



The
Fertility Society
of Australia

Pre-Conception Health Special Interest Group



Reproductive carrier screening

Reproductive carrier screening (RCS) is the testing of healthy adults to determine if they have an increased chance of having a child with a severe recessively inherited genetic condition [1, 2]. RCS is specifically targeted at individuals without a family history of a genetic condition who are therefore at population chance of being carriers. People who have known family history should be offered referral to a specialised genetic service.





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Evidence review

The genetic conditions targeted by RCS are mostly those with autosomal recessive inheritance, where a couple only have a chance of having an affected child when both parents are carriers of the same autosomal recessive condition. In this setting, each conception has a one in four chance of being affected by the condition. Most, if not all, people are carriers of multiple autosomal recessive conditions, but the likelihood of their partner being a carrier of the same condition is low. RCS targets X-linked conditions, where the gene mutation lies on the X-chromosome, males are usually more severely affected than females, and female carriers are frequently asymptomatic.

RCS was first performed for haemoglobinopathies using red blood cell indices and haemoglobin electrophoresis, and Tay-Sachs disease using enzyme analysis pre-dating the availability of genetic tests [3]. Genetic RCS initially tested for one or several genetic conditions, and was frequently targeted at individuals whose ancestry indicated a higher than average chance of being carriers. Examples include testing for cystic fibrosis in people with European ancestry and testing for Tay-Sachs disease in people with Ashkenazi Jewish ancestry. More recently, advances in 'next generation' gene sequencing technology have made it possible to test for hundreds, or even thousands of recessive genetic conditions in a single test, leading to the provision of *pan-ethnic* carrier screens.

In Australia, RCS is currently available in two main forms, supplemented by haematological screening for haemoglobinopathies. The first is a three-condition screen that targets the three most common recessive conditions for which prenatal testing is performed: cystic fibrosis (CF), spinal muscular atrophy (SMA) and Fragile X syndrome (FXS) [4]. This test has the advantage of being relatively inexpensive whilst detecting a large number of carriers because the conditions are common. The second type of test is 'expanded carrier screening (ECS)' which typically targets several hundred recessive genes. The main advantages of ECS is that it detects a larger number of carrier couples, although it is notable that many of the conditions included in ECS gene panels are exceptionally rare, and overall, the number of at-risk couples detected by ECS is only approximately double that detected by three condition screening for CF/SMA/FXS [5]. Additional challenges presented by ECS include that most of the conditions tested are less well understood than CF/SMA/FX, and more heterogeneous in their severity, predictability of phenotype and response to treatment [5]. In addition, there is a small chance that ECS will identify that the person tested is themselves affected by one of the conditions tested, a possibility that should be discussed in pre-test counselling. The field of expanded carrier screening is evolving rapidly, and currently available ECS panels vary in the conditions screened and reporting practices, according to the provider [6]. At present there is no clear consensus on the criteria for inclusion of conditions in ECS panels [1].

Reproductive carrier screening can be offered as couple screening, where both members of a couple are screened simultaneously, or sequential screening when one member of the couple is tested first, and testing is only performed in their partner if carrier status is detected in the first person screened. Usually sequential screening is initiated in the woman to enable detection of carrier status for X-linked conditions. In general, couple screening is favoured for ECS because of the much higher likelihood of identifying carrier status in the first person screened.

If both members of a couple are found to be carriers of the same autosomal recessive condition, or if the woman is found to be a carrier of an X-linked condition, couples may benefit from the opportunity to discuss

the condition with a clinician with specific expertise in managing children with that condition [4]. The following reproductive options may be available [2]:

1. Having a child naturally and accepting the possibility of having an affected child with confirmatory testing available after birth.
2. Conceiving naturally and having testing during the pregnancy (chorionic villus sampling or amniocentesis) to determine if the fetus is affected, followed by the option of pregnancy termination or continuing with the pregnancy.
3. Conceiving using in vitro fertilisation (IVF) and using preimplantation genetic testing (PGT-M) to select for transfer embryos that are not affected by the condition. PGT can now be applied for most recessive conditions, and for many people is more acceptable than undergoing prenatal diagnosis and termination of pregnancy [7].
4. Using donor sperm, egg or embryo from individuals who are not carriers.
5. Adoption.
6. Not having children.

The preconception period is the preferred timing for carrier screening because this allows the greatest number of reproductive options to avoid the chance of having a child with a serious genetic condition. It should be noted that reproductive carrier screening is optional, and people may choose to decline some or all screening [1].

RCS has been shown to reduce the chance of a couple having a child with certain genetic conditions [8, 9], and is predicted to reduce the burden of Mendelian disease in a cost-effective manner [10], however it cannot eliminate risk. It is important to note that even expanded carrier screening panels only include a fraction of known recessive genetic conditions, and even for those conditions tested, some carriers may not be detected due to limitations of gene testing technology and interpretation [1]. Moreover, many genetic conditions arise not from inherited gene variants, but from de novo autosomal dominant gene mutations that arise in the sperm or egg and therefore cannot be predicted by RCS.

Summary

RCS provides people with information about their chance of having a child with a genetic condition, allowing them to make informed decisions about pregnancy planning based on their personal values. Information on RCS should be offered to all women who are planning a pregnancy or in the first trimester of pregnancy, emphasising that all testing is optional. Preconception testing is favoured because it allows the greatest range of reproductive options, including PGT. Acceptable tests include those that target a small number of common and severe conditions, and an expanded carrier test that targets a large number of conditions, including those that are more rare or variable in outcome.

Recommendations

As per RANZCOG guidelines [2], it is recommended that information on RCS be offered to all women who are planning a pregnancy or in the first trimester of pregnancy. This should include information about screening for a limited selection of the most frequent conditions and ECS. Ideally RCS is offered prior to conception because this allows the greatest range of reproductive options. In addition to genetic screening, family history should be actively sought and individuals with an existing family history of a genetic condition should be offered referral to a specialised genetic service.



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It is important that RCS is accompanied by informed consent about the advantages and disadvantages of screening and the costs involved. Couples wishing to receive more information about RCS should be given the opportunity to speak to a genetic counsellor or other informed clinician. All couples with a high chance of having a child with one of the conditions tested should be referred for genetic counselling to discuss reproductive options.

For more information about pre-conception health visit



www.yourfertility.org.au

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