Genetic carrier screening

This statement has been developed and reviewed by the Genomics Advisory Working Group & Women's Health Committee and approved by the RANZCOG Board and Council.

A list of Women's Health Committee Members & Genomics Advisory Working Group can be found in Appendix A.

Disclosure statements have been received from all members of this committee.

Disclaimer This information is intended to provide general advice to practitioners. This information should not be relied on as a substitute for proper assessment with respect to the particular circumstances of each case and the needs of any patient. This document reflects emerging clinical and scientific advances as of the date issued and is subject to change. The document has been prepared having regard to general circumstances.

First endorsed by RANZCOG: March 2019
Current: March 2019 (Interim update specific t o Australia - July 2024)
Review due: March 2022

Objectives: To provide health professionals with advice on the counselling of women and couples prior to and in the early stages of pregnancy in relation to genetic carrier screening.
[i]See: RANZCOG's Interim statement on gendered language (below)

Target audience: All health professionals providing care to women and couples prior to and in the early stages of pregnancy.

Values: The evidence was reviewed by the Women's Health Committee (RANZCOG), and applied to local factors relating to Australia and New Zealand.

Background: This statement was first developed by the Genomics Advisory Working Group & Women's Health Committee in March 201 9.

Funding: The development and review of this statement was funded by RANZCOG.

[i] RANZCOG currently uses the term 'woman' in its documents to include all individuals needing obstetric and gynaecological healthcare, regardless of their gender identity. The College is firmly committed to inclusion of all individuals needing O&G care, as well as all its members providing care, regardless of their gender identity.

The College would like to acknowledge the contribution of Prof Lisa Hui to the July 2024 interim update of C-

1. Plain language summary

There are many hundreds of inherited genetic conditions that can affect human health, and most are very rare. However, when all these inherited conditions are considered together, they affect up to 1 in 400 people. The majority of children born with such conditions are born into families with no other affected family members. This occurs because a healthy couple can pass on genetic changes to their child without knowing that they are carriers of that condition. The two major types of inheritance that can lead to a healthy couple having children with serious genetic conditions are called autosomal recessive and X-linked recessive.

In autosomal recessive inheritance, a person inherits a faulty gene from each parent. Genes are the inheritance particles. We have about 23,000 pairs of genes, one in each pair inherited from each parent. For an autosomal recessive condition, if a person has one faulty gene and one healthy gene, they will not have the condition. They are a so-called "carrier" of the condition. We are all carriers of on average two severe autosomal recessive conditions. It is only if both members of a couple are carriers of the same faulty gene that there is a 1 in 4 chance of having a child affected by that condition. The most common types of autosomal recessive conditions in our community are thalassaemia and cystic fibrosis.

X-linked inheritance is closely related to the sex of the individual, with males generally being more severely affected than females. Genes lie on chromosomes, which can be thought of as long strings with the genes as beads on the string. Males have an X and a Y chromosome

4. Using donor sperm, egg or embryo from unaffected individuals.
5. Adoption.
6. Not having children.

Carrier screening can be performed at any time, but it is preferable to screen before a couple conceives so that they have time to understand and consider their reproductive options, such as preimplantation genetic diagnosis. The most common conditions for which carrier screening is available are thalass d1y675-5325 0 TD 13 >>Ba

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3. Introduction

Population carrier screening is defined as the detection of carrier status of autosomal and X-linked recessive diseases in couples or people who do not have an a priori increased chance of being a carrier based on their or their partners' personal or family history [1]. It does not refer to testing an individual with a strong family history of a known or possible genetic condition – these people should be offered direct referral to a specialist clinical genetics service.

Carrier screening for genetic conditions has been available since the 1970s with screening for Tay Sachs disease by testing of hexosamindase A level9.96 -0l[[2 >>BDC 4 t lingie434 (l9.96ie434 (l9.96l8 (e)94 (a)10

^ = based on a meta -analysis of data [4]

Prenatal diagnosis has been available for inherited genetic conditions since 1977. The current rate of prenatal diagnosis for an increased chance of single gene condition is approximately 1 in 500 births [5]

4.3 What conditions should be offered?

The conditions for which genetic screening is offered should be a cause of major diminution of quality of life and/or reduction in lifespan.

Information on carrier screening for the most common inherited genetic conditions in our population, that is thalass aemia , cystic fibrosis, spinal muscular atrophy, and fragile X syndrome, should be offered to all women planon inTc -0.005 Tw [(,)45( )]TJ(n)0AS.4 (t)63 (li1)6.7 (y)-1.7 (u)10.4 (n)0.

4.4 How should screening be performed?

Screening is usually provided as either (i) sequential screening, or (ii) couple screening.

(i) Sequential screening (also called two step screening) refers to where one member of the couple is offered testing first (usually the woman). If she/he is a carrier of an autosomal recessive condition, the other member of the couple is then offered screening. It is generally the female member of the couple who is offered screening in the first instance since for X-linked conditions such as fragile X syndrome, it is the female member's carrier status that is important. The advantage of sequential screening is that it reduces overall costs of testing for most couples (as most couples only require one member to be tested). It also allows for cascade testing of relatives of carriers. Cascade testing refers to testing of relatives of a person who is affected by or is a carrier of a genetic condition and who therefore has a higher probability of being a carrier than an unrelated individual.

