Genetic carrier screening

An update for GPs

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Reproductive genetic carrier screening is an essential part of preconception and early pregnancy counselling. As the first point of contact for couples planning pregnancy or during early pregnancy, GPs are well placed to discuss genetic screening and recommend tests based on a couple's risk factors, such as ethnicity, and personal preferences.

Genetic testing has rapidly expanded over the past decade, with a well-established genetic basis for more than 5000 conditions.[1] The option of genetic carrier screening is an important part of preconception counselling and should be routinely discussed with all couples and individuals planning and in the early stages of pregnancy.[2] However, many prospective parents are not offered reproductive genetic carrier screening. GPs are often the first point of contact for women planning pregnancy, and as such, are perfectly placed to discuss genetic carrier screening. As advances in technology allow genetic testing to be more easily accessible, an understanding of genetic carrier screening is increasingly relevant to GPs. Resources to help GPs and patients improve their understanding of genetic testing are listed in Box 1.

What is carrier screening?

Genetic mutations may occur spontaneously or they may be inherited. Common modes of inheritance include autosomal dominant, autosomal recessive, X-linked, Y-linked, codominant and mitochondrial patterns.[3]

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1. RESOURCES ON GENETIC SCREENING

Healthcare professionals

- **Royal Australian College of General Practitioners (RACGP) 'Beware the rare' online education modules** (https://bewaretherare.com.au)
  - **fact sheet:** A quick guide to carrier screening for hereditary rare diseases (https://bewaretherare.com.au/wp-content/themes/bewaretherare/pdfs/A-quick-guide-to-carrier-screening-for-hereditary-diseases.pdf)
  - **guide for health professionals:** Genetic carrier screening: a guide to preconception and early pregnancy carrier screening for hereditary rare diseases (https://bewaretherare.com.au/wp-content/themes/bewaretherare/pdfs/Genetic-carrier-screening.pdf)
  - **online CPD activity:** Spinal muscular atrophy and other paediatric neuromuscular disorders
- **RACGP clinical guidelines:** Genomics in general practice (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics)
- **Australian Government Department of Health Standing Committee on Screening, population based screening framework** (https://www.health.gov.au/resources/publications/population-based-screening-framework)
- **Royal Australian and New Zealand College of Obstetricians and Gynaecologists statement on genetic carrier screening** (https://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)

Patients and families

- **Genetic and Rare Disease Network** (www.gardn.org.au)
- **Genetic Alliance Australia** (www.geneticalliance.org.au)
- **Centre for Genetics Education** (www.genetics.edu.au)

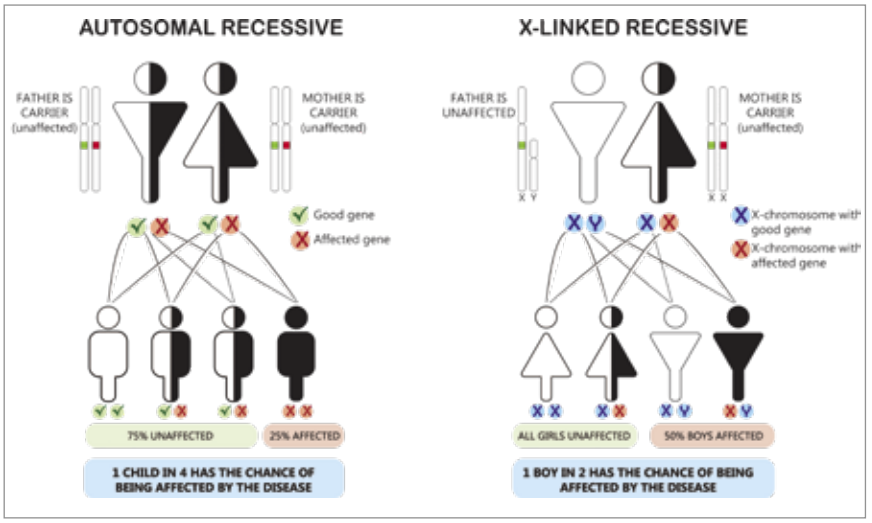


Figure. Inheritance pattern of autosomal recessive and X-linked conditions.

Reproductive genetic carrier screening assesses for autosomal recessive and X-linked mutations, which may go on to affect the health of a child. Examples of autosomal recessive diseases include cystic fibrosis, spinal muscular atrophy, Tay Sachs disease and sickle cell anaemia. If both partners are carriers for the same mutation, they have a one in four chance of having a child affected by the disease (Figure).

