Genetic carrier screening

A guide to preconception and early pregnancy carrier screening for hereditary rare diseases

What is carrier screening?

Carrier screening is a form of genetic testing that can detect if an individual or couple are carriers of an autosomal recessive and/or X-linked genetic condition, when there is no a priori increased risk based on either partner's personal or family history.[1,2] Involving a simple mouth swab or blood test, it allows a woman or couple to understand their risk of passing an inherited condition on to their children.

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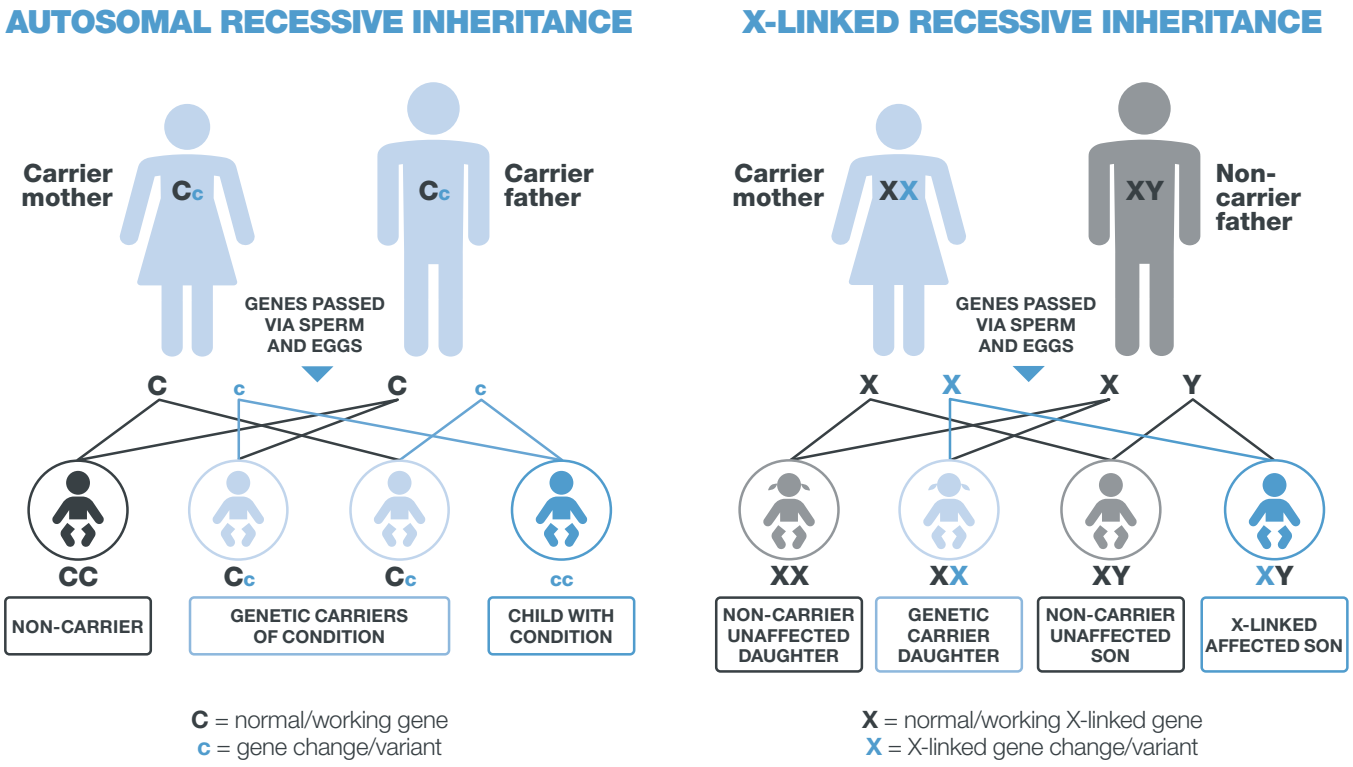
Autosomal recessive conditions

In autosomal recessive conditions, an individual must carry two copies of a faulty gene to be affected by the disorder.[1] An individual who has only one copy of the gene variant is generally asymptomatic but can pass the mutated gene on to their children. When both members of a couple are carriers ('carrier couple'), there is a one in four chance that a pregnancy will result in an affected child. Autosomal recessive conditions can be inherited by either sex equally, and often occur in the absence of any family history of disease.

