RACGP
Royal Australian College
of General Practitioners

Genomics in general practice

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Genomics in general practice

Background

Background

Genomics in general practice was developed by general practitioners (GPs) and subject matter experts to ensure that the content is the most valuable and useful for health practitioners. The guide is a suite of concise summaries on various clinical topics in genetics and genomics and is based on the best-available current evidence.

Aim of the resource

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 then refer to specialist services as required.

Development process

Development process

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

A literature search was conducted for each topic, and new evidence was identified. Members of the Expert Advisory Group reviewed the 2018 edition of the guide and updated the content based on current evidence available. 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

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

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.

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.

In this edition, topics have been re-organised into three categories:

Genetic tests and technologies which includes

- Chromosome microarray (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/genetic-tests-and-technologies/chromosome-microarray)
- Newborn screening (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/genetic-tests-and-technologies/newborn-screening)
- Personal genomic testing (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/genetic-tests-and-technologies/personal-genomic-testing)
- Pharmacogenomics (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/genetic-tests-and-technologies/pharmacogenomics)
- Prenatal testing (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/genetic-tests-and-technologies/prenatal-testing)
- Reproductive carrier screening (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/genetic-tests-and-technologies/reproductive-carrier-screening)

Family history (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/family-history)

Disease-specific topics which includes

- Alzheimer's disease (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/disease-specific-topics/al

zheimer-disease)
- Autism spectrum disorder (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/disease-specific-topics/autism-spectrum-disorder)
- Cystic fibrosis (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/disease-specific-topics/cystic-fibrosis)
- Developmental delay and intellectual disability (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/disease-specific-topics/developmental-delay-and-intellectual-disability)
- Diabetes (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/disease-specific-topics/diabetes)
- Familial breast and ovarian cancer (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/disease-specific-topics/familial-breast-and-ovarian-cancer)
- Familial colorectal cancer (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/disease-specific-topics/familial-colorectal-cancer)
- Familial hypercholesterolaemia (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/disease-specific-topics/familial-hypercholesterolaemia)
- Familial melanoma (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/disease-specific-topics/familial-melanoma)
- Familial prostate cancer (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/disease-specific-topics/familial-prostate-cancer)
- Fragile X syndrome and associated conditions (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/disease-specific-topics/fragile-x-syndrome-and-associated-conditions)
- Haemoglobinopathies (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/disease-specific-topics/haemoglobinopathies)
- Hereditary haemochromatosis (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/disease-specific-topics/hereditary-haemochromatosis)
- Hereditary thrombophilia (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/disease-specific-topics/hereditary-thrombophilia)
- Mental health conditions (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/disease-specific-topics/mental-health-conditions)
- MTHFR gene testing (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/disease-specific-topics/mthfr-gene-testing)
- Neurofibromatosis type 1 (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/disease-specific-topic

s/neurofibromatosis-type-1)
- Neurological conditions (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/disease-specific-topics/neurological-conditions)
- Sudden arrhythmic death syndrome (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/disease-specific-topics/sudden-arrhythmic-death-syndrome)

What's new

What's new

The majority of the topics have been updated with new links to resources and minor changes to the content so the existing information has not changed significantly. New information has been included on:

- Personal genomics testing
- Pharmacogenomics
- The new MBS item numbers for carrier screening, fragile X syndrome, SMA and cystic fibrosis
- Polygenic risk scores

Scope

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

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:

- 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) 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
- 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.

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.

Further reading

- Beauchamp TL. The 'four principles' approach to health care ethics. In: Ashcroft RE, Dawson A, Draper H, McMillan JR, editors. Principles of health care ethics. 2nd edn. Chichester, UK: John Wiley & Sons, 2007.
- Andorno R. The right not to know: An autonomy based approach. J Med Ethics 2004;30(5):435–39.
- Weaver M. The double helix: Applying an ethic of care to the duty to warn genetic relatives of genetic information. Bioethics 2016;30(3):181–87.
- Human Genetics Society of Position statement: Predictive and Pre-symptomatic genetic testing in adults and children (https://www.hgsa.org.au/documents/item/11030) . Sydney: HGSA, 2020.[Accessed 14 April 2022].
- AMA Position Statement Genetic Testing and Genomics in Medicine 2020 (https://www.ama.com.au/articles/genetic-testing-and-genomics-medicine-2020) .

Resources for general practitioners

- Centre for Genetics Education, Ethical issues in human genetics and genomics (https://www.genetics.edu.au/SitePages/Ethical-issues-in-human-genetics-and-genomics.aspx)
- Human Genetics Society of Australasia, Policies and position statements (https://www.hgsa.org.au/resources/hgsa-policies-and-position-statements)
- Financial Services Council, FSC Standard no. 16: Family medical history policy (https://fsc.org.au/resources-category/standard/1297-ifsastandardno16/file)

Clinical Genetics and Genetic Counselling

Clinical Genetics and 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 clinical geneticists and genetic counsellors available at genetics services in each state or territory. The process of professional clinical genetics and genetic counselling involves:

- assessment to advise if genetic testing is indicated and to facilitate genetic testing for diagnosis of a genetic condition
- assisting the person 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
- understanding the options for dealing with the risk of recurrence
- choosing the course of action that seems appropriate in view of their situation, and risk and values, and act in accordance with that decision
- making 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 consultation, the geneticist/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

Genetics support groups and organisations

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- 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' Health Centre for Genetics Education maintains a list of genetics services (https://www.genetics.edu.au/SitePages/Genetic-Services.aspx)

Health and life insurance issues

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 product (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'. 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 that would be relevant to the assessment of their risk, over and above the questions asked. This includes information about any health condition(s) that were diagnosed in first-degree relatives (ie parents, children, brothers, sisters) and the age at which they were diagnosed. It does not include any other information, including their genetic test result(s), if known to you, their name or date of birth.

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.

The Financial Services Council has implemented a moratorium on the disclosure of genetic test results in life insurance (https://www.fsc.org.au/resources-category/standard/1779-standard-11-moratorium-on-genetic-tests-in-life-insurance/file) product applications at a level below $500,000 for death and total and permanent disability, $200,000 for trauma, and $4000 a month for income protection. This commenced in July 2019.

Further reading

- Commonwealth of Australia. Insurance Contracts Act 1984 (http://austlii.edu.au/au/legis/cth/consol_act/ica1984220/s21.html) . Canberra: Commonwealth of Australia, 1984; Section 21. [Accessed 13 December 2017].

Resources for general practitioners

- Centre for Genetics Education, : Life insurance products and genetic testing in Australia (https://www.genetics.edu.au/SitePages/Life-insurance-products-and-genetic-testing-in-Australia.aspx)
- Financial Services Council. Genetic tests and applying for life insurance – Key Facts (https://fsc.org.au/resources-category/standard/1779-standard-11-moratorium-on-genetic-tests-in-life-insurance/file)
- Newson AJ, Ayres S, Boyle J, Gabbett MT, Nisselle A. (2018) “Human Genetics Society of Australasia Position Statement: Genetic testing and personal insurance products in Australia.” Twin Research and Human Genetics, 21(6):533-537.

Misconceptions about genetics

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	Gene variants in BRCA1 and BRCA2 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 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 penetrance (ie less than 100% of people with that gene variant manifest the condition), 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

Misconception	Fact
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 family history for a variety of reasons. For example, reduced or incomplete penetrance, recessive conditions, small family size, and new mutations (eg de novo, 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

Genetic tests and technologies

Chromosome microarray

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 quantify the number of copies of thousands of segments of DNA 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 conditions, while others represent normal human variations. Some CNVs are associated with an increased risk of morbidity but can be seen in healthy individuals. There are also some CNVs for which the clinical impact is unknown or uncertain.

Why use it?

CMAs are commonly used in two clinical situations, as a:

- prenatal diagnostic test
- first-line test for individuals presenting with developmental delay (DD), intellectual disability (ID) with or without facial dysmorphism, autism spectrum disorder (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/disease-specific-topics/autism-spectrum-disorder) (ASD) or multiple congenital anomalies

The use of CMAs 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 a traditional karyotype which involves examination of chromosomes under the microscope).

What does CMA test for?

CMA only tests for variations in DNA copy number. It can identify:

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

However, it does not identify:

- single gene mutations
- fragile X syndrome (FXS) (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/disease-specific-topic

s/fragile-x-syndrome-and-associated-conditions)
- balanced rearrangements (eg: translocations and inversions).

How does it work?

CMAs are 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'.

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 CMAs; the section on interpretation of results below may be useful.

There are no clear guidelines about whether GPs should be ordering CMAs for investigating DD or ID in children. A CMA has been identified as a first-line test for investigating non-syndromic DD and ID. A Medicare Benefits Schedule (MBS) rebate is available (http://www9.health.gov.au/mbs/fullDisplay.cfm?type=item&q=73292&qt=ItemID) for CMAs in the paediatric setting where a patient has DD, ID, ASD or at least two congenital abnormalities.

While GPs are able to order CMAs 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

No clinically significant copy number variants (CNVs)	Pathogenic or likely pathogenic CNV	CNVs of uncertain Significance	Secondary or unexpected findings

Normal result	Known copy number variant identified	Copy number variant(s) of uncertain significance (VOUS) identified. Clinical impact is unknown or uncertain	Copy number variant identified 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)	Laboratory report will suggest next steps (eg referral to genetics, family testing)

Further reading

- Martin CL, Ledbetter DH. Chromosomal Microarray Testing for Children With Unexplained Neurodevelopmental Disorders. JAMA. 2017;317(24):2545-2546. doi:10.1001/jama.2017.7272
- Palmer EE, Peters GB, Mowat Chromosome microarray in Australia: A guide for paediatricians. J Paediatr Child Health 2012;48(2):E59–67.
- Miller DT, Adam MP, Aradhya S, et 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, Chromosome microarray (CMA) testing in children and adults (https://www.genetics.edu.au/SitePages/Chromosome-microarray-fact-sheet.aspx)
- Jackson Laboratory, What you need to know before ordering chromosomal microarray (http://jax.org/education-and-learning/clinical-and-continuing-education/cancer-resources/deciding-to-test)

Newborn screening

Newborn screening

PRACTICE POINT

Screening is available to all newborns in Australia free of charge, and almost all babies are screened. There is a very small proportion of babies (1-2%) who may be lost to follow up or whose parents may refuse consent for screening. 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 of a conditions included in newborn screening 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 reduce morbidity and mortality.

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.

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

Less than 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 through newborn screening.

The newborn screening programs are being expanded to increase the number of conditions screened for. Refer to the Department of Health and Aged Care website for further details.

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.

Class	Condition
Amino acids	Argininaemia or arginase deficiency
	Argininosuccinic aciduria
	Citrullinaemia
	Tyrosinaemia type 1
	Homocystinuria
	Maple syrup urine disease
	Phenylketonuria
	Pterin defects
	Tyrosine aminotransferase deficiency
Organic acids	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 acidaemia

Class	Condition
	Methylmalonic acidurias
	Propionic acidaemia
	2-methylbutyryl-CoA dehydrogenase deficiency
	3-methylglutaconyl-CoA hydratase deficiency
Fatty acid oxidation	Carnitine or acylcarnitine translocase deficiency
	Carnitine transporter defect
	Carnitine palmitoyl transferase I and II deficiency (CPTID, CPTIID)
	3-hydroxy long chain acyl-CoA dehydrogenase deficiency (LCHADD)
	Medium chain acyl-CoA dehydrogenase deficiency (MCADD)
	Multiple acyl-CoA dehydrogenase deficiency (MADD)
	Short chain hydroxy acyl-CoA dehydrogenase deficiency (SCHADD)
	Trifunctional protein deficiency (TFPD)
	Very long chain acyl-CoA dehydrogenase deficiency (VLCADD)
Other	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.

There are other disorders currently being considered including congenital adrenal hyperplasia (CAH), spinal muscular atrophy (SMA) and severe combined immune deficiency (SCID).