X-linked conditions are those linked to a mutation on the X chromosome. Men are disproportionately affected by X-linked conditions as they receive only one copy of the X chromosome. As women receive two copies of the X chromosome, they are more often carriers or may have mild symptoms only of an X-linked condition. If a woman is a carrier for an X-linked disease, she has a 50% chance of having a son affected by the disease (Figure).[4] Examples of X-linked conditions include fragile X syndrome, haemophilia A and B and Duchenne muscular dystrophy.

Why screen?

Although individually rare, the combined risk of autosomal recessive and X-linked conditions is comparatively common. One in 200 children is born with an autosomal recessive or X-linked condition. In comparison, one in 800 children is born with Down syndrome.[2] Inherited rare genetic conditions account for 10% of infant mortality and 20% of paediatric inpatient admissions.[5]

On average, every individual is a carrier for two recessive genes known to be associated with severe disease.[3] Around 1 to 2 % of non-consanguineous couples will share the same autosomal recessive mutation or carry an X-linked disease; such couples have a 25% chance of having an affected child.[5] This risk is significantly higher in consanguineous couples.

Most parents who have a child affected by a genetic condition have no prior family history of the disease.[5] Reproductive genetic carrier screening gives couples the opportunity to find out if they have an increased chance of having a child with a serious genetic condition and allows the opportunity to make informed reproductive choices.

When to screen

The best time to offer genetic carrier screening is before conception, to allow couples the greatest opportunity to make informed choices regarding reproductive options. Screening can also be offered in early pregnancy; however, reproductive choices are much more limited, and it is important to consider state and territory laws regarding pregnancy termination.

2. TYPES OF REPRODUCTIVE CARRIER SCREENING

Haemoglobinopathy screening
- RANZCOG recommends all pregnant women be offered basic screening for thalassaemia carrier status by a full blood examination (FBE) at initial presentation[4]
- Screening with specific assays for haemoglobinopathies (such as haemoglobin [Hb] electrophoresis and haemoglobinopathy DNA testing) should be considered in high-risk ethnic groups (e.g. Asian, African, Mediterranean)
- Medicare funding exists for FBE and Hb electrophoresis but not for DNA analysis

Ashkenazi Jewish population screening
- Genetic panels screen for more than eight recessive conditions more common in this population
- In NSW, philanthropically funded community and high school screening programs are available
- Screening is available through private laboratories (no Medicare rebate)
- Dor Yeshorim Institute subsidises testing for couples and is accessible worldwide

Single condition screening
- Usually offered if there is a family history of a specific inherited condition, or if the patient's ethnicity puts them at higher risk of certain conditions (e.g. Tay Sachs disease)
- Cost $100 to $200

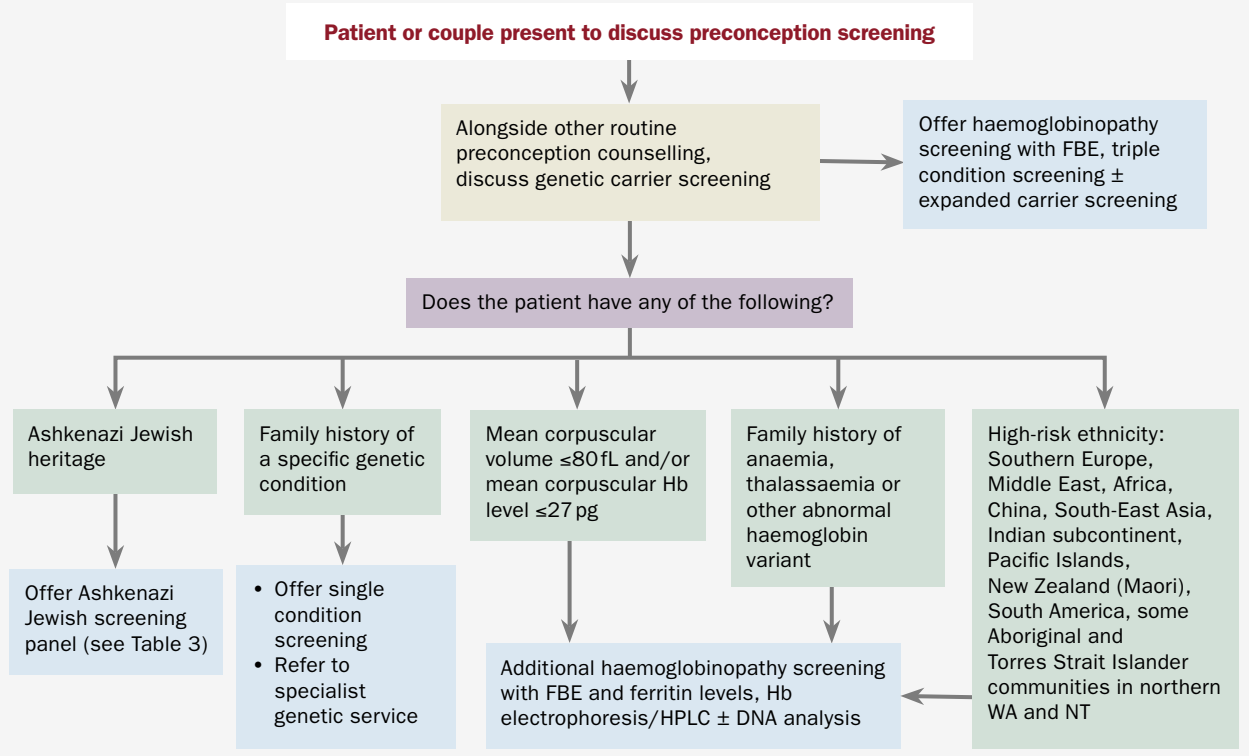
Triple condition screening
- Screens for cystic fibrosis, spinal muscular atrophy, fragile X syndrome
- Cost $350 to $400 per individual
- 2 to 3 week turnaround for results

