Preconception and prenatal genetic screening

Clinical Guideline Presentation v1

45 minutes

Towards CPD Hours

Clinical Excellence Queensland

Queensland Government

References:

Queensland Clinical Guideline: Preconception and prenatal genetic screening is the primary reference for this package.

Recommended citation:

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Disclaimer:

This presentation is an implementation tool and should be used in conjunction with the published guideline. This information does not supersede or replace the guideline. Consult the guideline for further information and references.

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Learning objectives

- Relevant to Queensland:
  - Identify recommended screening options for reproductive genetic carrier screening (RGCS) and prenatal chromosome screening
  - Identify options for diagnostic testing
  - Increase knowledge of commonly screened genetic conditions in the preconception and perinatal period

Abbreviations

Term	Meaning
β-hCG	Beta human chorionic gonadotropin
CRL	Crown rump length
CF	Cystic fibrosis
CFTS	Combined first trimester screen
CFTR	cystic fibrosis transmembrane conductance regulator
CGG	cytosine-guanine-guanine
CVS	Chorionic villus sampling
FXS	Fragile X syndrome
NIPT/NIPS	Non-invasive prenatal test/screen
PAPP-A	Pregnancy associate plasma protein A
RGCS	Reproductive genetic carrier screening
SMA	Spinal muscular atrophy
USS	Ultrasound scan

Definitions

Term	Meaning
Genetic condition	A phenotype associated with: • A pathogenic or likely pathogenic variation in DNA sequence affecting the expression or coding of a protein (a single gene condition) or • A missing or additional DNA region (a chromosome condition).
Genotype (genome)	A person's unique combination of genetic sequence or genetic makeup. It is a complete set of instructions on how that person's body synthesizes proteins and thus how that body is built and functions.
Mosaicism	The occurrence of two or more genetically different sets of cells within an individual.
Phenotype	How the genotype manifests in a person including appearance, development and behaviour. Not all the instructions or variations in the genotype may be expressed as differences in phenotype.
Single gene condition	A phenotype associated with a pathogenic or likely pathogenic variant in a specific gene. Patterns of inheritance include (but are not limited to) autosomal dominant, autosomal recessive and X-linked (X-linked can be recessive or dominant). May also be inherited or arise de novo.
Chromosome condition	A phenotype associated with a change in the number or structure of chromosomes.

Result interpretation

- All screening tests have the potential to give false positive or false negative results
- Threshold measures aim to achieve a low false negative rate (which may increase the risk of false positive)

Term	Screening result is	True status is
False positive	Increased-chance	Condition not present
False negative	Low-chance	Condition present
True positive	Increased-chance	Condition present
True negative	Low-chance	Condition not present

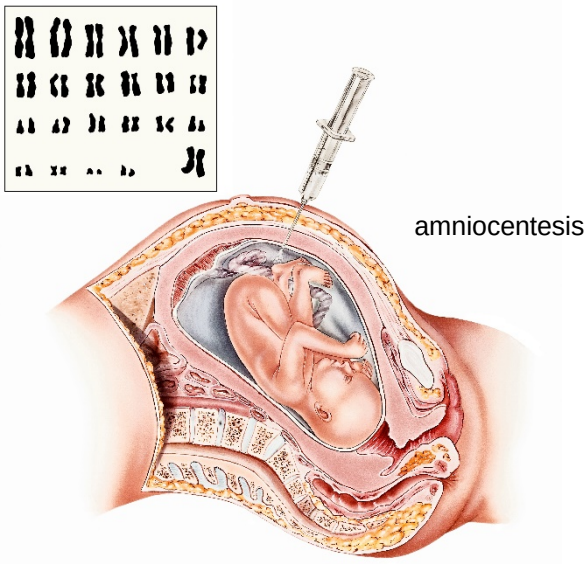
Screening versus diagnosis

What is a preconception or prenatal screening test?

- A test that identifies the chance (possibility or probability) of a genetic or chromosome condition occurring in the baby of this pregnancy or in a future pregnancy
- May be reported by laboratories as high or low risk, high or low chance, increased or decreased probability
- Has the potential to give false positives or false negative results
- Does not confirm the presence or absence of a chromosome or genetic condition

What is a prenatal diagnostic test?

- A test that confirms the presence of a genetic or chromosome condition (a diagnosis) in the baby
- Diagnostic tests include amniocentesis or chorionic villus sampling (CVS)



Types of screening

Who is offered screening?

