain about a genetic diagnosis or recurrence in another pregnancy</li> <li>• No further testing required at this stage</li> </ul>	<ul style="list-style-type: none"> <li>• Known copy number variant (CNV) identified</li> <li>• Consider referral to genetics clinic for genetic counselling</li> <li>• No further testing required at this stage</li> </ul>	<ul style="list-style-type: none"> <li>• Copy number variant of unknown significance (VOUS) identified</li> <li>• Consider referral to genetics clinic for interpretation of report and diagnostic review</li> <li>• Further testing such as parental studies may be useful</li> </ul>	<ul style="list-style-type: none"> <li>• Copy number variant of unexpected significance identified</li> <li>• Consider referral to genetics clinic for interpretation of report and genetic counselling</li> <li>• Further testing such as parental studies may be useful</li> </ul>

# Chromosomes anomalies



Genetic Health Queensland

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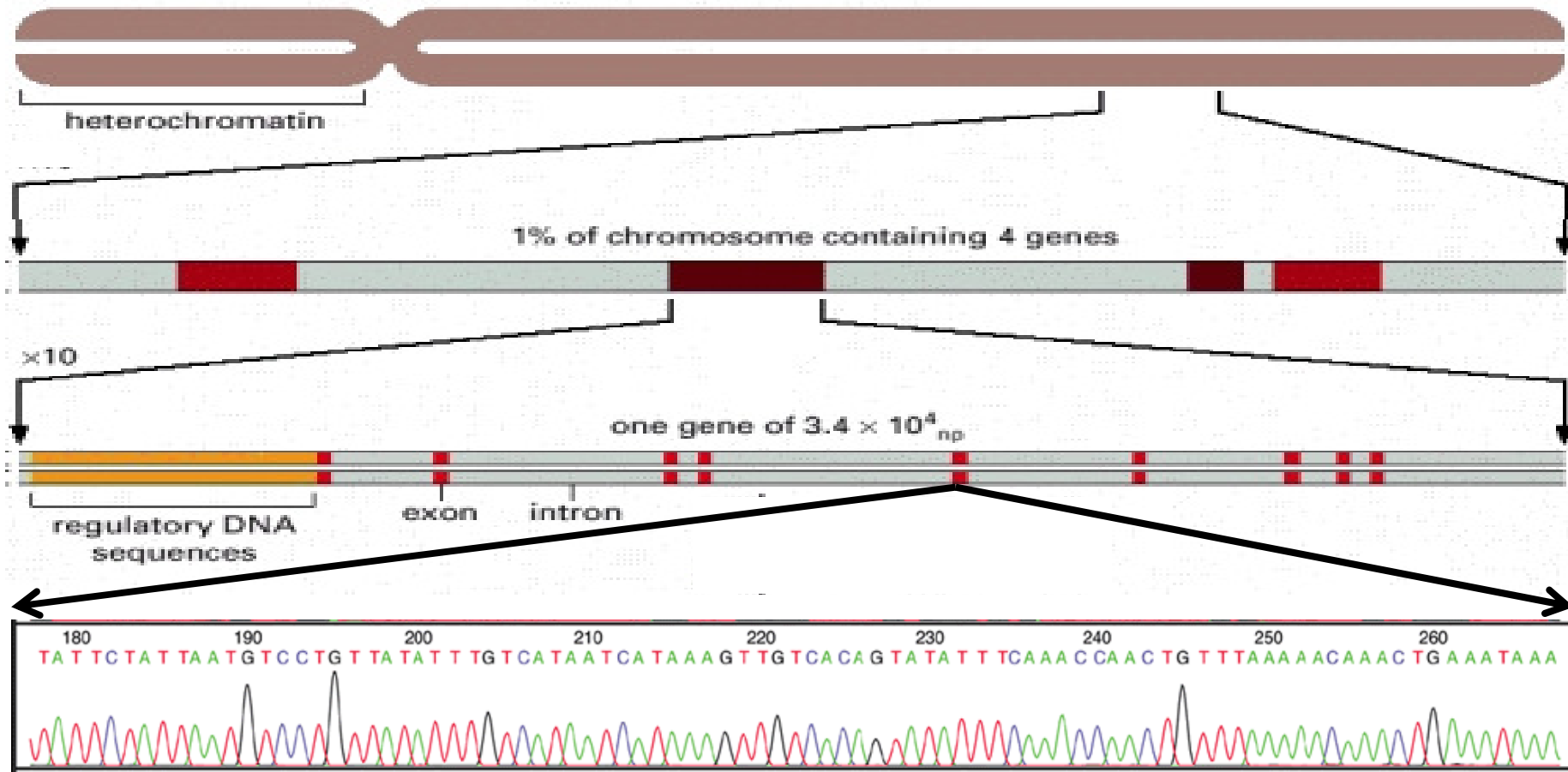




