Prenatal Screening and Diagnostic Testing for Fetal Chromosomal Abnormality

Summary This Policy Directive outlines requirements for prenatal screening and diagnostic testing for fetal chromosomal abnormality for clinical and care providers.

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Policy Directive

Prenatal Screening and Diagnostic Testing for Fetal Chromosomal Abnormality

Policy Statement

NSW Health is committed to providing prenatal screening, testing and related support services to all clinical and care providers. Included in this document is the provision of appropriate counselling and resources to assist pregnant women in making timely informed decisions.

Summary of Policy Requirements

Antenatal care providers must offer prenatal screening and diagnostic testing for fetal chromosomal abnormalities as part of routine care. A variety of screening and diagnostic tests can identify pregnancies at high risk of, or affected by, a chromosomal abnormality.

All pregnant women must be given the opportunity to opt into prenatal screening and/or prenatal diagnosis as early as possible in their pregnancy. Appropriate pre-and post-test counselling resources need to be available to allow informed consent for testing.

Screening tests

Screening tests can be performed throughout pregnancy from 10 weeks' gestation. These are done to identify sub-groups of pregnancies considered to be at increased risk of being affected by a form of aneuploidy.

Screening tests do not provide a definitive diagnosis. Individuals identified as being at increased risk are typically offered a diagnostic test.

Screening tests that can be offered at different gestation timepoints include:

- Combined first trimester screening, which is restricted to a fetus with a crown-rump length of 45–84 mm (approximately 11–13^{+6} weeks gestation).
- Second trimester biochemical screening, which can be used at 14–20 weeks' gestation.
- Non-invasive prenatal screening, which can be performed from 10 weeks' gestation onwards. There is no upper gestational limit for this test.

Diagnostic tests

Diagnostic tests for fetal aneuploidy involve tissue sampling for cytogenetic or molecular genetic analysis. Almost all prenatal diagnoses are now performed on placental tissue (chorionic villus sampling) or amniotic fluid (amniocentesis).

Revision History

Version	Approved By	Amendment Notes
PD2024_013 April-2024	Deputy Secretary, Health System Strategy and Patient Experience	Recommendations updated to apply to all pregnant women; no distinction between women considered to be at increased risk and those not at increased risk. Addition of non-invasive prenatal screening (NIPS). Abbreviation of laboratory testing procedures and requirements.
PD2007_067 August-2007	Director-General	Policy directive
GL2005_012 January-2005	Director-General	Guideline

Contents

1. Background

Chromosomal abnormalities affect approximately 1% of pregnancies, are responsible for a significant proportion of miscarriages and are the most common cause of structural and neurodevelopmental anomalies in infants.

A variety of screening and diagnostic tests can identify pregnancies at high risk of, or affected by, a chromosomal abnormality. These screening tests have varying efficacy, advantages and disadvantages, and the same screening tool will not necessarily suit all pregnant women.

Prenatal screening options should be discussed and offered in the first trimester whenever possible. Screening or diagnostic testing for fetal chromosomal and genetic conditions is voluntary and should only be undertaken if part of an informed decision by the pregnant woman. Decision-making should involve informed financial consent if the pregnant woman is to incur a cost.

Appropriate pre-and post-test counselling resources need to be available to allow informed consent for testing. Decisions regarding testing for pregnant women who present >24 weeks gestation are complex and must be managed on a case-by-case basis.

Screening tests for trisomies 21, 18 and 13 potentially identify 50% of pregnancies affected by all types of aneuploidies. Newer forms of screening can potentially identify pregnancies at higher risk of other chromosomal abnormalities such as Turner syndrome and other sex chromosome aneuploidies, rare autosomal aneuploidies, and microdeletions and/or duplications. The benefits and disadvantages of screening for forms of chromosomal abnormality beyond common trisomies need to be carefully considered and communicated to those contemplating extended screening, as it may be of limited clinical utility and cause unwarranted concern.

1.1. About this document

This Policy Directive describes the process to be followed when prenatal screening and testing are conducted. It provides direction on access to, and provision of prenatal testing and screening, so pregnant women are informed about screening options and how to access appropriate clinical and support services. Each test has advantages, disadvantages, and limitations. Offers of screening must be accompanied by the relevant information relating to testing and support to enable informed decision making and consent.

This Policy describes screening and diagnostic testing options for common forms of chromosomal abnormalities, such as trisomies 21, 18 and 13. It also reviews the potential of screening for sex chromosome aneuploidy, rare autosomal chromosomal abnormalities such as trisomies and microdeletions.