X-linked recessive conditions

X-linked recessive conditions are caused by mutations in genes on the X chromosome. A woman who is a carrier of an X-linked recessive condition ('carrier woman') has a one in two chance of passing on the variant with each pregnancy.[1] Since males inherit only one X chromosome (from the mother) and females two (one from each parent), there is a higher prevalence of X-linked recessive conditions in males than in females. However, some females with a mutated gene on one of their X chromosomes will have symptoms of the condition – this can be related to the gene itself, or to skewed X inactivation. The latter occurs when there is an excess of cells in which the mutation is on the active X chromosome, rather than a relatively even split between both the active and inactive X chromosome.[3]



Inheritance patterns: A. autosomal recessive and **B.** X-linked recessive inheritance. For some X-linked conditions (such as fragile X syndrome), females who carry a mutation may display some features of the condition.

Source: Delatycki MB, Laing NG, Moore SJ, et al. Preconception and antenatal carrier screening for genetic conditions: The critical role of general practitioners. Aust J Gen Pract 2019;48(3):106–10. doi: 10.31128/AJGP-10-18-4725.[4]

The burden of inherited rare diseases

Despite being individually rare, inherited rare diseases are collectively common. Approximately 1–2% of non-consanguineous couples have a one in four chance of having a child with a severe autosomal recessive or X-linked recessive genetic condition with each pregnancy.[4] This means around one in 200 babies are born with an autosomal recessive or X-linked recessive condition, which represents approximately four times the frequency of pregnancies affected by Down syndrome (one in 800).[4,5] Rare diseases are often complex and can cause severe disability, impaired quality of life and premature death.[6] Around 20% of infant mortality and 10% of paediatric hospital admissions are associated with inherited disorders.[7]

Carrier screening can help decrease the burden

Studies have shown that preconception carrier screening has led to a decline in several severe recessive conditions, including Tay–Sachs disease (90% reduction in cases in Jewish communities where screening is routinely offered) and cystic fibrosis.[7] In 2019, the Australian Government made a commitment to develop genomics testing in the primary care setting to transform prevention, prediction, diagnosis and treatment of inherited conditions.[8]

Why offer carrier screening to patients?

Carrier screening enables women and couples who are planning a family, or in early pregnancy, to make informed reproductive choices in line with their personal wishes and values. Clinicians involved in family planning and antenatal care, such as general practitioners, fertility specialists, obstetricians and genetic health professionals, are ideally placed to have these conversations with patients.

Options available for carrier women and couples following preconception screening include:[9]

- proceeding to a pregnancy but accepting the possibility that they may give birth to an affected child – in which case, they may be better placed to optimise the child's health and wellbeing (through early diagnosis and intervention)
- undergoing fetal diagnostic testing (via amniocentesis or chorionic villus sampling) and terminating affected pregnancies or preparing for the possibility that they may give birth to an affected child
- undergoing in vitro fertilisation (IVF) with preimplantation genetic testing (PGT) to screen embryos before they are implanted in the uterus
- undergoing IVF with donor eggs, sperm or embryos
- choosing to adopt or not have children.

Options available for carrier women and couples identified during early pregnancy include:[9]

- undergoing fetal diagnostic testing (via amniocentesis or chorionic villus sampling) and terminating affected pregnancies or preparing for the possibility that they may give birth to an affected child
- proceeding without fetal diagnostic testing and preparing for the possibility that they may give birth to an affected child.

What are the different types of carrier screening available?

The following carrier screening strategies are all considered acceptable methods for preconception and early pregnancy screening. Clinicians should establish a standard approach to carrier screening based on the needs of the local population and ease of access to genetic counselling services.[9]

Single-condition screening

Available since the 1970s, single-condition 'targeted' screening is typically offered to women and couples with a known family history of a specific inherited disorder, or from particular ethnic backgrounds that are known to have a high prevalence of certain conditions.[1,4] This includes Tay–Sachs disease, as well as haemoglobinopathies (eg α- and ß-thalassaemia, sickle cell disease). Many women and couples who are planning, or in the early stage of, pregnancy opt to be screened for haemoglobinopathies.

Three-condition screening

Other than haemoglobinopathy screening, the three-condition panel is the most widely used carrier screen performed today in Australia. It screens for three of the most common inherited rare diseases, namely cystic fibrosis (CF), spinal muscular atrophy (SMA) and fragile X syndrome (FXS).[10]

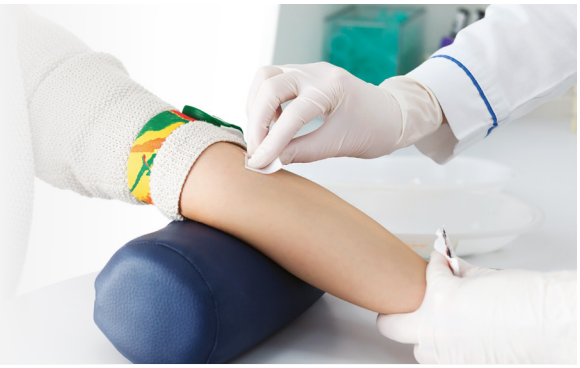
Expanded carrier screening

A new technique called massively parallel sequencing, or next-generation sequencing, can simultaneously detect numerous different mutations, such that we can now screen for over 1000 recessive and X-linked genes.[9,11,12] Expanded carrier screening is based on this technique, meaning that individuals and couples can now choose to be screened for hundreds of different inherited disorders.[4] Expanded carrier screening removes the need for ethnic-specific gene mutation panels and allows couples to explore their level of risk beyond the three-condition screen.[13] The specific disorders tested for varies between laboratories.

