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# Prenatal genetic screening and counselling

**Many women in Australia are offered information early in pregnancy on the risks of a genetic disorder or chromosomal aneuploidy occurring in the fetus. The growing number of higher-risk pregnancies in older women and our increasing cultural diversity in Australia makes the provision of accurate advice both before and during pregnancy ever more important.**

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Until quite recently, the uterus was an opaque box. It was only after birth (which was often accompanied by a ritual counting of fingers and toes) that parents, and their obstetrician or midwife, might find that the baby was affected by one of the many genetic or acquired clinical conditions that manifest at birth or early in life.

Over the past 30 years, this situation has changed completely. High-quality ultrasound images (Figure 1) allow doctors to take a non-invasive view of the fetus from a very early stage (often reinforced in practice by the offer of a DVD for the parents to take home). An ultrasound scan provides:

- a necessary clinical test for every woman because it determines whether there is a multiple pregnancy, a placental placement that could pose a problem or even a fetal death *in utero*
- a preliminary test that could indicate an abnormality, such as Down syndrome or a cardiac defect
- a bit of fun – the 'wow' moment for the parents to be.

**IN SUMMARY**

- **An ultrasound scan acts as a preliminary test that could indicate an abnormality, such as Down syndrome or a cardiac defect.**
- **Genetic screening is best carried out before pregnancy to allow time to offer the couple information, and time for them to discuss and think about the possible choices.**
- **Most couples will choose to avoid having a child with a 'serious disability' either by using IVF to achieve pregnancy with pretested embryos or, if they find out their fetus is affected once pregnant, by terminating the pregnancy.**
- **Cystic fibrosis and thalassaemia are the two recessive diseases for which there is a high existing level of awareness, and prenatal testing is often offered.**
- **For most (but not every) dominant disease, a full clinical and family history will show if one of the parents is affected.**
- **Down syndrome is the most common genetic disorder, with an increasing incidence with increasing maternal age.**
- **The role of genetic counselling is, primarily, to provide accurate information and to let a couple know what medical options and other strategies they can legally use to deal with the situation they face.**

An ultrasound scan is offered to, and taken up by, the vast majority of pregnant women, usually towards the end of the first trimester, often combined with a biochemical maternal serum test that screens for many possible abnormalities, including Down syndrome and neural tube defects. When there is a suspicion of an abnormality (whether genetic, chromosomal or sporadic), it is possible to follow ultrasound screening with definitive diagnostic testing, using chorionic villus sampling or amniocentesis, each with a very low risk of miscarriage (less than 1%).

Key practice points are presented in the box on page 20.

## The future is coming fast

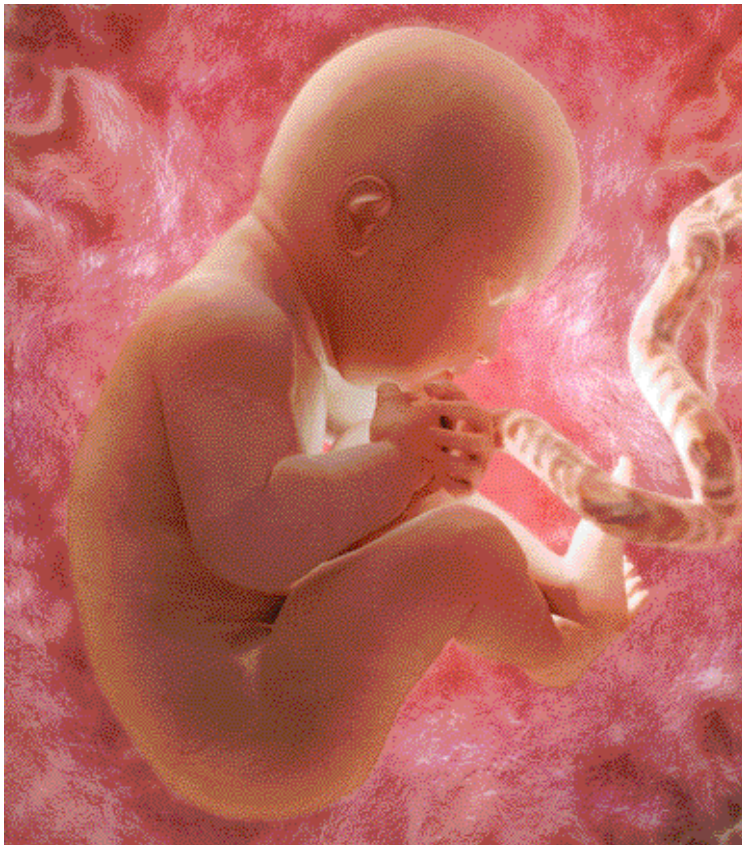
Couples often ask what they can do to ensure a healthy outcome for their pregnancy. Although the importance of folic acid supplementation, limiting alcohol intake, consuming a healthy diet and not smoking are usually discussed, this is also the time to discuss population genetic screening. The best time to screen is before pregnancy; this will allow time to offer the couple information, and time for them to discuss and think about the possible choices. Detection of a high genetic risk prior to pregnancy allows for family planning and investigation of alternative options such as *in vitro* fertilisation (IVF) combined with the use of preimplantation genetic diagnosis. However, many women do not consult a clinician until they are pregnant. Screening early in pregnancy is also a viable option, although it allows less time for consideration of diagnostic testing if this is required.