Further reading

- Human Genetics Society of Policy: Newborn bloodspot testing. Sydney: HGSA, 2020 (https://www.health.gov.au/resources/publications/newborn-bloodspot-screening-national-policy-framework) . Accessed 14 March 2022.
- Newborn Bloodspot Screening. National Policy Framework (https://www.health.gov.au/resources/publications/newborn-bloodspot-screening-national-policy-framework) . Accessed 14 March 2022.
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Personal genomic testing

Personal genomic testing

PRACTICE POINT

At this time, the clinical utility of personal genomic testing, or online DNA testing, is considered variable and depends on the specific variants that are reported. 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 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 individuals themselves, and represents the new world of personal genomic testing.

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 varaints** 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. Asymptomatic individuals now have the opportunity to access 'direct-to-consumer' (DTC), 'at-home' testing, or 'online DNA 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. While personal genomic testing has predominantly been offered as a direct-to-consumer service through international companies, in Australia clinicians can order certain types of personal genomic test for their patients through commercial laboratories. This includes panels for carrier screening for autosomal recessive conditions, pharmacogenomics and some polygenic risk scores (eg for certain cancers).

What do I need to know?

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

- identification of susceptibility to a wide range of diseases using polygenic risk scores
- **carrier screening** for autosomal recessive conditions
- pharmacogenomics (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/genetic-tests-and-technologies/pharmacogenomics)
- nutrigenomics (ie diet, nutrition, wellness)
- fitness and sporting abilities
- ancestry
- relationship (eg paternity) testing

The cost of personal genomic testing varies according to the type of test (eg SNP **Single nucleotide polymorphism/single nucleotide variant**, **genotyping** , **exome sequencing** , whole genome sequencing) and how much information is provided with the results. Personal genomic testing is not funded by the Medicare Benefits Schedule (MBS), so consumers incur the full cost. Personal genomic testing 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 some 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.

What is tested?

Personal genomic testing can provide information that is health or non-health related. 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 associated with high risk for disease with greater certainty (eg *BRCA1*, familial breast and ovarian cancer (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/disease-specific-topics/familial-breast-and-ovarian-cancer))
- are associated with a wide range of disease risks with variable levels of evidence (eg polygenic risk scores for cancers, heart disease)
- are limited predictors of disease (eg *APO-ε4*, Alzheimer disease (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/disease-specific-topics/alzheimer-disease))
- identify carrier status for recessive conditions (eg cystic fibrosis (https://www.racgp.org.au/cli

nical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/disease-specific-topics/cystic-fibrosis))
- can inform response to drugs (refer to 'Pharmacogenomics (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/genetic-tests-and-technologies/pharmacogenomics) ').

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. These tests might include genetic variants that are:

- 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* (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/disease-specific-topics/mthfr-gene-testing) gene testing (#_bookmark65)). In Australia, these tests are advertised as 'genomic wellness' tests, and are increasingly available through naturopaths and nutritionists.

How do I manage personal genomic testing in general practice?

Advising patients who want personal genomic testing

Patients may ask a GP to order personal genomic testing on their behalf. GPs asked to arrange personal genomic testing should consider the following:

- 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' (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/genomics-in-general-practice/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 personal genomic testing

Patients who have already had personal genomic testing 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. 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.

Implications for general practice

The uptake of personal genomic testing is likely to continue, and GPs will increasingly encounter patients who are curious about or have used personal genomic testing.

Commercial companies may begin to promote personal genomic testing to GPs, especially as the evidence builds for the clinical validity and utility of some components of these tests.

Some personal genomic testing 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 personal genomic testing 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.

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

Further reading

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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 (http://nhmrc.gov.au/guidelines-publications/g9)
- NSW Centre for Genetics Education. Online direct to consumer testing (https://www.genetics.edu.au/SitePages/Direct-to-consumer-testing.aspx)
- Pathology Tests Explained. Online DNA tests (https://pathologytestsexplained.org.au/inside-the-lab/genetic-testing/online-dna-tests) .

Pharmacogenomics

Pharmacogenomics

PRACTICE POINT

There are international guidelines about potential uses of pharmacogenomic testing, and growing evidence from randomised controlled trials of the clinical utility for these tests to inform some prescribing decisions; their precise role in Australian general practice is still under consideration.

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.

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 may be more susceptible to adverse drug effects.

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

Table 1. Examples of drugs affected by common gene variants

Gene name	Examples of drugs affected	Clinical consequence
CYP2D6 (5–10% of Caucasians are poor metabolisers; 1–2% of Caucasians are ultrarapid metabolisers)	Codeine	Poor metabolisers have no response to codeine; ultra- 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
CYP2C19 (poor metabolisers 2–15%)	Clopidogrel	Poor metabolisers may require alternative anti-platelet therapy
VKORC1 and *CYP2C9*	Warfarin	*CYP2C9* and *VKORC1* genotypes may be useful in determining the optimal initial dose of warfarin
SLCO1B1	Simvastatin (not other statins)	Low-function genotype associated with increased risk of myopathy; consider alternative statin or lower dose

How genetic polymorphisms/variants affect drug metabolism

Genetic variation can affect:

- 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).

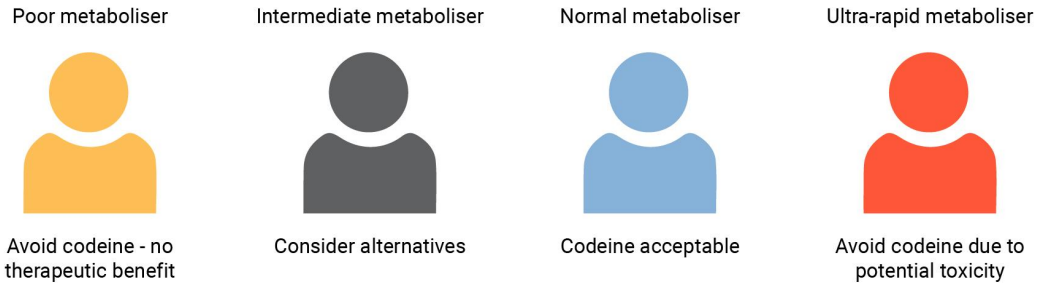
Pharmacogenomic testing analyses genes involved in these two processes.

One example is the cytochrome P450 multi-gene family, which produce enzymes involved in drug metabolism. P450 enzymes account for 70–80% of enzymes involved in drug metabolism. Common variations in P450 genes can affect the function of the enzymes produced, which in turn affects the metabolism of some drugs.

Genetic variations give rise to four different phenotypes in terms of drug response:

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

Figure 1. Codeine recommendation according to metaboliser status[8]



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:

- 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
- Evidence is accumulating from randomized controlled trials for some of these benefits for particular uses of pharmacogenomic testing (eg for antidepressants).

Limitations of pharmacogenomics

At present, there are several limitations of pharmacogenomic testing:

- Cost – there are currently only two pharmacogenetic tests funded through an MBS rebate: MBS item 73327 (http://www9.health.gov.au/mbs/fullDisplay.cfm?type=item&q=73327&qt=ItemID) for the detection of genetic variants in the thiopurine S-methyltransferase gene for the prevention of dose-related toxicity during treatment with thiopurine drugs and MBS item 73323 (http://www9.health.gov.au/mbs/fullDisplay.cfm?q=73323.) for HLAB5701 testing prior to prescribing Abacavir therapy.
- Testing turnaround time – some results can take between five and ten working days to reach the clinician who ordered the 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

Confidence in the clinical utility of pharmacogenomic testing is slowly growing, but there is a need for more evidence about the cost-effectiveness of pharmacogenomic testing to inform specific prescribing decisions.

Genetic testing

Pharmacogenomic testing may be considered for patients with:

- significant side-effects from drugs for which 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.

Further reading

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- Rollinson V, Turder R, Pirmohamed M. Pharmacogenomics for Primary Care: An Overview. Genes 2020, 11, 1337; doi:10.3390/genes11111337
- Abbasi J. Getting pharmacogenomics into the clinic. JAMA 2016;316(15):1533–35.

Resources for patients

- Centre for Genetics Education, Pharmacogenetics/pharmacogenomics (https://www.genetics.edu.au/ SitePages/Pharmacogenomics.aspx)
- Garvan Institute of Medical Research, DNA and medications:pharmacogenomics (https://www.garvan.org.au/research/kinghorn-centre-for-clinical-genomics/learn-about-genomics/dnabase/collection1/pharmacogenomics)
- National Library of Medicine, What is pharmacogenomics? (https://medlineplus.gov/genetics/understanding/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 and for autosomal and X-linked conditions. Screening options should be discussed in the first trimester whenever possible.

Prenatal screening tests should not be considered routine, but offered as a choice to women. 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.

What do I need to know?

Prenatal vs carrier screening. Carrier screening involves testing of the biological parents to see if they are carriers of a genetic condition vs prenatal screening which involves testing the pregnant woman and/or baby to look for the presence of a genetic condition in the baby.

Pre-pregnancy and pregnancy counselling that are relevant to genetics should include:

- Any known genetic conditions among close family members (refer to 'Family history (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/family-history) ').
- History of intellectual disability (ID), multiple pregnancy loss, stillbirth, children with congenital abnormalities
- **Consanguinity** ('are you and your partner blood relatives? Eg cousins').
- Pre-pregnancy and pregnancy folic acid intake
- Information about carrier screening for inherited conditions (ideally pre-conception but if not possible then early in first trimester).

All women should be provided information about prenatal screening for chromosomal conditions. These cannot be screened for as part of preconception screening.

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) 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 the possibility of an invasive diagnostic procedure such as chorionic villus sampling (CVS) and amniocentesis, thinking about the possibility of having a child with special needs or pregnancy termination, the availability of preimplantation genetic diagnosis).

Other important considerations:

- Screening tests can determine who is at increased risk of having a baby with a chromosomal or inherited 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 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).
- There is no increased risk of miscarriage from screening tests.
- Every screening test has a false positive rate: some women will receive an 'increased risk' result even though their baby is unaffected
- '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
- 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 offence. 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 ß-subunit of human chorionic gonadotrophin (ß-hCG). Levels of these proteins vary, but tend to be different in women carrying fetuses with Down syndrome or trisomy Increased free ß-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 the presence or absence of nasal bone on ultrasound is added to the algorithm.

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.

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, trisomy 18 or neural tube defects (eg spina bifida).

CFTS and NIPT have largely replaced second trimester screening. 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 DNA found circulating in maternal blood. Testing is usually available 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 aneuploidy 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 aneuploidies.

While the accuracy of NIPT in identifying Down syndrome is very high, the accuracy is not as high for trisomy 13 or 18 or for sex chromosome aneuploidy. 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 in whom the prevalence of chromosome aneuploidies is lower.

NIPT does not screen for:

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

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 tests

	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), ß-subunit of human chorionic gonadotrophin (ß-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 ≥15 weeks
Conditions detected	Trisomies 21, 18, 13; structural anomalies	Trisomies 21 and 18; neural tube defects	Trisomies 21, 18, 13; sex chromosome conditions* and other aneuploidies for some tests	Many chromosome and genetic conditions
Detection rate for trisomy 21	90%	75-80%	99%	99.9%

	Screening tests			Diagnostic procedures*
False positive rate for trisomy 21	3-5%	7-8%	<1%	<1%†
Test failure rate	<1%	<1%	1-5%	<1%
Risk to pregnancy	None	None	None	Small risk of miscarriage (≤1%)

*Though not highly accurate and can be confounded by underlying maternal and fetal factors.

** There are many different commercial tests available with varying characteristics (what is tested for, sensitivity, specificity and PPV), costs, etc.

†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 (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/genetic-tests-and-technologies/chromosome-microarray) (CMA).

