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Genetic screening

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Case study 1

Vanessa and John are planning a family. They see their general practitioner and ask whether they should have any tests prior to falling pregnant to maximise the chance of having a healthy child. What should be the response of the doctor?

Case study 2

Max goes to his general practitioner for a health check-up. His doctor measures his blood pressure and orders a battery of blood tests. Max tells his doctor that he has heard of genetic screening and that tests are available on the internet, and he asks if he should do such testing. What should his general practitioner advise?

The explosion of knowledge in relation to the genetic basis of multiple conditions means that screening for the risk of preventable disease as well as for the risk of having a child with a genetic condition is increasingly possible. Genetic screening is defined as a systematic attempt to identify and counsel as many people at genetic risk in a population as possible, whether or not they have a genetic family history. In 1968, Wilson and Jungner from the World Health Organization identified ten criteria to be met for the introduction of a screening program (Table 1). Critical among these criteria are that there is an intervention that can be instituted to reduce the impact of the condition for which screening is being conducted.

Table 1: 10 criteria that are required to be met for a screening program to be introduced (Wilson & Jungner, World Health Organization, 1968)

1.	The condition being screened for should be an important health problem
2.	The natural history of the condition should be well understood
3.	There should be a detectable early stage
4.	Treatment at an early stage should be of more benefit than at a later stage
5.	A suitable test should be devised for the early stage
6.	The test should be acceptable
7.	Intervals for repeating the test should be determined
8.	Adequate health service provision should be made for the extra clinical workload resulting from screening
9.	The risks, both physical and psychological, should be less than the benefits
10.	The costs should be balanced against the benefits

Genetic screening for conditions affecting individuals

There are a number of conditions where a person can be diagnosed as being at genetic risk prior to permanent problems from the condition and for which an intervention is possible. Hereditary haemochromatosis (HH) is the best example of this.

Hereditary haemochromatosis

Hereditary haemochromatosis refers to a group of genetic conditions where there is excess iron in the body. Untreated, the iron can deposit in organs, causing damage to those organs. The organs most at risk are the liver, heart, pancreas, pituitary gland and joints. This can lead to liver fibrosis, cirrhosis and cancer, damage to the heart (cardiomyopathy), diabetes, reduced libido, and infertility and arthritis.

Most haemochromatosis is caused by a mutation affecting both copies of the *HFE* gene. One particular mutation, p.C282Y, accounts for most significant haemochromatosis in the Caucasian community. Up to 1 in 150 individuals have the p.C282Y mutation in each copy of their *HFE* gene. Around 80% of men and 65% of women who have this genetic predisposition

will develop high body iron. Up to 50% of men and 10% of women with the genetic predisposition will develop significant problems from iron overload. If a person knows that they are at risk of hereditary haemochromatosis they can take steps to ensure their iron levels do not reach dangerously high levels and therefore prevent significant disease from the condition. Removal of blood (venesection) reduces body iron since the red blood cells contain iron in haemoglobin. The blood obtained by donation can be used to benefit the community in many jurisdictions, including in Australia, as long as the donor has no other contraindications to being a donor such as having hepatitis.

Studies have shown that adults and individuals of late high school age can be successfully screened for hereditary haemochromatosis. Adults who are found to be at genetic risk with high iron levels can take steps to reduce their iron levels. There is no evidence of significant negative psychological impact of such screening. The main barriers to widespread introduction of screening for haemochromatosis relate to concerns around health economics (will the government save money from screening or not?) and the fact that not all individuals who have the genetic predisposition will develop significant problems from iron overload.

Newborn screening

In many countries, virtually all children have a blood test in the first few days of life that is tested for multiple, mainly genetic, conditions for which intervention exists to prevent problems for the child. Newborn screening was first instituted to test for phenylketonuria. Phenylketonuria is an autosomal recessive condition where the affected individual cannot break down the amino acid phenylalanine. The build-up of phenylalanine results in progressive damage to the brain. Untreated, phenylke-

tonuria results in severe intellectual disability and behavioural issues. Dietary treatment, which consists of exclusion of phenylalanine, can largely prevent this. Subsequently, newborn screening was introduced for hypothyroidism (under-functioning of the thyroid gland), cystic fibrosis and multiple inborn errors of metabolism.

Other conditions for which screening has been proposed

With genetic testing becoming cheaper, suggestions have been made that screening could occur for multiple different genetic conditions through the use of next generation sequencing. Examples of conditions that could be diagnosed and for which interventions exist include testing for cancer predisposition and for the risk of sudden cardiac death.