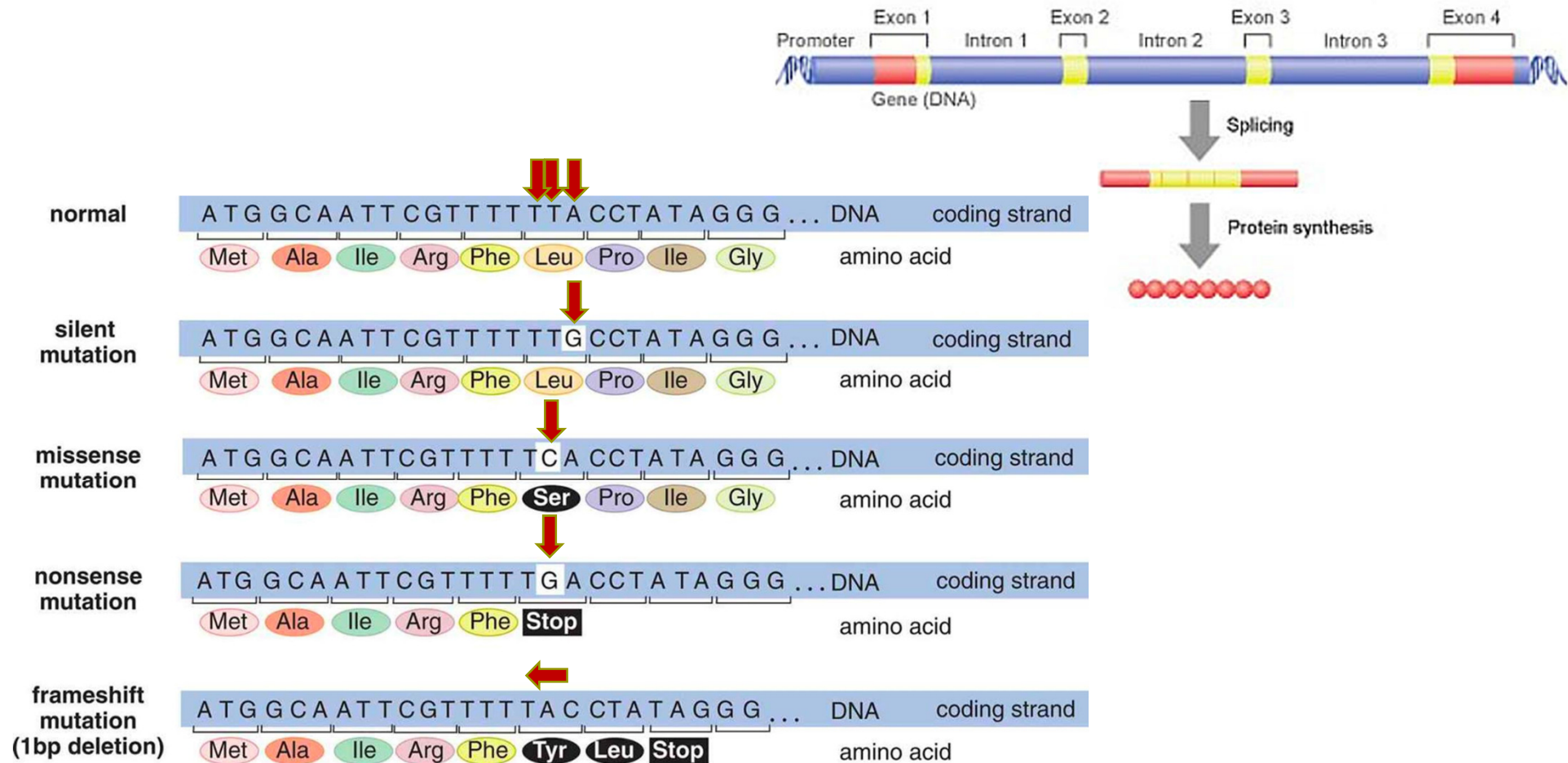
# Chromosome → Gene → Nucleotide



human chromosome 22— $48 \times 10^8$  nucleotide pairs of DNA

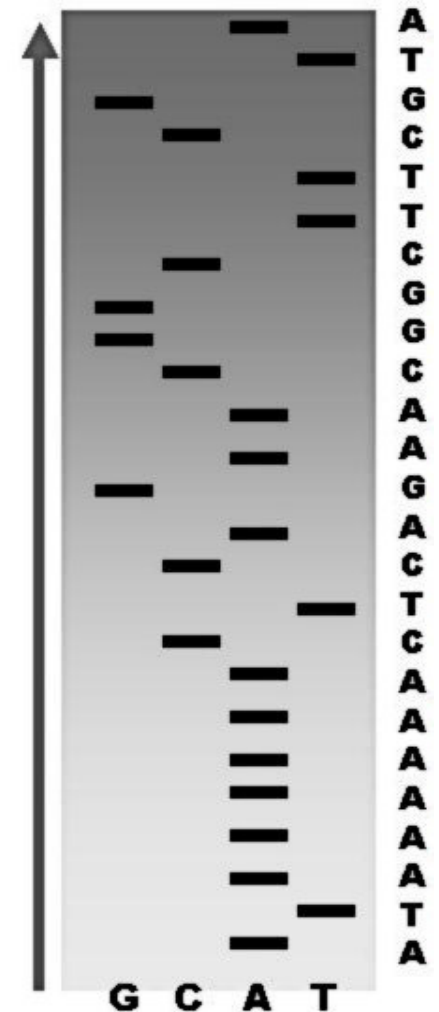
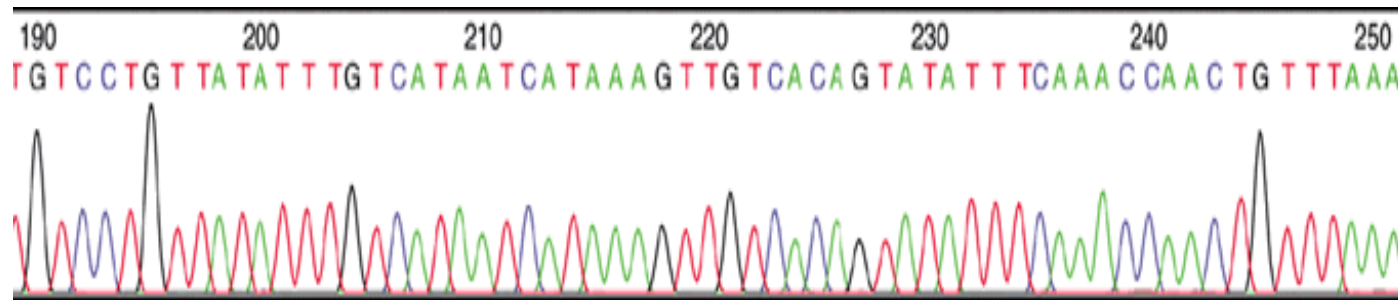


# Single gene mutations



# Genetic testing - Single gene

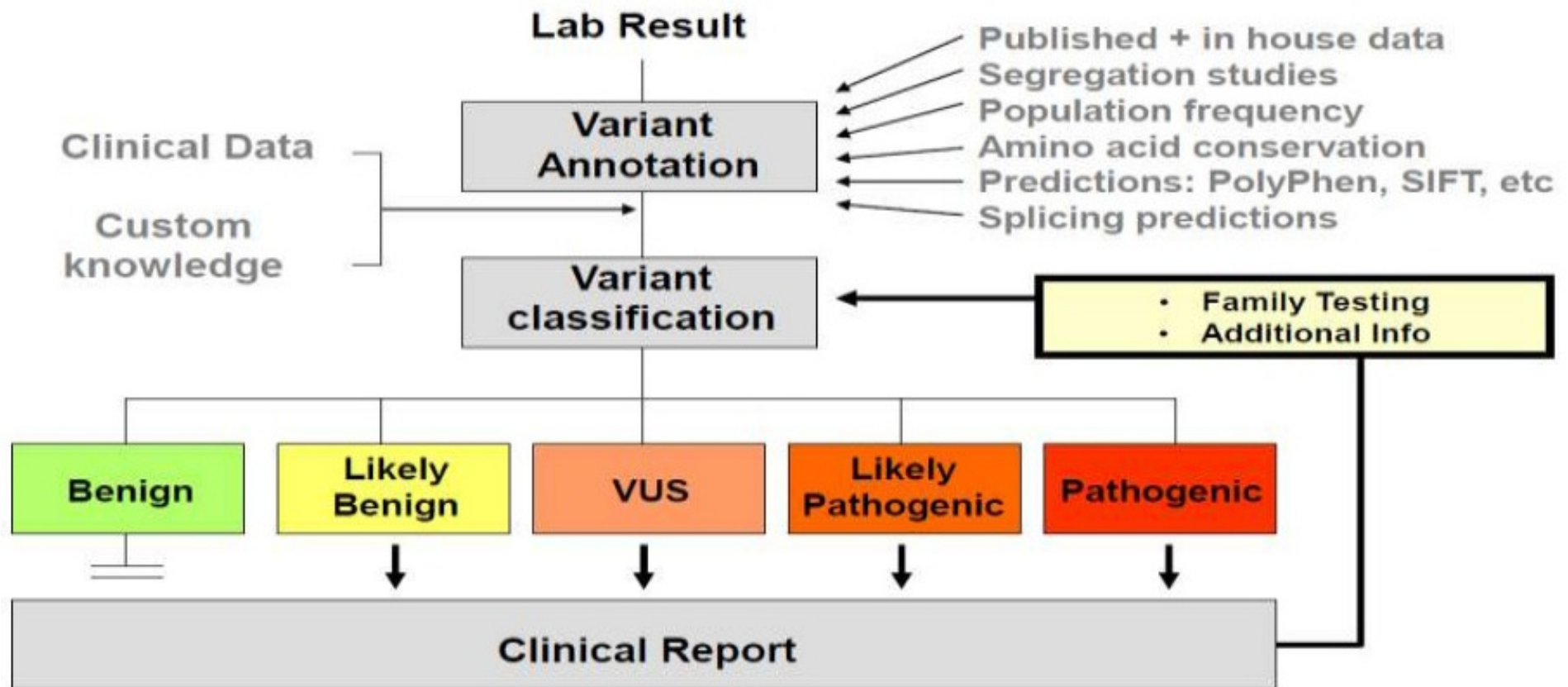
- **Sanger sequencing (1970's)**
  - Gold standard
  - Basis of Human Genome Project
    - (cost \$3billion over 13 years)
  - One gene at a time
  - Low error rate
  - Evolved from 'gel' → 'capillary' electrophoresis with fluorescent tags