- Preconception and prenatal genetic screening is offered to every woman who is planning a pregnancy *or* who is already pregnant
- The decision to proceed with any form of screening test is an individual choice

Reproductive genetic carrier screening (RGCS)

- Is ideally offered preconception when planning a pregnancy
- May also be offered during pregnancy, (ideally first trimester)

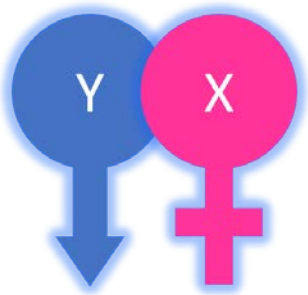
Prenatal chromosome screening

- Is offered during pregnancy from 10 weeks gestation

Reproductive genetic carrier screening (RGCS)

RGCS results can:

- Give information about the chance of having a child with an inherited autosomal or X linked genetic condition
- Inform preconception decisions and increase reproductive choices
- Inform pregnancy management and neonatal preparation



What conditions are screened for?

- Spinal muscular atrophy (SMA)
- Fragile X syndrome (FXS)
- Cystic fibrosis (CF)

Male and female partner testing

- If the female partner is a carrier of CF or SMA, testing of the male reproductive partner is also required
- If the female partner is a carrier of FXS, testing of the male reproductive partner testing is not required

Prenatal chromosome screening

Prenatal chromosome screening results give information:

- About the chance of a chromosomal condition in the developing baby
- To inform choices about continuing or terminating the pregnancy
- To inform pregnancy management and preparation for care of the baby after birth

What conditions are screened for?

- Trisomy 21 (Down syndrome)
- Trisomy 18 (Edward syndrome)
- Trisomy 13 (Patau syndrome)
- Sex linked conditions (e.g. Turner Klinefelter or Jacob syndromes, Triple X)

What tests are used?

- Combined first trimester screen (CFTS)
- Non-invasive prenatal screening test (NIPT/NIPS)
- 2nd trimester serum screening (Triple test)

When screening is offered

What are some of the discussion points when offering screening?

- Screening is a choice not a requirement
- The conditions being screened
- Difference between screening and diagnosis
- Process of screening (how, when, where, what)
- Financial costs (if any)
- Result interpretation (including false positive, false negative and test failure)
- Unanticipated findings (e.g. female FXS carrier)

What if the screening is declined?

- Respect choice
- Advise decisions can be reviewed/revised at any time
- Offer counselling (if relevant to the circumstances)
- Continue to offer usual/routine care

Combined first trimester screening (CFTS)

What does CFTS include?

An algorithm that incorporates:

- PAPP-A and free/total β-hCG at 9—13+6 weeks gestation
- Fetal nuchal translucency and crown rump length measurements on USS in late first trimester (11+3 to 13+6 weeks gestation)
- Maternal demographic information (e.g. age)
- Fetal characteristics (e.g. nasal bone variations, tricuspid valve flow)

What are other considerations?

- Detects about 85% of T21
  - False positive rate of about 5%
- Can also screen for T18 and T13
- Not as accurate as cell free DNA (cfDNA) screening (NIPT/NIPS)

Non-invasive prenatal test (NIPT/NIPS)

What does this include?

- Cell-free DNA screening of short fragments of maternal and fetal DNA that are released into the maternal circulation from the placenta
- The chance of a trisomy is estimated based on the expected percentage contribution of each chromosome and adjusted for the percentage of fetal DNA fragments in the maternal blood (fetal fraction)
- Performed from 10 weeks gestation (fetal fraction increases with gestation)

What are other considerations?

- Higher test performance compared to CFTS
- Incurs a financial cost
- Can be used as a second-tier screening test before progressing to diagnostic tests in some circumstances
- Requires diagnostic test to confirm presence of a chromosome condition in the fetus

Triple test

What does this include?

- Maternal serum testing (triple test)
  - Alpha-fetoprotein (AFP)
  - Free beta (β) human chorionic gonadotrophin(β-hCG)
  - Unconjugated oestriol (uE3)

When is it performed?

- 15 to 20 weeks gestation

What are other considerations?

- Combined test result performs better than any single individual result
- Confirm gestational age prior to screening
- Individual results outside of normal parameters may suggest neural tube defect
- Detection rates vary by laboratory

Diagnosis

Amniocentesis

- From 16 weeks gestation
- Needle aspirate of amniotic fluid for fetal cells

CVS

- From 11 completed weeks gestation
- Needle aspirate of placenta for placental cells
- May be performed transabdominal or transvaginal

What are other considerations?