Expanded carrier screening
- Screens for hundreds of conditions with variance in testing panels across different providers
- Cost $580 to more than $900 unless funded via Mackenzie's Mission (see Box 4)
- 4 to 6 week turn around for results

Types of screening

The Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) and The Royal

A GUIDE TO INCORPORATING GENETIC SCREENING AS A PART OF PRECONCEPTION COUNSELLING



Abbreviations: FBE = full blood examination; Hb = haemoglobin; HPLC = high-performance liquid chromatography; NT = Northern Territory; WA = Western Australia.

Australian College of General Practitioners (RACGP) guidelines state that all couples planning pregnancy should have a comprehensive family history recorded, and those with a relevant family history or who are known carriers for a genetic condition should be offered referral for specialised genetic counselling. RACGP guidelines recommend offering low-risk couples screening for the more common conditions (triple condition screening).[6] RANZCOG also recommends that all women be offered basic haemoglobinopathy screening and genetic carrier screening via triple or expanded testing, regardless of ethnicity or family history.[2]

Carrier screening is offered in Australia by many private companies by a simple blood test or buccal swab. The cost can vary depending on provider and testing panels. There is no Medicare rebate for genetic carrier screening, although haemoglobinopathy screening may be partially funded by state and territory governments. Reproductive carrier screens that should be considered for couples planning, or in the early stages of pregnancy are summarised in Box 2. An algorithm for incorporating genetic screening during preconception counselling is presented in the Flowchart.

Haemoglobinopathy screening

The RANZCOG recommends that all women should be offered basic haemoglobinopathy screening with full blood examination, with further testing for people of certain ethnicities (Table 1).[2,9] Haemoglobinopathy screening is performed inconsistently across Australia because of differences in state and territory guidelines and funding. Australia has long been an ethnically diverse population with a significant number of carriers of beta thalassaemia mutations, particularly in individuals of Mediterranean, Middle Eastern and African backgrounds.[7] Alpha thalassaemia mutations are common among people of South-East Asian descent. With increasing immigration from this region, testing for alpha thalassaemia should be considered as a part of standard thalassaemia testing.[8]

Although Medicare funding for thalassaemia testing with haemoglobin electrophoresis and high-performance liquid chromatography has been available since 1998, specific alpha thalassaemia DNA testing is not currently covered.[8] Funding for alpha thalassaemia screening varies across states and territories, with the Victorian government currently the only state to offer fully subsidised alpha thalassaemia testing.[9]