Most couples will choose to avoid having a child with a 'serious disability' either by using IVF to achieve pregnancy with pretested embryos (using preimplantation genetic diagnosis) or, if they find out their fetus is affected once pregnant, by terminating the pregnancy. However, the definition of 'serious' is not the same for all couples, and not every positive diagnosis of a fetal abnormality is necessarily followed by a decision to terminate the pregnancy.

Should a couple wish to continue with an affected pregnancy, they can do so knowing the probable outcomes, and knowing there is an opportunity to intervene clinically (if this is helpful) from birth or occasionally *in utero*. Intervention can include attendance of a paediatrician at the delivery, preplanned transfer of the baby to a paediatric tertiary centre, meeting with surgeons during the pregnancy and ensuring appropriate support services are put in place. This knowledge also gives a certain level of control back to the parents who have made informed decisions based on all the relevant information.

It is important for all health professionals, particularly GPs who are often in the best position to offer advice to couples contemplating pregnancy or early in pregnancy, to be aware of how rapidly technology is transforming available screening options before birth. In future, the choices may be widened when gene analysis of parents can define both the

### Prenatal genetic screening and counselling



Prenatal screening for genetic disorders is often discussed early in a pregnancy. However, addressing the issue before conception can give the couple more choices and make *in vitro* fertilisation with preimplantation genetic diagnosis a realistic option.

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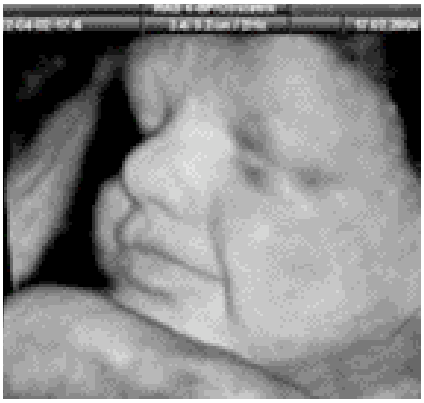

Figure 1. Three-dimensional ultrasound image of a fetus.

risks of abnormalities and the opportunities to choose desirable characteristics. However, at present diagnosis is confined to severe disorders caused by mutations in single genes. Over the coming decade, chorionic villus sampling and amniocentesis might be replaced with an analysis of fetal DNA from the maternal circulation, perhaps as early as seven weeks into pregnancy. This is not available at present in Australia, although it is used to predict fetal gender in some European countries.

## Recessive genetic conditions

For a recessive disorder, a mutation causing dysfunction of a gene must be inherited from both parents. It is important to note that the number of carriers for such diseases is always much higher than the number of affected individuals. For example, for more than 90% of babies born with cystic fibrosis in Australia, there is no prior family history of the disease.

Cystic fibrosis and thalassaemia are the two recessive diseases for which there is a high existing level of awareness and prenatal testing is often offered. In the case of cystic fibrosis, there are about one million carriers of the mutated dysfunctional gene in Australia, but only about 4000 people living with the disease. One in 25 healthy individuals of Northern European background are carriers of a cystic fibrosis mutation. Carrier status can be determined from a simple, self-administered cheek brush swab (Figure 2). Either partner can be screened in the first instance. Most, but not all, carriers will be detected and thus screening reduces, but does not completely eliminate, the chance of being a cystic fibrosis carrier.