(ii) Couple screening

4.5 Informed consent

Recommendation 5	Grade
Women wanting more information about carrier screening should be given the opportunity to have a more detailed discussion about carrier screening with an informed clinician. Informed consent for screening should be obtained and this should include any out of pocket expenses that are required for this testing.	Consensus-based Recommendation

All individuals/couples having screening should provide written informed consent that should include:

(i) Acknowledgement that screening will not identify carrier status for all mutations in the tested genes and therefore that there is a residual chance of the couple having a child with one of the conditions screened for.

(ii) Acknowledgement that there is a small chance of identifying the individual tested as affected by one of the conditions screened for. An example is the identification of homozygous/compound heterozygous mutations in the CFTR gene in an individual with no symptoms, congenital bilateral absence of the vas deferens and/or pulmonary symptoms.

(iii) If couple screening is offered, the members of the couple need to be informed that if they have children with a different partner that they require rescreening to define the reproductive risk for that new couple.

4.6 What genetic findings should laboratories report?

Recommendation 6	

Laboratories should only report carrier status for class 4 (likely pathogenic) and 5 (pathogenic) mutations. Variants of unknown/uncertain significant (VUS) should not be reported.

4.7 Carrier couples of autosomal recessive conditions / female carriers of X-linked conditions

All couples found to have a higher chance of having a child with one of the conditions screened for should be referred for genetic counselling to be informed of available reproductive options.

4.7.1 The preconception period is the preferred timing for carrier screening as advances in preimplantation genetic diagnosis (PGD) now provide couples with a means to avoid having a pregnancy affected by a heritable disorder altogether. For many couples, undergoing in vitro fertilisation (IVF), PGD and selective transfer of an

Individuals and couples should be informed that there is an out -of-pocket expense for expanded carrier screening.

4.9 Laboratory accreditation and standards

All laboratories currently undertaking carrier screening should be accredited by the National Association of Testing Authorities (NATA) in Australia, and International Accreditation New Zealand (IANZ) in New Zealand.

Laboratories that undertake carrier testing should undertake audit and monitoring of their carrier screening programs and participate in external quality assurance activities.

All pathology laboratories in Australia receiving funding via Medicare must be accredited by the National Association of Testing Authorities (NATA)/RCPA Laboratory Accreditation Program. The Standards are set by the National Pathology Accreditation Advisory Council (NPAAC). The Standards are based on the international standard ISO 15189 Standard for Medical Laboratories. In New Zealand laboratories are accredited via IANZ using the same ISO 15189 as their basis(https://www.rcpa.edu.au/Patients/Lab -Accreditation).

4.10 Implications for maternity and genetics workforce

Reproductive carrier screening on a population basis is a new area of practice for many maternity clinicians. Educational resources and training for health professionals should be developed prior to the introduction of screening into routine clinical care.

Health professionals caring for reproductive age women should have up- to-date knowledge of the options available for carrier screening, awareness of appropriate patient resources (a)1.2 (e)4.4 (n)6.6 ((f)4 (n)0

9. Appendices

Appendix A Women's Health Committee Membership

Name	Position on Committee
Professor Yee Leung	Chair and Board Member
Dr Gillian Gibson	Deputy Chair, Gynaecology
Dr Scott White	Deputy Chair, Obstetrics and Subspecialties Representative
Associate Professor Ian Pettigrew	Member and EAC Representative
Dr Kristy Milward	Member and Councillor
Dr Will Milford	Member and Councillor
Dr Frank O'Keeffe	Member and Councillor
Professor Sue Walker	Member
Dr Roy Watson	Member and Councillor
Dr Susan Fleming	Member and Councillor
Dr Marilyn Clarke	ATSI Representative

Genomics Advisory Working Group

Appendix B Overview of the development and review process for this statement

i. Steps in developing and updating this statement

This statement was originally developed in March 2018. The Genomics Advisory Working Group & Women's Health Committee carried out the following steps in reviewing this statement:

- Declarations of interest were sought from all members prior to reviewing this statement.
- Structured clinical questions were developed and agreed upon.
- An updated literature search to answer the clinical questions was undertaken.
- At the March 2018 face-to-face committee meeting, the existing consensus-based recommendations were reviewed and updated (where appropriate) based on the available body of evidence and clinical expertise. Recommendations were graded as set out below in Appendix B part iii)

ii. Declaration of interest process and management

Declaring interests is essential in order to prevent any potential conflict between the private interests of members, and their duties as part of the Women's Health Committee.

A declaration of interest form specific to guidelines and statements was developed by RANZCOG and approved by the RANZCOG Board in September 2012. The Women's Health Committee members were required to declare their relevant interests in writing on this form prior to participating in the review of this statement.

Members were required to update their information as soon as they become aware of any changes to their interests and there was a standing agenda item at each meeting where declarations of interest were called for and recorded as part of the meeting minutes.

There were no significant real or perceived conflicts of interest that required management during the process of updating this statement.

iii. Grading of recommendations

Each recommendation in this College statement is given an overall grade as per the table below, based on the National Health and Medical Research Council (NHMRC) Levels of Evidence and Grades of Recommendations for Developers of Guidelines.[14] Where no robust evidence was available but there was sufficient consensus within the Women's Health Committee, consensus-based recommendations were developed or existing ones updated and are identifiable as such. Consensus-based recommendations were agreed to by the entire committee. Good Practice Notes are highlighted throughout and provide practical guidance to facilitate implementation. These were also developed through consensus of the entire committee.

Appendix C Full Disclaimer

This information is intended to provide general advice to practitioners, and should not be relied on as a substitute for proper assessment with respect to the particular circumstances of each case and the needs of any patient.