1.2. Key definitions

Counselling	A communication process, which aims to help individuals, couples and families understand and adapt to the medical, psychological, familial, and reproductive implications of the genetic contribution to specific health conditions.
Deoxyribonucleic acid (DNA)	A self-replicating material which is present in nearly all living organisms as the main constituent of chromosomes. It is the carrier of genetic information.
Gene	The basic physical and functional unit of heredity. Genes, which are made up of DNA, act as instructions to make molecules called proteins.
Genetics	The study of genes, genetic variation, and heredity in living organisms.
Testing	A type of medical test that identifies changes in chromosomes, genes, or proteins.

1.3. Legal and legislative framework

This Policy is underpinned by the requirements of Legal and Legislative frameworks including related NSW Health strategies, guidelines, policies, and procedures (Refer to Attachment 1: Related Resources).

2. Consent and Counselling

All prenatal screening and testing for chromosomal and genetic conditions is voluntary. Pregnant women must provide consent for testing and must have been provided with relevant information (e.g., nature of the test, possible results, and options available) to give informed consent.

The individual being tested must be legally competent to give consent; must consent freely without coercion by professional staff, family members, employers, insurers, or others; and be adequately informed about all relevant issues and available testing options. The person may withdraw consent at any time.

For individuals, their partners or support people from culturally, linguistically, and diverse backgrounds and/or hearing impairment, professional interpreter services must be engaged, if required. The provision of care must be inclusive and sensitive to intersectionality, including (dis)ability, race, and Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual (LGBTQIA) persons.

Some screening protocols such as combined first trimester screening include an ultrasound scan that assesses multiple aspects of pregnancy. Pregnant women electing not to have

screening for aneuploidy must be made aware of the other important benefits of routine scanning, e.g. confirmation of gestational age, placental localisation, early identification of a multiple pregnancy and structural anomalies.

2.1. Pre-test counselling

Issues for consideration and discussion before any screening test is undertaken include:

- Recognising a woman's values and preferences, to ensure counselling is culturally sensitive and respectful.
- The difference between screening and diagnostic testing.
- Potential outcomes and options for further testing if indicated.
- Discussion of the benefits and limitations of tests that can be completed now or at a different stage in their pregnancy.
- Identifying the conditions that can be screened/tested for and those not assessed.
- Identification of patient-specific factors that will impact the appropriateness of a test.
- Discussion of baseline levels of risk based on maternal age and family history.
- Establishing how and when test results will be communicated before completing the test.
- Facilitation of shared decision-making and respecting a woman's choice.
- The potential costs of testing, including whether the tests are Medicare-rebated.

2.2. Post-test counselling

Considerations for discussion after receipt of screening results:

- Provision of the result(s) and an interpretation of ongoing risk in a timely manner. If a screening test describes an '*increased chance'* (may also be referred to in screening test reports as ‘high risk’ or ‘increased risk’) then the likelihood of the pregnancy being affected (positive predictive value) must be discussed.
- If relevant, discussion of options for further testing includes relative benefits and limitations of different options, including risks associated with invasive procedures.
- Establishing whether the woman wishes to proceed with any further testing and supporting and respecting autonomy in decision making.
- Ensuring that other health professionals involved in managing the pregnancy are aware of the tests that have been performed, their results, and the decisions made in relation to the pregnancy.

3. Prenatal Screening

3.1. Prenatal screening tests

Screening tests are designed to identify sub-groups of pregnancies considered to be at increased risk of being affected by a form of aneuploidy and do not provide a definitive diagnosis. These at-risk sub-groups would typically be offered a diagnostic test.

Screening tests can be performed throughout pregnancy from ten weeks' gestation. Different screening tests can be offered at different gestation timepoints.

Screening tests may be based on maternal history and characteristics, biomarkers, ultrasound markers or genomic markers or may involve a combination of these approaches.

All women must be offered at least one screening test for chromosomal abnormality. The most common chromosomal abnormality is trisomy 21, and screening tests are typically judged by performance in the assessment of this condition.

Screening must be restricted to high efficacy tests (traditionally >75% detection for the condition for a 5% or lower screen positive rate). The screening tests described below and summarised in Table 1 are limited to those involving assessment at a single time point.

3.1.1. Combined first trimester screening

Combined first trimester screening is widely available and is the screening test currently used for many pregnancies.

The test includes measurement of the ultrasound marker 'nuchal translucency' and this must be assessed by an accredited sonographer/sonologist.

The test also includes measurement of the biochemical markers free beta-human chorionic gonadotropin, and pregnancy associated plasma protein-A. These must be tested and reported on by an accredited pathology service.