Mutations in a number of different genes are known to increase the risk of cancer. The most prominent among these are mutations in *BRCA1* and *BRCA2,* which predispose to breast and ovarian cancer in women and breast and prostate cancer in men. Individuals can take steps to reduce the risk of dying from cancer if they are known to have a mutation in one of these genes. Options include screening for breast cancer and/or undertaking surgery to remove breast and ovarian tissue. Mutations in a number of genes are known to predispose to bowel cancer. Individuals with a mutation in one of these genes can have regular surveillance by colonoscopy to identify precancerous and cancerous lesions that can be removed and therefore prevent advanced cancer and death from this condition.

A number of studies have been conducted in the Ashkenazi Jewish community where three mutations in *BRCA1* and *BRCA2* are common. Around 1 in 40 (2.5%) individuals in this community have one of the three mutations compared to about 1 in 400 (0.25%) individuals in the non-Ashkenazi Jewish population

who have a mutation in *BRCA1* or *BRCA2*. These studies have shown that individuals can be screened for these mutations in a manner that is acceptable to the community. Expanding such testing to non-Ashkenazi Jewish individuals is more complex since there are many different mutations that can result in an increased risk of cancer in the non-Ashkenazi Jewish community. Nevertheless, the cost of testing these genes is dramatically reducing with technological advances and therefore such testing will become increasingly possible.

Mutations in a number of different genes can predispose to sudden cardiac death. The main two categories are long QT syndrome and hypertrophic cardiomyopathy. In long QT syndrome there is a predisposition to irregular heart rhythm that includes ventricular fibrillation that can lead to sudden cardiac death. A number of triggers are known to predispose to an irregular heart rhythm in those with such a mutation. Triggers can include sudden noise and exercise. There are steps an individual can take to prevent sudden death if they have such a mutation. These include medication and insertion of an automatic defibrillator that will revert the irregular heart rhythm back to normal heart rhythm. Issues with screening for such conditions by genetic testing include the need to test multiple different genes and the risk of calling a benign sequence alteration a disease-causing one and therefore causing unnecessary intervention and anxiety for individuals and families.

Hypertrophic cardiomyopathy refers to a group of conditions where there is increased thickness of the heart wall that can lead to sudden cardiac death. Interventions include medication, surgery and insertion of an automatic defibrillator that can reduce the risk of sudden cardiac death in individuals with such a mutation.

Genetic screening for risk of genetic disease in offspring

In autosomal recessive conditions, each parent has a single faulty gene. When a couple are both carriers of the same recessive condition there is a one in four chance for each child to have the condition. All people are carriers of a number of autosomal recessive conditions, but it is only if both parents are carriers of a mutation in the same gene that a child can have a recessive condition. Recent studies have estimated we all carry one or two recessive mutations that if a child had mutations in both copies of that gene would result in a condition of sufficient severity to prevent that child having children. In X-linked recessive conditions, if a woman has a faulty gene on the X chromosome there is a one in two chance for each son to have the condition. If individuals and couples are identified as carriers prior to having children, there are a number of reproductive options available to prevent the birth of a child with that condition. These include testing an established pregnancy and terminating the pregnancy if the developing baby is identified as having a genetic condition, as well as preimplantation genetic diagnosis using IVF and only placing embryos in the woman's uterus that are unaffected by the genetic condition (see Chapter 8).

Until recently, reproductive carrier screening involved testing for the most common mutation(s) in the genes of interest. Increasingly, it is now tested by next generation sequencing of the genes. The latter has the advantage of identifying more carriers but it risks diagnosing a person as a carrier of a condition where the identified alteration in the gene is a benign change rather than a mutation. Some years ago the American College of Medical Genetics published a panel of 25 recommended *CFTR* mutations to screen. Mutations in the *CFTR* gene can result in cystic fibrosis. It later came to light that one of the recommended alterations is a benign change and not a

mutation. This illustrates that carrier screening is not always a straightforward process.

Testing is often offered to the female in the couple in the first instance and then to the male partner if the female is found to be a carrier of one or more autosomal recessive conditions. The reason for testing the female first is that for X-linked conditions, only the mother needs to be a carrier to have an affected child. Another way of screening is couple screening. Here, both members of the couple are tested together and they are provided with the result as a couple — high risk where both are carriers of the same autosomal recessive condition or the female is a carrier of an X-linked condition, or low risk where the couple are not both carriers of the same autosomal recessive condition and the female is not a carrier of any of the X-linked conditions. The advantage of couple screening is that it reduces the time to get a result for those couples where the female is a carrier of one or more conditions and reduces the amount of time required for counselling couples where the female is a carrier of one or more conditions since for most the male will not be a carrier of that condition, and thus reduces anxiety for those couples since they will not have to wait to find out if the male is a carrier. The disadvantages are that it has a greater upfront cost and it means low risk couples don't know the conditions they are carriers of, and so there is missed opportunity to test their relatives for carrier status of those conditions, so-called cascade testing.

