



RACGP

Royal Australian College of General Practitioners

# *Genomics in general practice*



## **Genomics in general practice**

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*We acknowledge the Traditional Custodians of the lands and seas on which we work and live, and pay our respects to Elders, past, present and future.*



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*Genomics in general practice*

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In 2015, the RACGP inherited the 2007 publication *Genetics in family medicine: The Australian handbook for general practitioners*, which was produced under the auspices of the now defunct agency, Biotechnology Australia, with support from the National Health and Medical Research Council (NHMRC). The RACGP is grateful to the authors of the original 2007 resource and its contributors for their work, which formed the foundation of *Genomics in general practice*.

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### Conflicts of interest

This publication has been produced in accordance with the rules and processes outlined in the RACGP's Conflict of interest policy ([www.racgp.org.au/support/policies/organisational](http://www.racgp.org.au/support/policies/organisational)).

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## Background

In 2015, The Royal Australian College of General Practitioners (RACGP) took ownership of *Genetics in family medicine: The Australian handbook for general practitioners*, a 2007 resource produced by the now defunct Biotechnology Australia, with support from the National Health and Medical Research Council (NHMRC). Developed in collaboration with a broad range of national stakeholders, *Genetics in family medicine: The Australian handbook for general practitioners* provided comprehensive and authoritative advice on a range of issues in genetic medicine for general practitioners (GPs) at a time of burgeoning interest in this field.

In the 10 years since it was published, the field of genetics and genomics has developed rapidly. Advances in genetics and genomics offer great potential for identifying patients at risk of disease and targeting treatment. GPs need up-to-date knowledge and skills in this domain.

To determine how best to update the 2007 resource, ensuring the material remains relevant to general practice, the RACGP convened a panel of experts (the Advisory Group), which comprised representatives from the original development consortium and new members. The result is *Genomics in general practice*, a suite of concise summaries on various clinical topics in genetics and genomics.

## Aim of the resource

*Genomics in general practice* is intended to be used as a point-of-care reference for GPs. It is designed to assist in clinical decision-making by presenting a snapshot view of the identification and diagnosis of a range of genetic conditions, and the use of genetic testing and technologies encountered in general practice. It is hoped *Genomics in general practice* will assist GPs to provide information on genetics and genomics to patients and their families, and refer to specialist services as required.

## Development process

*Genomics in general practice* was developed in accordance with RACGP procedures.

Members of the Advisory Group reviewed *Genetics in family medicine: The Australian handbook for general practitioners* to determine the scope and purpose of the new publication.

A literature search was conducted for each topic, and relevant research papers and grey literature were identified.

Successive drafts of the resource were produced by the writer under the direction of the Advisory Group. Subject matter experts were consulted during this content-development phase. Where contention existed within the literature or among subject matter experts, the Advisory Group determined how to address this within the resource by consensus.

A broad range of GP and non-GP stakeholders were invited to review and provide feedback on a draft. Comments were considered by the Advisory Group and amendments made prior to publication.

## A note on the title of the resource

The terms 'genetic' and 'genomic' are sometimes used interchangeably. The term genetic refers to the study of single genes, whereas genomic refers to the study of multiple genes. Traditional genetic testing involves the examination of individual genes that are known to cause or increase risk for a particular disease. The new field of genomic testing allows for the testing of a number of different genes at once, even a person's entire genetic makeup (genome). As such, genomic testing can provide a wealth of information about a patient's health, including predisposition to common conditions and response to particular drugs. The title for this resource, *Genomics in general practice*, reflects the possibilities inherent to genomic testing for the practice of medicine.

## Format

*Genomics in general practice* consists of short, practical summaries with key information that a GP might need to manage common genetic conditions and issues of testing in primary care.

For two of the topics where there have been significant developments in the past 10 years, 'Pharmacogenomics' and 'Personal genomic testing', more detailed information is presented alongside the summary.

This resource is intended as a 'guide' rather than a 'guideline' with weighted recommendations for clinical decision-making. Where appropriate clinical guidelines exist (ie they are recent and applicable to an Australian general practice context), they have been referenced in the text.

The most important information for GPs is listed at the beginning of each chapter under the heading 'Practice point'. The issues considered in each chapter vary, but many include discussion of relevant tests and when GPs should refer to another health professional or genetics services. Where relevant, useful websites and other resources to access for further information for GPs and patients are listed at the end of the chapter.

## Scope

*Genomics in general practice* is primarily intended for use by GPs and other primary care staff. Although it has not been designed for use by patients and consumers, this resource does contain some information for that audience.

The resource does not include a discussion of very rare genetic conditions that are unlikely to be encountered in general practice, or give comprehensive information about genetics services or use of the Medicare Benefits Schedule for billing purposes.

## Ethical principles

The ethical principles that guide all medical care apply in genomics. However, ethical dilemmas arise when there is tension or conflict between the rights of different family members. Key ethical principles include:<sup>1</sup>

- Justice – Patients should be treated equally, and there should be equity of access to services regardless of place of residence, ethnicity, gender, religion, age or disability.
- Respect for autonomy – The right of an individual to self-determination, including privacy and confidentiality.
- Beneficence – Taking positive action to do good.
- Non-maleficence – Do no harm.

There may be tension when these principles are considered with respect to the right of an individual to:

- know, or not to know, information relevant to their own health (autonomy)
- disclose, or not to disclose, personal information (privacy)
- make an informed decision regarding genetic testing.

Genetic counselling emphasises that an autonomous choice be made; that is, a choice that is informed and reflective of the individual's own values, and made freely (without coercion). However, ethical dilemmas may arise. For example:

- as a result of genetic testing, an individual's result may disclose the genetic status of another family member (eg a monozygotic [identical] twin)<sup>2</sup> who has not had testing (and may not wish to)
- an individual refuses to disclose to other family members that they are at risk of particular diseases<sup>3</sup>
- parents request that their child (<18 years of age) be tested for an adult-onset condition where there is no health benefit for the child, thus affecting the child's future autonomy.<sup>4</sup>

In any of these situations, it is important to explore with the patient the potential harms and benefits, and the reasons for their request. Referral to genetic services for counselling is strongly recommended.

## References

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2. Andorno R. The right not to know: An autonomy based approach. J Med Ethics 2004;30(5):435–39.
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4. Human Genetics Society of Australasia. Policy: Pre-symptomatic and predictive testing for children and young adults. Sydney: HGSA, 2014. Available at [www.hgsa.org.au/documents/item/272](http://www.hgsa.org.au/documents/item/272) [Accessed 13 December 2017].

## Resources for general practitioners

- Centre for Genetics Education, Fact sheet 19: Ethical issues in human genetics and genomics, [www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-19-ethical-issues-in-human-genetics-and-genomics/view](http://www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-19-ethical-issues-in-human-genetics-and-genomics/view)
- Financial Services Council, FSC Standard no. 16: Family medical history policy, [www.fsc.org.au/resources/standards/16s-family-history.pdf](http://www.fsc.org.au/resources/standards/16s-family-history.pdf)
- National Health and Medical Research Council, Genetic discrimination, [www.nhmrc.gov.au/\\_files\\_nhmrc/publications/attachments/g001\\_genetic\\_discrimination\\_150622.pdf](http://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/g001_genetic_discrimination_150622.pdf)



## Genetic counselling

Genetic counselling is a communication process that aims to provide information and supportive counselling to members of families regarding problems in growth, development and health that may have a genetic basis.

Patients can be referred to genetic counsellors available at genetics services in each state or territory.

The process of professional genetic counselling involves assisting patients to:

- comprehend the medical facts regarding a genetic condition, including the diagnosis, probable course of condition and available management
- appreciate the way heredity contributes to the condition and risk of occurrence in relatives
- understand the options for dealing with the risk of recurrence
- choose the course of action that seems appropriate in view of their situation, and risk and values, and act in accordance with that decision
- make the best possible adjustment to the condition in an affected family member and/or to the risk of recurrence of that condition.

During a genetic counselling consultation, the counsellor may discuss the following issues with the patient:

- Information about the condition
  - key clinical features
  - genetic contribution to the cause of the condition, including gene(s) involved, inheritance pattern, likelihood that a person who inherits the genetic susceptibility will develop the condition
  - interactions between genes and the interplay between genes and the environment.
- Information about genetic testing
  - availability of testing
  - advantages and disadvantages for deciding whether to undergo genetic testing
  - understanding and using genetic test results.
- Implications for family members
  - medical and psychological implications
  - implications for future reproductive choices, employment and insurance
  - issues concerning the privacy and confidentiality of genetic information.

## Resource for patients

- New South Wales's Centre for Genetics Education maintains a list of genetics services, [www.genetics.edu.au/genetic-services](http://www.genetics.edu.au/genetic-services)

## *Genetics support groups and organisations*

In addition to support from general practitioners, genetic services and professional counselling, patient referral to support groups or organisations can be beneficial and, in some cases, necessary for the wellbeing of the patient and/or their family.

Support groups and organisations can be an important source of peer support and empowerment, and provide practical information and advice about living with a genetic condition. Families can benefit from contact with other people in similar situations, regardless of their level of coping or need for support.

Support groups and organisations can have state-based or territory-based, national or international memberships, allowing families to appreciate that they are not alone in the challenges they may face living with a particular genetic condition.

### Resource for patients

- New South Wales's Centre for Genetics Education maintains a list of genetics services, [www.genetics.edu.au/genetic-services](http://www.genetics.edu.au/genetic-services)

## Health and life insurance issues

General practitioners (GPs) are well placed to advise patients to consider the implications around health and life insurance for themselves and their families before embarking on genetic testing.

Private health insurance is community-rated (ie based on population risk), and does not take into account genetic information, but will take into account any existing condition.

However, individuals applying for a new life insurance policy (eg cover for death, disability, income protection) are required by law to disclose 'every matter known to the applicant, or could reasonably be expected to be known, that is relevant to the insurer's decision'.<sup>1</sup> This includes the results of any genetic tests.

While some insurance companies will ask for more specific details than others, applicants must disclose all known genetic information about themselves and their relatives that would be relevant to the assessment of their risk, over and above the questions asked. This includes predictive test results of their relatives, and a failure to do so may render a claim invalid.<sup>2</sup>

This information may have a range of consequences, depending on the condition involved and whether the genetic test was positive, uninformative or negative.

If an application for health and/or life insurance is held or taken out before a genetic condition is diagnosed, or before a risk is identified through a predictive genetic test, the applicant does not have to disclose this new information. Life insurance cover is guaranteed renewable and, so as long as the premiums are paid, that cover will apply.

### References

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2. Financial Services Council. FSC Standard no. 11: Genetic testing policy. Sydney: FSC, 2016. Available at [www.fsc.org.au/resources/standards/11s-genetic-testing-policy-final.pdf](http://www.fsc.org.au/resources/standards/11s-genetic-testing-policy-final.pdf) [Accessed 13 December 2017].

### Resources for general practitioners

- Centre for Genetics Education, Fact sheet 20: Life insurance products and genetic testing in Australia, [www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-20-life-insurance-products-and-genetic-testing-in-australia/view](http://www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-20-life-insurance-products-and-genetic-testing-in-australia/view)
- National Health and Medical Research Council, Genetic discrimination, [www.nhmrc.gov.au/\\_files\\_nhmrc/publications/attachments/g001\\_genetic\\_discrimination\\_150622.pdf](http://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/g001_genetic_discrimination_150622.pdf)

## Misconceptions about genetics

General practitioners (GPs) can use the information below to address common misconceptions about genetic issues during discussion with patients.

### Information for patients

Misconception	Fact
If your father has a genetic condition, but you look more like your mother, you will not develop it	An individual's physical similarity to other relatives (or lack thereof) does not affect their risk of developing a condition
You can only inherit a 'female' cancer like breast or ovarian cancer from your mother's side	<b>Gene variants</b> in <i>BRCA1</i> and <i>BRCA2</i> can be passed through the paternal line (a person's father and his relatives) and maternal line (a person's mother and her relatives)
If you have the gene for a particular disease, you will eventually get the disease	The presence of a pathogenetic variant does not always mean an individual will develop the condition. If the gene variant shows variable <b>penetrance</b> (ie penetrance less than 100%), the risk of disease can be uncertain
A 'one-in-four' chance of having a child with the variant means that after you have one affected child, the next three children will be unaffected	A 'one-in-four' chance of having a child with the variant applies to each pregnancy (for autosomal recessive conditions)
Female carriers of X-linked conditions are never affected	This is not always the case and is influenced by X-inactivation. Carriers may have a mild phenotype and are manifesting heterozygotes. For example, female carriers of Duchenne muscular dystrophy may show mild symptoms of a cardiomyopathy; female carriers of haemophilia may have a bleeding diathesis
If you have no family history of a genetic condition, you are not at risk of developing one and neither are your children	There may be no <b>family history</b> for a variety of reasons. For example, reduced or incomplete penetrance, recessive conditions, small family size, and new mutations (eg <b>de novo</b> , sporadic)
Genetic conditions can 'skip' a generation	In the case of autosomal recessive and X-linked conditions, affected family members may be scattered across a generation, giving the appearance of skipping generations

## Summary of genetic tests

The following table provides information about genetic tests that may be encountered in general practice and the tests' indications.

Genetic test	Indications
G-banded (conventional microscopic) karyotype – Chromosomes are stained to reveal patterns of alternating light and dark bands	Suspected chromosome rearrangement; investigate multiple miscarriages
Fluorescent in situ hybridisation (FISH) – Using fluorescent dyes or tags specific to a chromosome, FISH can visualise chromosomes to identify abnormalities	Determine physical arrangement of chromosomal conditions or correct number of chromosomes (eg rapid method of aneuploidy screening in prenatal setting)
Chromosomal microarray (CMA) or molecular karyotype (eg single nucleotide polymorphism [SNP] microarray) – CMA uses a microchip-based platform to perform a genome-wide assay that looks for sub-microscopic copy number variants (CNVs). These variants are extra (duplications) or missing (deletions) segments of deoxyribonucleic acid (DNA). Many CNVs are common and benign, while some are pathogenic	Unexplained intellectual disability or developmental delay; prenatal investigation of abnormality on ultrasound
Sanger sequencing – The exact order of base pairs A, G, T and C in an individual's genetic makeup is known as the DNA sequence. Sanger sequencing is old, low through-put, but reliable technology, and sequences just one gene at a time	Suspect condition with a known single-gene cause (eg cystic fibrosis, thalassaemia)
Next generation sequencing (NGS) or massively parallel sequencing – NGS sequences millions of small DNA fragments, which are then mapped to a reference genome. NGS can sequence the entire genome, just the exome (coding genes) or a panel of selected genes	Genome sequencing: A comprehensive approach that captures the entire genome Exome sequencing: A more cost-effective approach to capture and analyse all known disease-causing genes (eg rare childhood syndromes) Panel sequencing: A more targeted approach focusing on a large number of key genes related to a clinical indication (eg cancer, cardiac conditions)
SNP genotyping or genomic profiling or scan – Testing that analyses single nucleotide variations in the genome	Determine ability to metabolise certain drugs (eg CYP2D6, codeine), paternity testing, personal genomic testing (direct to consumer)
Polymerase chain reaction (PCR) – A method for amplifying DNA (ie making millions of copies of a particular sequence of DNA)	Disorders caused by triplet repeat expansions (eg Fragile X syndrome, Huntington's disease)
Multiplex ligation-dependent probe amplification (MLPA) – A PCR method of detecting copy number variants and SNPs	Suspect disorder caused by large deletions or duplications of specific genes (eg Duchenne muscular dystrophy)
DNA methylation studies of specific chromosome region	Suspect disorder caused by abnormal gene methylation which affects gene expression (eg Beckwith–Wiedemann syndrome)
<b>Maternal serum screening</b>	
Combined first trimester screening – Biochemical screening of maternal blood combined with ultrasound	First trimester: Screening at 11–13 weeks to estimate risk for trisomy 21, trisomy 18, trisomy 13
Second trimester serum screening – Biochemical screening of maternal blood	Second trimester: screening at 14–20 weeks to estimate risk for trisomy 21, trisomy 18 and neural tube defects
Non-invasive prenatal testing (NIPT) – Analysis of cell-free fetal DNA (cfDNA) in maternal plasma	Pregnancy screening from 10 weeks to detect evidence of trisomy 21, 18 or 13 in fetus with higher sensitivity and specificity than maternal serum screening
Adapted from Donoghue S, Downie L, Stutterd C. Advances in genomic testing. Aust Fam Physician 2017;46(4):200–05. Available at <a href="http://www.racgp.org.au/afp/2017/april/advances-in-genomic-testing">www.racgp.org.au/afp/2017/april/advances-in-genomic-testing</a> [Accessed 27 July 2017].	

# Glossary

## Anticipation

Anticipation describes a situation where a genetic condition appears at an earlier age with successive generations. The severity of the condition can also increase. This phenomenon is often seen in conditions caused by trinucleotide repeats, such as Huntington's disease, myotonic dystrophy and [Fragile X syndrome](#). In these cases, the size of the trinucleotide repeat increases when it is passed from parent to child, which can result in earlier onset and more severe disease.

For more information, refer to the Genetics Home Reference's explanation 'What do geneticists mean by anticipation?' (<https://ghr.nlm.nih.gov/primer/inheritance/anticipation>) and 'What are the different ways in which a genetic condition can be inherited?' (<https://ghr.nlm.nih.gov/primer/inheritance/inheritancepatterns>).

## Autosomal dominant inheritance

When a condition follows an autosomal dominant pattern of inheritance, the family tree will usually reveal multiple affected members on the same side of the family. Dominant conditions or traits are expressed when only a single [gene variant](#) is inherited. They are usually inherited on one side of the family and can be seen in multiple generations.

Wide variability in clinical expression is common in many autosomal dominant conditions, even within the same family.

Early onset of conditions, such as cancer, can be indicative of autosomal dominant inheritance within a family.

Not all dominant conditions show 100% [penetrance](#) (eg *BRCA1* gene mutations).

## Autosomal recessive inheritance

Autosomal recessive conditions affect either sex, and often occur in the absence of any family history. Recessive conditions or traits appear when an individual inherits two copies of the same [gene variant](#) (one from each parent).

Parents of a child with an autosomal recessive condition are usually asymptomatic [carriers](#). The affected child will carry two copies of the particular gene change.

The recurrence risk of autosomal recessive conditions is one in four for each pregnancy.

Wide variability in clinical expression is common in many autosomal recessive conditions, even within the same family.

[Consanguinity](#) is noted to occur more often among the parents of individuals with rare autosomal recessive conditions.

## Balanced translocation

A balanced translocation is a rearrangement of the chromosome with no apparent loss or gain of chromosomal material. Individuals with balanced translocations are not usually affected.

## Carrier

Recessive genetic conditions such as cystic fibrosis (CF) occur when a person inherits a particular genetic variant from each parent. A carrier is an individual who only has one copy of the [gene variant](#) and generally does not have symptoms, but can pass the variant to their children.

Some conditions are linked to the X chromosome ([X-linked recessive inheritance](#)). Typically, these conditions affect more males (who have the sex chromosomes XY) than females (who have the sex chromosomes XX). A woman who is a carrier of an X-linked condition has the variation on one of her X chromosomes, which she can pass on to her children. However, if the biological male partner is a carrier, he will not pass it to his sons, but will pass it to his daughters.

## Carrier screening

Carrier screening is a test to determine whether an individual carries a genetic variant or chromosomal alteration that does not generally affect that individual's health, but increases his or her chance of having children with the condition in question. The outcome of such testing can influence future reproductive decisions. Carrier screening is performed on individuals who are not necessarily known to be at increased risk for a particular genetic condition. Screening tests can be conducted on individuals, groups such as those from a common ethnic background and entire populations (eg newborn screening).

## Cascade screening

Cascade screening involves testing the close biological relatives of an individual who has a genetic condition in order to determine whether these relatives carry the genetic variant or chromosomal alteration (thereby increasing their chances of developing the condition or having a child with the condition).

## Compound heterozygote, compound heterozygous and compound heterozygosity

A compound heterozygote is an individual with two different pathogenic alleles at a particular location in a pair of chromosomes. For example, in hereditary haemochromatosis, compound heterozygotes have both a *C282Y* and an *H63D* variant, and are less likely to develop iron overload than *C282Y* homozygotes. However, the impact will be assessed on a case-by-case situation as it depends on the variant (allele) and its pathogenicity. Additionally, as one allele will have come from the mother and the other from the father, there might be implications in terms of cascade testing within the family.

## Consanguinity

Consanguinity describes a relationship between two people who are related to each other because of a common ancestor. Consanguineous relationships occur in all population groups, but may occur more frequently in certain cultures. The most common form of consanguineous relationships is between first cousins.