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

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 Such couples could access **pre-implantation genetic testing** 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

Further reading

- The Royal Australian and New Zealand College of Obstetricians and Prenatal screening and diagnostic testing for fetal chromosomal and genetic conditions (http://www.ranzcog.edu.au/Statements-Guidelines) . Melbourne: RANZCOG, 2018. [Accessed 14 March 2022].
- The Royal Australian College of General Guidelines for preventive activities in general practice. 9th edn (http://www.racgp.org.au/your-practice/guidelines/redbook) . Melbourne: RACGP, 2016. [Accessed 6 September 2022].
- Screening for Fetal Chromosomal Abnormalities: ACOG Practice Bulletin, Number 226. Obstetrics & Gynecology 2020; 136(4): 859-867.
- Murdoch Childrens Research Your choice – Prenatal screening tests in pregnancy. (http://www.mcri.edu.au/prenatal-screening) Melbourne: MCRI, 2017. [Accessed 14 March 2022].

Resource for general practitioners

- Centre for Genetics Education and The Royal Australian College of General Practitioners, First trimester screening in general practice (https://www.genetics.edu.au/SitePages/FTS-module.aspx) or on the RACGP *gplearning* site

Resources for patients

- Better Health Channel, Pregnancy – Prenatal tests (http://betterhealth.vic.gov.au/health/healthyliving/pregnancy-prenatal-tests)
- Centre for Genetics Education, Prenatal testing overview (https://www.genetics.edu.au/SitePages/Prenatal-testing-overview.aspx)
- Centre for Genetics Education, Screening tests during pregnancy (https://www.genetics.edu.au/SitePages/Screening-tests-during-pregnancy.aspx)

Reproductive carrier screening

PRACTICE POINT

All women/ couples planning a pregnancy, or who are already pregnant, should have a comprehensive **family history** (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/family-history) recorded.

Women/ 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** Carrier screening and offered referral to specialist services (ie genetics or obstetrics). Information on carrier screening for at least the more common genetic conditions that affect children (eg cystic fibrosis (#_bookmark41) <link to chapter> [CF], spinal muscular atrophy [SMA], fragile X syndrome [FXS]) should be offered to low-risk women and couples (ie regardless of family history and ethnicity). Women/couples can be offered larger panels of genes for carrier screening (expanded carrier screening, ECS). The decision to have screening is a personal choice to be made by the individual/couple.

What do I need to know?

Reproductive carrier screening is used to identify carriers of genetic conditions with an **autosomal recessive inheritance** or X-linked inheritance pattern.

Information about carrier screening should 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 testing**
- use of donor gametes
- prenatal diagnostic testing

Traditionally, reproductive carrier screening for inherited recessive conditions was offered on the basis of ethnicity. However, this is known to lead to significant under-identification of carrier couples. Given the multicultural nature of society and people of different ethnic backgrounds having children, ethnicity is poorly predictive of carrier frequency in Australia.

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

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). From November 2023, there will be an MBS item available for carrier screening, fragile X syndrome, SMA and cystic fibrosis. Depending on the test provider:

- screening may look for a limited number of conditions (eg CF, fragile X syndrome (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/disease-specific-topics/fragile-x-syndrome-and-associated-conditions) [FXS], spinal muscular atrophy) or screen for an expanded range of conditions (ie >100)
- genetic counselling may or may not be available from the pathology provider.

Note: Carriers of haemoglobinopathies may be initially identified through a routine full blood examination (FBE). Mackenzie's Mission, a national research project funded by the Federal Government, is in progress but closed for further recruitment.

It aims to identify how reproductive carrier screening for an expanded range of conditions can best be made available to Australian couples who want it.

When should I refer?

Couples identified as high risk of having a child with a genetic condition should be offered referral to specialist services (ie genetics or obstetrics), that is couples where both are carriers of the same autosomal recessive condition and/or where the woman is a carrier of an X-linked condition.

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.

Further reading

- The Royal Australian and New Zealand College of Obstetricians and Prenatal screening and diagnostic testing for fetal chromosomal and genetic conditions (http://www.ranzcog. edu.au/Statements-Guidelines) . Melbourne: RANZCOG, 2018. [Accessed 14 March 2022].
- Delatycki M, Laing N, Moore S, et al. Preconception and antenatal carrier screening for genetic conditions. The critical role of general practitioners. AJGP 2019. 3; 106-110.
- Sparks T. Expanded carrier screening: counseling and considerations (https://doi.org/10.1007/s00439-019-02080-y) . Human Genetics (2020) 139:1131–1139

Resources for patients

- Mackenzie's Mission (https://www.mackenziesmission.org.au/)
- Centre for Genetics Education. Reproductive carrier screening (https://www.genetics.edu.au/SitePages/Reproductive-carrier-screening.aspx)
- Cystic Fibrosis Community Care, cystic fibrosis carrier screening (http://cysticfibrosis.org.au/vic/carrier-screening)
- Spinal Muscular Atrophy (SMA) Australia (https://smaaustralia.org.au)
- The Fragile X Association of Australia (https://fragilex.org.au)

Family history

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). The use of a family history screening questionnaire (Table 1) can help identify individuals who may require a more detailed assessment of their family **history** of cancer, heart disease or diabetes.

Table 1. Family history screening questionnaire

This risk assessment focuses on your close relatives including parents, children, brothers and sisters who are either living or dead.	Yes	No
Have any of your close relatives had heart disease before 60 years of age? 'Heart disease' includes cardiovascular disease, heart attack, angina and bypass surgery.		
Have any of your close relatives had diabetes? 'Diabetes' is also known as type 2 diabetes or non-insulin dependent diabetes		
Do you have any close relatives who had melanoma?		
Have any of your close relatives had bowel cancer before 55 years of age?		
Do you have more than one relative on the same side of the family who had bowel cancer at any age? Please think about your parents, children, brothers, sisters, grandparents, aunts, uncles, nieces, nephews and grandchildren.*		
Have any of your close male relatives had prostate cancer before 60 years of age?		

This risk assessment focuses on your close relatives including parents, children, brothers and sisters who are either living or dead.	Yes	No
Have any of your close female relatives had ovarian cancer?		
Have any of your close relatives had breast cancer before 50 years of age?		
Do you have more than one relative on the same side of your family who has had breast cancer at any age? Please think about your parents, children, brothers, sisters, grandparents, aunts, uncles, nieces, nephews and grandchildren.*		

*Only first-degree and second-degree relatives need be considered in this screening questionnaire

Reproduced with permission from Emery JD, Reid G, Prevost AT, Ravine D, Walter FM. Development and validation of a family history screening questionnaire in Australian primary care. Ann Fam Med 2014;12(3):241–49.

Taken from a Guideline for preventative activities in general practice (https://www.racgp.org.au/download/Documents/Guidelines/Redbook9/Appendix-2A-Family-history-screening-questionnaire.pdf)

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 (#_bookmark41) [CF]).

General information to collect in a family history includes:

- age of patient
- age at diagnosis of conditions in the family
- ancestry and cultural background
- step-relationships and adoption (ie: family members not genetically related to the individual)
- children born to parents who are blood-related (**consanguinity**)
- known genetic conditions.

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

Markers of possible genetically determined conditions in a family history include:

- birth defects, multiple stillbirths and multiple miscarriages – consider referral to genetics services
- developmental delay (DD) – consider referral and ordering a chromosome microarray (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/genetic-tests-and-technologies/chromosome-micro

array) (CMA) and fragile X syndrome <link to chapter> (FXS) testing (DD and intellectual disability (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/disease-specific-topics/developmental-delay-and-intellectual-disability) [ID], FXS, autism spectrum disorder (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/disease-specific-topics/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 (https://www.eviq.org.au/) 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	
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)			

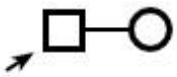
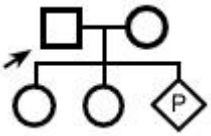
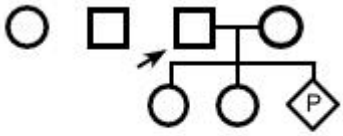
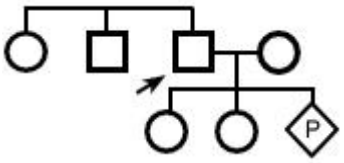
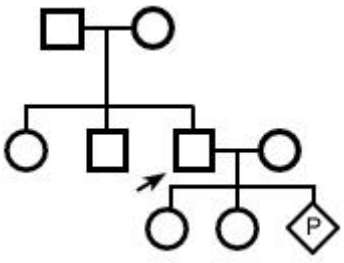
*Use a key or legend to define the condition(s) denoted by the shading in the pedigree.

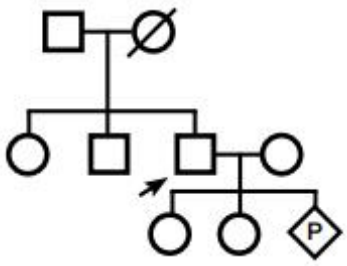
Record the date on which the pedigree is drawn and update it as new information becomes available.

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

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 partner, 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 'T'	
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	

Further reading

- The Royal Australian College of General Guidelines for preventive activities in general practice (http://www.racgp.org.au/your-practice/guidelines/redbook) . 9th edn. Melbourne: RACGP, 2016. [Accessed 6 September 2022].
- Cancer Institute eviQ. Sydney: Cancer Institute NSW, 2017 (http://www.eviq.org.au) [Accessed 6 September 2022].
- Bennett RL, French KS, Resta RG, Doyle 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.
- Ginsburg GS, Wu RR, Orlando LA. Family health history: underused for actionable risk assessment. The Lancet. 2019 (https://doi.org/10.1016/S0140-6736(19)31275-9) .

Resources for general practitioners

- National Genetics and Genomics Education Centre (UK), Taking and recording a family history (http://primarycaregenetics.org)
- The Royal Australian College of General Practitioners, Guidelines for preventive activities in general 9th edn, Family history screening questionnaire (http://www.racgp.org.au/your- practice/guidelines/redbook/appendices/appendix-2a-family-history-screening-questionnaire)

Disease specific topics

Alzheimer disease

Alzheimer disease

PRACTICE POINT

Currently, genetic testing of *APOE* **gene variants** considered to have limited clinical utility for diagnostic purposes, and is not recommended in clinical practice. Genetic testing is available for variants in three genes *APP, PSEN1, PSEN2* that confer a very high risk for early onset familial Alzheimer disease (AD). However, pathogenic variants in these genes are responsible for only a small percentage of AD.

What do I need to know?

The average lifetime risk of developing AD is estimated to be about 10% (until the age of 75–80 years). The ε4 variant of the *APOE* gene is associated with an increased risk of late-onset AD, but this risk is confounded by other factors. These factors include those that cannot be modified (eg other genetic variants, sex, family history, possibly ethnicity) and modifiable risk factors (eg diet, exercise, cardiovascular health, environment). The clinical utility of knowing ε4 status is uncertain.

Research suggests that heterozygous **carriers** of the ε4 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.

The ε4 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 for this is uncertain.

Genetic testing

While the association of the *APO-ε4* variant with AD is significant, genetic testing has limited sensitivity and specificity. The *APO-ε4* variant may be included in some commercial test panels (refer to '[Personal genomic testing (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/genetic-tests-and-technologies/personal-genomic-testing)](https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/genetic-tests-and-technologies/personal-genomic-testing) '). Given the lack of predictive value of *APO-ε4* for AD, this information may cause unnecessary anxiety for some individuals, especially given the lack of preventive or therapeutic interventions. There may be broader implications for the individual and family members (ie [ethical principles (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/genomics-in-general-practice/ethical-principles)](https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/genomics-in-general-practice/ethical-principles) ,

health and life insurance issues (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/genomics-in-general-practice/health-and-life-insurance-issues)).

When should I refer?

Genetic testing of APP, PSEN1 and PSEN2 may be appropriate for individuals with a family history of early onset AD particularly if there is more than one person affected in a family (≥2 affected family members; age at onset <65 years of age), and referral to genetics services is appropriate.