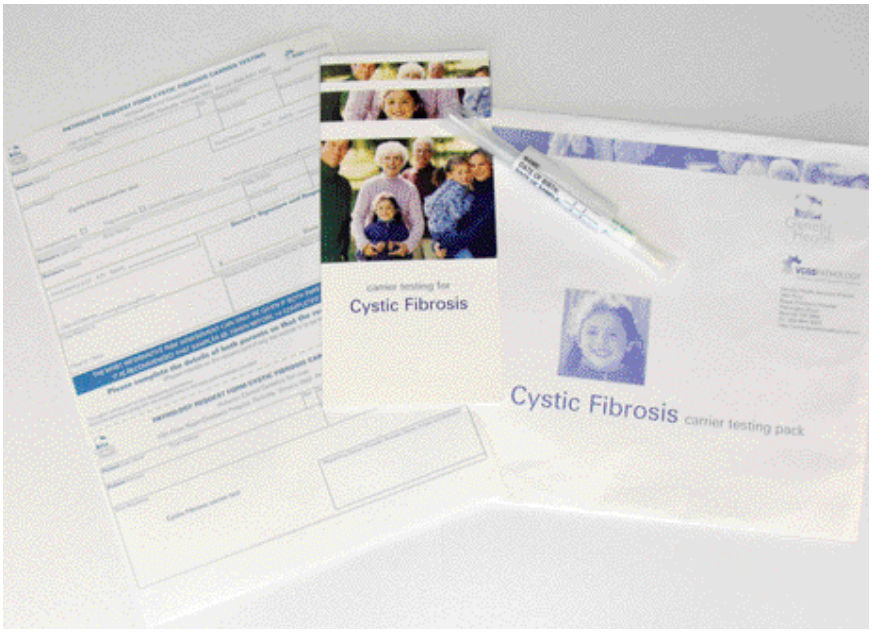


Figure 2. Cystic fibrosis carrier testing pack.

If there is a family history of a condition or a person comes from an ethnic group at risk of specific conditions, the state or territory genetic services will usually carry out the DNA screening test among family members for free. In the absence of a family history, there is currently no Medicare rebate for screening, so out-of-pocket costs are incurred.

## Ethnicity and our multicultural population

Beta-thalassaemia is common in Mediterranean countries such as Cyprus, Greece and Italy and in the Middle East, and both alpha-thalassaemia and (to a lesser extent) beta-thalassaemia are common in South East Asian countries such as Thailand and parts of Vietnam and China. Many people now come to Australia from the Indian subcontinent, and in some regions of India both thalassaemia and sickle cell anaemia are found. Tay-Sachs disease is particularly common in Ashkenazi Jews, and children who attend Jewish schools in NSW and Victoria are usually tested for carrier status between the ages of 16 and 18 years.

Thirty years ago it might have been possible to use names as a predictor of ethnicity, but today there are many 'Smiths' and 'Andersons' with genes from Italian or Greek grandparents. A couple may no longer be aware of a risk due to ethnicity until they are counselled by their GP or obstetrician.

Some cultures place a high social value on marriages between cousins. Cousins are more likely to share a genetic mutation (about one chance in eight for first cousins) than unrelated individuals because they are closely related. The risk of a birth defect occurring in a marriage between cousins is, therefore, double that in the wider population, but even then the risk of having a defect is only about 6% compared with 3% in the general population. The risk is increased, but not by as much as is often thought.