# Genetic testing - gene

## Interpretation/report

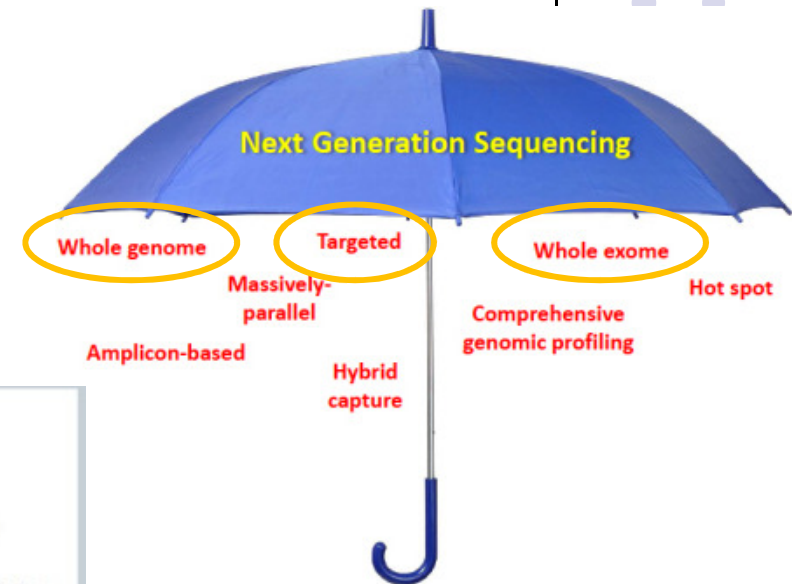
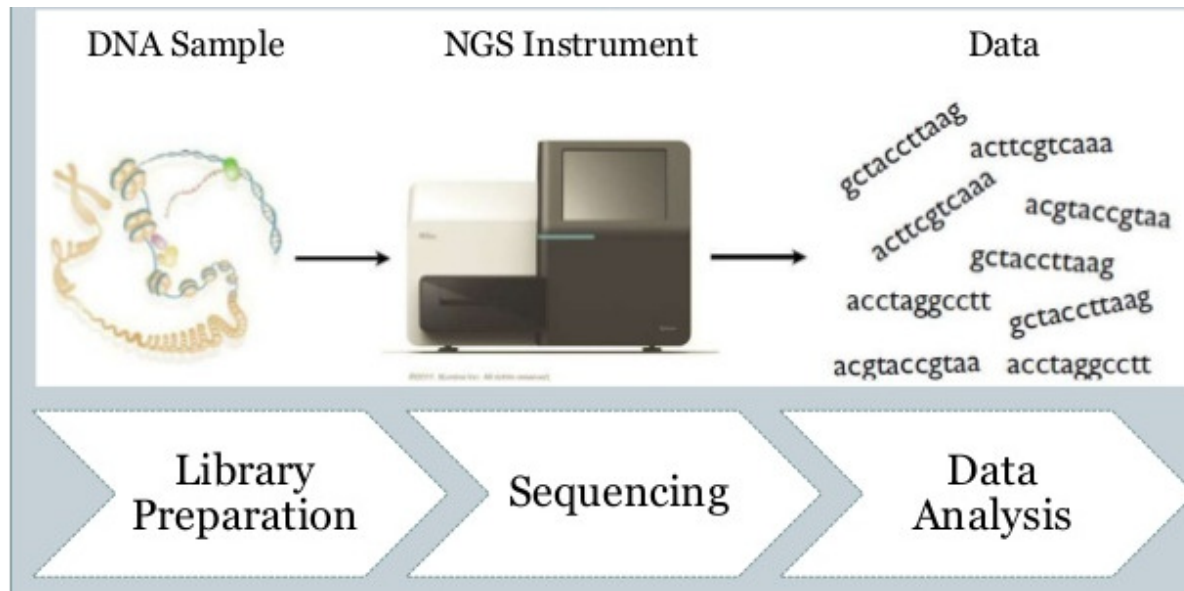


# Genetic testing - Next generation sequencing (NGS)



## ● NGS pipeline

- Cost effective
  - automated, cheaper, faster
- High throughput
  - more samples/genes in one experiment



