



## College Statement

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Title	<b>Prenatal screening tests for trisomy 21 (Down syndrome), trisomy 18 (Edwards syndrome) and neural tube defects</b>
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*A Guideline developed by the Human Genetic Society of Australasia (HGSA) and the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG).*

## Statement

### **Prenatal screening tests for trisomy 21, trisomy 18 and neural tube defects**

In Australia and New Zealand, prenatal screening tests are available to identify pregnancies at increased risk of chromosome anomalies such as trisomy 21, trisomy 18 and some structural anomalies such as neural tube defects. Ultrasound and maternal serum screening tests identify fetuses with an increased likelihood of having one of these conditions. Sometimes these conditions are not compatible with live birth, some are associated with long-term and serious morbidity, and some require neonatal investigation or treatment. There is usually no intrauterine fetal therapy.

Screening tests lead to an offer of a diagnostic test (ultrasound, chorionic villus sampling or amniocentesis) to women with pregnancies identified at increased risk of fetal anomaly. In the event of the diagnosis of an anomaly, the woman and her partner may choose to terminate or continue with the pregnancy.

Prenatal screening is best implemented in the context of a comprehensive program that coordinates pre-test counselling and information, biochemical and ultrasound measurements, post-test interpretation, counselling and support during decision making and, where indicated, follow-up consultations and diagnostic testing.

### **1 Pre-test counselling and information**

- a) All pregnant women should be advised of the availability of prenatal screening as early as possible in pregnancy to allow time to discuss the options available and facilitate an informed choice.

- The term 'informed choice' is used in the context of shared decision-making. The ability to make an informed choice is particularly important because of the value-laden implications of prenatal screening.
  - The information provided should include written and verbal explanations that are based on current evidence.
- b) Information on the relative advantages and disadvantages of the available screening tests should be provided to pregnant women (and their partners). Information should be provided in a way that is easily understood and culturally appropriate. Information should include details of the nature, purpose, limitations and consequences of screening. The offer of screening needs to take into account both the tests that are available to the woman and the stage of her pregnancy. There should be information on:
- The understanding that screening is entirely voluntary and that there will be no change to pregnancy management if a woman and her partner choose not to have any screening tests.
  - The practical aspects of screening including the conditions that are being screened for, the type of tests, the timing of tests and the approximate costs involved.
  - The possibility that ultrasound scans may be diagnostic of anomalies other than those for which the screening programs are designed.
  - The probabilistic nature of results including residual risk and the offer of a follow up diagnostic test if an 'increased risk' (positive) result is obtained.
  - The understanding that a termination of pregnancy would be available in the event an abnormality was diagnosed, and that the mode of termination available will be influenced by gestational age. There should be an assurance that continuation of the pregnancy is a valid option should an abnormality be diagnosed, and that couples would receive appropriate counselling and care in preparation for birth.
- c) Health professionals caring for pregnant women should undertake continuing education regarding options available for prenatal screening, and should:
- Know about the current screening modalities available and in what settings they can be implemented.
  - Be able to provide pre-test information including written resources developed for this purpose.
  - Participate in Continuing Professional Development (CPD) and courses that provide current evidence based information on prenatal screening.

**BEST PRACTICE NOTE:**

*Resources available to health professionals include websites and professional organisations, seminars, courses and printed material which are regularly revised and updated so that they reflect current practice. Pamphlets and other information are available from local genetic services and obstetric ultrasound / radiology practices.*

- d) Informed practitioners should be available for consultation. These may include:
- Ultrasound specialists, specialist Obstetricians & Gynaecologists, Clinical Geneticists, Genetic Counsellors, General Practitioners and Midwives. Women may also choose to access consumer organisations that provide specific information about various conditions.

## 2. Recommended screening tests

### a) First trimester for trisomy 21 and trisomy 18

#### **Combined first trimester screening:**

The risk assessment incorporates NT, crown-rump length (CRL) and maternal age. This test must be done when the fetus has a CRL of 45 to 84mm, which approximately corresponds to **11W to 13W 6D**.