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## Key practice points

- GPs often have a continuing relationship with a patient, couple or family over many years, which makes them particularly suitable to identify most genetic counselling issues during pregnancy.
- At present, the 'standard of care' for prenatal testing requires a clinician to advise a woman early in pregnancy that accurate diagnosis is available for many single-gene disorders, such as cystic fibrosis and thalassaemia (and to ascertain whether there are any reasons, in terms of family history or ethnicity, why there might be a suspicion that testing is required), and for chromosomal disorders, such as Down syndrome.
- There are limits to what can be achieved using prenatal tests: there is still a background risk of 3% of having a baby with a major birth defect or developmental problem, and no couple can be guaranteed a healthy outcome.
- Parent support groups and many health professionals want population screening for carriers to be expanded to include other relatively common monogenic conditions such as spinal muscular atrophy and fragile X syndrome.
- If there is any family history of a serious genetic condition, if a couple want information about what population screening is currently available (in this rapidly changing field) or if a couple want to find out about diagnostic testing, GPs should consider referral to a genetics service.
- For couples who know they are at risk of transmitting a serious monogenic disease, preconception testing for carrier status followed by *in vitro* fertilisation and direct preimplantation genetic testing of embryos before their use is an increasing practical alternative to prenatal testing and possible repeated termination of affected pregnancies.
- Families may raise concerns about general genetic issues with a primary care physician: does cancer, obesity or even dementia run in my family? Late-onset diseases often have a genetic component, but are rarely due to a single-gene mutation, and therefore cannot yet be assigned a risk through gene analysis. However, this may provide an opportunity for general health advice to a concerned family; it has been shown that pregnancy is a time when a couple is more likely to follow advice on health issues. If there is a strong family history that raises medical suspicion (as for familial hypercholesterolaemia, or breast or colon cancer), a referral to the clinical genetics service might be considered.
- A pregnant woman should be advised that an ultrasound scan combined with first-trimester maternal serum screening, which will be carried out as part of routine prenatal care, can detect the majority of fetuses affected by Down syndrome or another chromosomal disorder, and some single-gene diseases. Many women will indicate an over-arching desire to have a healthy baby and will abort a fetus affected by a serious abnormality. A few will indicate that they would be very reluctant to consider a termination of pregnancy under any circumstances, and may prefer not to have the scan. Others will decide to continue the pregnancy but want the information to manage their own expectations at and after delivery.
- Although termination of pregnancy still raises controversy within the wider community, it is considered by most to be a personal and private matter, and remains an inescapable component of preventing abnormal births through prenatal testing. As Professor Bernadette Modell, one of the founders of community genetics, commented to Professor Williamson many years ago: 'Our shoulders are not broad enough to take a decision of this magnitude on behalf of others; we must leave it to them, because only they will have to live with the consequences for the rest of their lives'.

## Dominant genetic conditions

There are several thousand diseases where a person is affected, or at risk, if he or she has just one copy of a mutation (and the other copy of the gene, from the 'other parent', functions normally). These are 'dominant disorders', and one that receives much attention is Huntington disease. Another that is more likely to come to the attention of GPs is familial hypercholesterolaemia.

For most (but not every) dominant disease, a full clinical and family history will show if one of the parents is affected. Serious dominant diseases are relatively rare. Where they manifest later in life (as for Huntington disease), the family often knows the risk and family members have often already considered their views about prenatal or presymptomatic testing (although they might not have considered preimplantation genetic diagnosis). This is an area where professional advice from a clinical geneticist or genetic counsellor can often be of great value.

## Chromosomal aneuploidies and dysmorphology

Down syndrome is the most common genetic disorder, caused in most cases by an extra normal copy of chromosome 21 (Figure 3). Remarkably, it is not 'inherited'; if a woman has a child with Down syndrome, she is not (in general) at increased risk of having another in future pregnancies. However, the incidence of Down syndrome does increase with advanced maternal age, and because many women (about 20% in Australia) now

have children in their late 30s and early 40s, there is an increase in the number of Down syndrome conceptions.

Most pregnant women have a combination of high-resolution ultrasound (measuring nuchal translucency) plus a biochemical analysis of maternal serum (to measure levels of pregnancy-associated plasma protein A and the beta subunit of human chorionic gonadotrophin) between 10 weeks and 13 weeks and six days of pregnancy. This offers a very good prediction of whether a fetus is at high or low risk of Down syndrome when the pregnant woman is of any age, and is a test of particular value to younger women who are often described as 'low risk'. In addition to Down syndrome, maternal serum screening plus high-resolution ultrasound identifies an almost equal number of pregnancies at high risk of many other less common chromosomal or single-gene disorders.

At this point, a pregnant woman and her partner will usually be referred to a specialist, public genetic service for a definitive diagnosis by a clinical geneticist and counselling from a genetic counsellor.

## What will the future bring?

It is already possible to test anyone's DNA for thousands of gene variations (or single nucleotide polymorphisms). There are several companies that will perform the analysis for about US$1000 (A$1155); and the price of the cheapest has come down to under US$400 (A$462), using the DNA from cells taken from a cheek swab with a cotton bud. The test is carried out using highly sensitive DNA chips, or using new DNA sequence techniques with thousands of specific primers. The same test can be carried out on DNA from chorionic villi or cells from amniocentesis (but not, as of yet, using fetal DNA from maternal blood, or from the amount of DNA that can be obtained from one or a few cells taken for preimplantation diagnosis).

