Population genetic screening

BACKGROUND
Genetic screening programs in Australia are primarily carried out during pregnancy for maternal thalassaemia carrier status, chromosomal conditions and neural tube defects in the fetus, and for a number of conditions in the newborn.

OBJECTIVE
This article describes these programs and the general practitioner's role, particularly around offering prenatal screening that includes nongenetic aspects (eg. smoking, alcohol), to enable good practice.

DISCUSSION
General practitioners can be involved in offering prenatal screening and in giving increased risk results from prenatal and newborn screening, with due consideration of informed decision making and counselling about the meaning of the result. Increased risk results from these screening programs are followed up by further testing where required. As genetic contribution to diseases, especially complex common conditions, becomes better understood, more genetic tests will become available. This may impact on the role of the GP in population genetic screening programs.

Sylvia A Metcalfe
BSc(Hons), PhD, is Group Leader, Genetics Education and Health Research, Murdoch Childrens Research Institute, and Associate Professor in Medical Genetics, Department of Paediatrics, The University of Melbourne, Victoria. sylvia.metcalfe@mcri.edu.au

Kristine Barlow-Stewart
FHGSA(GenCounsel), PhD, is Director, The Centre for Genetics Education of NSW Health, and Associate Professor, Faculty of Medicine, University of Sydney, New South Wales.

Martin B Delatycki
MBBS, FRACP, PhD, is Director, Bruce Lefroy Centre for Genetic Health Research, Murdoch Childrens Research Institute, and Consultant Clinical Geneticist, Genetic Health Services Victoria.

Jon Emery
MA, MBBCh, MRCGP, FRACGP, DPhil, is Professor, Discipline of General Practice, University of Western Australia.

While advances in genetic testing have meant that now more than 1000 gene tests are available,[1] there are still a limited number of genetic conditions included in population based screening. Population based genetic screening identifies individuals at risk of having, or of passing on, a genetic condition. Screening may be followed by more definitive genetic testing.

In every state and territory in Australia, genetic screening occurs most often during the prenatal and newborn periods for a number of conditions, although as yet there is no single national approach. Carrier genetic screening occurs less commonly and genetic susceptibility screening is even more sporadic. In this article, we focus on the current screening programs that exist in Australia and have adapted information from several sections of *Genetics in family medicine: the Australian handbook for general practitioners*.[2]

Prenatal screening

When blood is taken from a pregnant woman, a number of tests can be performed that are, in essence, genetic screening tests that might require follow up with more definitive testing. Reduced mean cell volume/mean cell haemoglobin (MCV/MCH) in a full blood examination (FBE) can be suggestive of thalassaemia carrier status, which require further tests for confirmation (see the article 'Genetics and blood' this issue). Although the FBE is performed routinely, this result may be unexpected unless there is specific discussion about what may be revealed by the blood tests.

Increasingly, women are offered screening tests for fetal chromosomal conditions (predominantly Down syndrome) and structural anomalies that may involve blood tests, ultrasound or a combination of both. *Table 1* outlines these different screening tests together with their advantages and disadvantages. It is clear from a number of studies[3–6] that women are often unsure of the meaning of their result from these screening tests and of the possible consequences of being offered a diagnostic test, such as termination of pregnancy following diagnosis of an affected fetus or miscarriage due to having an invasive procedure to sample fetal cells. It is essential that the health practitioner provides information about these tests, and discusses that such tests are offered as a choice to women rather than considered routine. Ideally, where possible, opportunities for prepregnancy counselling should be identified as this allows for greater time to consider the ramifications of testing and reproductive options. Suggestions for areas of discussion before and/or during pregnancy are listed in *Table 2* and

Table 1. Advantages and disadvantages of screening tests during pregnancy

Screening test[a]	Gestation (weeks)	% Down syndrome pregnancies detected	Advantages	Disadvantages
Combined first trimester screening	10–12 (blood test) 11^{3}–13^{6} (ultrasound with nuchal translucency)	85–90%	• Early screen and therefore early diagnosis • Highest detection rate • No added risk of miscarriage • Detection of some fetal abnormalities • Benefits relating to early scan: – accurate dating – diagnosis of multiple pregnancy – diagnosis of early pregnancy failure (miscarriage)	• Will detect some affected pregnancies that may spontaneously miscarry • Does not provide risk for neural tube defects but ultrasound may detect anencephaly • Women may not access services so early in the pregnancy • Ultrasound requires accredited operator for accuracy[b] • Out of pocket expenses vary[c]
Second trimester maternal serum screening	14–20 (15–17 ideal)	70–75%[d]	• Available to women presenting in second trimester • No added risk of miscarriage • No out of pocket expenses for public patients if arranged through a public hospital	• Later screening test • Inaccurate dates can result in inaccurate risk by calculations. A dating scan should be considered if dates are uncertain • Lower detection rate • No neural tube risk can be given if test done at 14 weeks • Out of pocket expenses vary