TABLE 1. SUMMARY OF HAEMOGLOBINOPATHIES

Disease	At-risk ethnicity	Symptoms
Alpha thalassaemia	• Most common in people of Chinese, South-East Asian descent • Also occurs in people of Southern European, Middle Eastern, Indian subcontinental, Pakistani, African, Pacific Islander and Maori (of New Zealand) descent • Identified in some Aboriginal and Torres Strait Islander communities in NT and WA	Causes Bart's hydrops fetalis – fatal in utero or soon after birth
Beta thalassaemia	People of Middle Eastern, Southern European, Indian subcontinental, Central and South-East Asian, African descent	Symptoms range from mild anaemia to severe anaemia requiring lifelong blood transfusions
Sickle cell anaemia	People of African, Middle-Eastern, Southern European, Indian, Pakistani, South American, Caribbean descent	Chronic anaemia, poor growth, bone and chest pain, organ damage, recurrent infections, peripheral oedema

TABLE 2. TRIPLE CONDITION GENETIC SCREENING

Condition	Carrier frequency	Clinical features
Cystic fibrosis	1 in 35	Respiratory disease, pancreatic insufficiency Life expectancy: childhood to middle aged
Spinal muscular atrophy	1 in 50	Progressive muscle weakness Life expectancy: childhood
Fragile X syndrome	1 in 330	Intellectual disability

Triple condition screening and expanded carrier screening

Triple condition screening is offered via many private companies for the three most common hereditary conditions – cystic fibrosis, spinal muscular atrophy and fragile X syndrome (Table 2). Additionally, expanded carrier testing is available through private laboratories, which allows testing for hundreds of genetic conditions (Box 3). Next generation sequencing is now widely available and can screen for a rapidly increasing number of conditions, at a fraction of its previous cost.[2]

3. PRIVATE GENETIC SCREENING OPTIONS

Australian Clinical Labs
- Gene access carrier screen (triple screening)
- Comprehensive carrier screening (expanded carrier screening)

Genomic Diagnostics
- Core genetic carrier screen
- Myriad Foresight expanded carrier screening

Sonic Genetics
- 3-gene carrier screen
- Beacon expanded carrier screen

Victorian Clinical Genetics Services
- Prepair genetic carrier screening
- Expanded carrier screening

Virtus Diagnostics
- Genetic carrier screen – 3-gene panel
- Expanded carrier screen

Eugene
- Expanded carrier screening

Genomics For Life
- Expanded carrier screening

Screening for ethnicity-specific conditions: monogenetic recessive conditions in the Ashkenazi Jewish community

Further ethnicity-specific screening is suggested for certain at-risk groups. For instance, in Australia, Jewish people with Ashkenazi (Eastern European) ancestry have an increased incidence of severe monogenetic recessive conditions, including cystic fibrosis, Tay Sachs disease and Bloom syndrome, for which screening is recommended (Table 3).[2,10,11] Around one in five Ashkenazi Jewish individuals screened will be carriers for one or more of these conditions. With wide uptake of screening in Jewish communities, the prevalence of Tay Sachs disease has reduced by 90%.[2,3,5]

If an Ashkenazi Jewish individual is diagnosed as a carrier for one or more conditions, their partner should be offered screening for the condition(s) in question, regardless of heritage. There is no Medicare rebate for Ashkenazi Jewish screening panels but some state genetic services may subsidise testing. In NSW, school screening is offered to Jewish students for free in select high schools, and community screening is available to Jewish adults who are planning pregnancy via the Community Genetics Program. Dor Yeshorim is an international Jewish genetic screening program that provides screening at reduced cost

and is accessible to Ashkenazi Jewish couples worldwide.

Mackenzie's Mission

In 2018, the Australian government announced $20 billion in funding for reproductive genetic carrier screening via Mackenzie's Mission, named after Mackenzie Casella, who passed away from spinal muscular atrophy at 7 months of age. Mackenzie's mission is aiming to recruit 10,000 couples across Australia for expanded carrier screening, with the goal of making genetic carrier screening freely available and easily accessible to all couples (Box 4). Couples enrolled in Mackenzie's Mission are offered expanded carrier screening with no out-of-pocket cost. If found to be at increased risk, couples will be offered free genetic counselling, as well as the option to access one funded cycle of IVF with preimplantation genetic testing.