Individuals who are blood relatives share a greater proportion of their genes than unrelated people, thus, these individuals potentially share **pathogenic variants** for recessive conditions. When individuals are first cousins and there is no **family history** of a specific condition, or of other consanguineous relationships in previous generations, the risk of them having a child with a genetic condition is approximately 5–6%, compared with 3–4% in the general population. This risk will increase in communities where there is a multi-generational tradition of first-cousin marriages, rendering couples closer in genetic relationship.

## De novo

A de novo variant is a new genetic variation that arises in the fetal stage of development (ie was not present in either parent).

## Exome

The exome is the part of the genome that contains protein-coding genes only. The exome represents less than 2% of the genome, but contains about 85% of known disease-causing gene variants.

## Gene variants

Gene variants are small deoxyribonucleic acid (DNA) sequence changes (ie additions, duplications, deletions, substitutions). These variants can have a range of effects: some may cause disease (**pathogenic variant**), while others do not cause disease but may modify an individual's risk of disease (eg increase risk, provide a protective effect).

## Genome

The genome is the entire set of genetic material, including all coding and non-coding genes.

## Genotyping, genomic profiling and genomic scan

Genotyping (also known as genomic profiling or genomic scanning) is a test to determine an individual's [single nucleotide polymorphism \(SNP\)](#) profile. A SNP profile may be used to predict disease susceptibility, tailor treatment and provide non-health related information (eg paternity, ancestry).

## Heterozygote, heterozygous and heterozygosity

Heterozygosity refers to the presence of two different alleles (form of a [gene variant](#)) at a given location on a pair of chromosomes (eg [carrier](#) for a pathogenic gene variant).

## Homozygous, homozygous and homozygosity

Homozygosity refers to the presence of two identical alleles (form of a gene variant) at a given location on a pair of chromosomes.

## Incomplete penetrance

Refer to '[Penetrant and penetrance](#)'.

## Multifactorial inheritance and complex inheritance

Multifactorial inheritance, also called complex inheritance, can be attributed to a combination of genetic (ie single gene, multiple genes), environmental and lifestyle factors.

The number of necessary factors, and the impact those factors have on the presence or severity of a condition, will vary for different conditions and individuals.

Often, when there are multiple susceptibility genes involved, there is an additive effect on the outcome.

Early onset of conditions, such as cancer, cardiovascular disease or type 2 diabetes, may be indicative of multifactorial inheritance within a family.

This type of inheritance does not follow a characteristic pedigree pattern, but may look like [autosomal dominant inheritance](#) with [incomplete penetrance](#).

## Pathogenic variant and gene mutation

A [pathogenic variant](#) is a genetic variant that increases an individual's susceptibility or predisposition to certain diseases. Pathogenic variants are also known as mutations. Some are responsible for normal human variation, and these are known as polymorphisms (eg height).

There are variations that affect the way we metabolise drugs. For some variants, their effects are unknown or uncertain, while others have no effect.

## Penetrant and penetrance

Penetrance refers to the proportion of people with a particular genetic variant who will go on to develop the condition. It describes the extent to which disease or characteristics controlled by the gene, or variation within the gene, will be expressed. For example, people carrying an autosomal dominant variant may not always develop the condition – this is called 'incomplete penetrance'. If a condition is 100% penetrant, an individual will definitely develop the condition. If penetrance is 80%, most but not all individuals will develop the condition. Other genes and lifestyle factors, such as diet, exercise and smoker status, may affect the onset of some conditions.

For more information, refer to Genetics Home Reference's 'What are reduced penetrance and variable expressivity?' (<https://ghr.nlm.nih.gov/primer/inheritance/penetranceexpressivity>).



## Predictive testing

Predictive testing aims to determine whether a person who has no signs or symptoms of a specific condition at the time of testing has specific genetic variations that increase the likelihood they will later develop the condition. Predictive testing is often performed in relation to genetic conditions that are not evident at birth, but have their onset during adulthood, such as some cancers. Predictive genetic testing in conditions such as familial cancer can only be conducted when the family-specific genetic variant is known. Hence, genetic testing must first be done on a family member affected with the specific condition, as they are the most likely to carry the genetic variant.

## Pre-implantation genetic diagnosis

Pre-implantation genetic diagnosis (PGD) is cytogenetic testing, with or without molecular testing, performed on embryos used in assisted reproductive technology procedures. Prenatal testing of successful pregnancies may be recommended for confirmation of the test result.

## Pre-symptomatic testing

Pre-symptomatic testing aims to determine whether a person will develop a particular genetic condition (eg Huntington's disease) at some point in the future when symptoms of the condition have not yet manifested.

## Sensitivity

Sensitivity is the true positive rate for a test. For example, if the person has the condition, how often will the test give a positive result?

## Single nucleotide polymorphism

A nucleotide is a single base pair unit of deoxyribonucleic acid (DNA). A **single nucleotide polymorphism** (SNP or 'snip') is a polymorphism in a single nucleotide occurring at a particular site in the genome. For example, one individual may have a 'G' at a particular location and another individual a 'T'. If two or more alternative DNA variants occur at a particular location at a population frequency of >1%, it is defined as a SNP. SNPs are the most common type of genetic variation in the human genome and account for approximately 0.02% of the genome.

## Specificity

Specificity is the true negative rate for a test. For example, if the person does not have the condition, how often will the test give a negative result?

## Variable expressivity

Variable expressivity refers to the range of signs and symptoms that an individual with a particular genetic condition will display.

Variable expressivity is a factor that influences the effect of particular genetic variants. While some genetic variants are consistent in terms of the effect they have on a disease or characteristic, other have a more variable effect. For example, Lynch syndrome (hereditary non-polyposis colorectal cancer [HNPCC]) shows variable expressivity. An individual's presentation of this disease is modified by their genetic, lifestyle and environment factors.

Variable expressivity is not the same as reduced penetrance.

For more information, refer to the Genetics Home Reference's 'What are reduced penetrance and variable expressivity?' (<https://ghr.nlm.nih.gov/primer/inheritance/penetranceexpressivity>).

## X-inactivation

Inactivation of most genes on the X chromosome in female somatic cells ensures that males and females have the same number of X chromosome genes instructing the body to perform particular functions.

This is usually a random process; thus, females will have a mixture of cells with respect to the inactivated X chromosomes being of maternal or paternal origin.

The usual random process of X-inactivation means that female **carriers** of the mutation will not usually show any signs of the condition as there are enough cells with the correct copy of the gene to instruct the body to perform particular functions.

Rarely, some female carriers may be mildly symptomatic because of unequal or skewed inactivation of the X chromosomes.

## X-linked recessive inheritance

Since a male inherits only one X chromosome (from his mother), in a family affected by a condition that follows a pattern of X-linked recessive inheritance, there will be more affected males than affected females. Males are usually more severely affected than females because of X-inactivation.

Since a male only passes his Y chromosome to his sons, there is no male-to-male transmission of X-linked conditions.

With each pregnancy, females who are carriers for a gene variant involved have a one-in-two chance of passing on the variant. Sons who inherit the variant will be affected and daughters who inherit the variation will be carriers like their mothers.

Daughters of affected males can only inherit the variation from their father and are known as 'obligate carriers'.

## Acronyms

<b>AD</b>	Alzheimer's disease	<b>MCH</b>	mean corpuscular haemoglobin
<b>AGHDR</b>	Australian Genetic Heart Disease Registry	<b>MCV</b>	mean corpuscular volume
<b>ASD</b>	autism spectrum disorder	<b>MLPA</b>	multiplex ligation-dependent probe amplification
<b>CA 125</b>	cancer antigen 125	<b>MODY</b>	maturity onset diabetes of the young
<b>CBAVD</b>	congenital bilateral absence of the vas deferens	<b>NF1</b>	neurofibromatosis type 1
<b>CF</b>	cystic fibrosis	<b>NGS</b>	next generation sequencing
<b>cfDNA</b>	cell-free fetal DNA	<b>NHMRC</b>	National Health and Medical Research Council
<b>CFTS</b>	combined first trimester screening	<b>NIPS</b>	non-invasive prenatal screening
<b>CMA</b>	chromosomal microarray	<b>NIPT</b>	non-invasive prenatal testing
<b>CNV</b>	copy number variant	<b>NT</b>	nuchal translucency
<b>COC</b>	combined oral contraceptive	<b>PAPP-A</b>	pregnancy-associated plasma protein A
<b>CPTI</b>	carnitine palmitoyl transferase deficiency types I and II	<b>PCR</b>	polymerase chain reaction
<b>CPVT</b>	catecholaminergic polymorphic ventricular tachycardia	<b>PGD</b>	pre-implantation genetic diagnosis
<b>CRC</b>	colorectal cancer	<b>PGT</b>	personal genomic testing
<b>CVD</b>	cardiovascular disease	<b>PKU</b>	phenylketonuria
<b>CVS</b>	chorionic villus sampling	<b>PPV</b>	positive predictive value
<b>CYP</b>	cytochrome P450 enzyme	<b>PSA</b>	prostate-specific antigen
<b>DD</b>	developmental delay	<b>QF-PCR</b>	quantitative fluorescence polymerase chain reaction
<b>DLCNC</b>	Dutch Lipid Clinic Network Criteria	<b>RACGP</b>	The Royal Australian College of General Practitioners
<b>DNA</b>	deoxyribonucleic acid	<b>SADS</b>	sudden arrhythmic death syndrome
<b>DTC</b>	direct-to-consumer	<b>SCAD</b>	short chain acyl-CoA dehydrogenase deficiency
<b>FAP</b>	familial adenomatous polyposis	<b>SCHAD</b>	short chain hydroxy acyl-CoA dehydrogenase deficiency
<b>FBE</b>	full blood examination	<b>SNP</b>	single nucleotide polymorphism
<b>FH</b>	familial hypercholesterolaemia	<b>β-hCG</b>	human chorionic gonadotrophin
<b>FISH</b>	fluorescent in situ hybridisation	<b>SSRI</b>	selective serotonin reuptake inhibitor
<b>FOBT</b>	faecal occult blood test	<b>TFP</b>	trifunctional protein deficiency
<b>FRA-BOC</b>	familial risk assessment – breast and ovarian cancer	<b>VLCAD</b>	very long chain acyl-CoA dehydrogenase deficiency
<b>FSH</b>	follicle-stimulating hormone	<b>VOUS</b>	variant(s) of unknown significance
<b>FXPOI</b>	Fragile X-associated primary ovarian insufficiency	<b>VTE</b>	venous thromboembolism
<b>FXS</b>	Fragile X syndrome		
<b>FXTAS</b>	Fragile X-associated tremor/ataxia syndrome		
<b>GP</b>	general practitioner		
<b>HbE</b>	haemoglobin E		
<b>HHC</b>	hereditary haemochromatosis		
<b>HNPCC</b>	hereditary non-polyposis colorectal cancer		
<b>ID</b>	intellectual disability		
<b>IVF</b>	in-vitro fertilisation		
<b>LCHAD</b>	3-hydroxy long chain acyl-CoA dehydrogenase deficiency		
<b>LDL-C</b>	low-density lipoprotein cholesterol		
<b>MADD</b>	multiple acyl-CoA dehydrogenase deficiency		
<b>MBS</b>	Medicare Benefits Schedule		
<b>MCAD</b>	medium chain acyl-CoA dehydrogenase deficiency		

# Alzheimer's disease

## Practice point

Currently, genetic testing of *APOE* gene variants is considered to have limited clinical utility for diagnostic purposes, and is not recommended in clinical practice.<sup>1,2</sup>

Genetic testing is also available for gene variants in three genes *APP*, *PSEN1*, *PSEN2* that confer a very high risk for early onset familial Alzheimer's disease (AD). However, these gene variants are responsible for only a small percentage of AD cases.<sup>2,3</sup>

## What do I need to know?

The average lifetime risk of developing AD is estimated to be between 10 and 12% (until the age of 75–80 years).<sup>3–5</sup> The  $\epsilon 4$  variant of the *APOE* gene is associated with an increased risk of late-onset AD,<sup>5,6</sup> but this risk is confounded by other factors. These factors include those that cannot be modified (eg other genetic variants, gender, family history, possibly ethnicity) and modifiable risk factors (eg diet, exercise, cardiovascular health, environment). The clinical utility of knowing  $\epsilon 4$  status is uncertain.<sup>3,5–7</sup>

Research suggests that heterozygous carriers of the  $\epsilon 4$  variant have an approximately threefold increase in risk of developing AD, while homozygous carriers have an approximately 15-fold increase in risk. Having a first-degree relative with AD doubles the risk of developing the disease.<sup>3,7,8</sup>

The  $\epsilon 4$  variant is neither necessary nor sufficient to cause AD, and risk estimates are problematic given the range of confounding factors. Therefore, the clinical utility of genetic testing is uncertain.<sup>2,3</sup>

## Genetic testing

While the association of the *APO- $\epsilon 4$*  variant with AD is significant, genetic testing has limited sensitivity and specificity.<sup>2</sup> The *APO- $\epsilon 4$*  variant may be included in some commercial test panels (refer to 'Personal genomic testing: Summary'). Given the lack of predictive value of *APO- $\epsilon 4$*  for AD, this information may cause unnecessary anxiety for some individuals, especially given the lack of preventive or therapeutic interventions.<sup>3</sup> There may be broader implications for the individual and family members (ie ethical principles, health and life insurance issues).<sup>3</sup>

## When should I refer?

Genetic testing may be appropriate for families with a history of early onset AD ( $\geq 2$  affected family members; age at onset  $< 65$  years of age), and referral to genetics services is appropriate.<sup>2</sup>

## References

1. Human Genetics Society of Australasia and Choosing Wisely Australia. Tests, treatments and procedures clinicians and consumers should question. Sydney: NPS MedicineWise, 2016. Available at [www.choosingwisely.org.au/recommendations/hgsa](http://www.choosingwisely.org.au/recommendations/hgsa) [Accessed 14 December 2017].
2. Bird TD. Alzheimer disease overview. In: Pagon RA, Adam MP, Ardinger HH, et al, editors. GeneReviews. Seattle, WA: University of Washington, 1998. Available at [www.ncbi.nlm.nih.gov/books/NBK1161](http://www.ncbi.nlm.nih.gov/books/NBK1161) [Accessed 14 December 2017].
3. Goldman JS, Hahn SE, Catania JW, et al. Genetic counseling and testing for Alzheimer disease: Joint practice guidelines of the American College of Medical Genetics and the National Society of Genetic Counselors. *Genet Med* 2011;13(6):597–605.
4. Cummings JL, Cole G. Alzheimer disease. *JAMA* 2002;287(18):2335–38.
5. Seshadri S, Drachman DA, Lippa CF. Apolipoprotein E  $\epsilon 4$  allele and the lifetime risk of Alzheimer's disease: What physicians know, and what they should know. *Arch Neurol* 1995;52(11):1074–49.
6. Ashford JW. *APOE* genotype effects on Alzheimer's disease onset and epidemiology. *J Mol Neurosci* 2004;23(3):157–65.
7. Van Cauwenberghe C, Van Broeckhoven C, Sleegers K. The genetic landscape of Alzheimer disease: Clinical implications and perspectives. *Genet Med* 2016;18(5):421.
8. Guerreiro RJ, Gustafson DR, Hardy J. The genetic architecture of Alzheimer's disease: Beyond *APP*, *PSENs* and *APOE*. *Neurobiol Aging* 2012;33(3):437–56.

## Resources for patients

### Information

- National Library of Medicine (US), Alzheimer disease, <https://ghr.nlm.nih.gov/condition/alzheimer-disease>
- National Library of Medicine (US), *APOE* gene: Normal function, <https://ghr.nlm.nih.gov/gene/APOE#normalfunction>
- National Library of Medicine (US), *APOE* gene, <https://ghr.nlm.nih.gov/gene/APOE>

### Support

- Alzheimer's Australia, [www.fightdementia.org.au](http://www.fightdementia.org.au)

# Autism spectrum disorder

## Practice point

Referral to a paediatrician for a clinical genetics evaluation of children with autism spectrum disorder (ASD) can provide a specific diagnosis in between 30 and 40% of cases.<sup>1</sup> General practitioners (GPs) can order a **chromosome microarray (CMA)** at the point of referral to a paediatrician in order to speed up this process.

## What do I need to know?

ASD is an umbrella term for a collection of pervasive developmental disorders. This term replaces previously used diagnostic terminology, including autistic disorder, Asperger syndrome, Rett syndrome, childhood disintegrative disorder and pervasive developmental disorder – not otherwise specified.<sup>2</sup>

ASD is characterised by impaired social communication and interaction, limited interests, and repetitive behaviours. Markers of ASD usually appear during the first two years of life, in particular, problems with language development and social relatedness.<sup>3</sup>

Some rare genetic conditions show clinical features that are characteristic of ASD. These include:

- tuberous sclerosis (*TSC1* or *TSC2* genes)
- **Fragile X syndrome** (FXS; *FMR1* gene)
- chromosomal abnormalities (eg inversions, duplications)
- metabolic conditions
- Rett syndrome (*MECP2* gene in many cases).

## Genetic testing

CMA is now considered a first-line genetic test for the investigation of developmental delay (DD) and intellectual disability (ID), ASD, and congenital abnormalities (CMA).<sup>4</sup> A CMA does not detect **gene variants** causing FXS (a single-gene cause of ASD), so an additional deoxyribonucleic acid (DNA) test must be ordered alongside.

While GPs are able to order CMAs, many choose not to, given the complex interpretation of the results. However, ordering CMA and FXS tests in parallel with referral to a paediatrician can reduce wait times for patients. A Medicare Benefits Schedule (MBS) rebate is available for CMA in situations where the patient has DD, ID, ASD or at least two congenital abnormalities. DNA testing for FXS is available with an MBS rebate when the patient:<sup>5</sup>

- exhibits ID, ataxia, neurodegeneration or premature ovarian failure consistent with an *FMR1* mutation
- has a relative with an *FMR1* mutation.

## When should I refer?

Refer to:

- a paediatrician for assessment of autistic features
- genetics services if the individual is dysmorphic
- a neurologist if regression of psychomotor skills occurs.

## Other considerations

If a diagnosis of ASD is made, referral to a genetic counsellor may be appropriate in terms of family planning. Research estimates the recurrence risk for siblings of children affected with ASD at up to 7%. If there are multiple affected siblings, the recurrence risk is higher (up to 50%).<sup>1</sup>

## References

1. Schaefer GB, Mendelsohn NJ. Clinical genetics evaluation in identifying the etiology of autism spectrum disorders: 2013 guideline revisions. *Genet Med* 2013;15(5):399–407.
2. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. 5th edn. Washington, DC: American Psychiatric Publishing, 2013.
3. Tonge B, Brereton A. Autism spectrum disorders. *Aust Fam Physician* 2011;40(9):672–77. Available at [www.racgp.org.au/download/documents/AFP/2011/September/201109tonge.pdf](http://www.racgp.org.au/download/documents/AFP/2011/September/201109tonge.pdf) [Accessed 15 December 2017].
4. Miller DT, Adam MP, Aradhya S, et al. Consensus statement: Chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. *Am J Hum Genet* 2010;86(5):749–64.
5. Department of Health. Medicare Benefits Schedule (MBS) Online. Canberra: DoH, 2017. Available at [www.mbsonline.gov.au](http://www.mbsonline.gov.au) [Accessed 15 December 2017].

## Resources for patients

### Information

- Autism Spectrum Australia (Aspect), What is autism?, [www.autismspectrum.org.au/content/what-autism](http://www.autismspectrum.org.au/content/what-autism)
- Centre for Genetics Education, Autism spectrum disorder, [www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-46-autism-spectrum-disorder/view](http://www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-46-autism-spectrum-disorder/view)

### Support

- Amaze, [www.amaze.org.au](http://www.amaze.org.au)
- Autism Spectrum Australia (Aspect), [www.autismspectrum.org.au](http://www.autismspectrum.org.au)

# Cystic fibrosis

## Practice point

The commonly used **newborn screening** tests will identify 85–90% of individuals with cystic fibrosis (CF), but will not identify individuals with rare (atypical) CF variants.<sup>1</sup> Such patients may present to the general practitioner (GP).

## What do I need to know?

CF is the most common life threatening genetic condition in Australia. CF primarily affects the lungs and digestive system, which become obstructed with excessive, thick mucus. It is a condition that follows an **autosomal recessive inheritance** pattern, meaning both parents must carry a CF-causing **gene variant** to be at risk of having a child with the disease.

About one in 25 Australians of northern European ancestry are **carriers** of the *CFTR* gene variant. The most common variant in the *CFTR* gene is the  $\Delta F508$  variant, which accounts for approximately 70% of all *CFTR* gene variant in those of northern European ancestry. While there are more than 2000 variants in the *CFTR* gene, around 40 variants contribute to approximately 90% of cases of CF in Australia.<sup>1,2</sup>

## Genetic testing

Almost all babies in Australia are screened at birth for CF. There are some who may be lost to follow up or refuse to consent for screening. Exact numbers in Australia are not available. Refer to '**Newborn screening**' for more information.