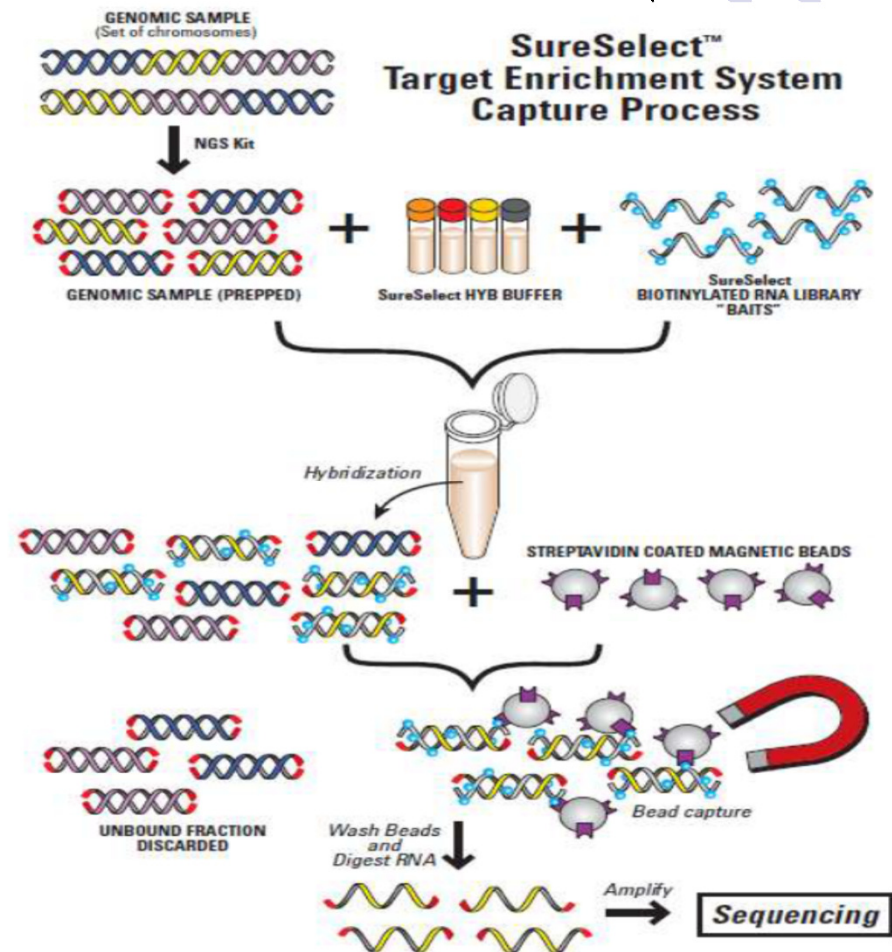


# Genetic testing - NGS



## Library prep/sequencing

- Patient DNA fragmented into smaller sizes
- Add 'baits/fragments' of target sequence  
Target = panel of genes OR  
exome OR  
genome
- Hybridized patient DNA/baits is captured (e.g. with beads)
- Sequence captured fragments using a platform/sequencing method/machine
- +++ platforms, capture/sequencing methods, machines available from different companies



# Genetic testing - NGS

## Target

Panel of genes

Clinical exome

(~5000 known disease genes)

Whole exome

(All ~24000 genes)

Genome

## Analysis

Panel of genes

Clinical exome

(~5000 known disease genes)

Whole exome

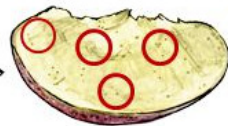
(All ~24000 genes)

Genome

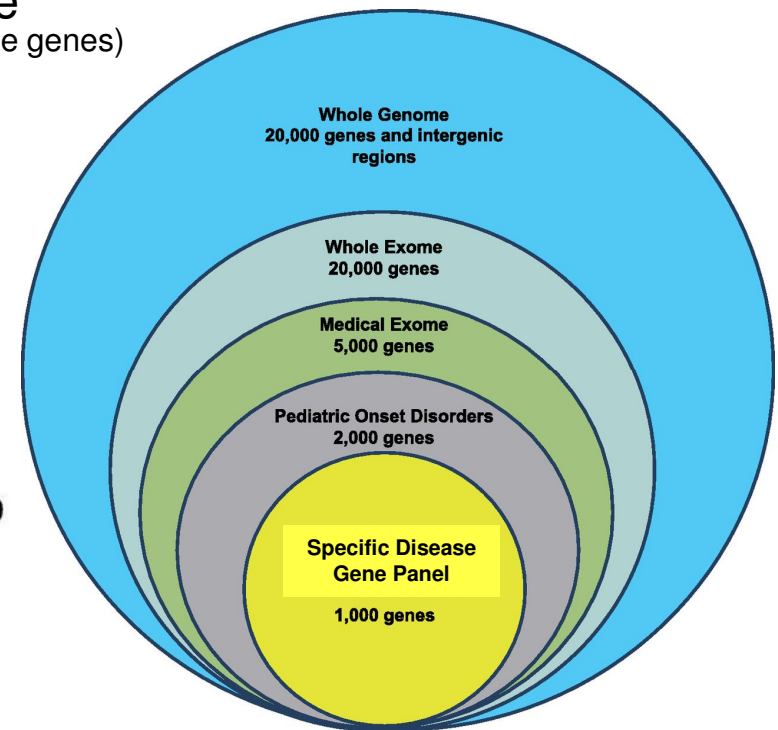
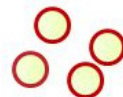
Whole  
Genome



Exome = 1 %



Targeted= 10 to 500  
epilepsy genes

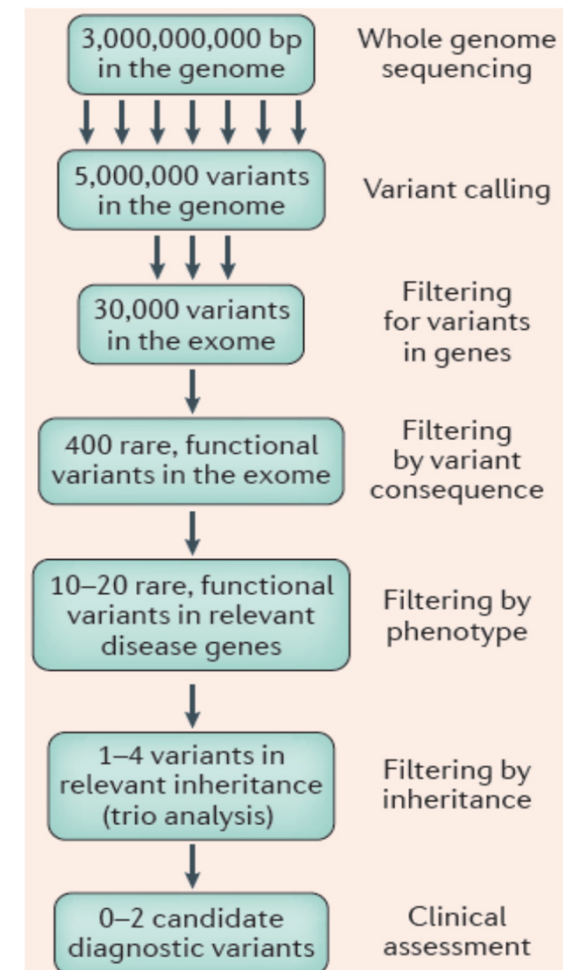
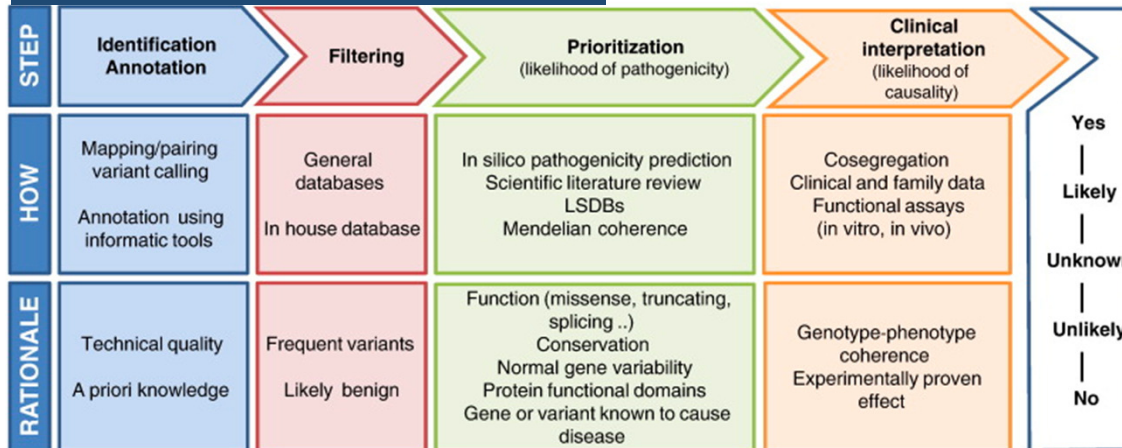
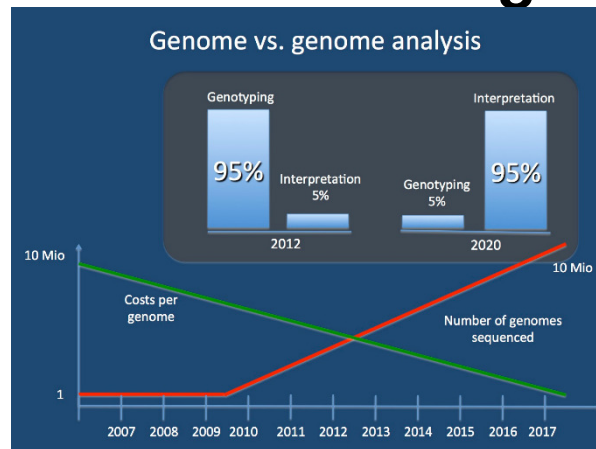