Further reading

- Human Genetics Society of Australasia and Choosing Wisely Australia. Tests, treatments and procedures (http://www.choosingwisely.org.au/recommendations/hgsa) Sydney: NPS MedicineWise, 2016. [Accessed 6 September 2022].
- Huq AJ, Sexton A, Lacaze P, et al. Genetic testing in dementia-A medical genetics perspective Int J Geriatr Psychiatry. 2021 Aug;36(8):1158-1170.
- 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 Genet Med 2011;13(6):597–605.
- Van Cauwenberghe C, Van Broeckhoven C, Sleegers The genetic landscape of Alzheimer disease: Clinical implications and perspectives. Genet Med 2016;18(5):421.

Resources for patients

Information

- National Library of Medicine (US), Alzheimer disease (https://medlineplus.gov/genetics/condition/alzheimer-disease/)
- National Library of Medicine (US), *APOE* gene: Normal function (https://medlineplus.gov/genetics/gene/apoe/#normalfunction)
- National Library of Medicine (US), *APOE* gene (https://medlineplus.gov/genetics/gene/apoe/)

Support

- Dementia Australia (https://www.dementia.org.au)

Autism spectrum disorder

Autism spectrum disorder

PRACTICE POINT

Referral to a paediatrician for evaluation of children with autism spectrum disorder (ASD) can provide a specific diagnosis in between 30 and 40% of affected individuals. General practitioners (GPs) can order a **chromosome microarray** (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/genetic-tests-and-technologies/chromosome-microarray) (CMA) and testing for fragile X syndrome 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, childhood disintegrative disorder and pervasive developmental disorder – not otherwise specified.

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

Some rare genetic conditions can show clinical features of ASD. These include:

- tuberous sclerosis (*TSC1* or *TSC2* genes)
- fragile X syndrome (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/disease-specific-topics/fragile-x-syndrome-and-associated-conditions) (FXS; *FMR1* gene)
- chromosomal abnormalities
- metabolic conditions
- Rett syndrome (*MECP2* gene variants in most 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. A CMA does not detect FXS (a single-gene cause of ASD), so genetic testing for FXS should be ordered as well as a CMA.

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 (http://www9.health.gov.au/mbs/fullDisplay.cfm?type=item&q=73292&qt=ItemID) 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:

- exhibits ID, ataxia, neurodegeneration or primary ovarian insufficiency consistent with an *FMR1* mutation
- has a relative with an FMR1 mutations

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 25%, with higher risk for male than female siblings. If there are multiple affected siblings, the recurrence risk is higher (up to 50%).

Further reading

- Schaefer GB, Mendelsohn Clinical genetics evaluation in identifying the etiology of autism spectrum disorders: 2013 guideline revisions. Genet Med 2013;15(5):399–407.
- Vorstman JAS, Parr JR, Moreno-De-Luca D, et al. Autism genetics: opportunities and challenges for clinical translation Nat Rev Genet. 2017 Jun;18(6):362-376.
- Thapar A, Rutter M. Genetic Advances in Autism. J Autism Dev Disord. 2021 Dec; 51(12):4321-4332
- Genovese A, Butler MG. Clinical Assessment, Genetics, and Treatment Approaches in Autism Spectrum Disorder (ASD). Int J Mol Sci. 2020 Jul; 21(13): 4726.

Resources for patients

Information

- Autism Spectrum Australia (Aspect), What is autism? (http://autismspectrum.org.au/content/what-autism)
- Centre for Genetics Education, Autism spectrum disorder (https://www.genetics.edu.au/SitePages/Autism-spectrum-disorder.aspx)

Support

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

Cystic fibrosis

Cystic fibrosis

PRACTICE POINT

Newborn screening will identify 85–90% of individuals with cystic fibrosis (CF), but will not identify individuals homozygous/compound heterozygous for rare CFTR (cystic fibrosis transmembrane conductance regulator) variants. Such patients may present to the general practitioner symptomatically (GP) symptomatically.

What do I need to know?

CF is the most common childhood onset 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 a *CFTR* pathogenic variant. The most common variant in the *CFTR* gene is the p.Phe508del variant, which accounts for approximately 70% of all *CFTR* pathogenic variants in those of northern European ancestry. While there are more than 2000 variants in the *CFTR* gene, most of which are benign or of uncertain significance, around 40 pathogenic variants cause approximately 90% of CF in Australia.

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' (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/genetic-tests-and-technologies/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 (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/family-history) or ethnicity. Refer to 'Reproductive carrier screening (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/genetic-tests-and-technologies/reproductive-carrier-screening) ' for more information.

When should I refer?

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

Children suspected of having CF (who have not been previously identified through newborn screening tests) should be referred to a respiratory paediatrician for a sweat test. Symptoms may include recurrent cough, failure to thrive, lower respiratory tract infections, 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. These men should be referred to a fertility specialist.

Other considerations

Cascade screening should be offered following a diagnosis of CF or of a *CFTR* pathogenic variant carrier in a family to identify other carriers.

Further reading

- RANZCOG policy on Genetic Carrier Screening (https://www.ranzcog.edu.au/RANZCOG_SITE/media/RANZCOG-MEDIA/Women%27s%20Health/Statement%20and%20guidelines/Clinical-Obstetrics/Genetic-carrier-screening(C-Obs-63)New-March-2019_1.pdf?ext=.pdf)
- Australasian Guideline (2nd Edition): an Annex to the CLSI and UK Guidelines for the Performance of the Sweat Test for the Diagnosis of Cystic Fibrosis *John Massie, Ronda Greaves, Michael Metz, Veronica Wiley, Peter Graham, Samantha Shepherd, Richard Mackay. Clin Biochem Rev 38 (3) 2017
- The Royal Australian College of General Guidelines for preventive activities in general practice (http://www.racgp.org.au/your-practice/guidelines/redbook) . 9th edn. Melbourne: RACGP, 2016. [Accessed 6 September 2022].
- Kessels SJM, Carter D, Ellery B, et al. Prenatal genetic testing for cystic fibrosis: a systematic review of clinical effectiveness and an ethics review. Genet Med. 2020 Feb;22(2):258-267.

Resources for patients

Information

- National Library of Medicine, Cystic fibrosis (https://ghr.nlm.nih.gov/condition/cystic-fibrosis)
- Better Health Channel, Cystic fibrosis (http://betterhealth.vic.gov.au/health/conditionsandtreatments/cystic-fibrosis-cf)
- Centre for Genetics Education, Cystic fibrosis (https://www.genetics.edu.au/SitePages/Cystic-Fibrosis.aspx)

Support

- Cystic Fibrosis Australia (http://cysticfibrosis.org.au)

Developmental delay and intellectual disability

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.

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)
  - conditions that follow an **autosomal dominant inheritance** pattern (eg tuberous sclerosis)
  - conditions that follow an **autosomal recessive inheritance** pattern (eg Joubert syndrome)
  - conditions that follow an **X-linked recessive inheritance** pattern (eg fragile X syndrome (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/disease-specific-topics/fragile-x-syndrome-and-associated-conditions) [FXS])

Genetic testing

Chromosome microarray (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/genetic-tests-and-technologies/chromosome-microarray) (CMA) is now considered a first-line genetic test for the investigation of DD, ID, autism spectrum disorder (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/disease-specific-topics/autism-spectrum-disorder) (ASD), and congenital abnormalities. CMA does not detect **gene variants** causing FXS (ie *FMR1* gene), so an additional DNA test for diagnosis of FXS 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 (http://www9.health.gov.au/mbs/fullDisplay.cfm?type=item&q=73292&qt=ItemID) 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:

- exhibits ID, ataxia, neurodegeneration, or primary ovarian insufficiency 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 or any of the following:

- dysmorphic features
- motor weakness and delayed motor milestones
- autistic features
- epilepsy
- congenital anomalies (eg cleft palate, heart defects)
- a family history (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/family-history) of autism, FXS or other developmental/learning disability

Patients with these features should be referred to a paediatrician.

Urgent referral to a paediatric neurologist is recommended if an infant or child with motor weakness and delay in the setting of normal cognition (eg suspected spinal muscular atrophy or muscular dystrophy). Delays in referral may delay access to new drug treatment for spinal muscular atrophy.

Further reading

- The Royal Australian College of General Practitioners. Guidelines for preventive activities in general practice (http://racgp.org.au/yourpractice/guidelines/redbook) . 9th edn. Melbourne: RACGP, 2016. [Accessed 6 September 2022].
- Canadian Task Force on Preventive Health Care. Recommendations on screening for developmental delay. CMAJ May 17, 2016 188 (8) 579-587
- 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.
- Department of Health. Medicare Benefits Schedule (MBS) Online (http://mbsonline.gov.au) . Canberra: DoH, 2022. [Accessed 11 February 2022].
- The Royal Australian College of General Practitioners. Beware the rare (https://bewaretherare.com.au/) .

Resources for patients

- Raising Children Network, Developmental delay in babies (http://raisingchildren.net.au/articles/developmental_delay_video.html)
- Centre for Genetics Education. CMA testing in Children and Adults (https://www.genetics.edu.au/SitePages/Chromosome-microarray.aspx)
- Centre for Genetics Education. Genetic causes of intellectual disability/childhood syndromes (https://www.genetics.edu.au/SitePages/Intellectual-disability-childhood-syndromes-Genetic-causes.aspx)

Diabetes

Diabetes

PRACTICE POINT

Types 1 and 2 diabetes are multifactorial.

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.
Polygenic risk scores for type 1 and type 2 diabetes exist but their clinical utility remains uncertain.

What do I need to know?

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

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.

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

- 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 (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/family-history) of diabetes

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

When should I refer?

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

Further reading

- Carroll RW, Murphy Monogenic diabetes: A diagnostic algorithm for clinicians. Genes (Basel) 2013;4(4):522–35.
- Bishay RH, Greenfield 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.
- Monogenic Diabetes: Genetics and Relevance on Diabetes Mellitus Personalized Medicine. Curr Diabetes Rev. 2020;16(8):807-819
- Systematic Review of Polygenic Risk Scores for Type 1 and Type 2 Diabetes. Int J Mol Sci 2020 Mar 2;21(5):1703.

Resource for general practitioners

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

Resource for patients

- Centre for Genetics Education, Diabetes types 1 and 2 (https://www.genetics.edu.au/SitePages/Diabetes-type-1-and-2.aspx)

Familial breast and ovarian cancer

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** (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/family-history) must be taken and regularly updated.

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.

What do I need to know?

Highly **penetrant and penetrance** **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. **Pathogenic variants** in *BRCA1* and *BRCA2* are associated with increased risk of other cancers including prostate cancer and pancreatic cancer.

The lifetime risk of breast cancer in Australian women is approximately one in eight. 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.

Several other genes (low-to-moderate penetrant variants) predisposing to breast and/or ovarian cancer can now also be tested. Features within a family that are suggestive of increased risk of having a pathogenic *BRCA1* or *BRCA2* variant include:

- 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.

Use existing risk criteria (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 having a pathogenic *BRCA1* or *BRCA2* variant (high risk), or women who may require additional screening or chemoprevention (moderately increased risk).

Genetic testing

Family cancer clinics can assess individual risk to determine the utility of genetic testing for BRCA1 and BRCA2 variants. As new genes in which variants predisposing to breast cancer are identified, testing of these genes 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.

A range of options are available to carriers of *BRCA1* and *BRCA2* variants to manage their increased cancer risks.

A rebate is available for *BRCA1 and BRCA2* gene testing (http://www9.health.gov.au/mbs/fullDisplay.cfm?type=item&q=73296&qt=item&criteria=BRCA1%20and%20BRCA2%20) under the Medicare Benefits Schedule (MBS).

Validated polygenic risk scores (PRS) for breast cancer are commercially available. In combination with other known risk factors (e.g. family history, lifestyle and hormonal risks) PRS may be used to provide individualised information about breast cancer risk. Their precise role in risk-based breast cancer prevention and screening in Australia is yet to be determined.