Risks are based on the *a-priori* risk derived from maternal age and history of previous pregnancy affected by trisomy 21. The ultrasound and biochemical markers need to be converted using a mixture model and/or multiple of medians for risk calculation. For biochemical markers this needs to be related to gestational age and maternal weight (at a minimum) and to plurality.

Combined first trimester screening detects 85–90% of trisomy 21 pregnancies for a 5% screen-positive rate. The test can be extended to include other ultrasound (e.g., nasal bone) or biochemical (e.g., placental growth factor markers to improve screening performance).

The ultrasound component of the test is also of value for accurate dating of the pregnancy, identification of multiple pregnancies, identification of major fetal structural abnormalities and development of risks for adverse pregnancy outcomes such as preeclampsia.

Combined first trimester screening is restricted to a fetus with a crown-rump length of 45–84 mm, which is approximately 11–13^{+6} weeks gestation.

3.1.2. Second trimester biochemical screening

Second trimester screening is biochemistry based and involves measurement of alpha feto-protein, total human chorionic gonadotropin and estriol; sometimes described as a 'triple test'. The incorporation of a fourth marker, Inhibin-A ('quadruple test'), improves test efficacy.

These tests report approximately 75% detection of pregnancies affected by trisomy 21 for a 5% screen-positive rate.

These tests are most effective if the absolute quantification of markers is adjusted for maternal weight and gestational age. The raw data also need to be adjusted for a multiple pregnancy.

Second trimester screening can be used at 14–20 weeks' gestation and therefore offers pregnancies who missed combined first trimester screening an opportunity to have a screening test. Screening efficacy is, however, poorer than cell-free DNA (cfDNA) screening (see below), and this may be a better alternative. Second trimester biochemical testing is becoming less widely used as cfDNA screening becomes more prevalent.

3.1.3. Non-invasive prenatal screening for chromosomal abnormalities

Non-invasive prenatal screening for chromosomal abnormalities is also known as cfDNA screening or non-invasive prenatal testing. Non-invasive prenatal screening can be performed from 10 weeks' gestation onwards. There is no upper gestational limit for this test.

Non-invasive prenatal screening for chromosomal abnormalities involves genomic analysis of fragments of cfDNA in maternal plasma. The majority (approximately 90%) of cell-free fragments are maternal in origin, but a significant minority (approximately 10%) are placental and identified as the fetal fraction.

Non-invasive prenatal screening for chromosomal abnormalities involves the collection of a single maternal blood sample. The mixed maternal and fetal DNA fragments are extracted from maternal plasma. Several technologies are used to identify these fragments and determine whether the pregnancy is likely affected by a chromosomal abnormality. Although there is variation between commercially available products, all currently available assays include screening for trisomies 13,18 and 21 as well as sex chromosome aneuploidies.

Non-invasive prenatal screening assays report the highest level of screening efficacy (~99% detection for trisomy 21; <1% screen positive tests), although these reports often exclude 'no-call' results. CfDNA tests also have higher efficacy for other common trisomies (trisomy 18 and trisomy 13).

Non-invasive prenatal screening may not be the most appropriate tool for determining fetal aneuploidy in several clinical situations, in which case diagnostic testing is to be considered. These include:

- Maternal age > 45 years
- The nuchal translucency measures ≥ 3.5mm
- The free β- human chorionic gonadotropin measures greater than ≥ 5.0 MoM or < 0.2 MoM
- The pregnancy-associated plasma protein-A measures < 0.2 MoM

- The combined first trimester screening risk is > 1:100
- A structural anomaly is detected on ultrasound
- There is repeated non-invasive prenatal screening failure.

Although non-invasive prenatal screening is highly sensitive, the relatively low prevalence of trisomies 13, 18 and 21 means that positive predictive values are 37-92%, not 100%. It is important to validate an increased risk non-invasive prenatal screening result with diagnostic testing, particularly if there is consideration of termination of pregnancy. Termination of pregnancy must not be offered based on non-invasive prenatal screening results alone.

'No result' is reported in 1–2% of pregnancies, typically due to low fetal fraction or failure of laboratory quality standards. The merits of repeat testing, alternative strategies for screening, or diagnostic testing are then to be considered.

Non-invasive prenatal screening can also be used to screen for other forms of aneuploidy (rare autosomal trisomies, segmental aneuploidies) and/or some recurrent microdeletions and duplications, as well as other rare chromosomal imbalances. Data describing test performance for these conditions exists; however, careful pre-test counselling is required to identify the advantages and disadvantages of adding these conditions to a screening regimen. Commercial providers offer various options for extended testing, and clinicians must be aware of how these perform if they are offering or referring for testing.