What does carrier screening cost?

Medicare provides rebates for some genetic tests.*
Patients can expect to pay fees in the range of:†

- single-condition screening: $100–$200
- three-condition screening: $350–$400
- expanded carrier screening: $580–$900.



Who should be offered carrier screening?

Traditionally, genetic testing was offered to adults with a family history of a recessive condition; partners and relatives of identified carriers; partners of people with the condition and/or people of a particular ethnicity.[2] However, this approach only identifies a minority of carriers, since the majority of affected children are born to parents with no previously known family history, and only a minority of relatives in high-risk families request carrier testing. Thus, it is now recommended that carrier screening be offered to all women planning a pregnancy or in the first trimester of pregnancy, regardless of family history or geographic origin.[9]

As with other types of genetic testing, carrier screening is associated with various ethical issues, including objections to pregnancy termination and/or embryo selection, and concerns about eugenics.[14] While every individual will have their own views on these topics, healthcare professionals have a duty to inform and counsel women and couples about the availability of carrier screening, as they already do for chromosomal screening (eg trisomy 21).[9]

*The cost of screening for haemoglobinopathies is generally covered by state/territory government funding. Relatives of affected individuals/carriers **may** be eligible to access funded testing via Medicare or state/territory government funding. Medicare rebates will be introduced in 2022–2023 to support access to carrier screening for cystic fibrosis, spinal muscular atrophy and fragile X syndrome.[15]

†Fee estimates are per person. Actual fees vary by provider.

It is now recommended that carrier screening be offered to **all women** planning a pregnancy or in the first trimester of pregnancy, regardless of family history or geographic origin.[9]

The Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) specifically recommends that clinicians:[9]

- offer information on carrier screening (both three-condition and expanded panel screening) to all women planning a pregnancy or in the first trimester of pregnancy
- offer basic screening for thalassaemia carrier status to all pregnant women (via full blood examination), with specific assays for haemoglobinopathies (such as serum electrophoresis and haemoglobinopathy DNA testing) considered if the patient is from a high probability ethnic or population group
- offer additional screening to individuals of Eastern European (Ashkenazi) Jewish descent, due to a higher incidence of conditions such as Tay–Sachs disease in this population
- offer a more detailed discussion about carrier screening with an informed clinician
- obtain informed consent for screening, this should include any out-of-pocket expenses that are required for the chosen test.

When should carrier screening be performed?

Preconception

Ideally, carrier screening should be offered to women or couples who are planning a family as early as possible to allow them time to consider a wider range of reproductive options.[4] As such, preconception carrier screening should be considered the 'gold standard' of care. When carrier status is determined before pregnancy, carriers should be referred for genetic counselling to review their options.[9] Carriers then have the option of taking steps to avoid having an affected child if they so choose.

Early pregnancy

If a woman or couple presents for the first time in pregnancy, they should be offered carrier screening if they are still within the first trimester. Those found to have a higher risk of having an affected child following screening should then be referred for genetic counselling to understand their options.[9]

Does carrier screening replace NIPT and combined first trimester testing?

Carrier screening **does not** replace non-invasive prenatal testing (NIPT) and combined first trimester screening (CFTS). These tests should still be offered to all pregnant women to screen for an increased risk of having a child with Down syndrome or other chromosomal disorder, as carrier screening **does not** detect chromosomal anomalies and NIPT and CFTS **do not** identify carrier status of single-gene disorders.[1,16]

Do both partners need to be screened?

Partners can be screened sequentially or simultaneously.

Sequential screening

This method involves testing one partner first – usually the woman, as carrier status is more relevant for X-linked conditions – and the male partner only if the female partner is found to be a carrier of an autosomal recessive condition.[4,9] Sequential screening is generally more cost-efficient when screening for one or few conditions given that many couples will find they do not need to test the second partner. This method may be preferred where time is not limited (preconception screening).