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# Genetic testing - NGS

## Variant filtering and interpretation

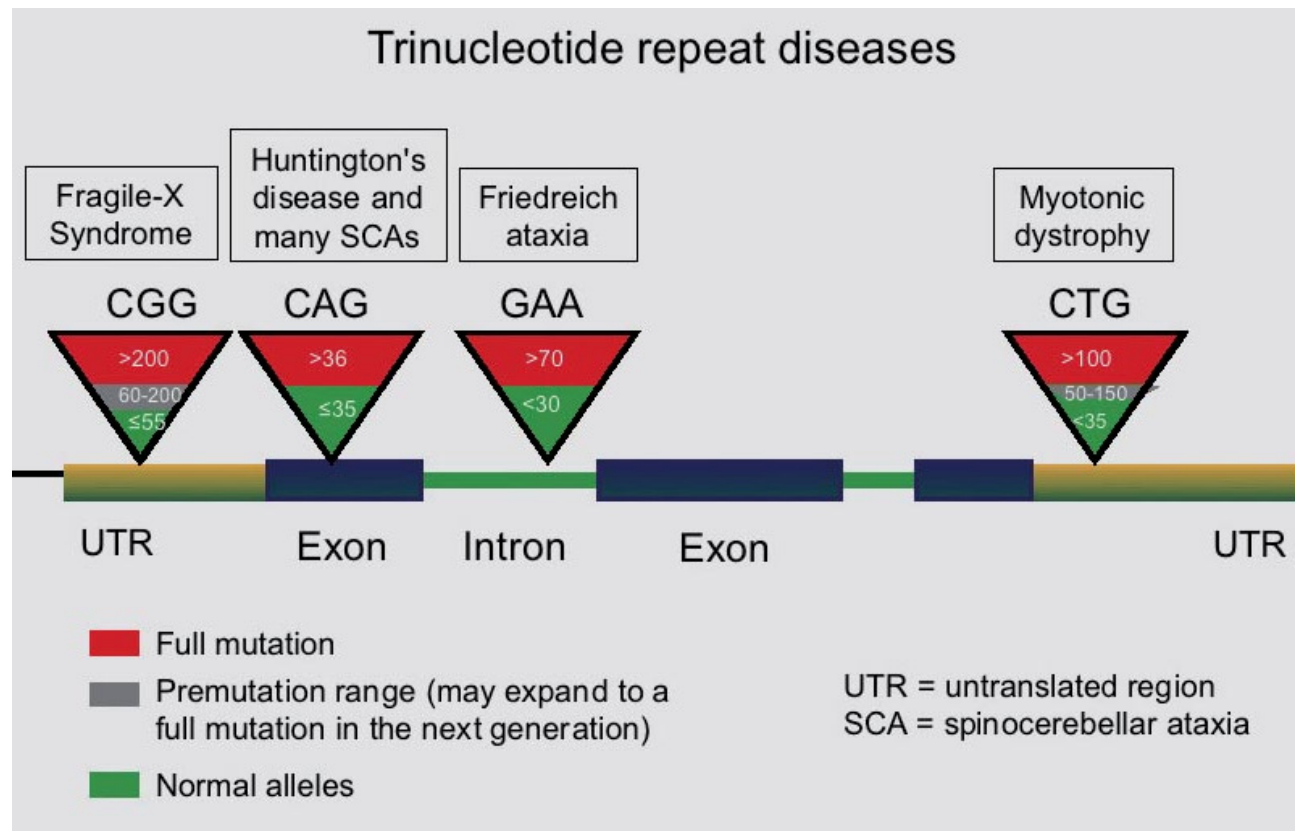




# Genetic testing - NGS - caveats



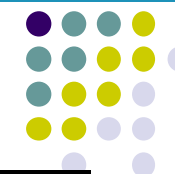
Understand the types of mutations with each gene



Not detected by:

- Sanger sequencing
- MLPA
- Panels
- Exomes
- Genomes

# Gene(tic) testing



	Single Gene	Panel	Exome	Genome
Targeted	+++	++	-	-
No. variants to interpret	minimal	few	many	numerous
Risk of incidental findings	unlikely	very low	possible	possible
Applicable to genetically heterogeneous diseases	no	yes	yes	yes
Complex lab process	-	+	++	+++
Turnaround time	+	++	+++	+++
Data can be reinterrogated	no	yes	yes	yes

# NGS testing

## • report

### TEST PERFORMED

#### Intellectual Disability

(499 Gene Panel; Including 3 Added Genes - *KAT6A*, *KAT6B*, *KMT2A*; gene sequencing with deletion and duplication analysis)

### RESULTS:



A heterozygous pathogenic variant consistent with a molecular diagnosis of a *FOXP2* related condition was identified.

Additionally, 7 variants of potential clinical relevance are identified.

#### Clinically Significant Variants

Gene Info		Variant Info		
GENE	INHERITANCE	VARIANT	ZYGOSITY	CLASSIFICATION
<i>FOXP2</i> NM_014491.3	Autosomal Dominant	c.1191dup p.Glu398Argfs*31	Heterozygous (maternally inherited)	Pathogenic

#### Additional Variants of Potential Clinical Relevance

Gene Info		Variant Info		
GENE	INHERITANCE	VARIANT	ZYGOSITY	CLASSIFICATION
<i>PPOX</i> NM_000309.4	Autosomal Dominant & Autosomal Recessive	c.82C>T p.Pro28Ser	Heterozygous	Unknown Significance
<i>COG7</i> NM_153603.3	Autosomal Recessive	c.1766G>A p.Arg589His	Heterozygous	Unknown Significance
<i>POMT1</i> NM_007171.3	Autosomal Recessive	c.1565G>A p.Arg522Lys	Heterozygous	Unknown Significance
<i>AHI1</i> NM_017651.4	Autosomal Recessive	c.2906C>G p.Thr969Ser	Heterozygous	Unknown Significance
<i>IGF1R</i> NM_000875.4	Autosomal Dominant & Autosomal Recessive	c.1940G>A p.Arg647His	Heterozygous	Unknown Significance
<i>PCNT</i> NM_006031.5	Autosomal Recessive	c.8431G>T p.Val2811Leu	Heterozygous	Unknown Significance
<i>SMARCA4</i> NM_001128849.1	Autosomal Dominant	c.829C>T p.Pro277Ser	Heterozygous	Unknown Significance