The first genetic condition for which widespread screening was introduced to reduce reproductive risk was Tay Sachs disease. Tay Sachs disease is an autosomal recessive condition where affected children appear healthy early in life but with time their development slows and then regresses, meaning they lose developmental skills. Affected individuals become blind,

develop seizures and generally die in the first few years of life. Tay Sachs disease occurs due to mutations in a gene called *HEXA*. *HEXA* produces a protein called hexosaminidase A, which is a protein that breaks down fatty substances in the brain. When there is insufficient hexosaminidase A there is a build-up of fatty substances that causes progressive damage to the brain. In the late 1960s, it was found that carriers of Tay Sachs disease have around half the level of hexosaminidase A in their blood as non-carriers. Therefore, carrier screening was possible and was introduced into communities in the early 1970s. Tay Sachs disease is around one hundred times more common in the Ashkenazi Jewish community than the general Caucasian community, and screening programs have generally been welcomed in Jewish communities.

The second condition for which widespread screening was introduced was beta-thalassaemia. Beta-thalassaemia is a recessive condition that is most common among individuals from Mediterranean regions. Affected individuals have severe anaemia and, untreated, die early in childhood. Beta-thalassaemia can be treated by regular blood transfusions. Carriers of beta-thalassaemia generally have abnormalities of the appearance of the red blood cells under the microscope. There is a simple non-genetic test to identify carriers called haemoglobin electrophoresis. Because the initial test to identify carriers of beta-thalassaemia is a common test called a full blood count, the majority of pregnant women are screened for beta-thalassaemia either before or in the early stage of pregnancy.

It is now possible to screen for many hundreds of autosomal recessive and X-linked recessive conditions. Companies are offering testing for these at an ever decreasing cost. Where both members of a couple are carriers of an autosomal recessive condition or the female is a carrier of an X-linked condition

there are a number of reproductive options available to avoid having a child with the particular genetic condition. These include testing an established pregnancy and terminating the pregnancy if the developing baby is identified as having the condition, or utilising preimplantation genetic diagnosis through IVF (see Chapter 8).

Case study 1

There are many different options for reproductive carrier screening for couples planning or in the early stages of pregnancy. Companies offer screening for carrier status for a few up to hundreds of autosomal and X-linked recessive conditions. Vanessa and John should be offered these options and allowed to make an informed decision on having testing. They should be offered screening for Vanessa in the first instance, or for both to be tested at once by couple screening.

Case study 2

There are an increasing number of companies offering direct to consumer genetic testing (see Chapter 9). Initially this was for multiple gene alterations, with the report providing risk estimates for various disorders (e.g. vascular disease, diabetes and dementia). Now there are companies offering whole genome sequencing directly to members of the public. The general practitioner should discuss the pros and cons of such testing, pointing out the possibility of identifying risk for conditions where there is no proven prevention (e.g. late onset neurodegenerative disease such as Alzheimer disease), that variants of unknown significance may be identified and that the algorithms used to calculate risk of common disorders, where the cause is influenced by multiple genes and the environment, are often based on a small number of studies and therefore risk estimates are likely to be quite inaccurate.

The future

It is very possible that in the medium term all newborns will have whole genome sequencing. This will identify genetic risk for treatable conditions such as those described in this chapter. In addition, it will identify carrier status to define risk for that individual's future offspring. It is likely that conditions that do not have preventive treatments in 2017 will do so in the future, and therefore the value of such testing will expand. There are ethical issues associated with such broad screening. Should the parents of a child with a mutation that predisposes to late onset neurodegenerative disease for which no preventive treatment exists be told about this? Will genetic traits that indicate talent in particular areas, or conversely lack of talent in other areas, be used to direct a child's interest and vocations? Will parents choose to use reproductive technologies such as PGD and IVF to select for particular traits?

Many genetic conditions that affect people are not inherited but rather are the result of a mutation that occurs in the egg or sperm and therefore cannot be predicted by genetic testing of parents. It is likely that such mutations will be identifiable in DNA from a fetus that is present in the mother's bloodstream early in pregnancy (non-invasive prenatal testing). In the future, it is likely that such testing will identify many different genetic conditions and couples will have the option of terminating a pregnancy when such conditions are identified.