TABLE 3. SUMMARY OF ASHKENAZI JEWISH SCREENING RECOMMENDATIONS

Condition	Carrier frequency	Clinical features	Life expectancy
Tay Sachs disease	1 in 25	Progressive neurodegeneration	6 months to 5 years
Cystic fibrosis	1 in 25	Respiratory disease, pancreatic insufficiency	Childhood to mid-life
Bloom syndrome	1 in 100	Intellectual disability, cancer susceptibility	Childhood to early adulthood
Fanconi anaemia	1 in 80	Cancer susceptibility, pancytopenia	Childhood to early adulthood
Familial dysautonomia	1 in 30	Progressive neurodegeneration, autonomic dysfunction	Childhood to early adulthood
Canavan disease	1 in 40	Neurodegeneration	Early childhood
Niemann-Pick disease (type A)	1 in 80	Neurodegeneration	Early childhood
Mucolipidosis type IV	1 in 100	Neurodegeneration	Early childhood

4. MACKENZIE'S MISSION RESEARCH STUDY

- Australian government-funded study providing expanded carrier screening for up to 10,000 couples
- No out-of-pocket cost for couples
- Screens for 1300 genes associated with more than 750 severe genetic conditions
- Couples can be recruited preconception or up to 9 weeks pregnancy
- Couple screening is performed via buccal swab
- Results typically received in 4 to 6 weeks
- Couples will receive a low risk or increased risk result
- Couples found to be at increased risk will be offered free genetic counselling via the study
- Healthcare professionals can apply to become study recruiters by contacting study organisers below*
  - **Email:** info@mackenziesmission.org.au
  - **Phone:** 1800 976 299

* Recruitment phase ending March 2022.

PRACTICE POINTS ON REPRODUCTIVE GENETIC SCREENING

- Reproductive genetic carrier screening assesses for autosomal recessive and X-linked mutations in couples planning pregnancy, which may go on to affect the health of a child.
- On average, each individual is a carrier for two recessive genes known to be associated with severe disease.
- Around 1 to 2% of non-consanguineous couples will share the same autosomal recessive or X-linked mutation.
- Most parents who have a child affected by a genetic condition have no prior family history of the disease.
- The Royal Australian and New Zealand College of Obstetricians and Gynaecologists recommends that all women be offered genetic carrier screening as part of preconception and early pregnancy counselling, regardless of family history or ethnicity.
- The Royal Australian College of General Practitioners suggests triple condition screening be offered to all low-risk women and couples, and that couples who are known carriers or have a relevant family history should be referred to specialist services.
- Various options for testing are available, depending on patient preference and ethnicity, which may indicate a greater risk of certain mutations.
- Funding options include state- and territory-specific funding, private funding and the recent federal government-funded scheme, Mackenzie's Mission.

Sequential *vs* couple screening

Sequential testing involves testing one partner first, with subsequent screening of the other partner only if an autosomal recessive mutation is identified. The woman is usually screened first given the relevance of her carrier status for X-linked conditions.[2] Sequential screening is the norm when testing for few conditions (e.g. triple condition screening) and when time is not a pressing factor (i.e. not late in first trimester of pregnancy).

Couple screening is more appropriate when many conditions are being screened for. Up to 75% of individuals will be a carrier for at least one of the many hundreds of conditions screened for in expanded carrier screening, so simultaneous screening of both partners is more efficient.[12] A couple is given a low-risk result if found not to have the same autosomal recessive mutation and no X-linked mutation is identified.

Follow up

Couples found to be at increased risk should be referred for genetic counselling to a clinical geneticist or genetic counsellor to ensure they fully understand the implications of their result and to discuss reproductive options. State-funded genetic counselling is available through the public health system, and most private testing companies offer genetic counselling as part of their testing service.

Reproductive options include:[2]

- proceeding with a natural pregnancy and accepting the child may be affected
- undergoing further screening with noninvasive prenatal testing or early pregnancy testing via chorionic villus sampling or amniocentesis and considering termination of an affected pregnancy
- undergoing IVF with pre-implantation genetic testing
- undergoing IVF with donor eggs or sperm or embryos
- choosing to adopt
- choosing not to have children.

Conclusion

Genetic carrier screening should routinely be offered to all women and couples planning and in the early stages of pregnancy to assess the risk of carrying shared autosomal recessive or X-linked mutations. Haemoglobinopathy screening and triple condition screening for cystic fibrosis, spinal muscular atrophy and fragile X syndrome should be discussed with all couples before conception and in early pregnancy, as well as the option of expanded screening. Couples with a known family history or known carrier status should be offered referral for genetic counselling. Genetic carrier screening gives couples the chance to make informed decisions regarding their reproductive options. The Practice Points summarise the importance of preconception and early pregnancy genetic screening. MT

References

A list of references is included in the online version of this article (www.medicinetoday.com.au).

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