a False positive rate set at 5% at these detection rates

b Nuchal translucency measurement should be performed by a Fetal Medicine Foundation or Royal Australian and New Zealand College of Obstetrics and Gynaecology (RANZCOG) accredited operator

c May be limited access in some states: in Victoria, it is currently not funded for public patients; in Queensland the blood test is not available publicly

d Assumes the use of the quadruple test (four analytes) and ultrasound dating

should include consideration of periconceptual folate to reduce the risk of neural tube defects (*Table 3*). It should be noted however, that while some of the topics in *Table 2* are mentioned for the sake of completeness, their inclusion does not imply a genetic effect on the health of the baby (eg. smoking and alcohol).

Ultrasound scanning

Ultrasound scans will screen for some birth defects and can also be a diagnostic tool for some birth defects (eg. neural tube defects). Ultrasound scans can be carried out in the first trimester, usually at 8–11 weeks gestation, to:

- confirm gestational age
- check the pregnancy viability when there has been a complication such as bleeding
- view the position of the placenta
- confirm the presence of a multiple pregnancy
- check fetal growth, physical development and viability
- as part of first trimester combined screening (see below).

In the second trimester, the fetal anomaly scan is usually conducted at 18–20 weeks and can detect a number of malformations including:

- neural tube defects (eg. anencephaly, spina bifida)
- cardiac defects
- gastrointestinal malformations (eg. gastroschisis, exomphalos)
- limb defects
- central nervous system (CNS) defects
- urinary tract anomalies.

It can also detect soft signs associated with underlying chromosomal or other genetic conditions. However, the second trimester ultrasound scan is not recommended as a primary screening test for Down syndrome.

Combined first trimester screening

This test combines nuchal translucency (NT) measurement (performed between 11 weeks/3 days and 13 weeks/6 days) with a biochemical maternal blood test at 10–12 weeks gestation. Nuchal translucency describes the appearance of a fluid filled space at the back of the fetal neck that can be measured by ultrasound and is associated with a greater risk of fetal anomalies such as Down syndrome, other chromosomal conditions, cardiac defects and some rare genetic conditions. Nuchal translucency screening alone is not recommended as a screening test for Down syndrome and should be combined with the biochemical blood test that measures pregnancy associated plasma protein (PAPP-A) and human chorionic gonadotrophin (free ß-hCG). By combining the blood test with the NT test results in conjunction with maternal age and weight, and gestational age, around 85–90% of babies who have Down syndrome, trisomy 18, and occasionally other problems, will be picked up compared with 70% or less using NT on its own. Depending on the state/territory, combined first trimester screening is not always available in the public sector and there may be out of pocket costs for the patient (*Table 1*). Where good quality NT measurement is not available, second trimester screening may be the best option.

Table 2. Counselling before or during pregnancy

- Collection of relevant family history
- Assessment of whether information in the family history places the current pregnancy at increased risk
- Recommendation of periconceptional folic acid supplementation
- Provision of information about screening and diagnostic tests during pregnancy
- Consideration of carrier tests for diseases specific to certain ethnic groups (eg. thalassaemia, sickle cell, cystic fibrosis, Tay-Sachs disease)
- Assessment of drug and medication use and implications for pregnancy
- Discussion of lifestyle changes (eg. alcohol and smoking cessation during pregnancy and change to diet)
- Provision of information about infectious diseases:
  - rubella vaccination status
  - varicella antibody status and immunisation if nonimmune
  - discussion about listeria infection and toxoplasmosis
- Provision of information about pre-implantation genetic diagnosis for couples who are known carriers of a genetic condition and/or couples undergoing IVF

Table 3. Recommendations about folic acid in pregnancy

Women at population risk for neural tube defects

- Women planning a pregnancy should take supplementary folic acid, 0.5 mg (500 µg) folic acid tablet or multivitamin appropriate for use in pregnancy and containing at least 0.4 mg (400 µg) of folic acid every day for at least 1 month before possible conception and continued for the first 3 months of pregnancy
- As many pregnancies are unplanned, all women of reproductive age should consider taking supplementary folic acid or a folate rich diet
- Folic acid tablets and multivitamins containing at least 0.4 mg (400 µg) folic acid are available from chemists, health food stores and some supermarkets

Women at increased risk for neural tube defects

- Women are at higher risk of having a baby with a neural tube defect if they:
  - have had a baby with spina bifida, anencephaly or other neural tube defect
  - have had a neural tube defect themselves
  - are on certain medications for epilepsy
  - have diabetes
  - have a close relative who has had a neural tube defect
- These women should take supplementary folic acid every day for at least 1 month before possible conception and continued for the first 3 months of pregnancy. Usual recommended dose is 5 mg (5000 µg)