**Carrier screening** for CF can be offered by GPs to all couples planning a pregnancy (or already pregnant), regardless of **family history** or ethnicity. Refer to '**Reproductive carrier screening**' for more information.

Carrier screening for CF is also available through some genetic screening programs for at-risk groups (eg people of Ashkenazi Jewish ancestry) and through commercial carrier screening tests.<sup>1</sup>

## When should I refer?

Couples who are CF carriers should be referred for genetic counselling if they are planning a pregnancy or in the first trimester of pregnancy.<sup>3</sup>

Children suspected of having CF (who have not been previously identified through newborn screening tests) should be referred to a paediatrician for a sweat test. Symptoms may include recurrent cough, failure to thrive, lower respiratory tract infection, bronchiectasis and/or rectal prolapse.

Males presenting with infertility due to congenital bilateral absence of the vas deferens (CBAVD) may have an atypical form of CF. Refer the patient to a fertility specialist.<sup>4</sup>

## Other considerations

**Cascade screening** should be offered following a diagnosis of CF in the family to identify other potential carriers.<sup>1</sup>

## References

1. Delatycki MB, Burke J, Christie L, et al. Human Genetics Society of Australasia. Position statement: Population-based carrier screening for cystic fibrosis. *Twin Res Hum Genet* 2014;17(6):578–83.
2. Cystic Fibrosis Foundation. The clinical and functional translation of *CFTR* (CFTR2). Baltimore, MD: Johns Hopkins University, 2011. Available at <http://cftr2.org> [Accessed 15 December 2017].
3. The Royal Australian College of General Practitioners. Guidelines for preventive activities in general practice. 9th edn. Melbourne: RACGP, 2016. Available at [www.racgp.org.au/your-practice/guidelines/redbook](http://www.racgp.org.au/your-practice/guidelines/redbook) [Accessed 15 December 2017].
4. Ong T, Marshall SG, Karczeski BA, et al. Cystic fibrosis and congenital absence of the vas deferens. *GeneReviews*. Seattle, WA: University of Washington, 2001. Available at [www.ncbi.nlm.nih.gov/books/NBK1250](http://www.ncbi.nlm.nih.gov/books/NBK1250) [Accessed 15 December 2017].



## Resources for patients

### Information

- National Library of Medicine, Cystic fibrosis, <https://ghr.nlm.nih.gov/condition/cystic-fibrosis>
- Better Health Channel, Cystic fibrosis, [www.betterhealth.vic.gov.au/health/conditionsandtreatments/cystic-fibrosis-cf](http://www.betterhealth.vic.gov.au/health/conditionsandtreatments/cystic-fibrosis-cf)
- Centre for Genetics Education, Fact sheet 41: Cystic fibrosis, [www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-41-cystic-fibrosis](http://www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-41-cystic-fibrosis).

### Support

- Cystic Fibrosis Australia, [www.cysticfibrosis.org.au](http://www.cysticfibrosis.org.au)

# Developmental delay and intellectual disability

## Practice point

Children with features of developmental delay (DD) or intellectual disability (ID) should be referred to a paediatrician for a clinical genetics evaluation.<sup>1</sup>

## What do I need to know?

The causes of DD and ID can be genetic, non-genetic (eg fetal alcohol spectrum disorder, congenital infection) or unknown.

Knowledge that DD and ID are caused by an underlying genetic condition may inform:

- the ongoing management of the child's condition
- parents of future reproductive risk.

There are several genetic causes of DD and ID:

- Chromosomal
  - abnormalities of chromosome number (eg Down syndrome)
  - loss (ie deletion) or gain (ie duplication) of part of a chromosome.
- Single-gene disorders
  - **de novo gene variants** (occurring in the child but not inherited from a parent; eg Rett syndrome)
- Inherited causes
  - conditions that follow an **autosomal dominant inheritance** pattern (eg tuberous sclerosis)
  - conditions that follow an **autosomal recessive inheritance** pattern (eg phenylketonuria [PKU])
  - conditions that follow an **X-linked recessive inheritance** pattern (eg **Fragile X syndrome** [FXS])

## Genetic testing

**Chromosome microarray** (CMA) is now considered a first-line genetic test for the investigation of DD, ID, **autism spectrum disorder** (ASD), and congenital abnormalities.<sup>2</sup> CMA does not detect **gene variants** causing FXS (ie *FMR1* gene), so an additional deoxyribonucleic acid (DNA) test must be ordered alongside.

While general practitioners (GPs) are able to order CMAs, many choose not to, given the complex interpretation of the results. However, ordering CMA and FXS tests in parallel with referral to a paediatrician can reduce waiting times for patients.

A Medicare Benefits Schedule (MBS) rebate is available for CMA in situations where the patient has DD, ID, ASD or at least two congenital abnormalities. DNA testing for FXS is available with an MBS rebate when the patient:<sup>3</sup>

- exhibits ID, ataxia, neurodegeneration, or premature ovarian failure consistent with an *FMR1* mutation
- has a relative with an *FMR1* mutation.

## When should I refer?

A genetic cause should be suspected in individuals with DD **and** any of the following:

- dysmorphic features
- autistic features
- epilepsy
- congenital anomalies (eg cleft palate, heart defects)
- a [family history](#) of autism, FXS or other developmental/learning disability.

Patients with these features should be referred to a paediatrician or genetics services.

Refer directly to a paediatric neurologist if there is regression of motor skills (eg suspected muscular dystrophy, spinal muscular atrophy).

## References

1. The Royal Australian College of General Practitioners. Guidelines for preventive activities in general practice. 9th edn. Melbourne: RACGP, 2016. Available at [www.racgp.org.au/your-practice/guidelines/redbook](http://www.racgp.org.au/your-practice/guidelines/redbook) [Accessed 24 July 2017].
2. Miller DT, Adam MP, Aradhya S, et al. Consensus statement: Chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. *Am J Hum Genet* 2010;86(5):749–64.
3. Department of Health. Medicare Benefits Schedule (MBS) Online. Canberra: DoH, 2017. Available at [www.mbsonline.gov.au](http://www.mbsonline.gov.au) [Accessed 19 December 2017].

## Resource for patients

- Raising Children Network, Developmental delay in babies, [http://raisingchildren.net.au/articles/developmental\\_delay\\_video.html](http://raisingchildren.net.au/articles/developmental_delay_video.html)

# Diabetes

## Practice point

Types 1 and 2 diabetes are multifactorial, and there are currently no indications for genetic testing.

Approximately 2% of people with diabetes have maturity onset diabetes of the young (MODY), which is caused by a dominantly inherited variant in one of several known genes. It is important to identify these patients and family members, as there are implications for clinical management, including choice of treatment, prognosis and reproduction.<sup>1</sup>

## What do I need to know?

MODY typically presents in the second to fourth decade of life, and does not fit the clinical picture of either types 1 or 2 diabetes. Presentation is often subacute or incidental. Many cases are misdiagnosed as types 1 or 2 diabetes.<sup>2,3</sup>

MODY is the only type of diabetes caused by a single gene mutation. Mutations in 13 genes are known to cause MODY. The most prevalent mutations are in the *HNF1A*, *GCK* and *HNF4A* genes. *GCK*-MODY constitutes 10–60% of all MODY cases.<sup>2</sup>

Testing for MODY should be considered in individuals with early onset diabetes with atypical features (ie not clearly type 1 or type 2):<sup>1</sup>

- atypical type 1 diabetes
- no history of diabetic ketoacidosis
- prandial plasma C-peptide >200 pmol/L and >5 years post-diagnosis of type 1 diabetes
- atypical type 2 diabetes
- <35 years of age
- absence of features of insulin resistance
- no obesity
- no dyslipidaemia
- no hypertension
- no polycystic ovary syndrome
- strong **family history** of diabetes.

If MODY is suspected, assess risk using the calculator available at [www.diabetesgenes.org/content/mody-probability-calculator](http://www.diabetesgenes.org/content/mody-probability-calculator)

## When should I refer?

Individuals with suspected MODY should be referred to an endocrinologist for assessment and consideration of genetic testing.

## References

1. Carroll RW, Murphy R. Monogenic diabetes: A diagnostic algorithm for clinicians. *Genes (Basel)* 2013;4(4):522–35.
2. Bishay RH, Greenfield JR. A review of maturity onset diabetes of the young (MODY) and challenges in the management of glucokinase-MODY. *Med J Aust* 2016;205(10):480–85.
3. Naylor R, Philipson LH. Who should have genetic testing for maturity-onset diabetes of the young? *Clin Endocrinol (Oxf)* 2011;75(4):422–26.

## Resource for general practitioners

- McElduff A. Non-type 1, non-type 2 diabetes: What's in a name?, [www.nps.org.au/australian-prescriber/articles/non-type-1-non-type-2-diabetes-what-s-in-a-name](http://www.nps.org.au/australian-prescriber/articles/non-type-1-non-type-2-diabetes-what-s-in-a-name)

## Resource for patients

- Centre for Genetics Education, Fact sheet 48: Diabetes types 1 and 2 and inherited predisposition, [www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-48-diabetes-type-1-and-2](http://www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-48-diabetes-type-1-and-2)

## Fragile X syndrome and associated conditions

### Practice point

General practitioners (GPs) can order a test for Fragile X syndrome (FXS) for the following people:

- Individuals with intellectual disability (ID), developmental delay (DD) or **autism spectrum disorder (ASD)**.
- Individuals seen for reproductive counselling who have a **family history** of FXS (or related conditions, such as Fragile X-associated primary ovarian insufficiency [FXPOI] or undiagnosed ID).
- Women with reproductive or fertility issues (associated with elevated follicle-stimulating hormone [FSH]).
- Older individuals (>50 years of age) with late-onset tremor or cerebellar ataxia of unknown origin.

### What do I need to know?

#### FXS

FXS is the most common known inherited cause of ID, and the second most common cause of ID overall (after Down syndrome). FXS affects approximately one in 3600 males and one in 6000 females.<sup>1</sup>

FXS presents clinically with a wide range of symptoms, including global DD; difficulties with learning, speech and language; problems with coordination and sensory overload; and notably a range of emotional and behavioural difficulties.<sup>2,3</sup>

FXS follows an **X-linked recessive inheritance** pattern and is caused by an increase in length of the *FMR1* gene on the X chromosome. The length of the *FMR1* gene is divided into four categories (Figure 1). The longer the gene, the more likely the individual will have symptoms of FXS.<sup>2,3</sup>

Figure 1. Length of gene associated with FXS<sup>3</sup>



Females who are premutation carriers of FXS can have a child affected with FXS. This is because the gene length can get longer when passed from mother to child: this lengthening only occurs in women. Therefore, it is unlikely males who are premutation carrier of FXS would have an affected child.<sup>4</sup>

#### Associated conditions

Females who are premutation **carriers** are at increased risk of FXPOI. Males (females to a lesser extent) are at increased risk of Fragile X-associated tremor/ataxia syndrome (FXTAS) later in life.<sup>2,3,4</sup>

#### Genetic testing

**Chromosome microarray (CMA)** is now considered a first-line genetic test for the investigation of DD or congenital abnormalities. CMA does not detect **gene variants** causing FXS, so an additional deoxyribonucleic acid (DNA) test for FXS must be ordered alongside.<sup>5</sup>

While GPs are able to order CMAs, many choose not to, given the complex interpretation of the results. However, ordering CMA and FXS tests in parallel with referral to a paediatrician can reduce waiting times for patients.

A Medicare Benefits Schedule (MBS) rebate is available for CMA in situations where the patient has DD, ID, ASD or at least two congenital abnormalities. DNA testing for FXS is available with an MBS rebate when the patient:<sup>6</sup>

- exhibits ID, ataxia, neurodegeneration, or premature ovarian failure consistent with an *FMR1* mutation
- has a relative with an *FMR1* mutation.

## When should I refer?

For symptomatic patients:

- A child with a test positive result should be referred to a paediatrician for further assessment.
- An adult with ataxic symptoms and a test positive result (ie premutation carrier) should be referred to a neurologist.
- A woman with FXPOI should be referred to an obstetrician and gynaecologist.<sup>2,3</sup>

Asymptomatic patients with a test positive result (eg received through pre-conception or prenatal [carrier screening](#) or cascade testing) should be referred to genetics services.

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1. Birch RC, Cohen J, Trollor JN. Fragile X-associated disorders: Don't miss them. *Aust Fam Physician* 2017;46(7):487–91. Available at [www.racgp.org.au/afp/2017/july/fragile-x-associated-disorders-don%E2%80%99t-miss-them](http://www.racgp.org.au/afp/2017/july/fragile-x-associated-disorders-don%E2%80%99t-miss-them) [Accessed 19 December 2017].
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4. Abrams L, Cronister A, Brown WT, et al. Newborn, carrier, and early childhood screening recommendations for fragile X. *Pediatrics* 2012;130(6):1126–35.
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6. Department of Health. Medicare Benefits Schedule (MBS) Online. Canberra: DoH, 2017. Available at [www.mbsonline.gov.au](http://www.mbsonline.gov.au) [Accessed 19 December 2017].

## Resources for patients

### Information

- National Library of Medicine (US), Fragile X syndrome, <https://ghr.nlm.nih.gov/condition/fragile-x-syndrome>

### Support

- Fragile X Association of Australia, <https://fragilex.org.au>

## Familial breast and ovarian cancer

### Practice point

To identify patients who may be at risk of familial breast and ovarian cancer, a comprehensive **family history** must be taken and regularly updated.<sup>1,2</sup>

Refer individuals and families who meet high-risk criteria to a family cancer clinic.

Women who are at average or only slightly higher risk of familial breast and ovarian cancer do not require additional surveillance beyond the National Breast Cancer Screening Program and National Cervical Screening Program nor referral to a family cancer clinic.<sup>2</sup>

### What do I need to know?

Highly **penetrant gene variants** in *BRCA1* and *BRCA2* genes are associated with increased risk of several cancers, particularly breast and ovarian. These show **autosomal dominant inheritance** pattern.<sup>1,3</sup> **Pathogenic variants** in *BRCA1* and *BRCA2* are associated with increased risk of other cancers including prostate (for men specifically) and pancreatic.

The lifetime risk of breast cancer in Australian women is approximately one in eight.<sup>4</sup> Inheriting pathogenic variants of the *BRCA1* and *BRCA2* genes increase the chance of developing breast cancer to about 70% (cumulative risk to 80 years of age). Despite this, *BRCA1* and *BRCA2* variants account for only about 5% of all breast cancer cases, because these variants are relatively rare.<sup>3-6</sup>

Several other genes (low-to-moderate penetrant variants) predisposing to breast and/or ovarian cancer can now also be tested.<sup>7</sup>

Features within a family that are suggestive of increased risk of carrying a pathogenic *BRCA1* or *BRCA2* variant include:<sup>5</sup>

- multiple affected relatives on the same side of the family (maternal or paternal)
- breast and ovarian cancer in the same woman
- breast cancer diagnosed <40 years of age
- Ashkenazi Jewish ancestry (from central and eastern Europe)
- bilateral breast cancer
- male breast cancer.

A three-generation family history is key to identifying high-risk families who are most likely to benefit from genetic testing. Such a history should include first-degree and second-degree relatives on both sides of the family, and ethnic background (eg Ashkenazi Jewish). Note that sex-specific cancer can be inherited through maternal or paternal sides of the family (eg *BRCA* variants can be passed from the paternal side). Type of cancer (including bilateral) and age of onset should be recorded where available.<sup>4</sup>

Use existing risk criteria (eg [www.racgp.org.au/your-practice/guidelines/redbook/9-early-detection-of-cancers/93-breast-cancer](http://www.racgp.org.au/your-practice/guidelines/redbook/9-early-detection-of-cancers/93-breast-cancer)) to identify families who are at increased risk of carrying a pathogenic *BRCA1* or *BRCA2* variant (high risk), or women who may require additional screening or chemoprevention (moderately increased risk).<sup>2</sup>

Alternatively, the 'Familial risk assessment – Breast and ovarian cancer' (FRA-BOC) tool can be used to assess risk (<https://canceraustralia.gov.au/clinical-best-practice/gynaecological-cancers/familial-risk-assessment-fra-boc>).<sup>8</sup>

### Genetic testing

Family cancer clinics can assess individual risk to determine the utility of genetic testing for *BRCA1* and *BRCA2* variants. As new genetic variants predisposing to breast cancer are identified, these new variants may be offered as part of a panel of genetic tests through the family cancer clinic. If a pathogenic variant is identified in an individual, testing will be offered to relatives.<sup>4</sup>

A rebate is available for *BRCA1* and *BRCA2* gene testing under the Medicare Benefits Schedule (MBS).<sup>9</sup>

There is currently no role in general practice for ordering a cancer-risk assessment based on a **single nucleotide polymorphism** (SNP) profile (**genotyping**).



## When should I refer?

The recommended breast cancer screening strategy for women and different high-risk individuals is outlined in the Royal Australian College of General Practitioners (RACGP's) 2016 *Guidelines for preventive activities in general practice* (Red Book; available at [www.racgp.org.au/your-practice/guidelines/redbook/9-early-detection-of-cancers/93-breast-cancer](http://www.racgp.org.au/your-practice/guidelines/redbook/9-early-detection-of-cancers/93-breast-cancer)).<sup>2</sup>

## Other considerations

A cancer antigen 125 (CA 125) blood test and transvaginal ultrasound are not recommended as screening tests for ovarian cancer, even in women who are at high risk.<sup>2</sup>

Women at increased risk for breast and ovarian cancer should be encouraged to:

- discuss their family history with all first-degree relatives
- advise family members to discuss their risk with their general practitioner (GP).

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3. National Cancer Institute (US). *BRCA1 and BRCA2: Cancer risk and genetic testing*. Bethesda, MD: National Institutes of Health, 2015. Available at [www.cancer.gov/about-cancer/causes-prevention/genetics/brca-fact-sheet](http://www.cancer.gov/about-cancer/causes-prevention/genetics/brca-fact-sheet) [Accessed 19 December 2017].
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6. National Breast and Ovarian Cancer Centre. *Breast cancer risk factors: A review of the evidence*. Sydney: NBOCC, 2009. Available at [https://canceraustralia.gov.au/system/tdf/publications/breast-cancer-risk-factors-review-evidence/pdf/rfrw-breast-cancer-risk-factors-a-review-of-the-evidence\\_1.15.pdf?file=1&type=node&id=3074](https://canceraustralia.gov.au/system/tdf/publications/breast-cancer-risk-factors-review-evidence/pdf/rfrw-breast-cancer-risk-factors-a-review-of-the-evidence_1.15.pdf?file=1&type=node&id=3074) [Accessed 19 December 2017].
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9. Department of Health. *Medicare Benefits Schedule*. Canberra: DoH, 2017. Available at [www.mbsonline.gov.au/internet/mbsonline/publishing.nsf/Content/Home](http://www.mbsonline.gov.au/internet/mbsonline/publishing.nsf/Content/Home) [Accessed 22 January 2018].

## Resource for general practitioners

- Cancer Institute NSW, eviQ, [www.eviq.org.au](http://www.eviq.org.au)

## Resources for patients

### Information

- Better Health Channel, Breast cancer, [www.betterhealth.vic.gov.au/health/conditionsandtreatments/breast-cancer](http://www.betterhealth.vic.gov.au/health/conditionsandtreatments/breast-cancer)
- Better Health Channel, Genetic testing for inherited cancer, [www.betterhealth.vic.gov.au/health/conditionsandtreatments/genetic-testing-for-inherited-cancer](http://www.betterhealth.vic.gov.au/health/conditionsandtreatments/genetic-testing-for-inherited-cancer)
- Centre for Genetics Education, Fact sheet 32: Breast and ovarian cancer and inherited predisposition, [www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-32-breast-and-ovarian-cancer-and-inherited-predisposition](http://www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-32-breast-and-ovarian-cancer-and-inherited-predisposition)

## Support

- Breast Cancer Network Australia, [www.bcna.org.au](http://www.bcna.org.au)
- Cancer Australia, <https://canceraustralia.gov.au>
- Cancer Council Australia, [www.cancer.org.au](http://www.cancer.org.au)
- Ovarian Cancer Australia, <https://ovariancancer.net.au>
- Pink Hope Australia, <http://pinkhope.org.au>

## Familial colorectal cancer

### Practice point

A comprehensive **family history** must be taken and regularly updated to identify patients who may be at risk of familial colorectal cancer (CRC).<sup>1</sup>

Refer individuals and families who meet high-risk criteria to a family cancer clinic.