- Consider the contribution the test will make to further decisions/ management
- Risk of miscarriage (up to 6%)
- Possibility of:
  - Repeat sample required
  - Maternal cell contamination
- Timing relevant to gestation and further decisions (e.g. medical versus surgical termination of pregnancy)

Trisomy 21

Genotype

- Additional copy of chromosome 21
- ~3% have an unbalanced translocation rather than complete extra chromosome 21
- ~1–2% have mosaic form where some but not all cells have an additional chromosome 21

Incidence

- Increases with maternal age
  - 1 in 400 at 20 years of age
  - 1 in 30 at 45 years of age

Common phenotype traits?

- Hypotonia (most consistent feature), short stature, protruding tongue, smaller ears, short broad hands, transverse palmar crease
- Intellectual disability
- Increased frequency of cardiac, gastrointestinal, urinary, endocrine, musculoskeletal and respiratory anomalies

Trisomy 18 and Trisomy 13

Genotype T18

- Additional copy of chromosome 18

Incidence

- High chance of fetal loss and stillbirth
- Prevalence 0.87 per 1000 pregnancies
- Live birth prevalence less than 0.01 per 1000 live births

Common phenotype traits

- Multiple anomalies
- Developmental and intellectual disability

Genotype T13

- Additional copy of chromosome 13

Incidence

- High chance of fetal loss and stillbirth
- Prevalence 0.66 per 1000 pregnancies
- Live birth prevalence 0.02 per 1000 live births

Common phenotype traits

- Considered a life-limiting condition
- Multiple congenital anomalies
- Developmental and intellectual disability

Sex chromosome conditions

Turner syndrome

- Only females affected
- Usually only one copy of the X chromosome (45, X or monosomy)

Triple X

- Only females affected
- Additional copy of the X chromosome (47, XXX)

Klinefelter syndrome

- Only males affected
- Additional copy of the X chromosome (47, XXY)

Jacob syndrome

- Only males affected
- Additional copy of the Y chromosome (47, XYY)

Cystic fibrosis

Inheritance mode

- Autosomal recessive
- Occurs equally in males and females

Genotype

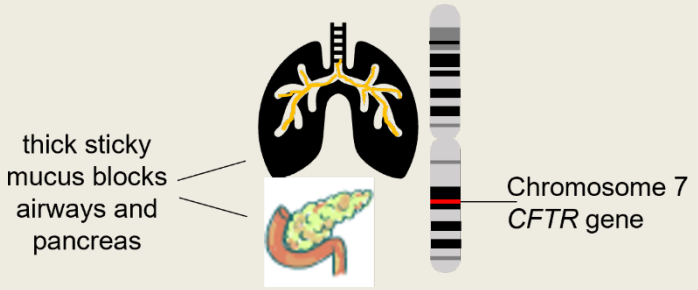
- Two copies of the *CFTR* gene with clinically significant variants
- Not all variants cause CF

Phenotype

- Classic CF chronic suppurative lung disease, pancreatic exocrine insufficiency, blocked biliary ducts, elevated sweat electrolytes, poor weight gain, male infertility

Life and health

- Most common life-limiting autosomal recessive condition in Australian children
- Median life expectancy significantly improved (~53 years)
- Rapidly evolving area for disease-modifying therapies that dramatically reduce symptoms (e.g. *CFTR* modulators)



Spinal muscular atrophy

Inheritance mode

- Autosomal recessive

Genotype

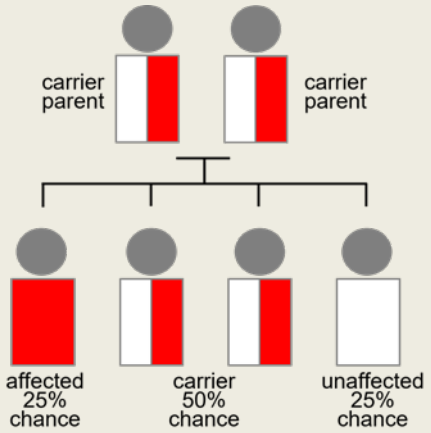
- 95% have homozygous deletions of the survival motor neuron gene *SMN1*

Phenotype

- Characterised by progressive muscle weakness and atrophy

Life and health

- Most frequent genetic cause of infant mortality
- Greater clinical benefit with early (pre-symptom onset) initiation of treatment
- Treatment landscape rapidly changing



Fragile X

Inheritance mode

- X linked

Genotype

- Expansion of CGG triplet repeat region of Fragile X Messenger Ribonucleoprotein1 (*FMR1)* gene

Phenotype

- Most common cause of inherited intellectual disability
- Features vary depending on mutation state (full versus premutation)
- Males more severely affected than females

Life and health

- Early intervention supports developmental outcomes
- Pharmacological treatments for hyperactivity, anxiety, aggression, and mood instability