Table 4. Factors to be noted on request form

Combined first trimester screening	Second trimester maternal serum screening
• Last menstrual period (LMP) and estimated due date	• Ultrasound based gestation or LMP
• Current weight	• Current weight
• Maternal age	• Maternal age
• Previous child with a chromosomal abnormality	• Previous child with a chromosomal abnormality, as well as previous child or close relative with a neural tube defect
• Date and location of ultrasound scan*	• Date of collection
• Any other information requested on the form (eg. ethnicity, IVF details)	• Any other information requested on the form (eg. ethnicity, IVF details)
	• If the woman has insulin dependent diabetes

* If the results of the scan are not received by the date on the form, the laboratory will contact the ultrasound practice or the requesting doctor

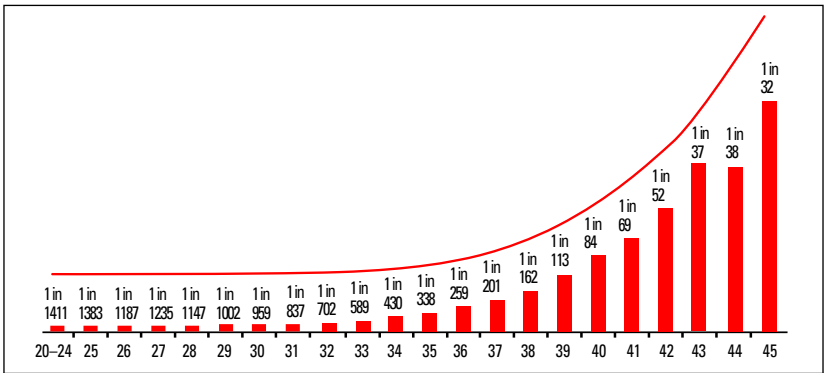

Figure 1. Maternal age risk of having a live born baby with Down syndrome

Second trimester maternal serum screening

Second trimester maternal serum screening is optimally performed at 15–17 weeks gestation (but can be performed until 20 weeks) using a blood test in conjunction with maternal age and weight and gestational age to calculate a risk figure for Down syndrome. This screening test may also detect pregnancies with an increased risk for trisomy 18 and neural tube defects. Detection rates are improved when four analytes (the quadruple test) are used:

- alpha-fetoprotein
- unconjugated oestriol
- free ß-hCG, and
- inhibin A.

Considerations when offering prenatal screening tests

When arranging either the combined first trimester or second trimester maternal serum screening tests, a number of factors should be noted on the request form to be used in the risk calculation algorithms (*Table 4*). It is important to note that all women are at risk of having a baby with a chromosomal abnormality, most commonly Down syndrome.

The risk of Down syndrome increases with maternal age (*Figure 1*). Screening tests give a risk figure for Down syndrome that modifies the risk based on maternal age alone, so screening tests should be offered to all pregnant women. It is important that the woman/couple understands that screening tests will not identify all pregnancies with Down syndrome; these can only be identified by performing a diagnostic test requiring a sample of fetal cells, either by chorionic villus sampling (CVS) or by amniocentesis. *Table 5* lists the advantages and disadvantages of these procedures. The result from a CVS or amniocentesis will still most likely be normal. The option of diagnostic testing and its consequences should be discussed. However, not all women decide to proceed to diagnostic testing for a range of reasons: concern about the risk of miscarriage, not wishing to know before the birth, or unacceptability of termination of pregnancy. However, it is still important to discuss and offer screening to women who would not choose to terminate a pregnancy, as some women value the information to prepare themselves for the birth of an affected child. Post-test counselling is available from specialist obstetricians and genetics services and referral should also be considered for discussion of diagnostic tests and counselling for women with increased anxiety.

Newborn screening

Newborn screening is a blood test provided free of charge that aims to detect certain rare genetic and/or metabolic conditions that may be life threatening and/or cause intellectual disability. The goal of screening is to prevent morbidity by implementing treatment before the onset of symptoms. Conditions include:

- cystic fibrosis
- phenylketonuria
- galactosaemia

- primary congenital hypothyroidism
- amino acidopathies
- fatty acid oxidation disorders
- organic acid disorders

(There is some variation between states and territories for which conditions are screened; galactosaemia is not part of newborn screening in Victoria).

About 0.1% of babies tested will be diagnosed with a condition as a result of newborn screening. Blood for testing is collected by heel prick 48–72 hours after birth (usually by a midwife in hospital or by a maternal child health nurse) and the blood is dried onto a newborn screening card (Guthrie card). Verbal agreement is required from the parents of the child before the test is performed, and must be recorded in the medical notes. When parents raise concerns, the opportunity is provided to discuss the test and address any concerns. It is rare for parents to refuse to give consent.