Individuals at average or only slightly higher risk do not require a colonoscopy, and should be encouraged to participate in the National Bowel Cancer Screening Program (ie faecal occult blood test [FOBT]).<sup>1,2</sup>

### What do I need to know?

Highly **penetrant gene variants** in several genes are associated with specific familial CRC syndromes:

- Lynch syndrome (associated with a range of cancers, including colorectal, endometrial, ovarian, gastric, renal pelvis, ureter, small bowel, biliary tract, brain) is caused by dominantly inherited pathogenic variants in the *MLH1*, *MSH2*, *MSH6* or *PMS2* genes. Lynch syndrome accounts for up to 6% of all colorectal cancer.<sup>3</sup>
- Familial adenomatous polyposis (FAP), associated with multiple adenomas in the large bowel, is caused by dominantly inherited pathogenic variants in the *APC* gene. FAP accounts for approximately 1% of colorectal cancer cases.<sup>3</sup>
- There are other rare inherited CRC syndromes that may be associated with specific polyp pathologies, phenotypic features or other cancer types in a family.<sup>4,5</sup>

Features **within a family** that are suggestive of increased risk of carrying a pathogenic variant for Lynch syndrome or FAP include:<sup>1,5</sup>

- multiple affected relatives on the same side of the family
- multiple CRCs in the same person (ie metachronous)
- CRC diagnosed <50 years of age
- other Lynch-syndrome related cancers (as above)
- >20 adenomas in the large bowel
- adenomas diagnosed <30 years of age.

A three-generation **family history** is key to identifying high-risk families who are most likely to benefit from genetic testing. Such a history should include first-degree and second-degree relatives on both sides of the family. Type of cancer (including whether the cancer is metachronous) and age of onset should be recorded where available.<sup>1</sup>

Use existing risk criteria (eg [www.racgp.org.au/your-practice/guidelines/redbook/9-early-detection-of-cancers/92-colorectal-cancer](http://www.racgp.org.au/your-practice/guidelines/redbook/9-early-detection-of-cancers/92-colorectal-cancer)) to identify families at increased risk of an inherited CRC syndrome (high risk), or individuals who may require additional screening or chemoprevention (moderately increased risk).<sup>1</sup>

### Genetic testing

Family cancer clinics will assess individual risk to determine the utility of genetic testing for Lynch syndrome or FAP. As new genetic variants predisposing to CRC are identified, these new variants may be offered as part of a panel of genetic tests through family cancer clinics.<sup>1</sup>

There is currently no role in general practice for ordering a cancer-risk assessment based on a **single nucleotide polymorphism (SNP) profile (genotyping)**.

### When should I refer?

The recommended CRC screening strategy and different individual risk categories are outlined in The Royal Australian College of General Practitioners' (RACGP's) 2016 *Guidelines for preventive activities in general practice (Red Book)*; [www.racgp.org.au/your-practice/guidelines/redbook/9-early-detection-of-cancers/92-colorectal-cancer](http://www.racgp.org.au/your-practice/guidelines/redbook/9-early-detection-of-cancers/92-colorectal-cancer)).<sup>1</sup>

## Other considerations

Individuals at increased risk for CRC should be encouraged to:

- discuss their **family history** with all first-degree relatives
- advise family members to discuss their risk with their general practitioners (GP).

## References

1. The Royal Australian College of General Practitioners. Guidelines for preventive activities in general practice. 9th edn. East Melbourne, RACGP, 2016. Available at [www.racgp.org.au/your-practice/guidelines/redbook](http://www.racgp.org.au/your-practice/guidelines/redbook) [Accessed 19 December 2017].
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4. Samadder NJ, Jasperson K, Burt RW. Hereditary and common familial colorectal cancer: Evidence for colorectal screening. *Dig Dis Sci* 2015;60(3):734–47.
5. Rubenstein JH, Enns R, Heidelbaugh J, Barkun A. American Gastroenterological Association Institute guideline on the diagnosis and management of Lynch syndrome. *Gastroenterology* 2015;149(3):777–82.

## Resources for general practitioners

- Department of Health, National bowel cancer screening program, [www.cancerscreening.gov.au/internet/screening/publishing.nsf/Content/bowel-screening-1](http://www.cancerscreening.gov.au/internet/screening/publishing.nsf/Content/bowel-screening-1)
- Cancer Council Victoria, Optimal care pathways, [www.cancervic.org.au/for-health-professionals/optimal-care-pathways](http://www.cancervic.org.au/for-health-professionals/optimal-care-pathways)
- Cancer Institute NSW, eviQ, [www.eviq.org.au](http://www.eviq.org.au)

## Resources for patients

### Information

- Better Health Channel, Genetic testing for inherited cancer, [www.betterhealth.vic.gov.au/health/conditionsandtreatments/genetic-testing-for-inherited-cancer](http://www.betterhealth.vic.gov.au/health/conditionsandtreatments/genetic-testing-for-inherited-cancer)
- Centre for Genetics Education, Fact sheet 33: Bowel cancer and inherited predisposition, [www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-33-bowel-cancer-and-inherited-predisposition](http://www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-33-bowel-cancer-and-inherited-predisposition)

### Support

- Bowel Cancer Australia, [www.bowelcanceraustralia.org](http://www.bowelcanceraustralia.org)
- Cancer Council Australia, [www.cancer.org.au](http://www.cancer.org.au)
- Cancer Australia, <https://canceraustralia.gov.au>
- Lynch Syndrome Australia, [www.lynchsyndrome.org.au](http://www.lynchsyndrome.org.au)

# Familial hypercholesterolaemia

## Practice point

General practitioners (GPs) are well placed to undertake opportunistic screening for familial hypercholesterolaemia (FH).<sup>1</sup> Family screening is critical when a diagnosis of FH is made in an individual.<sup>2,3</sup>

## What do I need to know?

FH is a lipid disorder that leads to premature cardiovascular disease (CVD). FH follows an **autosomal dominant inheritance** pattern. If FH is left untreated, males have a 50% chance of developing CVD before 50 years of age, and women have a 30% chance of developing CVD by 60 years of age. Early diagnosis and treatment of FH reduces the risk of CVD.<sup>1</sup>

The risk of FH can be assessed using the Dutch Lipid Clinic Network Criteria (DLCNC; [www.racgp.org.au/your-practice/guidelines/redbook/appendices/appendix-2b-dutch-lipid-clinic-network-criteria-for-making-a-diagnosis-of-familial-hypercholesterolaemia-in-adults](http://www.racgp.org.au/your-practice/guidelines/redbook/appendices/appendix-2b-dutch-lipid-clinic-network-criteria-for-making-a-diagnosis-of-familial-hypercholesterolaemia-in-adults)).<sup>4</sup>

FH assessment should be conducted when an individual presents with:

- clinical features such as xanthomata
- low-density lipoprotein cholesterol (LDL-C) >4.0 mmol/L or total cholesterol >7.5 mmol/L
- premature CVD or a **family history** of such (CVD <55 years of age for males and <65 years of age for females).<sup>1,2,5</sup>

## Genetic testing

While FH can be diagnosed clinically, a confirmatory deoxyribonucleic acid (DNA) test allows for **cascade screening** within the family of an affected patient.<sup>5</sup>

## When should I refer?

Refer individuals with a DLCNC score of  $\geq 3$  (ie possible-to-definite FH) to a cardiologist or lipid clinic for confirmation of diagnosis, including possible genetic testing.<sup>2,4</sup>

## Other considerations

Those diagnosed with FH should be encouraged to:<sup>1</sup>

- inform family members that they may be at increased risk of FH
- direct family members to further information about FH
- advise family members to discuss their risk of FH with their GP.

## References

1. Kirke A, Watts GF, Emery J. Detecting familial hypercholesterolaemia in general practice. *Aust Fam Physician* 2012;41(12):965–68. Available at [www.racgp.org.au/afp/2012/december/familial-hypercholesterolaemia](http://www.racgp.org.au/afp/2012/december/familial-hypercholesterolaemia) [Accessed 19 December 2017].
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5. Cardiac Society of Australia and New Zealand. Guidelines for the diagnosis and management of familial hypercholesterolaemia. Sydney: CSANZ, 2013. Available at [www.csanz.edu.au/wp-content/uploads/2014/12/Familial-Hypercholesterolaemia\\_2013-November.pdf](http://www.csanz.edu.au/wp-content/uploads/2014/12/Familial-Hypercholesterolaemia_2013-November.pdf) [Accessed 19 December 2017].

## Resources for patients

### Information

- Better Health Channel, Genetic factors and cholesterol, [www.betterhealth.vic.gov.au/health/conditionsandtreatments/genetic-factors-and-cholesterol](http://www.betterhealth.vic.gov.au/health/conditionsandtreatments/genetic-factors-and-cholesterol)
- Centre for Genetics Education, Fact sheet 56: Familial hypercholesterolaemia, [www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-56-familial-hypercholesterolaemia](http://www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-56-familial-hypercholesterolaemia)

### Support

- FH Australasia Network, [www.athero.org.au/fh](http://www.athero.org.au/fh)

## Familial melanoma

### Practice point

In order to identify patients who may be at risk of familial melanoma, a comprehensive **family history** must be taken and regularly updated. Genetic testing for melanoma risk is not routine as it does not alter the patient's management in most cases.<sup>1-3</sup>

### What do I need to know?

Rare, highly **penetrant** variants in a small number of genes (*CDKN2A* and *CDK4*) are associated with familial melanoma. These variants show an **autosomal dominant inheritance** pattern. Only 1–2% of melanomas are due to **pathogenic variants**.<sup>1,2</sup>

Having a first-degree relative with melanoma approximately doubles an individual's risk of developing melanoma. Having relatives who are affected with multiple melanomas or at a younger age further increases the risk of developing melanoma.<sup>3</sup>

Features within a family that are suggestive of increased risk of carrying a pathogenic variant for familial melanoma include having three or more relatives affected by melanoma on the same side of the family.

Other features and red flags within a family are:<sup>1</sup>

- multiple melanomas in the same person
- melanoma diagnosed <40 years of age
- ocular melanoma
- pancreatic cancer
- astrocytoma.

### Genetic testing

Genetic testing for *CDKN2A* **gene variants** has limited clinical utility in general practice. Testing should be restricted to selected families with a strong history of melanoma.<sup>1,3</sup> Assessment of individuals for genetic testing is performed by a family cancer clinic.

### When should I refer?

Individuals with more than one family member with melanoma should be referred to a dermatologist for clinical risk management.

Individuals with three or more relatives affected with melanoma and/or pancreatic cancer in the family should be referred to a family cancer clinic for genetic risk assessment.<sup>3,4</sup>

### Other considerations

Individuals with familial melanoma should be encouraged to advise family members to discuss their risk with their general practitioner (GP).

## References

1. Kefford R, Bishop JN, Tucker M, et al. Genetic testing for melanoma. *Lancet Oncol*. 2002;3(11):653–54.
2. National Cancer Institute (US). Genetics of skin cancer (PDQ) – Health professional version. Bethesda, MD: NIH, 2017. Available at [www.cancer.gov/types/skin/hp/skin-genetics-pdq](http://www.cancer.gov/types/skin/hp/skin-genetics-pdq) [Accessed 19 December 2017].
3. Australian Cancer Network Melanoma Guidelines Revision Working Party. Clinical practice guidelines for the management of melanoma in Australia and New Zealand. Sydney/Wellington: Cancer Council Australia/Australian Cancer Network/Ministry of Health, New Zealand, 2008. Available at [www.cancer.org.au/content/pdf/HealthProfessionals/ClinicalGuidelines/ClinicalPracticeGuidelines-ManagementofMelanoma.pdf](http://www.cancer.org.au/content/pdf/HealthProfessionals/ClinicalGuidelines/ClinicalPracticeGuidelines-ManagementofMelanoma.pdf) [Accessed 19 December 2017].
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## Resource for general practitioners

- Cancer Institute NSW, eviQ, [www.eviq.org.au](http://www.eviq.org.au)

## Resources for patients

### Information

- Centre for Genetics Education, Fact sheet 34: Genetics and melanoma, [www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-34-genetics-and-melanoma](http://www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-34-genetics-and-melanoma)

### Support

- Cancer Australia, [canceraustralia.gov.au](http://canceraustralia.gov.au)
- Cancer Council Australia, [www.cancer.org.au](http://www.cancer.org.au)
- Melanoma Institute Australia, [www.melanoma.org.au](http://www.melanoma.org.au)



## Familial prostate cancer

### Practice point

A comprehensive **family history** must be taken and regularly updated to identify patients who may be at risk of familial prostate cancer.<sup>1</sup>

Use existing risk criteria to identify individuals who are at increased risk of carrying a **pathogenic variant** of the *BRCA1* or *BRCA2* genes (high risk). These individuals should be referred to a family cancer clinic.

Men with family history of prostate cancer who decide to be tested should be offered prostate-specific antigen (PSA) testing every two years from 40 or 45 years of age, with the starting age depending on the strength of their family history.<sup>2</sup>

### What do I need to know?

Approximately 1–2% of prostate cancer is due to pathogenic variants in the *BRCA1* and *BRCA2* genes. These show an **autosomal dominant inheritance** pattern.<sup>3</sup>

Multiple genetic and environmental factors are likely to influence the risk of prostate cancer. Genetic testing for **gene variants** in men with multiple cases of prostate cancer only in their family is not widely available.

Features suggestive of increased risk of carrying a pathogenic *BRCA1* or *BRCA2* variant genes include two or more relatives affected by breast or ovarian cancer on the same side of the family (maternal or paternal) plus an additional high-risk feature:<sup>4,5</sup>

- relatives with breast or ovarian cancer
- breast and ovarian cancer in the same woman
- breast cancer diagnosed <50 years of age
- Ashkenazi Jewish ancestry
- bilateral breast cancer
- male breast cancer.

A three-generation family history is key to identifying high-risk families who are most likely to benefit from genetic assessment. Such a history should include first-degree and second-degree relatives on both sides of the family, and ethnic background (eg Ashkenazi Jewish). Type of cancer (eg metachronous) and age of onset of affected relatives should be recorded where available.

In men with a family history of prostate cancer, take a family history of other cancers to assess the risk of carrying a pathogenic *BRCA1* or *BRCA2* variant genes. In the absence of a positive breast or ovarian cancer family history, *BRCA1* and *BRCA2* testing is generally not warranted.

### Genetic testing

Family cancer clinics will assess individual risk to determine the utility of genetic assessment for *BRCA1* or *BRCA2* gene variants. As new genetic variants predisposing to prostate cancer are identified, these new variants may be offered as part of a panel of genetic tests through the family cancer clinic.

There is currently no role in general practice for ordering a cancer-risk assessment based on a **single nucleotide polymorphism** (SNP) profile (**genotyping**).

### When should I refer?

Refer men to a family cancer clinic if they have:<sup>1,4</sup>

- a family history suggestive of a *BRCA1* or *BRCA2* pathogenic gene variant.
- **three** first-degree or second-degree relatives with prostate cancer
- **two** first-degree or second-degree relatives with prostate cancer, one of whom was diagnosed <50 years of age.

## Other considerations

Individuals at increased risk of prostate cancer should be encouraged to:

- discuss their family history with all first-degree relatives
- advise family members to discuss their risk with their general practitioner (GP).

Recommendations for PSA testing vary according to family history of prostate cancer:<sup>2</sup>

Number of relatives with prostate cancer	Relative risk	Testing recommendation*
Father <b>or</b> one brother	2.5–3	PSA testing every two years for those aged 45–69 years
Father <b>and</b> two or more brothers	9–10	PSA testing every two years for those aged 40–69 years

\*After discussion of benefits and harms of PSA testing.

## References

1. The Royal Australian College of General Practitioners. Guidelines for preventive activities in general practice. 9th edn. Melbourne, RACGP, 2016. Available at [www.racgp.org.au/your-practice/guidelines/redbook](http://www.racgp.org.au/your-practice/guidelines/redbook) [Accessed 19 December 2017].
2. Prostate Cancer Foundation of Australia and Cancer Council Australia PSA Testing Guidelines Expert Advisory Panel. Clinical practice guidelines PSA testing and early management of test-detected prostate cancer. Sydney: Cancer Council Australia, 2015. Available at [http://wiki.cancer.org.au/australia/Guidelines:PSA\\_Testing](http://wiki.cancer.org.au/australia/Guidelines:PSA_Testing) [Accessed 19 December 2017].
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4. National Cancer Institute (US). Genetics of prostate cancer (PDQ) – Health professional version. Bethesda, MD: National Institutes of Health, 2017. Available at [www.cancer.gov/types/prostate/hp/prostate-genetics-pdq](http://www.cancer.gov/types/prostate/hp/prostate-genetics-pdq) [Accessed 19 December 2017].
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## Resource for general practitioners

- Cancer Institute NSW, eviQ, [www.eviq.org.au](http://www.eviq.org.au)

## Resources for patients

### Information

- Better Health Channel, Prostate cancer, [www.betterhealth.vic.gov.au/health/conditionsandtreatments/prostate-cancer](http://www.betterhealth.vic.gov.au/health/conditionsandtreatments/prostate-cancer)
- The Royal Australian College of General Practitioners, Patient information sheet – Should I have prostate cancer screening?, [www.racgp.org.au/your-practice/guidelines/prostate-cancer](http://www.racgp.org.au/your-practice/guidelines/prostate-cancer)

### Support

- Cancer Council Australia, [www.cancer.org.au](http://www.cancer.org.au)
- Cancer Australia, <https://canceraustralia.gov.au>
- Prostate Cancer Foundation of Australia, [www.prostate.org.au](http://www.prostate.org.au)

# Haemoglobinopathies

## Practice point

General practitioners (GPs) play an important role in identifying potential **carriers** of haemoglobinopathy. They also play an important role in identifying couples who are at risk of having a child with a haemoglobinopathy.

**Carrier screening** should be discussed with couples who are potential carriers of haemoglobinopathy because of their ethnicity, and are planning pregnancy or in the first trimester of pregnancy.<sup>1</sup>

To enable timely reproductive choices during early pregnancy, carrier screening should be offered to couples at the same time (ie both partners should be tested as early as possible).

## What do I need to know?

The term 'haemoglobinopathies' covers a range of conditions with an **autosomal recessive inheritance** pattern that affect haemoglobin, including  $\alpha$ -thalassaemia and  $\beta$ -thalassaemia, sickle cell disease and other abnormal haemoglobins, such as haemoglobin E (HbE).

Individuals with thalassaemia produce insufficient haemoglobin, while those with sickle cell disease produce structurally abnormal haemoglobin. The clinical implications range from mild through to death in utero.

Collectively, haemoglobinopathies are the most common single gene disorders in humans, and around 7% of the world's population are carriers.<sup>1</sup> Haemoglobinopathies are becoming more prevalent in Australia given immigration from endemic regions.<sup>2</sup>

While carriers are often asymptomatic, carrier status becomes clinically significant in women who are carriers and planning a pregnancy, where the biological male partner is also a carrier.<sup>1</sup> Screening for haemoglobinopathies is not part of the **newborn screening** program in Australia.

Carrier screening should be discussed as part of pre-pregnancy and prenatal care in the following individuals:<sup>1-4</sup>

- Those with **family history** of anaemia or haemoglobinopathy.
- Those from the following ethnic backgrounds (have increased carrier frequency)
  - southern European
  - African
  - Middle Eastern
  - Chinese
  - Indian subcontinent
  - central and south-east Asian
  - Pacific Islander
  - New Zealand Maori
  - South American
  - Caribbean
  - some northern Western Australian and Northern Territory Aboriginal and Torres Strait Islander communities.
- Those with a mean corpuscular volume (MCV) <80 fL or mean corpuscular haemoglobin (MCH) <27 pg.
- Biological male partners of known female carriers.

## Genetic testing

Order a haemoglobinopathy screen to include:<sup>1,2,4</sup>

- full blood examination (FBE) for MCV and MCH
- ferritin to exclude iron deficiency
- haemoglobin electrophoresis
- deoxyribonucleic acid (DNA) testing if indicated (Table 1).

There is an urgency to test the biological male partner concurrently when an at-risk woman who is a carrier is pregnant. DNA testing is required when  $\alpha$ -thalassaemia cannot be excluded and the partner is a known carrier of two-gene deletion  $\alpha$ -thalassaemia (Table 1).

**Table 1. Interpretation of haemoglobinopathy carrier testing results<sup>2</sup>**

MCH (pg)/MCV (fL)	Ferritin	Haemoglobin electrophoresis	Interpretation
MCH <27 and/or MCV <80	Normal	HbA <sub>2</sub> increased	$\beta$ -thalassaemia carrier
		HbA <sub>2</sub> normal HbH present	$\alpha$ -thalassaemia carrier
		HbA <sub>2</sub> normal HbH high	Possible HbH $\alpha$ -thalassaemia
		HbA <sub>2</sub> normal HbE present	HbE carrier or homozygote
		Normal	Possible $\alpha$ -thalassaemia carrier; DNA testing indicated
Low	Normal		Iron deficiency
			Thalassaemia may co-exist (treat iron deficiency then retest)
			If woman is pregnant, seek advice about further tests
MCH $\geq$ 27 and/or MCV $\geq$ 80	Normal	Normal	Thalassaemia unlikely but one-gene deletion $\alpha$ -thalassaemia not excluded; DNA testing indicated only if partner is carrier of $\alpha$ -thalassaemia
		Normal	HbS present
	Low	Normal	

HbA<sub>2</sub>, normal variant of haemoglobin with two  $\alpha$ -globin and two  $\beta$ -globin chains; HbE, abnormal variant of haemoglobin, due to abnormal  $\beta$ -globin; HbH, abnormal variant of haemoglobin, due to excess  $\beta$ -globin chains relative to  $\beta$ -globin chains, a type of  $\alpha$ -thalassaemia; HbS, abnormal variant of haemoglobin, due to abnormal  $\beta$ -globin; MCH, mean corpuscular haemoglobin; MCV, mean corpuscular volume

Adapted from Metcalfe SA, Barlow-Stewart K, Campbell J, Emery J. Genetics and blood – Haemoglobinopathies and clotting disorders. Aust Fam Physician 2007;36(10):812–19.