When should I refer?

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

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 as such screening has not been shown to improve prognosis.

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).

Further reading

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- The Royal Australian College of General Practitioners Guidelines for preventive activities in general practice (http://www.racgp.org.au/your-practice/guidelines/redbook) . 9th edn. Melbourne, RACGP, 2016. [Accessed 6 September 2022].
- National Cancer Institute (US). *BRCA1* and *BRCA2*: Cancer risk and genetic (http://www.cancer.gov/about-cancer/causes-prevention/genetics/brca-fact-sheet) Bethesda, MD: National Institutes of Health, 2015. [Accessed 6 September 2022].
- Cancer Australia. Advice about familial aspects of breast cancer and epithelial ovarian cancer: A guide for health (https://canceraustralia.gov.au/sites/default/files/publications/ advice-about-familial-aspects-breast-cancer-and-epithelial-ovarian-cancer/pdf/2015_bog_familial_aspects_int.pdf) Sydney: Cancer Australia, 2010. [Accessed 6 September 2022].
- Kuchenbaecker KB, Hopper JL, Barnes DR, et Risks of breast, ovarian, and contralateral breast cancer for *BRCA1*
- and *BRCA2* mutation carriers. JAMA 2017;317(23):2402–16.
- Cancer Australia. Recommendations for the management of early breast cancer in women with an identified BRCA1 or BRCA2 gene mutation or at high risk of a gene mutation (https://www.canceraustralia.gov.au/publications-and-resources/cancer-australia-publications/recommendations-management-early-breast-cancer-women-identified-brca1-or-brca2-gene-mutation-or-high) .
- Winship I, Southey Gene panel testing for hereditary breast cancer. Med J Aust 2016;204(5):188–90.
- Department of Medicare Benefits Schedule. Canberra: DoH, 20227 (http://www.mbsonline.gov.au/internet/ mbsonline/publishing.nsf/Content/Home) . [Accessed 14 February 2022].

Resource for general practitioners

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

Resources for patients

Information

- Better Health Channel, Breast cancer (http://betterhealth.vic.gov.au/health/conditionsandtreatments/breast-cancer)
- Better Health Channel, Genetic testing for inherited cancer (http://betterhealth.vic.gov.au/health/conditionsandtreatments/)
- Centre for Genetics Education, Breast and ovarian cancer and inherited predisposition (https://www.genetics.edu.au/SitePages/Breast-cancer-and-inherited-susceptibility.aspx)
- Cancer Institute NSW, eviQ, BRCA1 gene consumer information (https://www.eviq.org.au/cancer-genetics/consumer-information/3426-facts-for-people-and-families-with-a-faulty-b) and BRCA2 gene consumer information (https://www.eviq.org.au/cancer-genetics/consumer-information/3427-facts-for-people-and-families-with-a-faulty-b)

Support

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

Familial colorectal cancer

Familial colorectal cancer

PRACTICE POINT

A comprehensive **family history** (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/family-history) must be taken and regularly updated to identify patients who may be at risk of familial colorectal cancer (CRC).

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]).

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* These genes encode mismatch repair proteins. Lynch syndrome accounts for up to 6% of all colorectal cancer.
- Familial adenomatous polyposis (FAP), associated with multiple adenomas in the large bowel, is caused by dominantly inherited pathogenic variants in the *APC* FAP accounts for approximately 1% of colorectal cancer cases.
- There are other rare inherited CRC syndromes that may be associated with specific polyp pathologies, phenotypic features or other cancer types in a family

Features within a family that are suggestive of increased risk of having a pathogenic variant for Lynch syndrome or FAP include:

- multiple affected relatives on the same side of the family
- multiple CRCs in the same person (be they synchronous (occurring at the same time) or metachronous (occurring at different times))
- CRC diagnosed <50 years of age
- immunohistochemistry in a CRC showing absent staining for one or more mismatch repair proteins

- other Lynch–syndrome related cancers (as above)
- >20 adenomas in the large bowel
- adenomas diagnosed <30 years of age

A three-generation family history (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/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.

Use existing risk criteria (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.

Genetic testing

Family cancer clinics will assess individual risk to determine the utility of genetic testing for Lynch syndrome or FAP. As new genes in which pathogenic variants predispose to CRC are identified, testing of these new genes may be offered as part of a panel of genetic tests through family cancer clinics.

Validated polygenic risk scores for CRC are commercially available. In combination with other known risk factors (e.g. family history and lifestyle risks) PRS may be used to provide individualised information about CRC risk. Their precise role in risk-based CRC prevention and screening in Australia is yet to be determined

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 (http://www.racgp.org.au/your-practice/guidelines/redbook/9-early-detection-of-cancers/92-colorectal-cancer)* (Red Book) and The Cancer Council Australian Clinical Practice Guidelines for the Prevention (http://www.racgp.org.au/your-practice/guidelines/redbook/9-early-detection-of-cancers/92-colorectal-cancer)%20and%20The%20Cancer%20Council%20Australian%20Clinical%20Practice%20Guidelines%20for%20the%20Prevention,%20Early%20Detection%20and%20Management%20of%20Colorectal%20Cancer.%20https:/wiki.cancer.org.au/australia/Guidelines:Colorectal_cancer.) , Early Detection and Management of Colorectal Cancer (http://www.racgp.org.au/your-practice/guidelines/redbook/9-early-detection-of-cancers/92-colorectal-cancer)%20and%20The%20Cancer%20Council%20Australian%20Clinical%20Practice%20Guidelines%20for%20the%20Prevention,%20Early%20Detection%20and%20Management%20of%20Colorectal%20Cancer.%20https:/wiki.cancer.org.au/australia/Guidelines:Colorectal_cancer.) .

Other considerations

Individuals at increased risk for CRC should be encouraged to:

- discuss their family history (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/family-history) with

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

Further reading

- The Royal Australian College of General Guidelines for preventive activities in general practice (http://www.racgp.org.au/your-practice/guidelines/redbook) . 9th edn. East Melbourne, RACGP, 2016. [Accessed 6 September 2022].
- Cancer Council Australian Clinical Practice Guidelines for the Prevention, Early Detection and Management of Colorectal Cancer. https://wiki.cancer.org.au/australia/Guidelines:Colorectal_cancer
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- Rubenstein JH, Enns R, Heidelbaugh J, Barkun American Gastroenterological Association Institute guideline on the diagnosis and management of Lynch syndrome. Gastroenterology 2015;149(3):777–82.

Resources for general practitioners

- Cancer Council Australian Clinical Practice Guidelines for the Prevention, Early Detection and Management of Colorectal Cancer. https://wiki.cancer.org.au/australia/Guidelines:Colorectal_cancer
- Department of Health, National bowel cancer screening program (http://cancerscreening.gov.au/internet/screening/ publishing.nsf/Content/bowel-screening-1)
- Cancer Council Victoria, Optimal care pathways (http://cancervic.org.au/for-health-professionals/optimal-care-pathways)
- Cancer Institute NSW, eviQ (http://eviq.org.au) , General practitioner referral guidelines for cancer genetics assessment (https://www.eviq.org.au/cancer-genetics/referral-guidelines/1147-general-practitioner-referral-guidelines-for)

Resources for patients

Information

- Better Health Channel, Genetic testing for inherited cancer (http://betterhealth.vic.gov.au/health/conditionsandtreatments/ genetic-testing-for-inherited-cancer)
- Centre for Genetics Education, Bowel cancer and inherited susceptibility (https://www.genetics.edu.au/SitePages/Bowel-cancer-and-inherited-susceptibility.aspx)

Support

- Bowel Cancer Australia (http://bowelcanceraustralia.org)
- Cancer Council Australia (http://cancer.org.au)
- Cancer Australia (https://canceraustralia.gov.au)
- Lynch Syndrome Australia (http://lynchsyndrome.org.au)

Familial hypercholesterolaemia

Familial hypercholesterolaemia

PRACTICE POINT

General practitioners (GPs) are well placed to undertake opportunistic screening for familial hypercholesterolaemia (FH). Family screening is critical when a diagnosis of FH is made in an individual.

What do I need to know?

FH is a lipid disorder that leads to premature cardiovascular disease (CVD). FH most often 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.

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

FH assessment should be conducted when an individual presents with:

- clinical features such as tendon xanthomata
- untreated low-density lipoprotein cholesterol (LDL-C) >4.9 in adults mmol/L
- premature CVD or a family history (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/family-history) of such (CVD aged < 60 years).

Genetic testing

While FH can be diagnosed clinically, a confirmatory DNA test allows for **cascade screening** within the family of an affected patient. There is MBS funding for genetic testing (http://www9.health.gov.au/mbs/fullDisplay.cfm?type=item&q=73352&qt=item&criteria=familial%20hypercholesterolaemia) for FH. MBS item 73352 can only be ordered by specialist physician to make the diagnosis; GPs can order the test for cascade screening.

When should I refer?

Refer individuals with a DLCNC score of ≥3 (ie possible-to-definite FH) to a cardiologist or lipid clinic for confirmation of diagnosis, including possible genetic testing.

Other considerations

Those diagnosed with FH should be encouraged to:

- 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

Further reading

- The Royal Australian College of General Practitioners Guidelines for preventive activities in general practice (http://www.racgp.org.au/your-practice/guidelines/redbook) . 9th edn. Melbourne: RACGP, 2016. [Accessed 6 September 2022].
- Bell DA, Watts Progress in the care of familial hypercholesterolaemia: 2016. Med J Aust 2016;205(5):232–36.
- Watts GF, Sullivan DR, Poplawski N, et Familial hypercholesterolaemia: A model of care for Australasia. Atherosclerosis Supplements 2011;12(2):221–63.
- Cardiac Society of Australia and New Zealand. Diagnosis and Management of Familial Hypercholesterolaemia – Position Statement. 2016.
- Familial hypercholesterolaemia: indentation and management (http://www.nice.org.uk/guidance/cg71/chapter/Recommendations#case-finding-and-diagnosis) . Updated Oct 2019.

Resources for patients

Information

- Better Health Channel, Genetic factors and cholesterol, enetic-factors-and-cholesterol (http://betterhealth.vic.gov.au/health/conditionsandtreatments/)
- Centre for Genetics Education, Familial hypercholesterolaemia (https://www.genetics.edu.au/SitePages/Familial-hypercholesterolaemia.aspx)

Support

- FH Australasia Network (http://athero.org.au/fh)

Familial melanoma

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 is does not alter the patient's management in most cases.

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** in these genes.

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.

Genetic testing

Genetic testing for *CDKN2A* **gene variants** may be offered through specialist genetics or dermatology services in individuals with:

- Three or more relatives affected by melanoma on the same side of the family

Other features within the family:

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

Validated polygenic risk scores for melanoma are commercially available and may be used to provide individualised information about melanoma risk. Their precise role in risk-based melanoma prevention and screening in Australia is yet to be determined.

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.

Other considerations

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

Further reading

- J Newton-Bishop, T Bishop, M Harland. Melanoma genomics. Acta Derm Venereol. 2020. doi: 10.2340/00015555-3493
- Cancer Council Australia Clinical Practice Guidelines for the diagnosis and management of melanoma. Last updated Apr 2021. https://wiki.cancer.org.au/australia/Guidelines:Melanoma
- The Royal Australian College of General Practitioners Guidelines for preventive activities in general practice (http://www.racgp.org.au/your-practice/guidelines/redbook) . 9th edn. Melbourne: RACGP, 2016. [Accessed 6 September 2022].

Resource for general practitioners

- Cancer Institute NSW, eviQ, General practitioner referral guidelines for cancer genetics assessment (https://www.eviq.org.au/cancer-genetics/referral-guidelines/1147-general-practitioner-referral-guidelines-for)

Resources for patients

Information

- Centre for Genetics Education,Genetics and melanoma,
- Melanoma and inherited susceptibility (https://www.genetics.edu.au/SitePages/Melanoma-and-inherited-susceptibility.aspx)

Support

- Cancer Australia (http://gov.au)
- Cancer Council Australia (http://cancer.org.au)
- Melanoma Institute Australia (http://melanoma.org.au)

Familial prostate cancer

Familial prostate cancer

PRACTICE POINT

A comprehensive **family history** (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/family-history) must be taken and regularly updated to identify patients who may be at risk of familial prostate cancer.