Are these DNA variations meaningful? Perhaps fortunately, most of the variants are genetically harmless. At today's very incomplete level of understanding, the predictions are usually not very accurate, the data are difficult to interpret and results do not distinguish high from low risk for diseases such as cancer or coronary heart disease. However, the DNA tests do offer guidance on whether a person or fetus is, for example, at high or low risk of developing Alzheimer's disease when he or she is between 70 and 80 years of age, or at risk of developing haemochromatosis, or is likely to have red hair. Most of the tests can identify carriers of common mutations, such as cystic fibrosis or sickle cell anaemia.

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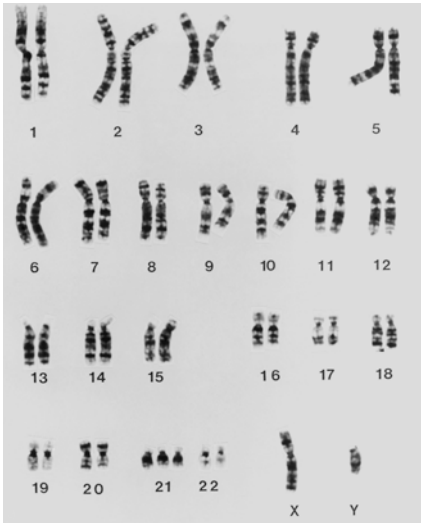


PHOTOLIBRARY

Figure 3. Down syndrome karyotype showing trisomy of chromosome 21.

## How common is common and how severe is severe?

Traditionally, prenatal genetic screening and testing have been offered in the context of severe diseases that affect infants and children, not to provide a test for red hair. However, now that mutations that cause or predispose to adult diseases such as Alzheimer's or Huntington disease, haemochromatosis or rare familial forms of breast or colorectal cancer can be identified, there are some couples at risk of these conditions who demand prenatal testing for these late-onset disorders. Others argue this is unethical for a disease that will not present for several decades, or might not present at all. It goes without saying that this is a complex issue that can only be decided on a case-by-case basis. However, if a loved family member has been known to be affected by a genetic disease, the person requesting screening will often have individual knowledge of the consequences. In the context of a society where women have a large measure of choice over their reproduction, they will request what works for them in terms of this personal knowledge.

## Genetic counselling

The role of genetic counselling is, primarily, to provide accurate information and to let a couple know what medical options and other strategies they can legally use to deal with the situation they face. A genetic counsellor will help the family, often at a time of great distress, interpret the medical information they are given, will provide support, can facilitate diagnostic testing, can act as patient advocate with third parties and can follow up with the family to provide information about risk of recurrence to future pregnancies or to other family members.

Genetic counselling is particularly useful when a high-risk pregnancy is identified using ultrasound and maternal serum screening or during gene screening in a population. This is because the couple are typically unaware of any risk before the test and, unlike the family with a history of the particular genetic disease such as cystic fibrosis or thalassaemia, will know little or nothing of the realities of the disorder.

## The ethics of choice

Australia is a multicultural community where there are a small number of individuals who oppose termination of pregnancy under any circumstances. Most people do not agree with this position. Each couple will have their own 'tipping point' and ultimately have a right to choose whether to continue or end a pregnancy.

Choice should be available for every couple, which is why we believe that screening should be available free of charge to those who wish to have it. The majority of women undertake screening during their pregnancy for reassurance that their baby is 'normal'. The aim of screening is to identify pregnancies at risk of a medical condition that causes disability, and to offer choice. In order to allow a definition of the choices that are realistic and achievable, all screening should be offered with accurate counselling.

In Victoria, when both members of a couple are identified as being carriers of cystic fibrosis from the cystic fibrosis population screening program, they may have no prior knowledge of the condition or what may be involved with the care of an affected child. The couple is offered a meeting with a respiratory physician, a genetic counsellor and the cystic fibrosis support group in Victoria to obtain reliable information in an unbiased manner, rather than depending on a lucky dip into the internet. The same principles apply to thalassaemia gene screening in all states and territories in Australia, as well as for the Tay-Sachs screening programs in Jewish schools. It is hoped these principles will continue to be followed for all genetic screening programs in the future. MT

## Further reading

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**COMPETING INTERESTS:** None.