## When should I refer?

Urgent referral should be made to genetics or haematology services when carrier couples are identified during pregnancy in order to allow for timely reproductive decisions, or when a pregnant woman is identified as a carrier and of testing the biological male partner has not been done.

Urgent referral should be made to haematology services if a pregnant woman is found to have abnormal variant of haemoglobin (HbH)  $\alpha$ -thalassaemia.

## Other considerations

Do not assume low MCV or MCH is due to iron deficiency alone, especially in at-risk individuals.<sup>1</sup> If the patient is not pregnant, treat for the iron deficiency then retest. If MCV or MCH remain low, the individual is possibly a carrier of a haemoglobinopathy. If the patient is pregnant, DNA testing for  $\alpha$ -thalassaemia is indicated.<sup>1</sup>

A woman only needs to have haemoglobinopathy screening once – if MCV or MCH is low but was previously normal, it is most likely due to iron deficiency.

## References

1. Tan YL, Kidson-Gerber G. Antenatal haemoglobinopathy screening in Australia. *Med J Aust* 2016;204(6):226–30.
2. Metcalfe SA, Barlow-Stewart K, Campbell J, Emery J. Genetics and blood: Haemoglobinopathies and clotting disorders. *Aust Fam Physician* 2007;36(10):812–19.
3. The Royal Australian and New Zealand College of Obstetricians and Gynaecologists. Prenatal screening and diagnosis of chromosomal and genetic conditions in the fetus in pregnancy (C-Obs 59). Sydney: RANZCOG, 2015. Available at [www.ranzcog.edu.au/Statements-Guidelines](http://www.ranzcog.edu.au/Statements-Guidelines) [Accessed 20 December 2017].
4. The Royal Australian College of General Practitioners. Guidelines for preventive activities in general practice. 9th edn. Melbourne: RACGP, 2016. Available at [www.racgp.org.au/your-practice/guidelines/redbook](http://www.racgp.org.au/your-practice/guidelines/redbook) [Accessed 20 December 2017].

## Resources for general practitioners

- Bender MA, Douthitt Seibel G, Sickle cell disease, [www.ncbi.nlm.nih.gov/sites/books/NBK1377](http://www.ncbi.nlm.nih.gov/sites/books/NBK1377)
- Origa R, Moi P, Alpha-thalassaemia, [www.ncbi.nlm.nih.gov/books/NBK1435](http://www.ncbi.nlm.nih.gov/books/NBK1435)
- Origa R, Beta-thalassaemia, [www.ncbi.nlm.nih.gov/books/NBK1426](http://www.ncbi.nlm.nih.gov/books/NBK1426)

## Resources for patients

- Centre for Genetics Education, Fact sheet 43: Thalassaemia, [www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-49-blood-clotting-conditions/view](http://www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-49-blood-clotting-conditions/view)
- Centre for Genetics Education, Fact sheet 44: Sickle cell disease, [www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-44-sickle-cell-disease](http://www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-44-sickle-cell-disease)
- National Library of Medicine (US), Alpha thalassaemia, <https://ghr.nlm.nih.gov/condition/alpha-thalassaemia>
- National Library of Medicine (US), Beta thalassaemia, <https://ghr.nlm.nih.gov/condition/beta-thalassaemia>
- National Library of Medicine (US), Sickle cell disease, <https://ghr.nlm.nih.gov/condition/sickle-cell-disease>

# Hereditary haemochromatosis

## Practice point

Hereditary haemochromatosis (HHC) is a common condition that affects an estimated one in 250 individuals of northern European backgrounds. Genetic testing for HHC should be performed in patients with proven iron overload. Cascade screening of relatives is also important when specific gene variants causing HHC are confirmed in the family.<sup>1</sup> Screening for HHC in the general population is currently not recommended given its variable expressivity and incomplete penetrance.<sup>2,3</sup>

## What do I need to know?

HHC is a condition with an autosomal recessive inheritance pattern where excessive iron absorption leads to increased blood iron stores. HHC is underdiagnosed as the symptoms are usually non-specific; however, early diagnosis and treatment reduces serious complications and possible early death.

The most common genetic cause of HHC (up to 90%) is homozygosity of the C282Y gene variant in the HFE gene (HFE-haemochromatosis). About one in 10 people are carriers of a C282Y variant, while one in every 200 carriers is homozygous for the C282Y variant. Another common variant in the HFE gene is H63D. Not all individuals with a genetic predisposition to HHC will develop iron overload (incomplete penetrance).<sup>2</sup>

The risk of iron overload varies according to genotype (Table 1).<sup>3-5</sup>

**Table 1. Varying genotypes and risk of iron overload**

Genotype	Risk of iron overload with genotype	Frequency of genotype*
Heterozygous C282Y	No increased risk	1 in 10
Homozygous C282Y	Greatly increased risk – 40–60% for females and 75–100% for males	1 in 200
Heterozygous H63D	No increased risk	1 in 4
Homozygous H63D	No increased risk	1 in 50
Compound heterozygous C282Y/H63D	Small increase in risk – 1%	1 in 50

\*Frequency data are approximate for those of northern European ancestry and ethnicity.

## Genetic testing

Genetic testing for the risk of HHC is recommended in individuals with suspected iron overload (ie elevated serum ferritin concentration >200 µg/L [(females)] or >300 µg/L [(males)], and a transferrin saturation >45% will identify almost all patients with HFE-haemochromatosis).<sup>2,6-8</sup>

Cascade screening is warranted for all first-degree relatives of patients with HHC who are C282Y homozygous or C282Y/H63D compound heterozygous.

A Medicare Benefits Schedule (MBS) rebate for the HFE gene test applies where the patient has an elevated transferrin saturation or elevated serum ferritin on repeat testing **or** a first-degree relative with haemochromatosis or is homozygous for the C282Y gene variant or a compound heterozygote.<sup>9</sup>

## Other considerations

Asymptomatic individuals (identified through cascade screening) who are *C282Y* homozygous or *C282Y/H63D* compound heterozygous should have their serum ferritin regularly monitored.<sup>2,6</sup>

Patients with *HFE*-haemochromatosis should be encouraged to:<sup>8</sup>

- inform all first-degree relatives of increased risk
- direct family to information about haemochromatosis (eg Haemochromatosis Australia)
- advise family members to discuss their risk with their general practitioner (GP).

## References

1. The Royal Australian College of General Practitioners. Guidelines for preventive activities in general practice. 9th edn. Melbourne: RACGP, 2016. Available at [www.racgp.org.au/your-practice/guidelines/redbook](http://www.racgp.org.au/your-practice/guidelines/redbook) [Accessed 20 December 2017].
2. European Association for the Study of the Liver. EASL clinical practice guidelines for *HFE* hemochromatosis. *J Hepatol* 2010;53(1):3–22.
3. US Preventive Services Task Force. Screening for hemochromatosis: Recommendation statement. *Ann Intern Med* 2006;145(3):204–08.
4. Allen KJ, Gurrin LC, Constantine CC, et al. Iron-overload-related disease in *HFE* hereditary hemochromatosis. *N Engl J Med* 2008;358(3):221–30.
5. Goot K1, Hazeldine S, Bentley P, Olynyk J, Crawford D. Elevated serum ferritin: What should GPs know? *Aust Fam Physician* 2012;41(12):945–49.
6. Allen K. Hereditary haemochromatosis: Diagnosis and management. *Aust Fam Physician* 2010;39(12):938.
7. St John AT, Stuart KA, Crawford DHG. Testing for *HFE*-related haemochromatosis. *Aust Prescr* 2011;34(3):73–76. Available at [www.nps.org.au/australian-prescriber/articles/testing-for-hfe-related-haemochromatosis](http://www.nps.org.au/australian-prescriber/articles/testing-for-hfe-related-haemochromatosis) [Accessed 20 December 2017].
8. Gastroenterological Society of Australia. Haemochromatosis. 3rd edn. Sydney: Digestive Health Foundation, 2007.
9. Department of Health. Medicare Benefits Schedule (MBS) Online. Canberra: DoH, 2017. Available at [www.mbsonline.gov.au](http://www.mbsonline.gov.au) [Accessed 20 December 2017].

## Resource for general practitioners

- Seckington R, Powell L. *HFE*-associated hereditary haemochromatosis. GeneReviews. Seattle, WA: University of Washington, 2000, [www.ncbi.nlm.nih.gov/books/NBK1440](http://www.ncbi.nlm.nih.gov/books/NBK1440)

## Resources for patients

### Information

- Centre for Genetics Education, Fact sheet 47: Hereditary haemochromatosis, [www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-47-hereditary-haemochromatosis](http://www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-47-hereditary-haemochromatosis)
- National Library of Medicine (US), Hereditary hemochromatosis, <https://ghr.nlm.nih.gov/condition/hereditary-hemochromatosis>

### Support

- Haemochromatosis Australia, <https://haemochromatosis.org.au>

# Hereditary thrombophilia

## Practice point

Individuals who may benefit from genetic testing for hereditary thrombophilia include:

- individuals with venous thromboembolism (VTE) <50 years of age **without** the following
  - major transient risk factor (eg surgery, immobility, trauma)
  - oestrogen provocation (eg pregnancy, prescribed oestrogens)
- individuals with VTE <50 years of age in an unusual site (eg central nervous system, abdominal veins, upper limb)<sup>1-3</sup>
- pregnant women who have had a previous episode of VTE or who have a strong **family history** of VTE (≥2 family members).<sup>1,4</sup>

Routine genetic testing for hereditary thrombophilia in individuals without any of the above features is not recommended in general practice.<sup>1</sup>

## What do I need to know?

Individuals with hereditary thrombophilia have an increased tendency to develop blood clots.

There are a number of different types of hereditary thrombophilia conditions (Box 1). At least half of thrombotic episodes in individuals with hereditary thrombophilia occur during periods of increased risk, such as during pregnancy, immobilisation or surgery.<sup>5</sup>

The risk of VTE in women taking a low-dose combined oral contraceptive (COC; <35 ug ethinyl oestradiol) is increased two to three times, compared with non-users. Despite this increase in risk, there is no indication for routine screening of women prior to prescribing a COC.<sup>5,7,8</sup>

## Genetic testing

Testing practices for hereditary thrombophilia are variable across Australia, in part due to a lack of local evidence-based guidelines.<sup>2</sup>

Factor V Leiden and prothrombin variant genetic testing is only available on the Medicare Benefits Schedule (MBS) if the patient has a:<sup>9</sup>

- personal history of VTE
- family history of a diagnosed inherited thrombophilic condition.

## When should I refer?

Refer women with hereditary thrombophilia who are pregnant or thinking about pregnancy. Management of hereditary thrombophilia in pregnancy requires specialised risk assessment, and patients should be under the direction of a specialist haematologist, obstetric physician or obstetrician.<sup>4,5</sup>

## Other considerations

Patients diagnosed with hereditary thrombophilia should be encouraged to inform all first-degree relatives of increased risk; however, the benefit of **cascade screening** of relatives is uncertain.<sup>2,5,8,10</sup>



### Box 1. Major hereditary thrombophilia conditions<sup>6</sup>

#### Group 1 conditions – Due to a defect or deficiency of an anticoagulant protein:

- Antithrombin deficiency
- Protein C deficiency
- Protein S deficiency

#### Group 2 conditions – Due to genetic mutations that result in an increased tendency towards thrombosis:

- Activated protein C resistance
- Factor V Leiden
- Prothrombin gene variant
- Elevated levels of factors VIII, IX and XI

#### Other conditions:

- Hyperhomocysteinaemia

The risk of thrombosis is higher for patients with Group 1 conditions than Group 2 conditions. Group 2 conditions occur approximately five times more frequently than Group 1 conditions.



## References

1. Baglin T, Gray E, Greaves M, et al. Clinical guidelines for testing for heritable thrombophilia. *Br J Haematol* 2010;149(2):209–20.
2. Ho WK, Hankey GJ, Eikelboom JW. Should adult patients be routinely tested for heritable thrombophilia after an episode of venous thromboembolism? *Med J Aust* 2011;195(3):139–42.
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6. Crowther MA, Kelton JG. Congenital thrombophilic states associated with venous thrombosis: A qualitative overview and proposed classification system. *Ann Intern Med* 2003;138:128–34.
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## Resources for patients

- Centre for Genetics Education, Fact sheet 49: Blood clotting conditions (hereditary thrombophilias), [www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-49-blood-clotting-conditions/view](http://www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-49-blood-clotting-conditions/view)
- NHS Choices (UK), Thrombophilia, [www.nhs.uk/conditions/thrombophilia/Pages/Thrombophilia.aspx](http://www.nhs.uk/conditions/thrombophilia/Pages/Thrombophilia.aspx)
- Varga E, The genetics of thrombophilia, [www.stoptheclot.org/article143.htm](http://www.stoptheclot.org/article143.htm)

## Mental health conditions

### Practice point

There are currently no specific high-risk **gene variants** that are associated with mental health disorders that are useful for **predictive testing** in clinical practice.<sup>1,2</sup>

Some companies that offer **personal genomic testing** may include variants that are associated with increased risk of certain mental health conditions. The results are unlikely to have any clinical utility.

### What do I need to know?

The causes of mental health conditions, such as schizophrenia, bipolar disorder and depression, are multifactorial, and include environmental, social and genetic factors.

Table 1 outlines the empirical risk according to **family history** for schizophrenia and bipolar disorder.

**Table 1. Empirical risk of schizophrenia according to family history<sup>3,4</sup>**

Affected relative	Risk (%)	
	Schizophrenia	Bipolar disorder
No close relative (general population risk)	1	2–3
Sibling	9	13
Parent	13	15
Sibling and one parent	15	20
Both parents	40	50
Second-degree relative	3	5
Monozygotic twin	40	70
Dizygotic twin	10	20

### Genetic testing

While some genetic variants have been shown to be associated with mental health conditions, there is no genetic test that can predict mental illness with certainty.

Some commercial genetic tests available are used to tailor drug treatments to individuals with a mental health disorder (**Pharmacogenomics: Summary**). There are currently no Australian clinical guidelines to support such use.<sup>1,5</sup>

### When should I refer?

There is no indication to refer patients with a family history of mental illness (eg couples considering pregnancy) to genetics services.

### References

1. International Society of Psychiatric Genetics. Genetic testing and psychiatric disorders: A statement from the International Society of Psychiatric Genetics. Brentwood, TN: ISPG, 2017. Available at <https://ispg.net/genetic-testing-statement> [Accessed 20 December 2017].
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3. Harper PS. *Practical genetic counselling*. 7th edn. London: Hodder Arnold, 2010.
4. Slater E, Cowie V. *The genetics of mental disorders*. London: Oxford University Press, 1971.
5. Hamilton SP. The promise of psychiatric pharmacogenomics. *Biol Psychiatry*. 2015;77(1):29–35.

## Resources for patients

- Centre for Genetics Education, Fact sheet 59: Mental illness – Schizophrenia and bipolar disorder, [www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-59-mental-illness-disorders](http://www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-59-mental-illness-disorders)
- National Library of Medicine (US), Bipolar disorder, <https://ghr.nlm.nih.gov/condition/bipolar-disorder>
- National Library of Medicine (US), Schizophrenia, <https://ghr.nlm.nih.gov/condition/schizophrenia>

# Neurofibromatosis type 1

## Practice point

The diagnosis of neurofibromatosis type 1 (NF1) is usually made on clinical grounds. While genetic testing is not needed to confirm a diagnosis, confirmation of a [gene variant](#) can be useful information for family members and family planning.<sup>1,2</sup>

## What do I need to know?

NF1 is a condition that follows an [autosomal dominant inheritance](#) pattern and affects nerve cell tissue, causing the growth of small tumours throughout the nervous system.

Symptoms usually appear during childhood and may become more pronounced during puberty, pregnancy and when hormonal changes take place. The severity of the condition can vary greatly, even within a family.

NF1 may be inherited, but up to 50% of cases are caused by a [de novo](#) mutation; therefore, [family history](#) may not be present.<sup>2</sup>

The diagnosis of NF1 is made on the basis of presence of specific physical findings.

Characteristic features of NF1 include:

- multiple café-au-lait spots
- inguinal or axillary freckling
- multiple neurofibromas.

Additional features can include:<sup>1,2</sup>

- optic glioma
- Lisch nodules (iris hamartomas)
- osseous lesions (eg sphenoid dysplasia)
- increased risk of various cancers
- precocious puberty or delayed sexual development
- specific learning disabilities
- short stature
- macrocephaly
- scoliosis
- renal artery stenosis.

## Genetic testing

While genetic testing is not needed to confirm a diagnosis, confirmation of a gene variant can provide useful information for family members or family planning (ie prenatal diagnosis, [pre-implantation genetic diagnosis](#)).<sup>1</sup>

## When should I refer?

Patients with NF1 (or a relevant family history) should be referred to genetics, paediatrics or neurology services.

## References

1. Ferner RE, Gutmann DH. Neurofibromatosis type 1 (NF1): Diagnosis and management. *Handb Clin Neurol* 2013;115:939–55.
2. Friedman JM. Neurofibromatosis 1. *GeneReviews*. Seattle, WA: University of Washington, 1998. Available at [www.ncbi.nlm.nih.gov/books/NBK1109](http://www.ncbi.nlm.nih.gov/books/NBK1109) [Accessed 20 December 2017].

## Resource for general practitioners

- BMJ Best Practice, Type 1 neurofibromatosis, <http://bestpractice.bmj.com/best-practice/monograph/410/highlights/summary.html>

## Resources for patients

- Centre for Genetics Education, Fact sheet 45: Neurofibromatosis type 1, [www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-45-neurofibromatosis-type-1/at\\_download/file](http://www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-45-neurofibromatosis-type-1/at_download/file)
- National Library of Medicine (US), Neurofibromatosis type 1, <https://ghr.nlm.nih.gov/condition/neurofibromatosis-type-1>

## Neurological conditions

### Practice point

A small number of adult-onset neurological conditions are due primarily to a single gene **mutation** (eg Huntington's disease). There are some more common neurological and neuromuscular conditions that have subsets due to specific **gene variants** (eg early-onset **Alzheimer's disease** and early-onset Parkinson's disease).<sup>1</sup>

Positive **family history** is important in diagnosing neurological conditions with a genetic cause (neurogenetic conditions).<sup>2</sup> Relevant history includes:

- two or more family members affected with the same condition
- a significantly earlier age of onset than average (ie <50 years old for Parkinson's disease and <65 years old for Alzheimer's disease).

### What do I need to know?

There are some neurological conditions that are caused by single gene variants that affect the normal function of muscles and the nervous system (eg neuropathies, myopathies, ataxias). There are also a large number of complex neurological conditions caused by an interplay of genetic and environmental factors.<sup>1,3</sup>

Genetic studies continue to identify variants that contribute to complex neurological conditions; however, there is currently no role for general practitioners (GPs) in ordering genetic testing for these conditions.

### Genetic testing

Genetic testing (diagnostic testing and **predictive testing**) is available through specialist services<sup>4</sup> for the following conditions:

- Creutzfeldt–Jakob disease and other prion diseases
- early onset Parkinson's disease
- familial epilepsy
- familial motor neurone disease
- Friedreich ataxia
- hereditary peripheral neuropathies (Charcot–Marie–Tooth disease)
- hereditary spastic paraparesis
- Huntington's disease
- mitochondrial disorders
- muscular dystrophies
- myotonic dystrophy
- spinal muscular atrophy
- spinocerebellar ataxias.

## When should I refer?

Individuals with suspected neurological conditions should be referred to a neurologist for clinical diagnosis, which may include genetic testing.

Referral to genetics services for predictive genetic testing of asymptomatic family members is appropriate in cases where:

- there is a proven (clinically or by genetic testing) family history of an inherited neurological or neuromuscular condition
- there is a suggestive family history as indicated by the presence of
  - two or more family members affected with the same condition
  - a significantly earlier age of onset than average.