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.

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.

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 having a pathogenic *BRCA1* or *BRCA2* variant 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:

- 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 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 having a pathogenic *BRCA1* or *BRCA2* variant. 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. *BRCA1* and *BRCA2* testing is also being used in men with prostate cancer to inform selection of treatment. As new genes in which variants predispose to prostate cancer are identified, testing of these new genes may be offered as part of a panel of genetic tests through the family cancer clinic.

There are validated polygenic risk scores for prostate cancer, including those that predict risk of aggressive disease. Their precise role in risk-based prostate cancer prevention and screening in Australia is yet to be determined.

When should I refer?

Refer men to a family cancer clinic if they have:

- 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:

Number of relatives with prostate cancer	Relative risk	Testing recommendations*
Father or one brother	2.5-3	PSA testing every two years for those aged 45–69 years

Number of relatives with prostate cancer	Relative risk	Testing recommendations*
Father and 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. If PSA result is greater than 95th percentile for age, offer further investigation and referral to urologist

Further reading

- The Royal Australian College of General Practitioners Guidelines for preventive activities in general practice (http://www.racgp.org.au/your-practice/guidelines/redbook) . 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 6 September 2022].
- Prostate Cancer Foundation of Australia and Cancer Council Australia PSA Testing Guidelines Expert Advisory 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 [Accessed 6 September 2022].
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- Rohith Arcot, MDa,*, Todd M. Morgan, MDb, Thomas J. Polascik. Genetically Informed Prostate Cancer Screening. Urol Clin N Am 48 (2021) 373–386 https://doi.org/10.1016/j.ucl.2021.04.001
- National Cancer Institute (US). Genetics of prostate cancer (PDQ) (http://www.cancer.gov/types/prostate/hp/prostate-genetics-pdq) – Health professional Bethesda, MD: National Institutes of Health, 2017. [Accessed 1 March 2022].
- National Cancer Institute (US). BRCA1 and BRCA2: Cancer risk and genetic Bethesda (http://www.cancer.gov/about-cancer/causes-prevention/genetics/brca-fact-sheet) , MD: National Institutes of Health, 2017. [Accessed 1 March 2022].

Resource for general practitioners

- Cancer Institute NSW, eviQ (http://eviq.org.au) , General practitioner referral guidelines for cancer genetics assessment (https://www.eviq.org.au/cancer-genetics/referral-guidelines/1147-general-practitioner-referral-guidelines-for)

Resources for patients

Information

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

Support

- Cancer Council Australia (http://cancer.org.au)
- Cancer Australia (https://canceraustralia.gov.au)
- Prostate Cancer Foundation of Australia (http://prostate.org.au)

Fragile X syndrome and associated conditions

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** (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/disease-specific-topics/autism-spectrum-disorder) (ASD).
- Individuals seen for reproductive counselling who have a **family history** (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/family-history) of FXS (or related conditions, such as fragile X-associated primary ovarian insufficiency [FXPOI]) or undiagnosed ID.
- Women with evidence of primary ovarian insufficiency (associated with elevated follicle-stimulating hormone [FSH]).
- Adults with tremor or cerebellar ataxia of unknown origin to diagnose fragile X-associated tremor/ataxia syndrome (FAXTAS). Mean onset of FAXTAS is ~60 years of age but can present before age 50.

What do I need to know?

FXS

FXS is the most common 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.

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.

FXS follows an X-linked dominant inheritance pattern and is caused by an increase in length of a CGG trinucleotide repeat in the *FMR1* gene on the X chromosome. The length of the *FMR1* CGG repeat is divided into four categories (Figure 1). The longer the repeat, the more likely the individual will have symptoms of FXS.

Figure 1. Lengh of gene associated with FXS

Females who are premutation carriers (55 – 199 CGG repeats) can have a child affected with FXS. This is because the repeat length can get longer when passed from mother to child: this lengthening only occurs in women. Therefore, it is very unlikely males who are premutation carrier of FXS would have a child with FXS.

Associated conditions

Females who are premutation **carriers** are at increased risk of FXPOI. Both males and females with a premutation are at increased risk of fragile X-associated tremor/ataxia syndrome (FXTAS) later in life with the risk being higher for males than females.

Genetic testing

Chromosome microarray (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/genetic-tests-and-technologies/chromosome-microarray) (CMA) is now considered a first-line genetic test for the investigation of DD or congenital abnormalities. However, CMA does not detect **gene variants** causing FXS, so an additional DNA test for FXS must be also ordered.

DNA testing for FXS is available with an MBS rebate when the patient:

- exhibits ID, ataxia, neurodegeneration, or primary ovarian insufficiency consistent with an *FMR1* mutation
- has a relative with an *FMR1* mutation

GPs should offer information on carrier screening for FXS to all couples planning a pregnancy (or who are already pregnant), regardless of family history or ethnicity. Refer to Reproductive carrier screening (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/genetic-tests-and-technologies/reproductive-carrier-screening) for more information.

When should I refer?

For symptomatic patients:

- A child with a test positive result should be referred to a paediatrician and clinical genetics team for further assessment
- An adult with ataxic symptoms and a test positive result (ie premutation carrier) should be referred to a neurologist and clinical genetics team.
- A woman with FXPOI should be referred to an obstetrician and gynaecologist and clinical genetics team.

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.

Further reading

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- Finucane B, Abrams L, Cronister A, et Genetic counseling and testing for *FMR1* gene mutations: Practice guidelines of the National Society of Genetic Counselors. J Genet Couns 2012;21(6):752–60.
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- Department of Medicare Benefits Schedule (MBS) Online (http://www.mbsonline.gov.au) . Canberra: DoH, 2022. [Accessed 11 February 2022].

Resources for patients

Information

- Centre for Genetice Education. Fragile X syndrome (https://www.genetics.edu.au/SitePages/Fragile-X-syndrome.aspx) .
- 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)

Haemoglobinopathies

PRACTICE POINT

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

Carrier screening should be offered to all couples who are planning pregnancy or in the first trimester of pregnancy.

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 α-thalassaemia and β-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. Haemoglobinopathies are becoming more prevalent in Australia given immigration from endemic regions.

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.1 Screening for haemoglobinopathies is not part of [newborn screening (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/genetic-tests-and-technologies/newborn-screening)](https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/genetic-tests-and-technologies/newborn-screening) programs in Australia.

Carrier screening should be discussed as part of pre-pregnancy and prenatal care with all individuals: Those at particular risk are listed below but these should not be relied upon to identify carriers of a haemoglobinopathy:

- Those with [family history (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/family-history)](https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/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.

Genetic testing

Order a haemoglobinopathy screen to include:

- full blood examination (FBE) for MCV and MCH
- ferritin to exclude iron deficiency
- haemoglobin electrophoresis
- 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 α-thalassaemia cannot be excluded and the partner is a known carrier of two-gene deletion α-thalassaemia (Table 1).

Table 1. Interpretation of haemoglobinopathy carrier testing results

MCH (pg)/MCV (fL)	Ferritin	Haemoglobin electrophoresis	Interpretation
MCH <27 and/or MCV <80	Normal	HbA_2 increased	β-thalassaemia carrier
		HbA_2 normal HbH present	α-thalassaemia carrier

MCH (pg)/MCV (fL)	Ferritin	Haemoglobin electrophoresis	Interpretation
		HbA_2 normal HbH high	Possible HbH α-thalassaemia
		HbA_2 normal HbE present	HbE carrier or homozygote
		Normal	Possible α-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 ≥27 and/or MCV ≥80	Normal	Normal	Thalassaemia unlikely but one-gene deletion α-thalassaemia not excluded; DNA testing indicated only if partner is carrier of 2-gene deletion α-thalassaemia
	Normal	HbS present	Carrier for sickle cell disease
	Low	Normal	Reduced iron stores or iron deficiency, thalassaemia unlikely but one-gene deletion α-thalassaemia not excluded. Treat iron deficiency then retest

HbA2, normal variant of haemoglobin with two α-globin and two β-globin chains; HbE, abnormal variant of haemoglobin, due to abnormal β-globin; HbH, abnormal variant of haemoglobin, due to excess β-globin chains relative to β-globin chains, a type of α-thalassaemia; HbS, abnormal variant of haemoglobin, due to abnormal β-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 and/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 testing of 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) α-thalassaemia.

Other considerations

Do not assume low MCV or MCH is due to iron deficiency alone, especially in at-risk individuals. 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 α-thalassaemia is indicated.

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.

Further reading

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- The Royal Australian College of General Practitioners Guidelines for preventive activities in general practice (http://www.racgp.org.au/your-practice/guidelines/redbook) . 9th edn. Melbourne: RACGP, 2016. [Accessed 6 September 2022].
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Resource for general practitioners

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- Origa R, Moi P, Alpha-thalassemia (http://ncbi.nlm.nih.gov/books/NBK1435)
- Origa R, Beta-thalassemia (http://ncbi.nlm.nih.gov/books/NBK1426)

Resources for patients

- Centre for Genetics Education, Thalassaemia (https://www.genetics.edu.au/SitePages/Thalassaemia.aspx)
- Centre for Genetics Education,Sickle cell disease (https://www.genetics.edu.au/SitePages/Sickle-cell-disease.aspx)
- National Library of Medicine (US), Alpha thalassemia (https://medlineplus.gov/genetics/condition/alpha-thalassemia/)
- National Library of Medicine (US), Beta thalassemia (https://medlineplus.gov/genetics/condition/beta-thalassemia/)
- National Library of Medicine (US), Sickle cell disease (https://medlineplus.gov/genetics/condition/sickle-cell-disease/)

Hereditary haemochromatosis

PRACTICE POINT

Hereditary haemochromatosis (HHC) is a common condition that affects an estimated one in 200 individuals of northern European background. 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.

Screening for HHC in the general population is currently not recommended given its **variable expressivity** and **incomplete penetrance**.

What do I need to know?

HHC is a condition with **autosomal recessive inheritanc** in which excessive iron absorption leads to increased body 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 p.Cys282Tyr (previously known as C282Y) gene variant in the *HFE* gene (*HFE*- haemochromatosis). About one in 10 people are carriers of a p.Cys282Tyr variant, while one in every 200 people is homozygous for the p.Cys282Tyr variant. Another common variant in the *HFE* gene is p.His63Asp (previously known as H63D). Not all individuals with a genetic predisposition to HHC will develop iron overload (incomplete penetrance).

The risk of iron overload varies according to genotype (Table 1).

Table 1. Varying genotypes and risk of iron overload

Genotype	Risk of iron overload with genotype	Frequency of genotype*
Heterozygous p.Cys282Tyr (previously known as C282Y)	No increased risk	1 in 10
Homozygous p.Cys282Tyr (previously known as C282Y)	Greatly increased risk – 40–60% for females and 75–100% for males	1 in 200

Genotype	Risk of iron overload with genotype	Frequency of genotype*
Heterozygous p.His63Asp (previously known as H63D)	No increased risk	1 in 4
Homozygous p.His63Asp (previously known as H63D)	No increased risk	1 in 50
Compound heterozygous p.Cys282Tyr/ p.His63Asp (previously known as 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%).

Cascade screening is warranted for all first-degree relatives of patients with HHC who are p.Cys282Tyr homozygous or p.Cys282Tyr/ p.His63Asp compound heterozygous.