Table 1. Characteristics of common screening tests for trisomy 21 detection

Test	Detection rate (sensitivity)	Screen positive rate	Comments
Combined first trimester screening	85–90%	5%	Limited to a fetus with a crown-rump length of 45–84 mm, which is 11–13^{+6} weeks' gestation Incorporates ultrasound (nuchal translucency) / biochemistry (free β- human chorionic gonadotropin and pregnancy-associated plasma protein-A with maternal age / previous history of trisomy 21. Robust test validated with large population-based datasets. Ultrasound valuable for detection of other pregnancy risk factors and prescribing risk of adverse pregnancy outcome. Needs skilled operator. Needs coordination of multiple parameters. Limited to <13^{+6} weeks' gestation.
Second trimester biochemical screening	70–75%	5%	15–20 weeks' gestation Incorporates biochemistry Alpha feto-protein, Total human chorionic gonadotropin, oestradiol +/- Inhibin A) with maternal age / previous history of Trisomy 21.

			Robust test validated with large population-based datasets. Needs scan to confirm gestational age. Relatively late (≥15 weeks' gestation). Less efficacious than other screening tools.
Non-invasive prenatal screening for chromosomal abnormalities (cfDNA)	99%	1–2%*	>10 weeks' gestation (no upper limit). DNA extracted from maternal plasma. Highest reported detection rate. Lowest reported screen positive rate. Limited performance data from population-based studies. A baseline scan is still needed.

*Includes 'no-calls' due to low fetal fraction and/or complications of DNA analysis

3.1.4. Screening with the routine 18–22 week morphology scan

The 18–22 week morphology scan can identify up to 70% of major structural abnormalities. It does not identify all structural anomalies and is not specifically designed to screen for chromosomal abnormalities. This is not recommended as a primary screening tool for chromosomal abnormality.

Most major structural anomalies are associated with an increased risk of aneuploidy, and diagnostic testing using an array-based approach is to be offered.

Minor markers (soft signs) are variations of normal that have an increased prevalence in some chromosomal abnormalities. Most markers have an insignificant impact on risk when found in isolation in an otherwise low-risk pregnancy and will not result in reassignment of risk to a high-risk group.

The presence of multiple markers, or of markers that have stronger associations with aneuploidy (nuchal oedema and hypoplastic nasal bone) may require reassignment of risk. The outcome of previous screening tests is to be reviewed, and the impact of this new finding(s) considered. This assessment may require the input of a specialist obstetrician or subspecialist in pregnancy imaging/maternal and fetal medicine.

3.1.5. Use of non-invasive prenatal screening within a contingent screening model

Although contingent screening is not currently recommended as the primary model for screening in NSW, this represents an alternative strategy, with this model, all pregnancies are offered combined first trimester screening.

The results of this test are interpreted using different thresholds to identify an 'intermediate' cohort that would benefit from second-tier screening by non-invasive prenatal screening. This process can enhance detection rates for trisomy 21 and reduce the screen-positive rate whilst minimising the number of non-invasive prenatal screening tests that are needed.

Alternatively, non-invasive prenatal screening can be used as a second-line test in pregnancies deemed high-risk using less specific screening tools (combined first trimester

and second trimester biochemistry). However, it is noted that some chromosomal anomalies that would be identified through diagnostic testing of these pregnancies will be missed if invasive testing is replaced by non-invasive prenatal screening.

4. Diagnosis of Fetal Aneuploidy

4.1. Diagnostic tests

Diagnostic tests for fetal aneuploidy involve tissue sampling for cytogenetic or molecular genetic analysis. A variety of tissues can be used to establish a diagnosis, including placenta, amniotic fluid (containing fetal squamous cells) and fetal blood. Almost all prenatal diagnoses are now performed on placental tissue (chorionic villus sampling) or amniotic fluid (amniocentesis).

4.1.1. Chorionic villus sampling

Chorionic villus sampling describes the collection of a placental sample. The test is either performed transabdominally (introducing a needle through the maternal abdomen, into the uterus and placenta) or transvaginally (introducing biopsy forceps through the cervix and into the placenta).

Chorionic villus sampling is usually performed at 11–14 weeks gestation but can be performed at later gestations.

The patient must be aware that the procedural risk of miscarriage is <1 in 200 procedures. The background risk of miscarriage at 12 weeks gestation is approximately 2%.

Chorionic villus sampling is performed by obstetric specialists in all tertiary NSW Local Health District and Speciality Health Network facilities and analysed in accredited laboratories.

4.1.2. Amniocentesis

Amniocentesis describes the collection of an amniotic fluid sample from the pregnant uterus. The test involves the introduction of a needle through the maternal abdominal wall and into the uterus.