## References

1. Biskup S, Gasser T. Genetic testing in neurological diseases. *J Neurol* 2012;259(6):1249–54.
2. Bird TD. Approaches to the patient with neurogenetic disease. *Clin Lab Med* 2010;30(4):785–93.
3. Toft M. Advances in genetic diagnosis of neurological disorders. *Acta Neurol Scand Suppl* 2014(198):20–25.
4. The Royal College of Pathologists Australia (RCPA). Genetic tests and laboratories. Available at [www.rcpa.edu.au/Library/Practising-Pathology/RCPA-Genetic-Testing/RGTL/Home](http://www.rcpa.edu.au/Library/Practising-Pathology/RCPA-Genetic-Testing/RGTL/Home) [Accessed 22 January 2018].

## Resource for patients

- Evans-Galea M, Delatycki M, Lockhart P. Explainer: What are neurogenetic diseases? Melbourne: The Conversation, 2014, <http://theconversation.com/explainer-what-are-neurogenetic-diseases-22497>

# Sudden arrhythmic death syndrome

## Practice point

Genetic heart disorders are an important cause of sudden arrhythmic death syndrome (SADS) in people <40 years of age.<sup>1</sup> In many cases, the death of a young person in the family can often be the first sign of a potential genetic heart disease within that family.<sup>2</sup> Identifying a genetic basis of sudden cardiac death is vital in being able to accurately manage families.<sup>3</sup>

## What do I need to know?

SADS is an umbrella term to describe unexpected deaths in young people (usually <40 years of age), whose cause of death following post mortem examination is 'undetermined' or 'unascertained'.<sup>3</sup>

The most common SADS conditions include genetic arrhythmia syndromes such as long QT syndrome, catecholaminergic polymorphic ventricular tachycardia (CPVT) and Brugada syndrome.

These conditions follow an [autosomal dominant inheritance](#) pattern. Therefore, first-degree relatives (ie parents, siblings, children) of an individual who has a genetic arrhythmogenic disorder are at a 50% risk of also having a [gene variant](#) for the condition, and thus, at risk of developing the condition. All these conditions show considerable clinical variability within families and have [incomplete penetrance](#).<sup>1,4,5</sup>

Of interest are individuals presenting with:<sup>3</sup>

- any first-degree relatives with unexplained sudden cardiac death <40 years of age
- episodes of unexplained syncope
- syncope or seizures during exercise, excitement or startle.

Collect a comprehensive [family history](#) (three generations), noting any relatives with the features above.<sup>3</sup>

## Genetic testing

Genetic testing can be arranged through a genetics clinic if appropriate.<sup>6</sup> There is currently no Medicare Benefits Schedule (MBS) rebate for testing.

## When should I refer?

Refer those with relevant family history to cardiology for cardiac screening tests, and to a cardiac genetics clinic for risk assessment.<sup>2</sup>

## Other considerations

Familial screening is vital when a genetic heart condition has been confirmed in an index case.

Emotional and psychological support is vital for families where sudden cardiac death has occurred and referrals for grief counselling should be offered.<sup>2</sup>



## References

1. Cardiac Society of Australia and New Zealand. Cardiac genetic investigation of young sudden unexplained death and resuscitated out of hospital cardiac arrest. Sydney: CSANZ, 2011. Available at [www.csanz.edu.au/wp-content/uploads/2014/12/Young\\_SUD\\_and\\_Resuscitated\\_OHCA.pdf](http://www.csanz.edu.au/wp-content/uploads/2014/12/Young_SUD_and_Resuscitated_OHCA.pdf) [Accessed 22 December 2017].
2. Ingles J, Semsarian C. Sudden cardiac death in the young: A clinical genetic approach. *Intern Med J* 2007;37(1):32–37.
3. Priori SG, Blomström-Lundqvist C, Mazzanti A, et al. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). *Eur Heart J* 2015;36(41):2793–867.
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5. Brugada R, Campuzano O, Sarquella-Brugada G, et al. Brugada syndrome. GeneReviews. Seattle, WA: University of Washington, 2005. Available at [www.ncbi.nlm.nih.gov/books/NBK1517](http://www.ncbi.nlm.nih.gov/books/NBK1517) [Accessed 22 December 2017].
6. Cardiac Society of Australia and New Zealand. Guidelines for genetic testing of inherited cardiac disorders. Sydney: CSANZ, 2011. Available at [www.csanz.edu.au/wp-content/uploads/2014/12/Genetic\\_testing\\_Inherited\\_Cardiac\\_Disorders.pdf](http://www.csanz.edu.au/wp-content/uploads/2014/12/Genetic_testing_Inherited_Cardiac_Disorders.pdf) [Accessed 22 December 2017].

## Resource for general practitioners

- Australian Genetic Heart Disease Registry (AGHDR), [www.heartregistry.org.au](http://www.heartregistry.org.au)

## Resources for patients

### Information

- AGHDR information sheets, [www.heartregistry.org.au/patients-families/genetic-heart-diseases](http://www.heartregistry.org.au/patients-families/genetic-heart-diseases)
- Centre for Genetics Education, Fact sheet 58: Primary arrhythmogenic disorders, [www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-58-primary-arrhythmogenic-disorders](http://www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-58-primary-arrhythmogenic-disorders)

### Support

- Sudden Arrhythmic Death Syndrome (SADS) Australia, [www.sads.org.au](http://www.sads.org.au)

# Chromosome microarray

## What is it?

A **chromosome microarray** (CMA; also known as a chromosomal microarray or molecular karyotype) is a powerful diagnostic tool that is used to identify genetic causes of illness and developmental problems. It is used to measure the expression of multiple genes simultaneously. A CMA can identify small segments of missing or extra deoxyribonucleic acid (DNA), known as copy number variants (CNVs).

Some CNVs have been linked with certain disabilities or conditions, while others represent normal human variations. There are also some CNVs for which the clinical impact is unknown or uncertain.<sup>1</sup>

## Why use it?

CMA is commonly used in two clinical situations, as a:<sup>2</sup>

- prenatal diagnostic test
- first-line test for individuals presenting with developmental delay (DD), intellectual disability (ID), **autism spectrum disorder** (ASD) or multiple congenital anomalies.

The use of CMA has grown given they have much greater resolution than traditional karyotypes (ie can detect much smaller variations and provide a greater diagnostic yield, compared with traditional karyotypes).

## What does CMA test for?

CMA only tests for variations in DNA copy number. It can identify:<sup>1</sup>

- microdeletions and duplications
- most abnormalities of chromosome number (eg Down syndrome)
- unbalanced rearrangements of chromosome (eg complex insertions or deletions).

However, it does not identify:<sup>1</sup>

- single gene mutations
- cases of **Fragile X syndrome** (FXS)
- balanced rearrangements (translocations and inversions).

## How does it work?

CMA is performed using a blood sample, or in some cases, saliva. Testing uses a microchip platform, which allows the analysis of many pieces of DNA at once. The microchip uses labels or probes that bind to certain chromosome regions. Analysis compares the patient's DNA sequence with a reference DNA sequence. Any differences are called 'variations'.<sup>1</sup>

## Should I order a CMA (or simply refer)?

In the prenatal setting, many women who undergo an invasive procedure (eg chorionic villus sampling [CVS], amniocentesis) will have their sample analysed using a CMA (in addition to fluorescence in situ hybridisation [FISH] or quantitative fluorescence polymerase chain reaction [QF-PCR]). General practitioners (GPs) working in this area may see the results from CMA; the section on interpretation of results below may be useful.

There are no clear guidelines about whether GPs should be ordering CMA for investigating DD or ID in children. A CMA has been identified as a first-line test for investigating non-syndromic DD and ID.<sup>2</sup> A Medicare Benefits Schedule (MBS) rebate is available for CMA in the paediatric setting where a patient has DD, ID, ASD or at least two congenital abnormalities.

While GPs are able to order CMA themselves, many choose not to given the complex interpretation of the results. However, ordering a CMA (together with an FXS test) alongside a referral to a specialist can reduce waiting times for patients. It is important to note that microarrays will not identify FXS; a separate DNA test is required.

## What do the results mean?

In general, the results of a CMA are shown in Table 1.

**Table 1. CMA results<sup>1</sup>**

No clinically significant copy number variants (CNVs)	Pathogenic or likely pathogenic CNV	CNVs of unknown or uncertain significance	Secondary or unexpected findings
Normal result or known, benign changes detected	Known copy number variant identified	Copy number variant(s) of unknown significance (VOUS) identified. Clinical impact is unknown or uncertain	Copy number VOUS identified. Usually a variant that is unrelated to the reason for testing
	Laboratory report will suggest next steps (eg referral to genetics, family testing)	Laboratory report will suggest next steps (eg referral to genetics, family testing)	Laboratory report will suggest next steps (eg referral to genetics, family testing)

## References

1. Palmer EE, Peters GB, Mowat D. Chromosome microarray in Australia: A guide for paediatricians. *J Paediatr Child Health* 2012;48(2):E59–67.
2. Miller DT, Adam MP, Aradhya S, et al. Consensus statement: Chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. *Am J Hum Genet* 2010;86(5):749–64.

## Resources for general practitioners

- Centre for Genetics Education, Fact sheet 16: Chromosome microarray (CMA) testing in children and adults, [www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-16-chromosome-microarray-cma-testing-in-children-and-adults](http://www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-16-chromosome-microarray-cma-testing-in-children-and-adults)
- Jackson Laboratory, What you need to know before ordering chromosomal microarray, [www.jax.org/education-and-learning/clinical-and-continuing-education/cancer-resources/deciding-to-test](http://www.jax.org/education-and-learning/clinical-and-continuing-education/cancer-resources/deciding-to-test)

## Family history

### Practice point

Ideally, a three-generation **family history** should be collected on all patients where possible, including first-degree relatives (ie children, siblings, parents) and second-degree relatives (ie aunts, uncles, grandparents).<sup>1</sup> The use of a family history screening questionnaire<sup>1</sup> ([www.racgp.org.au/your-practice/guidelines/redbook/appendices/appendix-2a-family-history-screening-questionnaire](http://www.racgp.org.au/your-practice/guidelines/redbook/appendices/appendix-2a-family-history-screening-questionnaire)) can help identify individuals who may require a more detailed assessment of their family history of cancer, heart disease or diabetes.

### What do I need to know?

Family history is particularly useful for assessing the risk of **autosomal dominant inheritance** and **multifactorial inheritance**. Conditions with an **autosomal recessive inheritance** or **X-linked recessive inheritance** pattern will often occur in the absence of family history (eg **cystic fibrosis [CF]**).

General information to collect in a family history include:<sup>4</sup>

- age of patient
- age at diagnosis of conditions in the family
- ancestry and cultural background
- step-relationships and adoption
- children born to parents who are blood-related (**consanguinity**)
- known genetic conditions.<sup>4</sup>

Update the patient's family history, including births, deaths and new diagnoses opportunistically.






















Markers of possible genetically determined conditions in a family history include:<sup>1,3,4</sup>

- birth defects, multiple stillbirths and multiple miscarriages – consider referral to genetics services
- developmental delay (DD) – consider referral and ordering a **chromosome microarray (CMA)** and **Fragile X syndrome (FXS)** testing (**DD and intellectual disability [ID]**, **FXS**, **autism spectrum disorder [ASD]**)
- neurodegenerative conditions, premature ischaemic heart disease, sudden death – consider referral to genetics services
- early onset of common cancers and/or unusual combinations of rare cancers – refer to **eviQ online**<sup>2</sup> for further information about familial cancer syndromes.

## Pedigree

Drawing a pedigree can be helpful in identifying patterns of inheritance (Table 1).

**Table 1. Common pedigree symbols**

	Male	Female	Sex unknown
Individual	 b.1925	 30 y	 4 mo
Affected individual*			
Affected individual with more than one condition*			
Carrier			
Deceased individual	 d. 35 y	 d. 4 mo	
Stillbirth (SB)	 SB 28 wk	 SB 30 wk	 SB 34 wk
Pregnancy (P)	 SP 28 wk	 SP 30 wk	

\*Use a key or legend to define the condition(s) denoted by the shading in the pedigree.

Record the date on which the pedigree is drawn and update it as new information becomes available.

At each step, ask about the health of the family member being discussed.

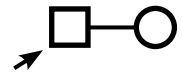
It may not always be possible to complete the pedigree because of complexities such as adoption, a lack of reliable information or family disruption. It is important to consider such issues in each family. Step-by-step instructions for drawing a pedigree is shown in Table 2.

**Table 2. Step-by-step instructions for drawing a pedigree<sup>3</sup>**

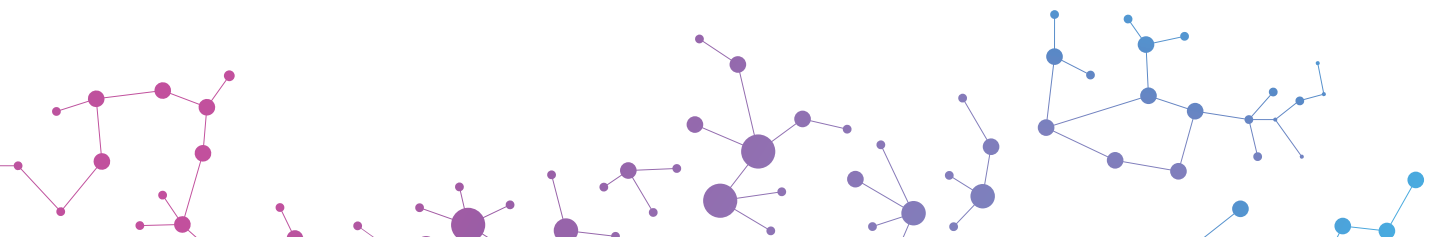
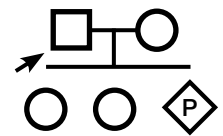
**Step 1** Draw the symbol for the family member being seen. Indicate this person with an arrow and enter any pertinent details (eg name, age)



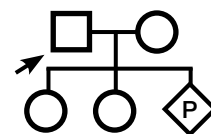
**Step 2** If the individual has a child or is pregnant, draw a line directly across to a symbol for the partner



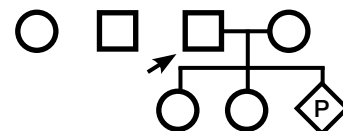
**Step 3** Ask about the number of pregnancies pertaining to the couple. Draw a reverse 'T' from the relationship line and add the symbol for each child and pregnancy



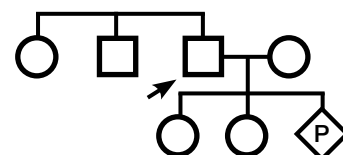
**Step 4** Add a line from each child or pregnancy to the reverse 'I'



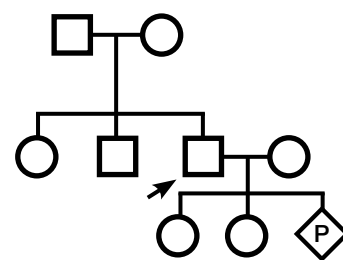
**Step 5** Ask about brothers and sisters for each partner. Add the relevant symbols alongside the corresponding person



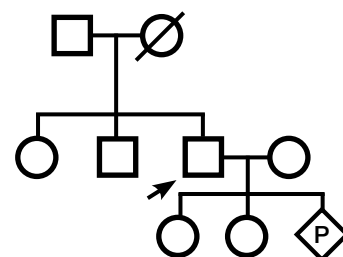
**Step 6** Indicate the relationship between siblings by drawing a vertical line stemming from each symbol and joining them together with a horizontal line



**Step 7** Add a vertical line from this sibship line and add parents



**Step 8** Indicate deceased family members by drawing a line through the symbol



**Step 9** Repeat steps 5–8 for each parent of the family member you are seeing to include the aunts, uncles and grandparents

## References

1. The Royal Australian College of General Practitioners. Guidelines for preventive activities in general practice. 9th edn. Melbourne: RACGP, 2016. Available at [www.racgp.org.au/your-practice/guidelines/redbook](http://www.racgp.org.au/your-practice/guidelines/redbook) [Accessed 22 December 2017].
2. Cancer Institute NSW. eViQ. Sydney: Cancer Institute NSW, 2017. Available at [www.eviq.org.au](http://www.eviq.org.au) [Accessed 22 December 2017].
3. Bennett RL, French KS, Resta RG, Doyle DL. Standardized human pedigree nomenclature: Update and assessment of the recommendations of the National Society of Genetic Counselors. *J Genet Couns* 2008;17(5):424–33.
4. Bennett RL. The family medical history as a tool in preconception consultation. *J Community Genet* 2012;3(3):175–83.

## Resources for general practitioners

- National Genetics and Genomics Education Centre (UK), Taking and recording a family history, [www.primarycaregenetics.org](http://www.primarycaregenetics.org)
- The Royal Australian College of General Practitioners, Family history screening questionnaire, [www.racgp.org.au/your-practice/guidelines/redbook/appendices/appendix-2a-family-history-screening-questionnaire](http://www.racgp.org.au/your-practice/guidelines/redbook/appendices/appendix-2a-family-history-screening-questionnaire)

# MTHFR gene testing

## Practice point

There is no substantial evidence to support the use of *MTHFR* gene testing in routine clinical practice. Knowledge of *MTHFR* gene status is unlikely to change patient management.<sup>1-3</sup>

## What do I need to know?

The *MTHFR* gene is involved in processing amino acids, specifically in relation to folate metabolism.

The *MTHFR* gene test identifies two **gene variants** associated with increased levels of homocysteine in the blood (C677T and A1298C). These variants are common in the general population.<sup>3</sup>

*MTHFR* gene testing is promoted by some complementary and alternative practitioners to investigate infertility, recurrent pregnancy loss and risk for particular diseases. However:<sup>1-3</sup>

- There is no significant evidence of a causal link between *MTHFR* gene variants and particular diseases.
- *MTHFR* status does not alter the recommendation that women who are planning a pregnancy or those in the first trimester of pregnancy take folic acid supplements to reduce the risk of neural tube defects.

Patients can obtain *MTHFR* gene testing through private providers at their own expense.

There is no indication to refer the patient to genetics services. Given the lack of clinical utility, some genetics service providers are no longer accepting patient referrals for consultations in relation to *MTHFR*.<sup>3</sup>

## How can I manage *MTHFR* gene testing in general practice?

### Advising patients who are considering *MTHFR* gene testing

The following points may be useful to raise in a discussion with patients who are interested in ordering a *MTHFR* gene test:

- *MTHFR* gene testing is not recommended when:
  - many people have one or both *MTHFR* gene variants (C677T and/or A1298C)<sup>3</sup>
  - there is a lack of strong scientific evidence to show that having one or both *MTHFR* gene variants causes particular health problems<sup>1,3,4</sup>
  - there are no evidence-based treatments that will improve the health of a patient with one or both of the *MTHFR* gene variants.<sup>3</sup>
- There is an association between the presence of *MTHFR* gene variants and increased homocysteine levels; however
  - while high homocysteine was once thought to increase risk of blood clots (thrombophilia), cardiovascular disease (CVD) and recurrent pregnancy loss, recent studies have found that this is not the case<sup>1,4</sup>
  - many other factors also increase homocysteine (ie diet, lifestyle, other gene variants). A person can reduce their risk of disease by following a healthy, balanced diet and avoiding well-known risk factors such as smoking and being overweight
  - having a biochemical test for homocysteine levels may provide more useful information. This is less expensive than having a *MTHFR* gene test, which in most cases is not covered under the Medicare Benefits Schedule (MBS).

## Managing patients who have had *MTHFR* gene testing

The following points may be useful in a discussion with a patient who has had a *MTHFR* gene test and is concerned about the results:

- The presence of one or both *MTHFR* gene variants (*C677T* and/or *A1298C*) is not associated with particular health problems
  - Individuals who have the *MTHFR* gene variant(s) might have increased homocysteine levels. While this was once thought to be associated with particular health problems (ie thrombophilia, CVD, recurrent pregnancy loss), recent studies have found that this is not the case.<sup>1,4</sup> Many other factors also increase homocysteine (ie diet, lifestyle, other gene variants). A person can reduce their risk of disease by following a healthy, balanced diet and avoiding well-known risk factors such as smoking and overweight.
  - Women who have *MTHFR* gene variant(s) may have a slightly increased risk of having a baby with neural tube defects (eg spina bifida). However, taking folic acid supplements before and during pregnancy decreases the risk, just as it does in women who do not have *MTHFR* gene variant(s).
- Genetic services are unlikely to accept referrals for consultations about the results of *MTHFR* gene testing because the presence of *MTHFR* gene variants is unlikely to significantly affect a patient's health.