#### **i) Blood collected at 9W to 13W 6D (ideally 9-12W) gestation for biochemical analysis of:**

- Pregnancy Associated Placental Protein-A (PAPP-A)
- Free  $\beta$ hCG

Currently the Fetal Medicine Foundation (FMF) software (Viewpoint and Astraia) accepts biochemistry results expressed in absolute values (U/L) or Multiples of the Median (MoM) when measured on Brahms Kryptor, Wallac, (Delfia Xpress, Autodelfia and Manual Delfia) platforms. Results from laboratories using other platforms should be entered into the FMF software as MoM measurements. Some laboratories may use their own biochemical data together with nuchal translucency measurements to report risks based on their own or commercially validated software.

#### **COMBINED WITH: -**

#### **ii) Ultrasound measurement of fetal nuchal translucency (NT) (11W to 13W 6D gestation)**

- NT measurements should only be performed by trained operators who are accredited with the Nuchal Translucency – Ultrasound, Education and Monitoring Program or FMF and who participate in regular audit (<http://www.nuchaltrans.edu.au/>).

#### **BEST PRACTICE NOTES:**

*For singleton pregnancies, risk assessment using combined first trimester screening including NT, free  $\beta$ hCG and PAPP-A is preferred to screening by NT alone. In multiple pregnancy, nuchal translucency assessment alone is the preferred modality for screening but may be combined with first trimester serology in twins. It is essential that the laboratory is notified of a twin pregnancy, and appraised of the chorionicity (monochorionic / dichorionic), in order that appropriately corrected PAPP-A and Free  $\beta$ hCG MoM values and/or aneuploidy risks are reported.*

*Biochemical screening cannot be used in triplet or higher order pregnancies. Interpretation of screening results, counselling and management of increased risk results in the setting of multiple pregnancy (twins and higher orders) are more complex than for singletons. It is therefore recommended that advice on screening and management in multiple pregnancies be sought from centres capable of performing diagnostic procedures.*

*Additional factors that modify risk assessment include previous pregnancy with trisomy 21, trisomy 18 multiple pregnancy, assisted reproduction and maternal weight. These should also be notified to the laboratory, when present.*

**b) Second trimester for trisomy 21, trisomy 18 and neural tube defects.**

**Maternal serum screening:**

**i) Blood is collected at 14W to 20W (ideally 15-17W) gestation for biochemical analysis of:**

- Alpha fetoprotein (AFP)
  - Free  $\beta$ hCG (or total hCG)
  - Unconjugated estriol (uE3)
- Some laboratories also include:
- Inhibin A

Commercial and 'in-house' software packages are used to calculate risks for trisomy 21, trisomy 18 and neural tube defects.

**BEST PRACTICE NOTES:**

*Other factors that modify risk assessment include maternal weight and history of previous pregnancy with trisomy 21, trisomy 18, or neural tube defect. These should be incorporated in the software algorithm that is used to generate risk.*

*Second trimester maternal serum screening is feasible in twin pregnancy. However, interpretation and management is more complex than for singletons. Advice on management should be sought from centres capable of performing the necessary diagnostic procedures in multiple pregnancies.*

**c) Screening for neural tube defects**

- The sensitivities and specificities of first and second trimester ultrasound and second trimester biochemical (alpha feto-protein; AFP) screening for neural tube defects (anencephaly and spina bifida) are shown in the table below:

	11–13 <sup>+6</sup> wk U/S <sup>1-3</sup>		≥15 wk AFP (≥2.0MoM) <sup>4</sup>		18–20 wk U/S <sup>5,6</sup>	
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
Anencephaly	100%	>99%	100%	97%	100%	>99%
Spina Bifida	10%	n/a	88%	97%	98%	>99%

- Anencephaly can be diagnosed at the 11W -13W 6D scan by assessing calcification of the fetal cranium in a transverse section. Ultrasound will also diagnose all fetuses with anencephaly at 18-20 weeks.
- Spina bifida is not commonly diagnosed by ultrasound at the 11W -13W 6D scan. AFP screening detects 88% of affected fetuses with a false positive rate of 3% in the second trimester.
- A positive screen result should be followed by a diagnostic scan in a tertiary unit. Although the data on the diagnostic performance of ultrasound is primarily based on assessment at 18-20 weeks, earlier evaluation may be considered.
- In many centres, the standard of the 18-20 week morphology scan is in effect a diagnostic test for spina bifida, and AFP screening has essentially been superseded.