# NGS testing - report

Variant nomenclature  
– nucleotide/amino acid change

Disease and clinical  
features linked to that gene

A heterozygous variant in the FOXP2 gene, NM\_014491.3:c.1191dup (p.Glu398Argfs\*31), was identified in the submitted specimen. Autosomal dominant mutations in FOXP2 have been associated with speech-language disorder-1 (SPCH1), which is also known as speech and language disorder with orofacial dyspraxia (PubMed: [20301615](#); OMIM: [602081](#)). The disorder is characterized by abnormal development of several brain areas critical for both orofacial movements and sequential articulation, resulting in marked disruption of speech and expressive language. Limited studies have suggested that variants in FOXP2 gene may be associated with autism spectrum disorders, but more recent data indicate that this association is unlikely (PubMed: [10889044](#), [11894222](#)). This frameshift variant, p.Glu398Argfs\*31, is the result of the insertion of one base pair which leads to an out of frame transcript, and the introduction of a premature stop codon. This variant is predicted to result in loss of function of the protein product of the FOXP2 gene either as the result of protein truncation, or of nonsense mediated mRNA decay. While this truncating variant has not, to our knowledge, been reported in the literature, truncating variants downstream of this position have been reported to be pathogenic (PubMed: [23918746](#), ClinVar:419394). This variant has not been reported in the Broad dataset (individuals without severe childhood onset disease). This frameshift is predicted to result in a premature truncation of the protein product encoded by this gene. The laboratory considers this variant to be pathogenic.

Predicted effect of variant

Control databases

Laboratory interpretation  
of variant



# Genetic testing costs

Test	Cost (\$)
Karyotype	400
FISH	150
Microarray	600
Cystic fibrosis (50 common mutations)	180
AS/PWS	400
Myotonic dystrophy	500
Gene panel test	1500
Whole genome	3000

Test	Cost (\$)
FBC	15
Urine metabolic	65
Lactate	15



# Genetic testing - consent

## **Consent with (diagnostic) clinical genomic/genetic testing:**

(ACMG recommendations)\*

- A clear distinction should be made between clinical and research testing
- Counselling should:
  - include written documentation of consent from the patient
  - be performed by a medical geneticist/affiliated genetic counsellor (if genomic)
- Pretest counselling should include a discussion of:
  - potential benefits and risks of test and alternatives to such testing
  - nature of and limitations of such testing
  - type of analysis performed
  - expected outcomes of testing (+ve, -ve, VOUS)
  - likelihood and type of incidental results that may be generated
  - potential implications for family members



# Challenges: DTC testing

- **NOT** available/funded in public system (GHQ)
- GHQ do not see patients who are considering or have had DTC
- Caution:
  - Do not test for all genetic disorders
  - Mostly tests for 'variations' not mutations in genes
  - Confers a 'relative risk' of common multifactorial diseases
  - Not useful for Mendelian rare genetic diseases



# Reproductive Genetics



## Key Components of Preconception Care

1. Reproductive life plan
2. Past reproductive history
3. Medical assessment
4. Medication use
5. Infections & immunizations
6. Genetic risks
7. Healthy weight & nutrition
8. Psychological & behavioral risks
9. Healthy environment
10. Physical assessment





# Carrier Screening

- Ideally screen before pregnancy
- Typical for AR and XL diseases
  - Haemoglobinopathies
  - Cystic fibrosis
  - Spinal muscular atrophy
  - Fragile X
- Particularly for those with a +ve family history
  - Available/funded in public system (via GHQ)
  - Requires prior identification of the specific familial gene mutation



# Carrier Screening

- Population screening for common conditions for those with NO family history
- Available/funded in public system (GHQ) when:
  - Condition is inherited in autosomal recessive manner  
**AND**
  - Partner of individual is proven carrier of condition  
(or at risk based on their family history)  
**AND**
  - Population frequency of being a carrier is  $>1/50$ 
    - e.g. cystic fibrosis, congenital adrenal hyperplasia,
    - e.g. spinal muscular atrophy, alpha/beta thalassaemia



# Carrier Screening

- Population screening for common conditions for those with NO family history
- **NOT** Available/funded in public system (GHQ) when:
  - Individuals have no family history of condition (AR or XL)
  - AND/OR**
  - Population frequency of being a carrier is  $<1/50$ 
    - e.g. autosomal recessive polycystic kidney disease ( $\sim 1/70$ )
    - e.g. galactosaemia ( $\sim 1/110$ )
    - e.g. Pompe disease ( $\sim 1/190$ )

## **REGARDLESS OF**

- Confirmation that partner of individual is proven carrier of disease



# Carrier Screening

- Population screening for common conditions for those with NO family history
- **NOT** Available/funded in public system (GHQ)
- Many self-funded 'carrier' genetic tests in the market
- Caution:
  - Do not test for all AR/XL disorders
  - Sometimes only test for common mutations in the genes listed
  - Negative result does not completely exclude being a carrier (residual risk may still present)



# Combined first trimester screening

- Primarily designed for fetal aneuploidy
  - Initially T21
  - Data now routinely available for T18 & T13
  - Note that screening is NOT diagnostic
- Most screening locally uses combination of:
  - Maternal age ( $\uparrow$  age  $\propto$   $\uparrow$  risk aneuploidy)
  - Nuchal translucency ( $\uparrow$  NT  $\propto$   $\uparrow$  risk aneuploidy)
  - B-hCG ( $\uparrow \propto$  T21,  $\downarrow \propto$  T18, T13)
  - PAPP-A ( $\downarrow \propto$  T21, T18, T13)
  - (fetal nasal bone)



## Combined first trimester screening

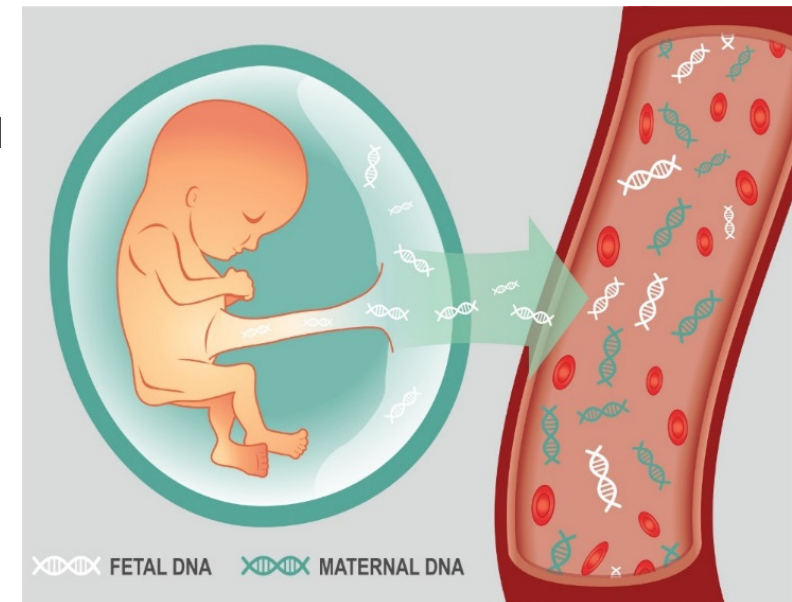
- Risk is expressed as being 'increased' or 'decreased'
- Less than 1 in 300 is traditionally considered 'increased'
- Women at increased risk can be offered invasive diagnostic testing (CVS or amniocentesis)