For the majority of babies, no condition will be suggested by newborn screening and parents and doctors are not notified of 'normal' results. However, as screening does not detect all affected babies, symptoms in a child warrant further investigation. Parents will be notified if follow up testing is required, either because there was a problem with the initial blood sample or because a result was abnormal. If possible, the Newborn Screening Service will contact the general practitioner who may prefer to notify the parents

Table 5. Advantages and disadvantages of diagnostic tests during pregnancy

Diagnostic test	Gestation (weeks)	% Down syndrome pregnancies detected	Advantages	Disadvantages
Chorionic villus sampling (CVS)[a]	From 11 weeks[b]	Greater than 99%	• Early detection • Definitive diagnosis • Results potentially available in time for termination of pregnancy (TOP) by curette	• Miscarriage risk (~1% above background in expert hands) • Detects chromosomally abnormal pregnancies that may otherwise spontaneously miscarry • 1% risk of equivocal results (placental mosaicism or maternal cell contamination of sample) • 0.1% failure to detect chromosome abnormality (abnormality is present in fetus but not in placenta, or maternal cell contamination of sample)
Amniocentesis[a]	From 15 weeks[c]	100%	• Test with lowest miscarriage rate • Definitive diagnosis	• Miscarriage risk (~0.5% above background in expert hands) • Diagnosis in second trimester when pregnancy is more established • Results available too late for TOP by curette (TOP may need to be performed by induction of labour or vaginal evacuation[c])
Second trimester fetal anomaly ultrasound scan (Also considered a screening test, see 'disadvantages')	18–20 weeks	Very low pick up rate on soft markers alone	• Detects many physical fetal abnormalities such as: neural tube, cardiac, limb, gastrointestinal, CNS • No added risk of miscarriage • Measures fetal growth and locates position of placenta	• Not all physical abnormalities can be detected • 'Soft markers' (risk factors for chromosomal abnormalities not definitive and difficult to interpret); 30% of babies with Down syndrome will have soft markers/signs • Not recommended as primary screening test for Down syndrome

a Out of pocket expenses vary for CVS, amniocentesis and scans according to each state/territory. Public patients attending a tertiary public hospital may not be charged if identified as 'increased risk'

b The timing of CVS is not uniform throughout Australia (eg. in South Australia it is sometimes offered from 10 weeks gestation)

c Procedures after 20 weeks gestation may not provide results in timeframe permitting second trimester termination of pregnancy. Refer to state/territory abortion laws, and policies of local perinatal units

Table 6. Criteria for screening for a disorder

- The disease must be an important health problem; it must be severe and/or common
- The disease must be preventable or treatable by acceptable methods
- The screening test must be simple, safe, reliable and acceptable
- Education and counselling facilities must be generally available

before follow up testing. About 1–2% of babies tested require repeat or subsequent diagnostic testing, although the majority will receive 'normal' results, in which case their GP will be sent the result. Treatment, counselling and support are provided free of charge by the services associated with newborn screening services in each state or territory.

Carrier screening

There are currently no national population based carrier screening programs for genetic conditions in Australia, although there are some specific programs offered. In Victoria, carrier screening for the autosomal recessive condition, Tay-Sachs disease, is offered to high school students in some Jewish schools free of charge. These students can also be tested for other conditions with a higher prevalence in this ethnic group as fee for service (see the article 'Family genetics' this issue). These tests, together with carrier screening for cystic fibrosis, are offered to students in all Jewish schools in New South Wales. Cystic fibrosis carrier screening is offered through obstetricians and GPs as fee for service through genetic services in Victoria and private laboratories.

What does the future hold for genetic screening?

As our understanding of the genetic contribution to conditions increases, so will the number of candidates for population genetic screening programs. It is important that such programs are evaluated according to the principles of population screening[7–10] (*Table 6*). This may require that they are offered within research studies before implementation, such as haemochromatosis screening[11] and carrier screening for fragile X syndrome.[12] In the future, it is likely that more conditions will be screened at a population level for genetic markers associated with susceptibility to common complex conditions such as thrombosis, emphysema, hypertension, osteoporosis, hypercholesterolaemia, type 2 diabetes, and coronary heart disease, as well as screening that harnesses developments in pharmacogenomics, introducing the concept of genetically personalised medicine.[10]

Summary of important points

- Identify opportunities for prepregnancy counselling.
- Assess whether information in the family history places the current pregnancy at increased risk.
- Consider carrier tests for those from specific ethnic groups.
- Prenatal screening should be offered to all pregnant women as a choice: provide information about screening and diagnostic tests.
- Provide information about newborn screening to parents before delivery.

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afp **CORRESPONDENCE** email: afp@racgp.org.au