A Medicare Benefits Schedule (MBS) rebate for the HFE gene test (http://www9.health.gov.au/mbs/fullDisplay.cfm?type=item&q=73317&qt=item&criteria=HFE%20gene%20) applies where the patient has an elevated transferrin saturation or elevated serum ferritin on repeat testing or has a first-degree relative with haemochromatosis or is homozygous for the p.Cys282Tyr gene variant or is compound heterozygous for p.Cys282Tyr/ p.His63Asp.

Other considerations

Asymptomatic individuals (identified through cascade screening) who are p.Cys282Tyr homozygous or p.Cys282Tyr/ p.His63Asp compound heterozygous should have their serum ferritin regularly monitored.

Patients with *HFE*-haemochromatosis should be encouraged to:

- 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)
- be blood donors.

Further reading

- The Royal Australian College of General Practitioners Guidelines for preventive activities in general practice (http://www.racgp.org.au/your-practice/guidelines/redbook) . 9th edn. Melbourne: RACGP, 2016. [Accessed 6 September 2022].
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- Department of Medicare Benefits Schedule (MBS) Online (http://www.mbsonline.gov.au) . Canberra: DoH, 2017. [Accessed 6 September 2022].

Resource for general practitioners

- Haemochromatosis Australia (https://haemochromatosis.org.au/health-professionals/)

Resources for patients

Information

- Centre for Genetics Education, Hereditary haemochromatosis (https://www.genetics.edu.au/SitePages/Hereditary-haemochromatosis.aspx)

Support

- Haemochromatosis Australia (https://haemochromatosis.org.au/haemochromatosis/resources/) ,

Hereditary thrombophilia

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)
- pregnant women who have had a previous episode of VTE or who have a strong **family history** (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/family-history) of VTE (≥2 family members).

Routine genetic testing for hereditary thrombophilia in individuals without any of the above features is not recommended.

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.

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 genetic screening of women prior to prescribing a COC.

Box 1. Major hereditary thrombophilia conditions

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 or 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.

Genetic testing

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

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

- 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.

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 for group 2 genetic variants (see box) is uncertain.

Further reading

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- Haematology Society of Australia and New Zealand and Choosing Wisely Tests, treatments and procedures clinicians and consumers should question (http://www.choosingwisely.org.au/ recommendations/hsanz) . Sydney: NPS MedicineWise, 2016. [Accessed 6 September 2022].
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- Department of Medicare benefits schedule book: Category 6 (http://www.mbsonline. gov.au/internet/mbsonline/publishing.nsf/Content/ED28842309B2CD13CA2580F7008294BE/$File/201705-Cat6.pdf) . Canberra: DoH, 2017. [Accessed 6 September 2022].

Resources for patients

- Centre for Genetics Education, Blood clotting conditions (hereditary thrombophilias) (https://www.genetics.edu.au/SitePages/Blood-clotting-conditions.aspx)
- Varga E, The genetics of thrombophilia (http://stoptheclot.org/article143.htm)

Mental health conditions

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. There are some genetic conditions with increased rates of mental health conditions. An example is the 22q11.2 deletion syndrome where there is an approximately 25% chance of schizophrenia. Generally, there are other features present that indicate the mental health condition is part of genetic syndrome. In such instances referral to a clinical geneticist should be considered.

Some companies that offer **personal genomic testing** may include polygenic risk scores for common mental health conditions such as depression. The clinical utility of such tests remains uncertain.

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.

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 commercially available genetic tests can be used to tailor drug treatments to individuals with a mental health disorder such as depression (Pharmacogenomics (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/genetic-tests-and-technologies/pharmacogenomics)). While there is evidence from trials that such tests have clinical utility, there are currently no Australian clinical guidelines relating to the use of pharmacogenomic tests in clinical practice.

When should I refer?

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

Further reading

- Bousman CA, Arandjelovic K, Mancuso SG, Eyre H, Dunlop BW. (2019). Pharmacogenetic tests and depressive symptom remission: A meta-analysis of randomized controlled trials. Pharmacogenomics, 20(1): 37-47
- International Society of Psychiatric Genetic testing and psychiatric disorders: A statement from the International Society of Psychiatric Genetics (https://ispg.net/genetic-testing-statement) . Brentwood, TN: ISPG, 2017. Available at https://ispg.net/genetic-testing-statement (https://ispg.net/genetic-testing-statement) [Accessed 10 Mar 2022].
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Resources for patients

- Centre for Genetics Education, Mental illness – Schizophrenia and bipolar disorder (https://www.genetics.edu.au/SitePages/Mental-illness.aspx)
- National Library of Medicine (US), Bipolar disorder (https://medlineplus.gov/genetics/condition/bipolar-disorder/)
- National Library of Medicine (US), Schizophrenia (https://medlineplus.gov/genetics/condition/schizophrenia/)

MTHFR gene testing

MTHFR gene testing

PRACTICE POINT

There is no substantial evidence to support the use of methylenetetrahydrofolate reductase (*MTHFR)* gene testing in routine clinical practice. Knowledge of *MTHFR* gene status is unlikely to change patient management.

What do I need to know?

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

There are two variants in *MTHFR* associated with mildly increased levels of homocysteine in the blood (*p.Cys677Thr* and *p.Ala1298Cys*). These variants are common in the general population with around 65% of people having at least one of these.

MTHFR gene testing is promoted by some complementary and alternative practitioners to investigate infertility, recurrent pregnancy loss and risk of particular diseases. However:

- 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*.

Note that other variants in *MTHFR* can lead to marked increase in homocysteine (homocystinuria) and testing for this condition differs to that outlined above for the two mild variants.

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 because:
    - many people have one or both *MTHFR* gene variants (*Cys677Thr* and/or *p.Ala1298Cys*)
    - there is a lack of strong scientific evidence to show that having one or both of these common *MTHFR* gene variants causes particular health problems
    - there are no evidence-based treatments that will improve the health of a patient with one or both of the common *MTHFR* gene variants
- There is an association between the presence of *MTHFR* gene variants and mildly increased homocysteine levels; however
    - while mild elevation in 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
    - 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 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 (*Cys677Thr* and/or *p.Ala1298Cys*) is not associated with particular health problems
    - Individuals who have the *MTHFR* gene variant(s) might have mildly 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 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 at standard recommended doses 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 for these mild variants because the presence of *MTHFR* gene variants is unlikely to significantly affect a patient's health.

Further reading

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Resources for general practitioners

- The Royal Australian College of General Practitioners, Position statement on responding to patient requests for tests not considered clinically appropriate (http://acgp.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, rcpa.edu.au/ (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 (http://racgp.org.au/your-practice/guidelines/redbook/15-screening-tests-of- unproven-benefit)
- The Royal Australian College of General Practitioners, First do no harm: A guide to choosing wisely in general practice - GP information MTHFR gene testing (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/first-do-no-harm/gp-resources/mthfr-gene-testing)
- The Royal Australian College of General Practitioners, First do no harm: A guide to choosing wisely in general practice - patient information MTHFR gene testing (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/first-do-no-harm/patient-resources/mthfr-gene-testing)

Resource for general practitioners

- Centre for Genetics Education, MTHFR gene test for patients (https://www.genetics.edu.au/SitePages/MTHFR-gene-testing.aspx)
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Neurofibromatosis type 1

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** . Gene variants can be useful information for family members and family planning.

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.

Features are present from 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, a family history (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/family-history) of NF1 may not be present.

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 and/or axillary freckling
- multiple neurofibromas

Additional features can include:

- optic nerve glioma
- Lisch nodules (iris hamartomas)
- osseous lesions (eg sphenoid wing dysplasia, tibial pseudoarthrosis)
- increased risk of various cancers
- precocious puberty or delayed sexual development
- specific learning disabilities
- short stature
- macrocephaly

- scoliosis
- hypertension that can be due to renal artery stenosis or phaeochromocytoma but is most often idiopathic.

Genetic testing

Genetic testing can be helpful to make a diagnosis of NF1 where there are insufficient features present to make a clinical diagnosis. An example is a child with multiple café au lait spots and no other clinical features and no family history of NF1. It is also necessary for prenatal diagnosis and **pre-implantation genetic testing**.

When should I refer?

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

Further reading

- Douglas R.Stewart, Bruce R.Korf, Katherine L.Nathanson, David A .Stevenson, KalebYohay. Care of adults with neurofibromatosis type 1: a clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). Genetics in Medicine 20(7), July 2018, Pages 671-682.

Resource for general practitioners

- Neurofibromatosis checklist (https://www.mangen.co.uk/wp-content/uploads/2019/01/NF1_review_checklist_.pdf)

Resources for patients

- Centre for Genetics Education, Neurofibromatosis type 1 (https://www.genetics.edu.au/SitePages/Neurofibromatosis-1.aspx)
- National Library of Medicine (US), Neurofibromatosis type 1 (https://medlineplus.gov/genetics/condition/neurofibromatosis-type-1/)
- Children's Tumour Foundation: Neurofibromatosis Type 1 (https://www.ctf.org.au/page/110/nf1)

Neurological conditions

Neurological conditions

PRACTICE POINT

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

Positive **family history** (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/family-history) is important in diagnosing neurological conditions with a genetic cause (neurogenetic conditions). 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 disease and <65 years old for Alzheimer 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, muscular dystrophies, ataxias). There are also a large number of complex neurological conditions caused by an interplay of genetic and environmental factors.

Genetic studies continue to identify variants that contribute to complex neurological conditions; however, genetic testing is generally arranged by specialists for these conditions.

Genetic testing

Genetic testing (diagnostic testing and **predictive testing**) is available through specialist services for the following conditions:

- Creutzfeldt–Jakob disease and other prion diseases
- familial and/or early onset dystonia
- early onset (50 years) Parkinson disease
- familial epilepsy
- familial motor neurone disease

- Friedreich ataxia
- hereditary peripheral neuropathies (Charcot–Marie–Tooth disease)
- hereditary spastic paraparesis
- Huntington 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 family history of an inherited neurological or neuromuscular condition (diagnosed clinically or by genetic testing)
- 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

Further reading

- Genetic testing in dementia-A medical genetics perspective Int J Geriatr Psychiatry. 2021 Aug;36(8):1158-1170. doi: 10.1002/gps.5535.
- The Role of Genetic Testing for Parkinson's Disease. Curr Neurol Neurosci Rep. 2021 Mar 8;21(4):17. doi: 10.1007/s11910-021-01100-7. Lola Cook , Jeanine Schulze , Anna Naito , Roy N Alcalay
- Genetic Testing in Epilepsy. Semin Neurol. 2020 Dec;40(6):730-738. doi: 10.1055/s-0040-1719070. Epub 2020 Nov 11. David M Ritter, Katherine Holland.
- Human Genetics Society of Australasia Position Statement: Predictive and Presymptomatic Genetic Testing in Adults and Children. Twin Research and Human Genetics (2020), 23, 184–189 doi:10.1017/thg.2020.51

Resource for patients

- Centre for Genetics Education Parkinson Disease (https://www.genetics.edu.au/SitePages/Parkinson-disease.aspx)
- Centre for Genetics Education. Huntington Disease (https://www.genetics.edu.au/SitePages/Huntington-disease.aspx)

Sudden arrhythmic death syndrome

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. In many cases, the death of a young person in the family can often be the first sign of a genetic heart disease within that family. Identifying a genetic basis of sudden cardiac death is vital in being able to accurately manage families.

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'.

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 sudden arrhythmic death. All these conditions show considerable clinical variability within families and have **incomplete penetrance** .

Important clinical features are:

- 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 (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/family-history) (three generations), noting any relatives with the features above.

Genetic testing

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

When should I refer?

Refer those with relevant clinical or family history to cardiology for cardiac screening tests, and to a cardiac genetics clinic for risk assessment.

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.