Couple screening

Couple screening involves testing both partners simultaneously to determine a combined 'low probability' or 'high probability' result.[4,9] A high probability is given when results identify both partners as carriers for the same autosomal recessive disorder or the woman is identified as a carrier for an X-linked disorder.[9] Couple screening is the preferred test in early pregnancy, when time is of the essence due to laws around timing of termination (which differ by state and territory).[4,17] It may also be preferred with expanded carrier screening due to the high chance of any individual being a carrier of one or more conditions.[9]

How can I best counsel patients about carrier screening?

Considerations for pre-test counselling

Healthcare professionals will need to explain the different carrier screening options now available and the disorders they test for. The woman or couple may benefit from the opportunity to return for a detailed discussion on the implications of screening, so they can make an autonomous, informed decision. Informed consent must be obtained and documented prior to issuing a referral for carrier screening.

The following list summarises the discussion points you should cover:[1,2,9,18–20]

- Highlight how the patient's personal or family history, including ethnic background, may place them at a higher risk of being a carrier for certain conditions. For those with no obvious risk, explain the rationale for carrier screening when no risk of genetic disorders exists.
- Reassure patients that there are a variety of reproductive options available to them if they are identified as carriers.
- Take care to inform patients on the implications and limitations of potential results, including the
  - ability for a test to accurately and reliably measure the genotype/s in question ('analytic validity')
  - ability for a test to predict carrier status ('clinical validity'), which may depend on the number of variants screened for each disorder
  - probability of having an affected child with each pregnancy if identified as a carrier
  - residual risk of having an affected child after a negative result.
- Inform patients of the cost implications of the different screening options, including out-of-pocket costs for tests, follow-up counselling or further investigations.
- Reinforce that screening is optional and will not be appropriate for all individuals/couples. It's important to note that carrier screening is associated with complex ethical issues, and not all women and couples will want to proceed.

Take a non-directive approach, allowing patient/s to consider the information provided in their own time before declining or accepting testing.

Considerations for post-test counselling

The implications of carrier screening are complex and often have significant emotional impact on individuals and couples identified as carriers. All couples found to be carriers for a genetic disorder should be educated on the risk associated with each pregnancy and offered specialist genetic counselling so that they can fully understand their reproductive options.

Key discussion points have been summarised below:[2,9,18,20]

- Ensure patients understand the significance of the test results.
- Remind patients with negative screening test results about clinical validity and residual risk (ie carrier screening does not test for all mutations/variants and the possibility of a false negative result).
- Encourage carrier individuals and couples to communicate results with their family to allow for cascade screening.

Refer all carrier women and couples to a genetic counsellor who can inform them of their reproductive options.

How might the carrier screening landscape change?

In 2018, the Australian Reproductive Genetic Carrier Screening Project ('Mackenzie's Mission') was allocated $20 million by the Australian Government to study the potential benefits and limitations of reproductive genetic carrier screening.[4] The research trial aimed to recruit 10,000 Australian couples and screen them for over 700 autosomal recessive and X-linked conditions.[21]

Couples were recruited by specific health practitioners. They could not self-refer or be referred by health practitioners not associated with the project. Couples were offered information and support to help them make informed choices regarding whether or not to have the test, as well as their reproductive options if they were identified as carriers. Researchers will evaluate the outcomes of screening, the psychosocial impacts reported by couples, the ethical issues raised by reproductive carrier screening, the health economic impacts of screening and health implementation issues.

It is anticipated that the research trial will finish at the end of 2022. The results of the trial will be used to help determine the value of a universal carrier screening program in Australia.

Further information for healthcare professionals

- Royal Australian College of General Practitioners, ***Genomics in general practice***
- Mackenzie's Mission, **Australian clinical labs offering carrier screening**
- Centre for Genetics Education, **Australian general genetics clinics**
- Australian Government Department of Health, **Genomics Health Futures Mission**
- Standing Committee on Screening, ***Population based screening framework***
- Australian Genomics Health Alliance, **Australian Reproductive Genetic Carrier Screening Project (Mackenzie's Mission)**

Key takeaway points

Autosomal recessive and X-linked genetic conditions are a major cause of death and serious long-term morbidity in children.

Carrier screening for those planning a family or in early pregnancy enables couples to make informed choices about their future offspring, according to their own personal wishes and values.

All healthcare professionals providing care to women and couples before and during early pregnancy now have a responsibility to provide advice on genetic carrier screening, as they already do for screening chromosomal disorders.

Some carrier screening tests are subsidised by Medicare.

Resources for healthcare professionals

Visit **bewaretherare.com.au** for useful clinical resources, including a video library and an RACGP-accredited CPD (Cat. 2) Activity suitable for general practitioners, practice nurses, obstetricians, fertility specialists, general paediatricians and maternal child health nurses.

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