A sample of approximately 20 ml is normally collected – which is replenished naturally within four hours. Amniocentesis is normally performed at 15–24 weeks gestation and can also be performed at later gestations.

The patient must be aware that the procedural risk of miscarriage is <1 in 200 procedures. The background risk of miscarriage at 16 weeks gestation is approximately 1%.

Amniocentesis is performed by obstetric specialists in all tertiary and some Level 5 NSW Local Health District facilities. The sample will normally be analysed in accredited laboratories.

4.1.3. Laboratory testing

Details of analysis and reporting of prenatal diagnostic samples and associated counselling issues are outside the scope of this document. Samples are routinely analysed in two stages.

Quantitative fluorescent polymerase chain reaction analysis for trisomy 13, trisomy 18, trisomy 21 and sex chromosome aneuploidies is typically performed first, with results generally available in less than three working days (once the sample is received by the laboratory). Due to the potential for confined placental mosaicism, quantitative fluorescent polymerase chain reaction results are to be interpreted in the context of the full clinical picture.

Microarray analysis will detect most aneuploidies as well as microdeletions and microduplications. Results are typically available in less than 14 days. Some microdeletions and microduplications are of uncertain clinical significance and parental samples may be required to aid interpretation.

Other laboratory methods, including karyotyping, Fluorescence *in situ* hybridisation and uniparental disomy studies may be useful in certain clinical scenarios.

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Attachment 1: Related Resources

Type	Published by	Publication
Legislation	NSW Act	*Human Tissue Act 1983*
Legislation	NSW Act	*Health Records and Information Privacy Act 2002*
Legislation	NSW Act	*NSW State Records Act 1998*
Legislation	NSW Act	*Privacy and Personal Information Protection Act 1998*
Legislation	NSW Act	*Children and Young Persons (Care and Protection) Act 1998*
Legislation	NSW Act	*Guardianship Act 1987*
Legislation	Federal Act	*Therapeutic Goods Act 1989*
Policy Directive	NSW Health	*Genetics Tests - Charging Policy Clinically Required Specialised-Non-Medicare Benefits Schedule Item* (PD2005_335)
Policy Directive	NSW Health	*Health Care Records - Documentation and Management* (PD2012_069)
Policy Directive	NSW Health	*NSW Register of Congenital Conditions – Reporting Requirements* (PD2018_006)
Policy Manual	NSW Health	*Consent to Medical and Healthcare Treatment Manual* (Consent Manual)
Policy Manual	NSW Health	Privacy Manual for Health Information (NSW Health Privacy Manual)
Other Guidelines	Australian Government Department of Health	Requirements for the Retention of Laboratory Records and Diagnostic Material (Ninth Edition 2022)
Resource	Australian Government Department of Health	National Pathology Accreditation Advisory Council (NPAAC)
Resource	Australian Government Department of Health	Clinical Practice Guidelines: Pregnancy Care 2020 Edition
Resource	NATA	National Association of Testing Authorities Australia
Resource	RANZCOG	Royal Australian and New Zealand College of Obstetricians and Gynaecologists Statements and Guidelines, available at https://ranzcog.edu.au/resources/statements-and-guidelines-directory/
Resource (Patient Information)	Centre for Genetics Education	Contact details of NSW Genetics Services and pregnancy information and testing available at http://www.genetics.edu.au
Resource (Patient Information)	Down Syndrome NSW	Down Syndrome NSW provide information about Down Syndrome that is useful to families and professionals, available at https://www.downsyndrome.org.au/nsw/

Type	Published by	Publication
Resource (Patient Information)	Genetic Alliance Australia	Genetic Alliance Australia provide peer support and information for individuals and families affected by a rare genetic condition/rare disease, available at http://www.geneticalliance.org.au/
Resource (Patient Information)	Multicultural Health Communication	Multilingual patient information, available at Multicultural Health Communication http://www.mhcs.health.nsw.gov.au/
Resource (Patient Information)	NSW Health	Pregnancy and the first five years https://www.health.nsw.gov.au/kidsfamilies/MCFhealth/Pages/default.aspx
Resource (Patient Information)	NSW Health	Having a baby is a key consumer resource for NSW pregnant women https://www.health.nsw.gov.au/kidsfamilies/MCFhealth/Pages/having-a-baby.aspx
Resource (Patient Information)	Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG)	Patient Information Pamphlets, available at https://www.ranzcog.edu.au
Resource (Patient Information)	Raising Children Network	The Raising Children Network website has scientifically validated information and resources, available at https://raisingchildren.net.au/pregnancy/health-wellbeing/tests-appointments/how-to-decide-tests-for-chromosomal-anomalies