## References

1. Hickie SE, Curry CJ, Toriello HV. ACMG Practice Guideline: Lack of evidence for *MTHFR* polymorphism testing. *Genet Med* 2013;15(2):153–56. Available at [www.acmg.net/docs/mthfr\\_gim2012165a\\_feb2013.pdf](http://www.acmg.net/docs/mthfr_gim2012165a_feb2013.pdf) [Accessed 22 December 2017].
2. Human Genetics Society of Australasia and Choosing Wisely Australia. 5 things clinicians and consumers should question. Sydney: NPS MedicineWise, 2016. Available at [www.choosingwisely.org.au/recommendations/hgsa](http://www.choosingwisely.org.au/recommendations/hgsa) [Accessed 22 December 2017].
3. Long S, Goldblatt J. *MTHFR* genetic testing: Controversy and clinical implications. *Aust Fam Physician* 2016;45(4):237–40. Available at [www.racgp.org.au/afp/2016/april/mthfr-genetic-testing-controversy-and-clinical-implications](http://www.racgp.org.au/afp/2016/april/mthfr-genetic-testing-controversy-and-clinical-implications) [Accessed 7 July 2017].
4. Levin BL, Varga E. *MTHFR*: Addressing genetic counseling dilemmas using evidence-based literature. *J Genet Couns* 2016;25(5):901–11.

## Resources for general practitioners

- The Royal Australian College of General Practitioners, Position statement on responding to patient requests for tests not considered clinically appropriate, [www.racgp.org.au/your-practice/guidelines/position-statement-on-responding-to-patient-requests-for-tests-not-considered-clinically-appropriate](http://www.racgp.org.au/your-practice/guidelines/position-statement-on-responding-to-patient-requests-for-tests-not-considered-clinically-appropriate)
- The Royal College of Pathologists of Australasia, Position statement: *MTHFR* genetic tests, [www.rcpa.edu.au/getattachment/7c454ef8-1dc2-4648-99a5-39d9354f55e3/MTHFR-Genetics-Tests.aspx](http://www.rcpa.edu.au/getattachment/7c454ef8-1dc2-4648-99a5-39d9354f55e3/MTHFR-Genetics-Tests.aspx)
- The Royal Australian College of General Practitioners, Chapter 15, Screening tests of unproven benefit – Guidelines for preventive activities in general practice, [www.racgp.org.au/your-practice/guidelines/redbook/15-screening-tests-of-unproven-benefit](http://www.racgp.org.au/your-practice/guidelines/redbook/15-screening-tests-of-unproven-benefit)

## Resources for patients

- Centre for Genetics Education, Fact sheet 64: *MTHFR* gene test for patients, [www.genetics.edu.au/health-professionals/FS64-MTHFR-GENE-TESTING-FOR-PATIENTS.pdf/view](http://www.genetics.edu.au/health-professionals/FS64-MTHFR-GENE-TESTING-FOR-PATIENTS.pdf/view)
- The Royal Australian College of General Practitioners, Appropriate diagnostic testing: Patient information, [www.racgp.org.au/download/Documents/Policies/Clinical/Patient-information-on-appropriate-diagnostic-testing.pdf](http://www.racgp.org.au/download/Documents/Policies/Clinical/Patient-information-on-appropriate-diagnostic-testing.pdf)



## Newborn screening

### Practice point

Screening is available to all newborns in Australia free of charge, and almost all babies are screened. There are some babies who may be lost to follow up or their parents may refuse consent for screening. Exact numbers in Australia are not available. Depending on the condition, not all affected babies will be identified (eg only the most common variants causing **cystic fibrosis** [CF] are included in the screening test). Therefore, any suggestive symptoms in a child warrant further investigation by the general practitioner (GP).

Depending on the program, GPs may or may not be notified of a positive screening result. Follow-up is usually handled by the screening program.

### What do I need to know?

Screening can identify a number of rare but serious medical conditions, where early detection and intervention can save lives or provide other benefits to the newborn.

Traditionally, conditions included in the program are based on the ability of clinicians to intervene early to avoid death, disability or other harm. With the advancement of genetic technology, there is some interest in expanding newborn screening panels to include a wider range of conditions.<sup>1-3</sup>

Newborn screening is optional in Australia,<sup>1</sup> and research suggests participation is very high.<sup>4</sup> Screening occurs two to three days after birth, and is usually arranged by midwives. In general, parents are not contacted when screening results are normal.

About 1–2% of babies tested require repeat or subsequent diagnostic testing. Screening programs in each state and territory are usually responsible for following up cases that require further testing. About one per 1000 (0.1%) babies tested will be diagnosed with a condition because of newborn screening.

Refer to Table 1 for a list of conditions currently included in newborn screening programs in Australasia.

**Table 1. Conditions screened in newborn screening programs in Australasia<sup>1,3</sup>**

Class	Condition
<b>Amino acids</b>	Argininaemia or arginase deficiency
	Argininosuccinic aciduria
	Citrullinaemia
	Tyrosinaemia type 1
	Homocystinuria
	Maple syrup urine disease
	Phenylketonuria
	Pterin defects
	Tyrosine aminotransferase deficiency
<b>Organic acids</b>	Beta-ketothiolase deficiency
	Cobalamin C defect
	Glutaric acidaemia type I
	Holocarboxylase synthetase deficiency
	3-hydroxy-3-methylglutaryl-CoA lyase (HMGCoA lyase) deficiency
	Isobutyryl-CoA dehydrogenase deficiency

Isovaleric acidemia
Methylmalonic acidurias
Propionic acidemia
3-methylcrotonyl-CoA carboxylase deficiency
2-methylbutyryl-CoA dehydrogenase deficiency
3-methylglutaconyl-CoA hydratase deficiency
<b>Fatty acid oxidation</b>
Carnitine or acylcarnitine translocase deficiency
Carnitine transporter defect
Carnitine palmitoyl transferase deficiency types I and II (CPTI)
3-hydroxy long chain acyl-CoA dehydrogenase deficiency (LCHAD)
Medium chain acyl-CoA dehydrogenase deficiency (MCAD)
Multiple acyl-CoA dehydrogenase deficiency (MADD)
Short chain acyl-CoA dehydrogenase deficiency (SCAD)
Short chain hydroxy acyl-CoA dehydrogenase deficiency (SCHAD)
Trifunctional protein deficiency (TFP)
Very long chain acyl-CoA dehydrogenase deficiency (VLCAD)
<b>Other</b>
Cystic fibrosis (CF)
Congenital hypothyroidism
Galactosaemia (not in Victoria)

## Other considerations

In addition to the implications for a child diagnosed with an inherited condition, there are also implications for future pregnancies in the family (ie carrier parents, siblings of the carrier parents). Information about [carrier screening](#) should be offered.

## References

1. Human Genetics Society of Australasia. Policy: Newborn bloodspot testing. Sydney: HGSA, 2011. Available at [www.hgsa.org.au/documents/item/29](http://www.hgsa.org.au/documents/item/29) [Accessed 8 January 2018].
2. Howard HC, Knoppers BM, Cornel MC, et al. Whole-genome sequencing in newborn screening? A statement on the continued importance of targeted approaches in newborn screening programmes. *Eur J Hum Genet* 2015;23(12):1593–600.
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## Personal genomic testing: Summary

### Practice point

At this time, the clinical utility of personal genomic testing (PGT) is considered variable.<sup>1</sup> If patients wish to pursue testing, ensure they opt for a full-service provider that includes the need for referral by a general practitioner (GP), test interpretation and genetic counselling support.

### What do I need to know?

PGT refers to the analysis of some or all of a person's genome. PGT is marketed for a variety of purposes, including:

- identification of susceptibility to a wide range of diseases
- [carrier screening](#) for autosomal recessive conditions
- [pharmacogenomics](#)
- nutrigenomics (ie diet, nutrition, wellness)
- fitness and sporting abilities
- ancestry
- relationship (eg paternity) testing.

PGT companies may or may not require a health professional to order the test. In situations where a referral is not required, individuals can request a test kit online and provide a saliva or cheek swab sample to the PGT company via post. This is referred to as 'direct-to-consumer' (DTC) or 'at-home' genetic testing.

PGT companies are mostly based overseas, but an increasing number are now based in Australia.

The cost of PGT varies according to the type of test (eg [genotyping](#), [exome sequencing](#), [whole genome sequencing](#)) and how much information is provided with the results. PGT is not available under the Medicare Benefits Schedule (MBS), so consumers incur the full cost (sometimes thousands of dollars).

PGT results may be provided with some clinical interpretation in the form of follow-up genetic counselling or a written report, or as raw sequence data. In many situations, the consumer is left to interpret the results without clinical guidance. This can prompt the individual to contact their GP for additional support. Referral of all such patients to public genetics services for assistance is not practicable given the resource implications.<sup>1-3</sup>

### How do I manage PGT in general practice?

#### Advising patients who want PGT

Patients may ask a GP to order PGT on their behalf. GPs asked to arrange PGT should consider the following:<sup>2,4</sup>

- How much does the patient understand about the test?
- What do they want to find out from the test and what will they do with that information?
- Has the patient thought about the possible impact of testing on life insurance? (Refer to '[Ethical principles](#)')
- Will the company help interpret the results?
- Do you feel able to assist the patient in interpreting results?

## Managing patients who have had PGT

Patients who have already had PGT might ask a GP for:

- help in interpreting the results
- further testing
- advice around treatment or management.

The majority of patients will have small variations in risks for a range of conditions, which will have limited clinical implications (eg *Alzheimer's disease*, *MTHFR gene testing*). In these circumstances, general preventive health advice is appropriate.

In a minority of patients, specific variants that put an individual at significantly increased risk of a condition (eg *BRCA* gene mutations, *HFE*-haemochromatosis, macular degeneration) will be identified. In these situations, referral to genetics or specialist services is appropriate.<sup>4</sup>

## More information

Refer to '[Personal genomic testing: More information](#)' for a detailed discussion of this topic.

## References

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## Resource for patients

- National Health and Medical Research Council, Direct-to-consumer (DTC) genetic testing: A statement from the National Health and Medical Research Council, [www.nhmrc.gov.au/guidelines-publications/g9](http://www.nhmrc.gov.au/guidelines-publications/g9)

## Personal genomic testing: More information

### What is personal genomics?

With the advancement of gene sequencing technology, genetic testing is increasingly moving beyond the clinic and tertiary medical centres, and into the community. This new form of testing is readily accessible via the internet, either through a health practitioner or by patients themselves, and represents the new world of personal genomic testing (PGT).<sup>1</sup>

Clinical genetic testing has traditionally been used to gather information or confirm a diagnosis of a condition in an individual showing symptoms. Testing has also been used to screen asymptomatic populations, such as [carrier screening](#) for recessive conditions. Until recently, these genetic tests have been targeted, looking for particular [gene variants](#) (or mutations) in specific genes. Clinical support, including genetic counselling, has generally been available to help individuals interpret and manage genetic test results.

However, new technology (eg [single nucleotide polymorphism \[SNP\] genotyping](#)) can now examine thousands of [gene variants](#) throughout a person's [genome](#). New sequencing technology also allows the entire sequencing of an individual genome ([whole genome sequencing](#)) at a relatively low cost. The availability of such technology is challenging the traditional model of genetic testing.<sup>2,3</sup>

Asymptomatic individuals now have the opportunity to access 'direct-to-consumer' (DTC) or 'at-home' testing through a range of private providers.

Some DTC companies require a health practitioner to order a test on behalf of the consumer and take delivery of the test results, while others do not. A test kit provided by the DTC company is used to collect a cheek swab or saliva sample and mailed back for analysis. In some cases, results are returned to the consumer without comprehensive interpretation and/or clinical support.

### What is tested?

PGT can provide information that is health or non-health related.<sup>4</sup> Non-health related information includes:

- physical traits (eg red hair, freckles)
- genetic relationship testing (eg paternity testing)
- ancestry.

Some tests offer information that have health-related implications to varying degrees. In some cases, the tests are the same as those offered in regular clinical settings. Personal genomic tests might include genetic variants that:

- are strong predictors of risk for disease (eg [BRCA1](#), [familial breast and ovarian cancer](#))
- are limited predictors of disease (eg [APO-ε4](#), [Alzheimer's disease](#))
- identify carrier status for recessive conditions (eg [cystic fibrosis \[CF\]](#))
- can inform response to drugs (refer to '[Pharmacogenomics: Summary](#)').

Some companies test for variants for other health-related information that are more uncertain, such as variants with low [penetrance](#), or with limited evidence to support associations with disease.<sup>3</sup> These tests might include genetic variants that are:

- much more weakly associated with susceptibility to disease (eg complex conditions such as type 2 diabetes, rheumatoid arthritis)
- marketed to predict sporting ability, including fitness and response to training regimens
- professed to provide information about response to diet and nutrition (nutritional genomics) or weight loss (eg [MTHFR gene testing](#)). In Australia, these tests are advertised as 'genomic wellness' tests, and are increasingly available through naturopaths and nutritionists.

## How are results reported?

Companies may report estimates of risk from test results in a variety of ways, including odds ratios, percentages, comparisons with average population risk (using a reference population) or lifetime risk. It is important to note that not all companies use the same reference population and consumers may be a different ethnicity to the reference population.

Companies may also vary in the way they produce their estimate of risk (eg use of different algorithms). Consequently, test results from one company may not match those from another company, even with the same deoxyribonucleic acid (DNA) sample.

Customers are often able to download their 'raw data' (ie the actual variant or SNP data), which may provide health-related information beyond what the original test results provide. This extra information often comes with no interpretation provided to the consumer. Consumers can also upload their raw data to online databases (or to genetic testing companies) where a further level of analysis is available. Again, this is often provided without appropriate clinical support.

## Considerations with PGT

### Questionable credibility

PGT companies use a combination of marketing rhetoric, and unsupported claims and research evidence to promote their product. In many cases, there is no clinical support. The ability of these tests to accurately predict outcomes (clinical validity) is variable. Consumers are faced with a difficult task of determining the credibility of these tests.

### Regulatory landscape

The technology around PGT is changing rapidly, as is the variety of testing. Given the international reach of PGT, regulation of the industry is challenging.

### Empowered patients

There are many who support PGT as a means of empowering consumers to proactively manage their health (ie clinical and personal utility). Others suggest individuals may be misled by information with poor clinical validity, leading to unnecessary costs that are a burden to the consumer and health system.

### Privacy and confidentiality

Information obtained by an individual can have implications for other family members, especially those who may not want to know. Given the ease of testing, some people (eg children) may be tested without full consent.

The ownership of the data from testing is another complex issue. If a testing company changes ownership, so does the data. Some consumers choose to share their genetic information or data (eg online) which can also allow for unintentional access by others.

### Personal utility

For many individuals, the concept of personal utility seems more relevant than the clinical utility of testing. Personal utility includes the value of increased knowledge about oneself (where curiosity often motivates individuals wanting to be tested), increased knowledge about the trait or condition tested, potential for anticipated coping, and altruism (eg helping research as a motivation for testing, with opportunities for data sharing through not-for-profit websites or organisations).<sup>5,6</sup>

## Implications for general practice

The uptake of PGT is likely to continue, and general practitioners (GPs) will increasingly encounter patients who are curious about or have used PGT.

Some PGT companies recommend using specific practitioners (ie those they nominate who may have undertaken some training) who will order the test on behalf of the consumer. Some of these companies may also provide genetic counsellors who can discuss the results with the consumer.

Other companies state that the PGT reports are provided for information or educational purposes only. They may state that the consumer should talk to their GP or other health practitioners about their results. However, practitioners themselves may have a limited understanding of the nature of the test or its interpretation.

Involving health practitioners in the process, either in ordering tests and/or interpreting results, may have positive and negative consequences. Some health practitioners, including GPs, may not feel confident in supporting patients to understand their results.<sup>1,5</sup>

There is also the potential to overburden the healthcare system with subsequent inappropriate ordering of health services, including referral to genetics services when it might not be warranted. Some genetic services no longer accept referral for most people who have had the *MTHFR* gene testing, as its clinical validity and utility is questionable.

The National Health and Medical Research Council (NHMRC) has developed a PGT resource entitled 'Understanding direct-to-consumer (DTC) genetic DNA testing: An information resource for consumers', available at [www.nhmrc.gov.au/guidelines-publications/g8](http://www.nhmrc.gov.au/guidelines-publications/g8). GPs can use this document to discuss PGT with patients who are interested in ordering a test.

Potential consumers of PGT testing should consider all aspects when they are thinking about having one of these tests and GPs can play an important role in raising these issues with their patients.<sup>7</sup>

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# Pharmacogenomics: Summary

## Practice point

While there are international guidelines about potential uses of pharmacogenomic testing, there is limited evidence from randomised controlled trials of the clinical utility and cost effectiveness of using pharmacogenomics to tailor prescribing, especially in primary care.<sup>1,2</sup>

## What do I need to know?

The term 'pharmacogenomics' describes how common **gene variants** influence drug metabolism and response.

There are common variants in cytochrome P450 enzymes (CYPs) and drug receptors that influence the rate of metabolism of many commonly prescribed drugs. Individuals are typically classified as 'poor', 'intermediate', 'extensive' or 'ultrarapid' metabolisers depending on their CYP variants. Poor and ultrarapid metabolisers may require different dosages, or be more susceptible to adverse drug effects.<sup>3</sup>

Table 1 provides examples of drugs that may be affected by common gene variants.

**Table 1. Examples of drugs affected by common gene variants<sup>1</sup>**

Gene name	Examples of drugs affected	Clinical consequence
<i>CYP2D6</i> (5–10% of Caucasians are poor metabolisers; 1–2% of Caucasians are ultrarapid metabolisers)	Codeine	Poor metabolisers have no response to codeine; ultrarapid metabolisers are at an increased risk of side effects
	Selective serotonin reuptake inhibitors (SSRIs; eg paroxetine, fluvoxamine)	Ultrarapid metabolisers have no response to SSRI; poor metabolisers may need 50% lower dose
<i>CYP2C19</i> (poor metabolisers 2–15%)	Clopidogrel	Poor metabolisers may require alternative anti-platelet
<i>VKORC1</i> and <i>CYP2C9</i>	Warfarin	<i>CYP2C9</i> and <i>VKORC1</i> genotypes may be useful in determining the optimal initial dose of warfarin
<i>SLCO1B1</i>	Simvastatin (not other statins)	Low-function genotype associated with increased of myopathy; consider alternative statin or lower dose

## Genetic testing

Pharmacogenomic testing may be considered for patients with:

- significant side effects from drugs for where pharmacogenomic variation in response is known (refer to Table 1)
- poor therapeutic response to specific medications
- potential suitability for using doses outside the usual range.

Pharmacogenomic testing is not subsidised under the Medicare Benefits Schedule (MBS), but can be ordered by general practitioners through a number of commercial providers.

## More information

Refer to 'Pharmacogenomics: More information' for a detailed discussion of this topic.

## References

1. Clinical Pharmacogenetics Implementation Consortium. CPIC guidelines. Stanford, CA: CPIC, 2014. Available at <https://cpicpgx.org> [Accessed 8 January 2018].
2. Relling MV, Evans WE. Pharmacogenomics in the clinic. *Nature* 2015;526(7573):343.
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## Resources for patients

- Centre for Genetics Education, Fact sheet 21: Pharmacogenetics/pharmacogenomics, [www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-21-pharmacogenomics-pharmacogenetics](http://www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-21-pharmacogenomics-pharmacogenetics)
- National Library of Medicine, What is pharmacogenetics?, <https://ghr.nlm.nih.gov/primer/genomicresearch/pharmacogenomics>

## Pharmacogenomics: More information

### What is pharmacogenomics?

Genetic variations play a role in our ability to metabolise and respond to drugs, both in terms of efficacy and toxicity. Pharmacogenomic testing assesses the type of response a patient may have to a particular drug. Testing before prescribing medication can provide information about the likely effectiveness or risk of side effects for the patient.<sup>1,2</sup>

### Pharmacogenetics versus pharmacogenomics

While pharmacogenetics examines the variability in response due to genetic variations in genes that metabolise drugs, pharmacogenomics is a broader term that refers to the involvement of all genes in determining drug response. The two terms are often used interchangeably.<sup>3-5</sup>

The ultimate goal of pharmacogenomics is the ability to target or 'tailor' drug therapy to individuals: being able to prescribe the right drug at an appropriate dose to maximise efficacy and avoid adverse effects. This goal feeds into the wider concept of personalised medicine, where an individual's genetic profile is used to make decisions about all aspects of healthcare (ie prevention, diagnosis, treatment).<sup>1,5</sup>

### How genetic polymorphisms affect drug metabolism

Genetic variation can affect:<sup>5</sup>

- pharmacokinetics – how the drug metabolised by the body is affected by genetic variations in metabolising enzymes
- pharmacodynamics – what effect the drug has on the body is influenced by genetic variations in drug targets (eg receptors).

Pharmacogenomics testing analyses genes involved in these two pathways.

One example is the cytochrome P450 genes, which produce enzymes involved in drug metabolism. P450 enzymes account for 70–80% of enzymes involved in drug metabolism.<sup>5</sup> Common variations in P450 genes can affect the function of the enzymes produced, which in turn affects the metabolism of some drugs. For example, drugs may be metabolised too quickly (ie higher dose needed for effect) or too slowly (ie lower dose needed for effect).