Method of screening	DR (%)
Maternal age (MA)	30
MA and maternal serum biochemistry at 15–18 weeks	50–70
MA and fetal nuchal translucency (NT) at 11–13 <sup>+</sup> <sub>6</sub> wks	70–80
MA and fetal NT and maternal serum free $\beta$ -hCG and PAPP-A at 11–13 <sup>+</sup> <sub>6</sub> wks	85–90
MA and fetal NT and fetal nasal bone (NB) at 11–13 <sup>+</sup> <sub>6</sub> wks	90
MA and fetal NT and NB and maternal serum free $\beta$ -hCG and PAPP-A at 11–13 <sup>+</sup> <sub>6</sub> wks	95



## Non-Invasive Prenatal Testing/Screening (NIPT/S)

- Screening NOT diagnostic test
- From 10 wks gestation
- Fragments of fetal DNA cross into maternal blood
- Maternal blood test can measure fetal DNA
- Screening test for some chromosome anomalies
  - Trisomy 13, Trisomy 18, Trisomy 21
  - Sex chromosomes - Turner syndrome
- Potentially avoids need for invasive testing
- Useful in gender identification for sex-linked disorders
  - Avoids invasive testing if fetus is female
- Not yet available to test single gene disorders (e.g. CF)







# Prenatal testing

- Invasive test to sample fetal cells
- Diagnostic test for couples with:
  - High risk pregnancies from NIPT and/or CFTS
  - Chromosomal analysis
- Predictive test for fetus/baby with:
  - Family history of genetic disease
  - Requires prior identification of the specific familial gene mutation or chromosome anomaly





# Prenatal testing

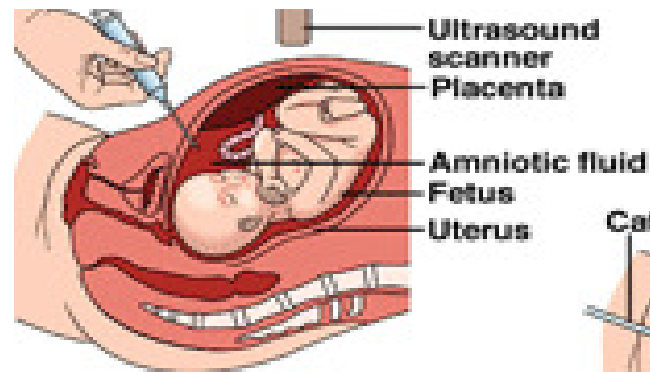
- Available in public and private systems

- **Chorionic villus sampling (CVS)**

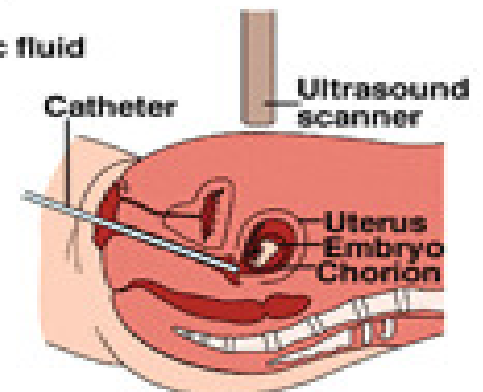
- from 11 wks gestation
- sample of placenta
- miscarriage risk 1-2%

- **Amniocentesis**

- from 16 wks gestation
- sample of amniotic fluid
- miscarriage risk 0.5-1%



(a) Amniocentesis

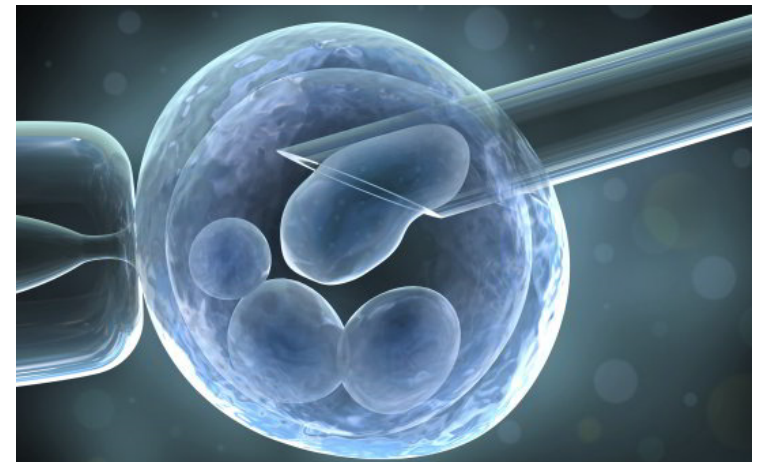


(b) Chorionic villus sampling



# Pre-implantation Genetic Diagnosis (PGD)

- Requires prior identification of the specific familial gene mutation or chromosome anomaly
- Private (self funded)
- Specialised PGD centres (not just any IVF specialist)
  - IVF process (fertile/non fertile couples)
  - Embryos tested for specific familial gene mutation
  - Unaffected embryos implanted
- Complex issues
  - Financial, time, success rates of IVF
  - Emotional, psychological
  - Prior lab work up
    - needs to know their technology will be able to find the mutation





# Options for family planning

- Be fully informed about risk to children
- Route taken depends on person/couple's own views
- **A) Do nothing (natural course)**
  - Parents with low risk to children (i.e. *de novo* cases)
  - Those who would not pursue pregnancy testing options
  - Where a specific familial gene mutation is unidentified/unknown
- **B) Sperm or egg donation**
  - Those who would not pursue pregnancy testing options
  - Where a specific familial gene mutation is unidentified/unknown
- **C) Detailed anomaly scans (USS/MRI) via maternal-fetal medicine**
  - Those who would not pursue pregnancy testing options
  - Where a specific familial gene mutation is unidentified/unknown
  - Where structural anomalies are part of condition and detectable antenatally
- **D) Prenatal (invasive) testing**
- **E) Pre-implantation genetic diagnosis (PGD)**





# Pregnancy management

- Affected females (with a genetic disease) should discuss family planning with their medical team
- If high risk, should be managed by obstetric medicine physician in tertiary centre
- Issues to clarify
  - Effects of their medication on fertility
  - Effects of their medication on baby
    - Teratogenic effects e.g. anti-epilepsy meds
  - Risk/effect of bearing a pregnancy on disease
    - based on severity of their disease
    - e.g. kidneys, heart, lungs





# Ethical, legal, & social issues



# Predictive testing

- **Predictive = at-risk pre-symptomatic child/adult**
- Role of clinical genetics service
- Testing and counselling offered in public system (GHQ)
- Requires prior identification of familial genetic mutation
- e.g. conditions
  - Marfan syndrome, cardiomyopathy, arrhythmia
  - Huntington disease, AD polycystic kidney disease
  - Spinocerebellar ataxia, genetic early onset dementia