Further reading

- Cardiac Society of Australia and New Cardiac genetic investigation of young sudden unexplained death and resuscitated out of hospital cardiac arrest (http://www.csanz.edu.au/wp-content/ uploads/2014/12/Young_SUD_and_Resuscitated_OHCA.pdf) . Sydney: CSANZ, 2011.[Accessed 14 March 2022].
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Resource for general practitioners

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

Resources for patients

Information

- AGHDR information sheets (http://heartregistry.org.au/patients-families/genetic-heart-diseases)

Support

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

Summary of genetic tests

Tests and indications

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
Fluorescence in situ hybridisation (FISH) – Using fluorescent tags specific to a chromosomal region, 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 (and therefore not reported by the laboratory), some are pathogenic and others are of uncertain significance	Unexplained intellectual disability or developmental delay; dysmorphic facial features; 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)

Genetic Test	Indications
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 (~3 billion nucleotides) Exome sequencing: A more cost-effective approach to capture and analyse all known disease-causing genes (eg rare childhood syndromes) (~30 million nucleotides) Panel sequencing: A more targeted approach focusing on 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)
Polygenic risk score	A polygenic risk score uses information about disease risk associated with multiple common variants, or SNPs, to estimate the risk for an individual of developing that disease. Indications. Personal genomic testing. Potential applications in cancer screening and chronic disease prevention. Currently polygenic risk scores may only be useful for people of European ancestry as there are not enough data available yet to reliably apply them to non-European populations.
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	Disorder caused by large deletions or duplications of specific genes (eg Duchenne muscular dystrophy)
DNA methylation studies of specific chromosome region	Disorders caused by abnormal gene methylation which affects gene expression (eg Prader Willi syndrome, Beckwith–Wiedemann syndrome)

Genetic Test	Indications
Maternal serum screening Combined first trimester screening – Biochemical screening of maternal blood combined with ultrasound Second trimester serum screening – Biochemical screening of maternal blood	First trimester: Screening at 11–13 weeks to estimate risk for trisomy 21, trisomy 18, trisomy 13 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 fetal aneuploidy 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 (http://www.racgp.org.au/afp/2017/april/advances-in-genomic-testing) ;46(4):200–05. Available at www.racgp.org.au/afp/2017/april/advances-in-genomic-testing [Accessed 27 July 2017].

Supplementary material

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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.

Acronyms

AD	Alzheimer's disease
AGHDR	Australian Genetic Heart Disease Registry
ASD	autism spectrum disorder
CA 125	cancer antigen 125
CAH	congenital adrenal hyperplasia
CBAVD	congenital bilateral absence of the vas deferens
CF	cystic fibrosis
cfDNA	cell-free fetal DNA
CFTS	combined first trimester screening
CMA	chromosomal microarray
CNV	copy number variant
COC	combined oral contraceptive
CPTID	carnitine palmitoyl transferase I deficiency
CPVT	catecholaminergic polymorphic ventricular tachycardia
CRC	colorectal cancer
CVD	cardiovascular disease
CVS	chorionic villus sampling
CYP	cytochrome P450 enzyme
DD	developmental delay
DLCNC	Dutch Lipid Clinic Network Criteria
DNA	deoxyribonucleic acid

DTC	direct-to-consumer
FAP	familial adenomatous polyposis
FBE	full blood examination
FH	familial hypercholesterolaemia
FISH	fluorescence in situ hybridisation
FOBT	faecal occult blood test
FRA-BOC	familial risk assessment – breast and ovarian cancer
FSH	follicle-stimulating hormone
FXPOI	Fragile X-associated primary ovarian insufficiency
FXS	Fragile X syndrome
FXTAS	Fragile X-associated tremor/ataxia syndrome
GP	general practitioner
HbE	haemoglobin E
HHC	hereditary haemochromatosis
HNPCC	hereditary non-polyposis colorectal cancer
ID	intellectual disability
IVF	in-vitro fertilisation
LCHADD	3-hydroxy long chain acyl-CoA dehydrogenase deficiency
LDL-C	low-density lipoprotein cholesterol
MADD	multiple acyl-CoA dehydrogenase deficiency
MBS	Medicare Benefits Schedule
MCADD	medium chain acyl-CoA dehydrogenase deficiency
MCH	mean corpuscular haemoglobin

MCV	mean corpuscular volume
MLPA	multiplex ligation-dependent probe amplification
MODY	maturity onset diabetes of the young
MTHFR	methylenetetrahydrofolate reductase
NF1	neurofibromatosis type 1
NGS	next generation sequencing
NHMRC	National Health and Medical Research Council
NIPS	non-invasive prenatal screening
NIPT	non-invasive prenatal testing
PAPP-A	pregnancy-associated plasma protein A
PCR	polymerase chain reaction
PGD	pre-implantation genetic diagnosis
PGT	personal genomic testing
PKU	phenylketonuria
PRS	polygenic risk score
PPV	positive predictive value
PSA	prostate-specific antigen
QF-PCR	quantitative fluorescence polymerase chain reaction
RACGP	The Royal Australian College of General Practitioners
SADS	sudden arrhythmic death syndrome
SCADD	short chain acyl-CoA dehydrogenase deficiency
SCHADD	short chain hydroxy acyl-CoA dehydrogenase deficiency
SCID	severe combined immune deficiency

SMA	spinal muscular atrophy
SNP/SNV	single nucleotide polymorphism/variant
ß-hCG	human chorionic gonadotrophin
SSRI	selective serotonin reuptake inhibitor
TFP	trifunctional protein deficiency
VLCADD	very long chain acyl-CoA dehydrogenase deficiency
VOUS/VUS	variant(s) of uncertain significance
VTE	venous thromboembolism

Glossary

Glossary

Allele

An allele is one of two or more versions of a gene or DNA sequence at a particular place on a chromosome. A person inherits two alleles, one from each parent.

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 repeat disorders, such as Huntington disease, myotonic dystrophy and fragile X syndrome (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/disease-specific-topics/fragile-x-syndrome-and-associated-conditions) . In these cases, the number of trinucleotide repeats increase when it is passed from parent to child, which can result in earlier onset and more severe disease.

For more information, refer to the MedlinePlus' explanation 'What do geneticists mean by anticipation? (https://medlineplus.gov/genetics/understanding/inheritance/anticipation/) ' and 'What are the different ways in which a genetic condition can be inherite (https://medlineplus.gov/genetics/understanding/inheritance/inheritancepatterns/) d?' .

Autosomal dominant inheritance

When a condition follows an autosomal dominant pattern of inheritance, the family tree will usually reveal multiple affected members in multiple generations on the same side of the family. Dominant conditions or traits are expressed when only a single **gene variant** is inherited.

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 pathogenic variants in the same **gene** (one from each parent). Parents of a child with an autosomal recessive condition

are usually asymptomatic **carriers** . The affected child has 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. Autosomal recessive conditions are more common when the parents are consanguineous.

Balanced translocation

A balanced translocation is a rearrangement of the chromosome with no apparent loss or gain of chromosomal material. Individuals with balanced translocations do not usually show any symptoms.

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 due to a pathogenic variant in a gene on the X chromosome (**X-linked 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 has a pathogenic variant in an X chromosome gene, he will not pass it to his sons, but will pass it to all of his daughters.

Carrier screening

Carrier screening is a test to determine whether an individual carries a genetic variant 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 from specific groups such as those from a common ethnic background (eg: screening for Tay-Sachs disease carrier status in the Ashkenazi Jewish community) or entire populations.

Cascade screening

Cascade screening involves testing the close biological relatives of an individual who has or is a carrier of a genetic condition in order to determine whether these relatives carry the genetic variant or chromosomal alternation (thereby increasing their chances of developing the condition or having a child with the condition). For example, cascade testing is available under the Medicare Benefits Schedule for genetic testing for familial hypercholesterolaemia (http://www9.health.gov.au/mbs/fullDisplay.cfm?type=item&q=73353&qt=ItemID) .

Compound heterozygote, compound heterozygous and compound heterozygosity

A compound heterozygote is an individual with two different alleles at a particular location in a pair of chromosomes. For example, in hereditary haemochromatosis, compound heterozygotes have both a p.Cys282Tyr (previously known as C282Y) and a p.His63Asp (previously known as H63D) variant, and are less likely to develop iron overload than p.Cys282Tyr homozygotes. However, the impact will be assessed on a case-by-case situation as it depends on the variant (allele) and its pathogenicity.

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 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 the same autosomal recessive condition. When individuals are first cousins and there is no family history (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/family-history) of a specific condition, or of other consanguineous relationships in previous generations, the risk of them having a child with a medical condition is approximately 5–6%, compared with 3–4% in the general population. This risk is higher in couples 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 usually arises in the ova or sperm from which the individual is conceived (ie is 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 DNA sequence changes (ie additions, duplications, deletions, substitutions). These variants can have a range of effects: some may cause disease (**pathogenic variants**), while others do not cause disease but may modify an individual's risk of disease (i.e may increase risk or provide a protective effect). The vast majority of gene variants are benign and do not result in disease but rather contribute to the differences between people.

Genome

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

Genotyping, genomic profiling and polygenic risk scores

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 by calculating polygenic risk scores, tailor treatment based on pharmacogenomic variants, or provide non– health related information (eg paternity, ancestry).Currently polygenic risk score may only be useful for people of European ancestry as there are not yet enough data available to reliably apply them to non-European populations.

Heterozygote, heterozygous and heterozygosity

Heterozygosity refers to the presence of a different allele (form of a **gene variant**) at a given location on a pair of chromosomes (eg a **carrier** for a pathogenic gene variant is heterozygous for that 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 or multiple genetic variants), 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 (e.g. when calculating polygenic risk scores). 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.

Penetrant and penetrance

Penetrance refers to the proportion of people with a particular genetic variant who will go on to develop the condition. 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 penetrance of some conditions. For more information, refer to MedlinePlus' 'What are reduced penetrance and variable expressivity? (https://medlineplus.gov/genetics/understanding/inheritance/penetranceexpressivity/) '.

Pharmacogenomic tests

Pharmacogenomic tests look for common variants that affect the way an individual responds to medications. They can be used to guide selection and dosage of several commonly used medications.

Pre-symptomatic testing and predictive testing

Pre-symptomatic testing aims to determine whether a person will almost certainly develop a particular genetic condition at some point in the future when symptoms of the condition have not yet manifested (eg Huntington disease). Predictive testing aims to determine whether a person who has no signs or symptoms of a specific condition at the time of testing has a specific pathogenic variant that increases 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 (eg BRCA 1 and 2 testing). Predictive genetic testing in familial cancer syndromes can only be conducted when the family-specific genetic variant is known. Hence, genetic testing must generally first be done on a family member affected with the specific condition.

Pre-implantation genetic testing

Pre-implantation genetic testing is testing performed on embryos produced by IVF. Prenatal testing of successful pregnancies may be undertaken as pre-implantation genetic testing is less than 100% accurate.

Single nucleotide polymorphism/single nucleotide variant

A nucleotide is a single base pair unit of DNA. A single nucleotide polymorphism (SNP or 'snip') or single nucleotide variant (SNV) is a variation 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 or SNV. SNPs/SNVs are the most common type of genetic variation in the human genome and account for approximately 0.02% of the genome.

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 MedlinePlus' 'What are reduced penetrance and variable expressivity? (https://medlineplus.gov/genetics/understanding/inheritance/penetranceexpressivity/) '.

Variant(s) of uncertain significance (VOUS/VUS)

A variant in a gene where the association with a particular condition is uncertain.

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 a mutation in a gene on the X-chromosome will not usually show any signs of the condition as there are enough cells with the functioning copy of the gene to instruct the body to perform particular functions. Rarely, some female carriers may be symptomatic because of unequal or skewed inactivation of the X chromosomes that results in the X chromosome with the pathogenic variant being active in the majority of cells.

X-linked recessive inheritance

Since a male inherits only one X chromosome (from his mother), when he has a pathogenic variant in a gene on the X-chromosome, he will have that condition. Males are usually more often and more severely affected because of X-inactivation in females. 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 of a pathogenic variant in a gene on the X-chromosome have a one-in-two chance of passing on the variant to each child. 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 pathogenic variant from their father and are known as ‘obligate carriers’.