#### d) Second trimester fetal morphology ultrasound scan

A second trimester fetal morphology ultrasound scan is not recommended as the primary screening tool for Trisomy 21 and Trisomy 18. However it can be used as primary screening for neural tube defects.

#### **BEST PRACTICE NOTE:**

*All women should be provided with the opportunity to have a detailed fetal morphology ultrasound scan at 18W to 20W gestation, to screen for structural fetal anomalies and pregnancy wellbeing.*

### 3. Management of screening results

#### i. Low risk screen results

- Women should be advised of the result in a timely manner.

#### ii. Increased risk results

#### **Trisomy 21**

##### *Combined first trimester screening*

- An increased risk should be considered as a risk of 1 in 300 or greater at the time of screening

##### *Second trimester maternal serum screening*

- An increased risk should be considered as a risk of 1 in 250 or greater at term. The cut-off used to define women at increased risk of a Trisomy 21 affected pregnancy should be 1 in 250 at term. This is consistent with the recommendations of the UK National Screening Committee, Antenatal Screening – Policy and Quality Issues (2003).

#### **Trisomy 18 (Edwards syndrome)**

##### *Combined first trimester screening and second trimester maternal serum screening*

- Trisomy 18 can be detected in both 1st and 2nd trimester screens. The detection rate varies between studies. Different detection rates and increased risk cut-offs are used by different laboratories.

#### **Neural Tube Defects (NTD)**

##### *Second trimester maternal serum screening*

- Women with a serum AFP > 2.0 MoMs should be defined as being 'increased risk' for a neural tube defect and should be referred for diagnostic ultrasound in a tertiary centre.

#### **BEST PRACTICE NOTES:**

*If an increased risk result is obtained for chromosome anomalies, the woman should have access to counselling services for support during the next decision-making phase and follow up. The option of prenatal diagnosis should be discussed and offered.*

*If the karyotype is normal, or there has been no prenatal diagnostic test, the woman should be advised of residual risks of non-chromosomal fetal anomalies and adverse pregnancy outcomes. She should be offered an 18 to 20 weeks gestation fetal morphology ultrasound scan by an experienced operator for assessment of pregnancy well-being and fetal structural anomalies.*

*If there is a prenatal diagnostic test and the karyotype is abnormal, appropriate counselling should be provided by a multidisciplinary team or suitably qualified person (with appropriate support), regarding the nature of the abnormality and the option of continuation or termination of the pregnancy.*

#### 4. Education and training for the measurement of nuchal translucency

All professionals working in diagnostic imaging measuring Nuchal Translucency and providing related services should be credentialed or engaged in a formal process to be credentialed in the measurement of the Nuchal Translucency.

In Australia and New Zealand, appropriate education and training for the measurement of nuchal translucency is recognised through the Fetal Medicine Foundation (FMF) London and the Australian Nuchal Translucency – Ultrasound, Education and Monitoring Program (co-located at RANZCOG). To become a credentialed operator in the performance of the nuchal translucency scan, operators must complete the following:

- Satisfactorily complete a theoretical course and complete the pre- and post- course Multiple Choice Questionnaires.
- Submit a logbook of images for assessment.
- Attend a clinical session in the presence of an approved examiner and be able to demonstrate ability to accurately measure: the CRL and the NT according to the FMF guidelines and the CRL.

To maintain the status of a credentialed operator, professionals need to:

- Submit data for the assessment of the distribution of their measurements annually.
- Submit five random images for assessment annually.

The theoretical course is open to all those involved in obstetric ultrasound, including obstetricians, radiologists, sonographers, general practitioners, genetic counsellors and midwives (<http://www.nuchaltrans.edu.au/>).

#### 5. Quality assurance

All laboratories must be accredited by the National Association of Testing Authorities (NATA) in Australia, and International Accreditation New Zealand (IANZ) in New Zealand. Laboratories performing first trimester screening should be encouraged to apply for accreditation with the FMF (London). Ideally, there should be a senior member of the laboratory staff responsible for the screening service, with defined lines of accountability for all laboratory aspects of the service.