Genetic variations give rise to four different phenotypes in terms of drug response:<sup>1</sup>

- Poor metabolisers who have markedly reduced or absent enzyme activity.
- Intermediate metabolisers with reduced enzyme activity.
- Extensive (or normal) metabolisers.
- Ultrarapid metabolisers who have high enzyme activity.

### Cytochrome P450 genes

Cytochrome P450 genes follow a certain naming system.<sup>6</sup> For example, *CYP2D6* is made up of the following codes:

- cytochrome P450 enzyme (CYP) – indicating it is part of the cytochrome gene family.
- 2 – a number associated with a specific group within the gene family.
- D – a letter which represents the gene subfamily.
- 6 – a number referring to the specific gene within the subfamily.

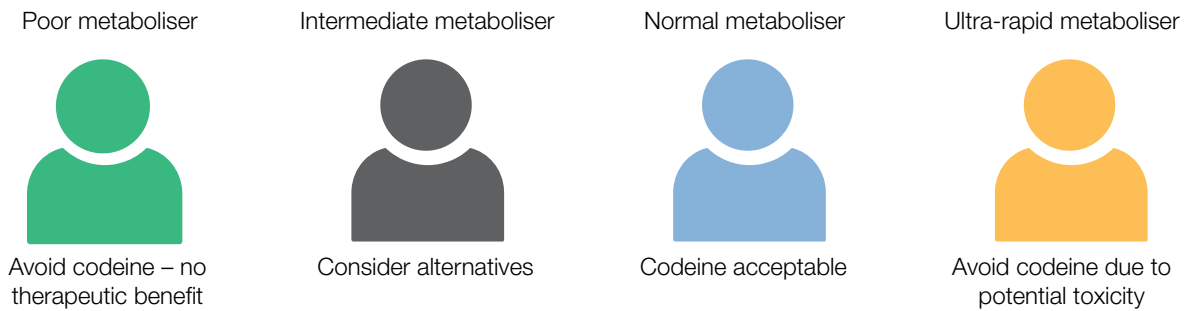
This gene can then have different forms or alleles. For example:<sup>6</sup>

- *CYP2D6\*1* – allele 1 produces normal enzyme function
- *CYP2D6\*4* – allele 4 produces enzyme with no activity
- *CYP2D6\*10* – allele 10 produces enzyme with decreased activity.

Codeine is a common analgesic metabolised by *CYP2D6* enzymes (Figure 1).<sup>7</sup>

Codeine → *CYP2D6* → morphine

Figure 1. Codeine recommendation according to metaboliser status<sup>8</sup>



## Benefits of pharmacogenomics

The benefits of pharmacogenomic testing arise from the ability to tailor medication to the individual: specifically, to predict the correct dose to avoid toxicity or adverse events, and to know whether a particular drug will be effective in any given patient.

The benefits of pharmacogenomics include:<sup>1,2</sup>

- achieving optimal drug doses quickly – the trial-and-error approach combined with repeated monitoring could be avoided
- minimising toxicity and adverse effects – knowledge of a patient's genetic profile could reduce the likelihood of adverse outcomes and help direct clinicians towards suitable alternatives
- efficacious medications – genetic variations can predict which patients are likely to respond to certain medications, allowing clinicians to personalise treatment.

## Limitations of pharmacogenomics

At present, there are several limitations of pharmacogenomic testing:<sup>1-4,9</sup>

- Cost – currently there is no Medicare Benefits Schedule (MBS) rebate for testing, therefore patients incur an out-of-pocket cost.
- Testing turnaround time – some results can take between five and 10 working days to reach the clinician who ordered the test. In some cases, the trial-and-error approach to dosage would be completed within this timeframe.
- Evolving science – our understanding of how genetics influences our response to drugs is incomplete. Confidence in the clinical utility of pharmacogenomic testing is slowly growing, with some parts of the world further advanced than others.
- Lack of compelling evidence from clinical trials.

## Current practice in Australia

While pharmacogenomics seem to offer the ability to improve patient care (and hence therapeutic outcomes), the clinical adoption of pharmacogenomic interventions has been slow.

While many of the drugs commonly prescribed in general practice (eg warfarin, fluoxetine) are influenced by genetic variation, there is currently no clear recommendation in Australia about the use of pharmacogenomic testing.

International guidelines exist about the potential use of pharmacogenomic testing;<sup>10</sup> however, there is limited evidence from randomised controlled trials of the clinical utility and cost effectiveness of using pharmacogenomics to tailor prescribing, especially in primary care.<sup>1,9</sup>

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1. Abbasi J. Getting pharmacogenomics into the clinic. *JAMA* 2016;316(15):1533–35.
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10. Clinical Pharmacogenetics Implementation Consortium (CPIC). Guidelines. Stanford, CA: CPIC, undated. Available at <https://cpicpgx.org/guidelines> [Accessed 8 January 2018].

## Resources for general practitioners

- Centre for Genetics Education, Pharmacogenetics, [www.genetics.edu.au/health-professionals/pharmacogenomics](http://www.genetics.edu.au/health-professionals/pharmacogenomics)
- Centre for Genetics Education, Fact sheet 21: Pharmacogenetics/pharmacogenomics, [www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-21-pharmacogenomics-pharmacogenetics](http://www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-21-pharmacogenomics-pharmacogenetics)
- National Library of Medicine, What is pharmacogenetics?, <https://ghr.nlm.nih.gov/primer/genomicresearch/pharmacogenomics>

## Prenatal testing

### Practice point

All pregnant women (ie regardless of age, ethnicity, family history) should be provided with information about prenatal screening tests for chromosomal conditions such as Down syndrome. Screening options should be discussed in the first trimester whenever possible.<sup>1,2</sup>

Prenatal screening tests should not be considered routine, but offered as a choice to women. General practitioners (GPs) should support women and couples to make informed, independent decisions about the utility of prenatal testing and reproductive options. Women who receive a high-risk screening result should be offered information about diagnostic testing.<sup>2</sup>

Those identified with a **family history** of inherited disorders should be made aware of the availability of **carrier screening** for recessive conditions.<sup>1</sup>

### What do I need to know?

Pre-pregnancy and pregnancy counselling that are relevant to genetics should include:<sup>1,2</sup>

- Any known genetic conditions among close family members (refer to 'Family history').
- History of intellectual disability (ID), multiple pregnancy loss, stillbirth, children with congenital abnormalities.
- **Consanguinity** ('Is there any chance that a relative of yours might be related to someone in your partner's family?').
- Pre-pregnancy and pregnancy folic acid intake.
- Information about carrier screening (ideally pre-conception or early in first trimester).

All women should be provided information about prenatal screening for chromosomal conditions.<sup>1,2</sup>

While chromosomal conditions such as Down syndrome are more common in pregnancies of women who are older (the chance of the baby having such a condition tends to increase with maternal age),<sup>3</sup> younger women can also have pregnancies with chromosomal conditions.

Prenatal screening information should include the following:

- Presenting the various screening options and their timing.
- An explanation of the meaning of results.
- A discussion of the potential implications of receiving a positive screening result (ie having to undergo an invasive diagnostic test, thinking about the possibility of having a child with special needs or pregnancy termination).

Other important considerations:

- Screening tests can determine who is at increased risk of having a baby with a chromosomal condition. Women who choose to undertake screening tests should be informed that they will be offered invasive diagnostic testing if they receive a high-risk screening result. Individuals may choose not to proceed with diagnostic testing for a number of reasons (eg concern about risk of miscarriage, not wishing to know prior to the birth, termination of pregnancy is not an option).
- Screening tests are non-invasive, so there is no increased risk of miscarriage from the procedure.
- Every screening test has a false positive rate: some women will receive an 'increased risk' result even though their baby is unaffected.
- In the majority of pregnancies with an 'increased risk' screening result, the baby is unaffected. A common misconception is that screening tests 'show' that the baby has Down syndrome.
- 'Low-risk' results do not exclude Down syndrome or other conditions.
- A second trimester ultrasound may detect some physical problems, but it is not recommended as a screening test for Down syndrome.
- Neural tube defects and other physical conditions may also be detected with second trimester serum screening.

- Use of the term 'risk' in relation to the probability of a diagnosis of Down syndrome (or other disability) should be avoided when discussing prenatal screening with patients because it implies a negative consequence, and can cause offense. The recommended terminology is 'chance' or 'probability'.

## Genetic testing

### Combined first trimester screening

Combined first trimester screening (CFTS) adds different measures together to provide a risk estimate for Down syndrome (trisomy 21), Edwards syndrome (trisomy 18) and Patau syndrome (trisomy 13).

These measures are as follows:

- Maternal blood to measure pregnancy-associated plasma protein A (PAPP-A) and free  $\beta$ -subunit of human chorionic gonadotrophin ( $\beta$ -hCG). Levels of these proteins vary, but tend to be different in women carrying fetuses with Down syndrome or trisomy 18. Increased free  $\beta$ -hCG with decreased PAPP-A is suggestive of Down syndrome, while decreased levels of both analytes is suggestive of trisomy 18.
- A nuchal translucency (NT) screening ultrasound.
- Maternal age, weight and gestation age.
- In some cases, an additional measurement called the nasal bone is included (presence or absence of nasal bone on ultrasound).

Approximately 5% of CFTS tests give an increased risk result. This figure varies depending on maternal age. Women with an increased risk result should be offered a diagnostic test. The majority of increased risk results are not due to Down syndrome, and most of these babies will be healthy.

There is a partial Medicare Benefits Schedule (MBS) rebate for the blood test component of CFTS; however, there are out-of-pocket expenses for the ultrasound.<sup>7</sup>

### Second trimester maternal serum screening

Second trimester maternal serum screening uses a blood test in conjunction with maternal age and weight, and gestational age to calculate a risk estimate of the chance a pregnancy is affected by Down syndrome, Edwards syndrome or neural tube defects (eg spina bifida).

Second trimester maternal serum screening is for women presenting late in pregnancy. The optimal time to have this test performed is between 15 and 17 weeks, but it can be performed until 20 weeks.

In some cases, there is no out-of-pocket cost for second trimester screening (ie public patient in a public hospital).

### Non-invasive prenatal testing or screening

Non-invasive prenatal testing (NIPT; also called non-invasive prenatal screening [NIPS], cell-free DNA [cfDNA] testing) analyses cell-free fetal deoxyribonucleic acid (DNA) found circulating in maternal blood. Testing is usually available anytime from 10 weeks' gestation. This test analyses the relative proportion of DNA fragments from different chromosomes. If the proportion of fragments from a specific chromosome is increased, then trisomy is suspected.

NIPT is the most accurate screening test available for detecting Down syndrome. Most available NIPT results will provide a risk estimate for trisomies 21, 18 and 13, and sex chromosome aneuploidies (eg monosomy X). Some also provide information about microdeletion syndromes, fetal sex and other autosomal trisomies.

While the accuracy of NIPT in identifying Down syndrome is very high, the accuracy is not as high for Edwards syndrome and Patau syndrome. The accuracy of NIPT is also influenced by the age of the woman and prevalence of the particular condition. For example, the [positive predictive value](#) (PPV) will be lower in younger women where the prevalence of chromosome aneuploidies is lower.

NIPT does not screen for:

- all chromosome aneuploidies
- single-gene disorders
- neural tube defects.

It is crucial to perform a 12-week ultrasound alongside, as NIPT is not diagnostic. High-risk results should be confirmed through diagnostic testing. False positive results are possible, and rates vary according to condition.

In some cases, NIPT can be performed as a second-tier screening test before progressing to chorionic villus sampling (CVS) or amniocentesis. Given the higher test sensitivity, a negative NIPT result can reduce the need for CVS or amniocentesis.

Currently, NIPT is not available through the MBS or covered by private health insurance.

**Figure 1. Summary of prenatal screening tests<sup>4</sup>**

	Screening tests			Diagnostic procedures*
	Combined first trimester screening (CFTS)	Second trimester serum screening	Non-invasive prenatal testing (NIPT)	Chorionic villus sampling (CVS); amniocentesis
Type of test	Blood test (maternal); ultrasound	Blood test (maternal)	Blood test (maternal)	Needle aspirate of placenta or amniotic fluid
Analytes	Nuchal translucency, pregnancy-associated plasma protein A (PAPP-A), $\beta$ -subunit of human chorionic gonadotrophin ( $\beta$ -hCG)	Estriol, beta-hCG, alphafetoprotein, inhibin A	Plasma cell-free DNA	Fetal cells
Timing of test (weeks)	Blood and ultrasound 11–13 weeks	15–20 weeks	From 10 weeks	CVS 11–13 weeks Amniocentesis $\geq$ 15 weeks
Conditions detected	Trisomies 21, 18, 13; structural anomalies	Trisomies 21 and 18; neural tube defects	Trisomies 21, 18, 13; sex chromosome conditions*	Many chromosome and genetic conditions
Detection rate for trisomy 21	90%	75–80%	99%	99.9%
False positive rate for trisomy 21	3–5%	7–8%	<1%	<1% <sup>†</sup>
Test failure rate	<1%	<1%	1–5%	<1%
Risk to pregnancy	None	None	None	Small risk of miscarriage ( $\leq$ 1%)

\*Though not highly accurate and can be confounded by underlying maternal and fetal factors.<sup>1</sup>

<sup>†</sup>Diagnostic tests performed using fetal cells collected by diagnostic procedures include fluorescence in situ hybridisation (FISH), quantitative fluorescence polymerase chain reaction (QF-PCR), karyotype, and [chromosome microarray \(CMA\)](#).

Adapted from Murdoch Childrens Research Institute. Your choice – Prenatal screening tests in pregnancy. Melbourne: Murdoch Childrens Research Institute, 2017. Available at [www.mcric.edu.au/prenatal-screening](http://www.mcric.edu.au/prenatal-screening)

## When should I refer?

The following people should be offered referral to specialist services (genetics or obstetrics):

- Couples who are known carriers of a genetic condition. Such couples could access [pre-implantation genetic diagnosis](#) through in-vitro fertilisation (IVF) for future pregnancies.
- Women with an increased probability of a pregnancy with a chromosomal condition
  - previous pregnancy with a chromosomal condition
  - positive screening test or diagnostic test
  - parent with chromosomal rearrangement (eg [balanced translocation](#)).
- Women with confirmed abnormality from diagnostic testing.

## References

1. The Royal Australian and New Zealand College of Obstetricians and Gynaecologists. Prenatal screening and diagnosis of chromosomal and genetic conditions in the fetus in pregnancy (C-Obs 59). Melbourne: RANZCOG, 2015. Available at [www.ranzcog.edu.au/Statements-Guidelines](http://www.ranzcog.edu.au/Statements-Guidelines) [Accessed 8 January 2018].
2. The Royal Australian College of General Practitioners. Guidelines for preventive activities in general practice. 9th edn. Melbourne: RACGP, 2016. Available at [www.racgp.org.au/your-practice/guidelines/redbook](http://www.racgp.org.au/your-practice/guidelines/redbook) [Accessed 8 January 2018].

- Loane M, Morris JK, Addor MC, et al. Twenty-year trends in the prevalence of Down syndrome and other trisomies in Europe: Impact of maternal age and prenatal screening. *Eur J Hum Genet* 2013;21(1):27.
- Murdoch Childrens Research Institute. Your choice – Prenatal screening tests in pregnancy. Melbourne: MCRI, 2017. Available at [www.mcri.edu.au/prenatal-screening](http://www.mcri.edu.au/prenatal-screening) [Accessed 8 January 2018].

## Resource for general practitioners

- Centre for Genetics Education and The Royal Australian College of General Practitioners, First trimester screening in general practice, [www.genetics.edu.au/health-professionals/online-learning/first-trimester-learning-module](http://www.genetics.edu.au/health-professionals/online-learning/first-trimester-learning-module)

## Resources for patients

- Better Health Channel, Pregnancy – Prenatal tests, [www.betterhealth.vic.gov.au/health/healthyliving/pregnancy-prenatal-tests](http://www.betterhealth.vic.gov.au/health/healthyliving/pregnancy-prenatal-tests)
- Centre for Genetics Education, Fact sheet 24: Prenatal testing overview, [www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-24-prenatal-testing-overview](http://www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-24-prenatal-testing-overview)
- Centre for Genetics Education, Fact sheet 25: Screening tests during pregnancy, [www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-25-screening-tests-during-pregnancy](http://www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-25-screening-tests-during-pregnancy)
- Centre for Genetics Education, Prenatal testing: Special tests for your baby during pregnancy – Includes NIPT, [www.genetics.edu.au/publications-and-resources/booklets-and-pamphlets/prenatal-testing-special-tests-for-your-baby-during-pregnancy](http://www.genetics.edu.au/publications-and-resources/booklets-and-pamphlets/prenatal-testing-special-tests-for-your-baby-during-pregnancy)



## Reproductive carrier screening

### Practice point

All women or couples planning a pregnancy, or who are already pregnant, should have a comprehensive **family history** recorded.<sup>1</sup>

Women or couples who are known **carriers** of a genetic condition or have a relevant family history should be made aware of the availability of **carrier screening** and offered referral to specialist services (ie genetics or obstetrics).<sup>1</sup>

Carrier screening for common recessive genetic conditions (eg **cystic fibrosis** [CF]) may be offered to low-risk women or couples (ie regardless of family history and ethnicity).

The decision to have screening is a personal choice to be made by the individual or couple.

### What do I need to know?

Carrier screening is used to identify carriers of genetic conditions with an **autosomal recessive inheritance** pattern.

Carrier screening can be offered to all women or couples during pre-conception and early in the pregnancy (ie first trimester). Identifying carrier couples before pregnancy provides greater reproductive options. For example:

- in-vitro fertilisation (IVF) with **pre-implantation genetic diagnosis**
- use of donor gametes
- prenatal diagnostic testing.

Traditionally, carrier screening for inherited recessive conditions was offered on the basis of ethnicity. However, given the multicultural nature of society and marriage between people of different ethnic backgrounds, ethnicity is less strongly predictive of carrier frequency in Australia. Therefore, carrier screening panels increasingly test for multiple conditions, irrespective of ethnicity.<sup>2</sup>

The decision to undertake carrier screening is a personal choice to be made by the individual or couple. Women or couples should be informed of the benefits, limitations and cost of screening. Ideally, this information is provided pre-pregnancy.<sup>1</sup>

### Genetic testing

A number of pathology services offer carrier screening, which can be ordered through general practice. However, carrier screening is not available through the Medicare Benefits Schedule (MBS). Depending on the test provider:

- screening may look for a limited number of conditions (eg CF, **Fragile X syndrome** [FXS], spinal muscular atrophy) or screen for an expanded range of conditions (ie >100)
- genetic counselling may or may not be available.

Note: Carriers of **haemoglobinopathies** may be initially identified through a routine full blood examination (FBE).

### When should I refer?

Couples identified as carriers of a genetic condition should be offered referral to specialist services (ie genetics or obstetrics).

### Other considerations

Carrier screening needs to occur in a timely manner to provide women or couples with reproductive options. The testing of biological male partners of pregnant female carriers is of particular importance.

## References

1. The Royal Australian and New Zealand College of Obstetricians and Gynaecologists. Prenatal screening and diagnosis of chromosomal and genetic conditions in the fetus in pregnancy (C-Obs 59). Melbourne: RANZCOG, 2015. Available at [www.ranzcog.edu.au/Statements-Guidelines](http://www.ranzcog.edu.au/Statements-Guidelines) [Accessed 8 January 2018].
2. American College of Obstetricians and Gynecologists. Committee Opinion no. 690: Carrier screening in the age of genomic medicine. *Obstet Gynecol* 2017;129(3):e35–40. Available at [www.acog.org/Resources-And-Publications/Committee-Opinions/Committee-on-Genetics/Carrier-Screening-in-the-Age-of-Genomic-Medicine](http://www.acog.org/Resources-And-Publications/Committee-Opinions/Committee-on-Genetics/Carrier-Screening-in-the-Age-of-Genomic-Medicine) [Accessed 8 January 2018].

## Resources for general practitioners

- Henneman L, Borry P, Chokoshvili D, et al. Responsible implementation of expanded carrier screening. *Eur J Hum Genet* 2016;24(6):e1–e12.
- The Royal Australian College of General Practitioners, Guidelines for preventive activities in general practice, [www.racgp.org.au/your-practice/guidelines/redbook](http://www.racgp.org.au/your-practice/guidelines/redbook)

## Resources for patients

### Information

- Cystic Fibrosis Community Care, Cystic fibrosis carrier screening, [www.cysticfibrosis.org.au/vic/carrier-screening](http://www.cysticfibrosis.org.au/vic/carrier-screening)

### Support

- Spinal Muscular Atrophy (SMA) Australia, <https://smaaustralia.org.au>
- The Fragile X Association of Australia, <https://fragilex.org.au>



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