# Predictive testing - issues

- Needs genetic counselling to discuss pros/cons of testing

## Pros

- › Management planning  
e.g. treatment, screening
- › Anxiety of not knowing
- › Reproductive planning
- › Career/lifestyle planning

## Cons

- › No treatment available
- › Anxiety of symptom development
- › Genetic guilt
- › Diagnostic label/stigma
- › Financial/employment/insurance discrimination
- › Effect on family dynamics/relationships
- › Altered parental rearing
- › Loss of autonomy for child



# Genetic testing - consent

## Consent with (predictive) clinical genetic testing:

- Counselling should:
  - include written documentation of consent from the patient
  - only be performed by a medical geneticist/affiliated genetic counsellor
- Pretest counselling should include a discussion of:
  - potential alternatives to such testing
  - expected outcomes of testing (+ve or -ve)
  - potential implications for family members
  - potential advantages of the test
  - potential disadvantages/risks of test

# HD predictive testing pathway



- Stage 1 (Genetic counsellor)
  - Disease information, genetics, risk,
  - Test characteristics
  - Predictive testing pros/cons
  - Clarify professional and family support systems
- Stage 2 (Psychologist)
  - Identify any pre-existing risk factor
  - Evaluate current mental state
  - Discuss/evaluate potential impact of result

# HD predictive testing pathway



- Stage 3 (Clinical Geneticist)
  - Clinical review and assessment
  - Review motivation for testing and any issues
  - Pathology request, consent for testing
- Stage 4 (Clinical Geneticist)
  - Results given face to face
- *Optional stage 5 (Psychology/Genetic Cllr)*
  - *Discuss impact/issues post results*



## Parliamentary Committee & life insurance industry

- Australian Joint Parliamentary Committee on Corporations and Financial Services held an Inquiry into the Life Insurance Industry in 2016-18.
- Recommendations in relation to genetic information:
  - **9.1** - The Financial Services Council, in consultation with the Australian Genetic Non-Discrimination Working Group, assess the consumer impact of imposing a moratorium on life insurers using predictive genetic information, unless the consumer provides genetic information to a life insurer to demonstrate that they are not at risk of developing a disease.
- Recommendations in relation to access to medical information:
  - life insurers request authorisation to access a consumer's medical information at the time of an application for an insurance policy and when making a claim.
  - the Financial Services Council and the **RACGP** collaborate to prepare and implement agreed protocols and standards for:
    - Requesting and providing relevant medical information only — not complete medical files;
    - uniform authorisation forms for access to medical information



## Ethical, legal, & social scenarios

- When children are found by the neonatal screening programme to be carriers of cystic fibrosis, it is best not to inform the family because of the unnecessary worry this can engender during childhood.

Strongly Disagree	Disagree	Undecided	Agree	Strongly Agree
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# Ethical, legal, & social scenarios



- A female carrier of X-linked haemophilia A has two daughters under 10 years.
- They are at 50% risk of being carriers.
- They should have a genetic test now to see if they are carriers.

Strongly Disagree	Disagree	Undecided	Agree	Strongly Agree
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# Ethical, legal, & social scenarios



- A man was recently diagnosed with autosomal dominant polycystic kidney disease (ADPKD).
- He realises that each of his children has a 50% chance of inheriting the condition from him
- He asks his GP to organise a kidney ultrasound for his two children aged 10 and 7, to see if they have inherited the condition.
- The GP should do so.

Strongly Disagree	Disagree	Undecided	Agree	Strongly Agree
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# Ethical, legal, & social scenarios



- The antenatal screening programme identified a pregnancy where the fetus had multiple anomalies caused by a chromosomal imbalance.
- The otherwise healthy father was found to be a carrier of a balanced chromosome rearrangement.
- The geneticist offered to see and test his relatives' chromosomes to see if they might be at high risk of having affected children, but the man did not want them contacted.
- The geneticist should attempt to contact them without the man's consent.

Strongly Disagree	Disagree	Undecided	Agree	Strongly Agree
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# Ethical, legal, & social scenarios



- A 20yr male is requesting predictive testing for HD.
- There is a strong family history of HD (genetically confirmed) on his maternal side.
- His mother (45yrs) is asymptomatic and does not want to be tested for HD.
- We should offer to test the young man.

Strongly Disagree	Disagree	Undecided	Agree	Strongly Agree
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# Conclusions



# Key learning points

- **Awareness of genetic disease:**
  - Increased patient requests
  - Take a family history and ascertain risk
  - Refer on for specialist advice
- **Genetics services/genetic counselling:**
  - Diagnostic and risk evaluation
  - Disease education and patient support groups
  - Identification of at risk family members
  - Reproductive options (CVS, amniocentesis, PGD)



# Key learning points

- **Genetic testing:**

- Indication
  - Diagnostic, predictive, carrier, reproductive, pharmacogenetic
- Mechanism and test type, and limitations
  - Chromosome - karyotype, FISH, microarray
  - Gene - Sanger, gene panel, exome, genome
- Consent
- Interpretation of report and notification of results
- Ethical and psychosocial implications

# Resources



*Genomics in general practice*



racgp.org.au

Healthy Profession.  
Healthy Australia.

## Health

Centre for Genetics Education

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## Genetic Health Queensland

Great state. Great opportunity.





# Any questions? Any feedback??



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## Genetic Health Queensland

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## Welcome to Genetic Health Queensland

Genetic Health Queensland (GHQ) is a statewide service that provides clinical genetic services across Queensland by a team of specialist health-care professionals. We see individuals and their families with a suspected or known inherited or genetic health condition.

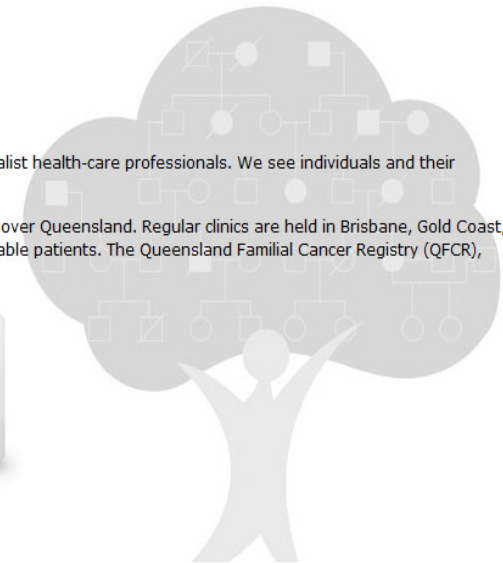
A team of medical specialists (clinical geneticists) and genetic counsellors work together at GHQ to look after patients and families all over Queensland. Regular clinics are held in Brisbane, Gold Coast, Toowoomba, Nambour, Bundaberg, Rockhampton, Mackay, Townsville and Cairns. Telehealth consultations are also available for suitable patients. The Queensland Familial Cancer Registry (QFCR), Queensland Cardiac Genetics Clinic, and RBWH Renal Genetics Clinic are also based within GHQ.

**Patients  
and Families**

**Health  
Professionals**

**Queensland  
Cardiac  
Genetics Clinic**

**Queensland  
Familial  
Cancer  
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## Genetic Health Queensland

Great state. Great opportunity.