- Data published by Australian service providers screening large populations for trisomy 21 confirm that detection rates of 85-93%, adjusted for a false positive rate of 5%, can be achieved using combined first trimester screening<sup>7-9</sup>. Currently, the significant majority of screening tests performed in states with large programs is combined first trimester screening.
- It is no longer appropriate to offer population based first trimester screening for trisomy 21 using maternal age and nuchal translucency alone.
- Data for second trimester maternal serum screening for trisomy 21 show lower detection rates of 64-78% adjusted for a 5% false positive rate<sup>4,8,10</sup>.
- External and internal quality control measures should be in place. Laboratories that measure risk for Trisomy 21 and neural tube defects during the second and/or first trimester must participate in an external quality assurance program (e.g. United Kingdom National External Quality Assurance Service [UKNEQAS] <http://www.ukneqas.org.uk/>).

Combined first trimester screening is dependent on the accuracy of results utilising standards of two usually independent providers, a serum laboratory and an ultrasound practice. The provider who inputs the data for risk calculation must know that the other provider has appropriate training, credentialing and ongoing audit for results to be valid.

- Laboratories should make every effort to be aware and state in the report if the NT measurements are performed by operators who are credentialed.
- If laboratories are performing small numbers of screening tests annually (1000 or less), they need to have an alignment with a larger laboratory in order to statistically review analytical parameters, such as overall patient MoM and median values. This alignment is necessary to assess if changes need to be made to their median values. This is consistent with the recommendations of the UK National Screening Committee, Antenatal Screening – Policy and Quality Issues (2003).  
<http://www.library.nhs.uk/screening/>

## 6. Performance quality standards and monitoring processes

There should be a national approach to developing and reviewing standards for performance measures both for pathology and ultrasound. For laboratories, examples of the minimum set of parameters that should be incorporated as performance measures are detection rate, screen positive rate, analytical and clinical validity (<http://www.cdc.gov/genomics/gtesting/ACCE.htm>).

For ultrasound, operators should participate in training to become credentialed in the performance of the nuchal translucency scan and participate in annual audit to monitor their performance.

- Those who provide risk assessment, whether laboratory or ultrasound units, should undertake overall audit and monitoring of their prenatal screening programs. Additional follow up of all pregnancies screened is necessary if providers are to have accurate and current information on the number of pregnancies screened, the detection rate and the screen positive rate.
- Monitoring screening program performance should include data on analyte medians, detection rate, screen positive rate, maternal age distribution of the screened population, uptake of screening and prenatal diagnosis tests, pregnancy outcome data and audits of women's understanding and experiences of screening.

## 7. Integrated Screening

- Integrated testing is where first and second trimester serum screening is combined with nuchal translucency and only one risk value is provided for all three tests. It has been proposed as a way to both increase the detection rate for Trisomy 21 and decrease the false-positive rate. The practical difficulty of this is that the results that allow for choice of intervention are not available until the second trimester. An additional problem has been poor attendance for the second trimester component of the screening as shown by Wiesz et al<sup>11</sup>. The evidence concerning achievable detection rates, false positive rates and compliance in practice is controversial. Therefore support for integrated screening remains under consideration at this time.

## NEW ZEALAND

It is recommended that in New Zealand those providing screening services for trisomy 21, trisomy 18 and neural tube defects attain the standards described above.

At the present time, there is no nationally coordinated prenatal screening program for Trisomy 21, Trisomy 18 or neural tube defects in New Zealand. However, a program is currently being developed. When information is available about the evolving New Zealand program it will be incorporated into this document.

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## **Useful Links**

Nuchal Translucency – Ultrasound, Education and Monitoring Program [www.nuchaltrans.edu.au](http://www.nuchaltrans.edu.au)

The Fetal Medicine Foundation (FMF) <http://www.fetalmedicine.com> credentials ultrasound operators and provides ongoing quality assurance for operators working outside Australia.

## **Disclaimer**

This College Statement is intended to provide general advice to Practitioners. The statement should never be relied on as a substitute for proper assessment with respect to the particular circumstances of each case and the needs of each patient.

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