Queensland Clinical Guidelines

Translating evidence into best clinical practice

Maternity and Neonatal **Clinical Guideline**

Preconception and prenatal genetic screening

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Acknowledgement

The Department of Health acknowledges the Traditional Custodians of the lands, waters and seas across the State of Queensland on which we work and live. We also acknowledge First Nations peoples in Queensland are both Aboriginal Peoples and Torres Strait Islander Peoples and pay respect to the Aboriginal and Torres Strait Islander Elders past, present and emerging.

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The guideline is not a substitute for clinical judgement, knowledge and expertise, or medical advice. Variation from the guideline, taking into account individual circumstances, may be appropriate.

This guideline does not address all elements of standard practice and accepts that individual clinicians are responsible for:

- Providing care within the context of locally available resources, expertise, and scope of practice
- Supporting consumer rights and informed decision-making, including the right to decline intervention or ongoing management
- Advising consumers of their choices in an environment that is culturally appropriate and which enables comfortable and confidential discussion. This includes the use of interpreter services where necessary
- Ensuring informed consent is obtained prior to delivering care
- Meeting all legislative requirements and professional standards
- Applying standard precautions, and additional precautions as necessary, when delivering care
- Documenting all care in accordance with mandatory and local requirements

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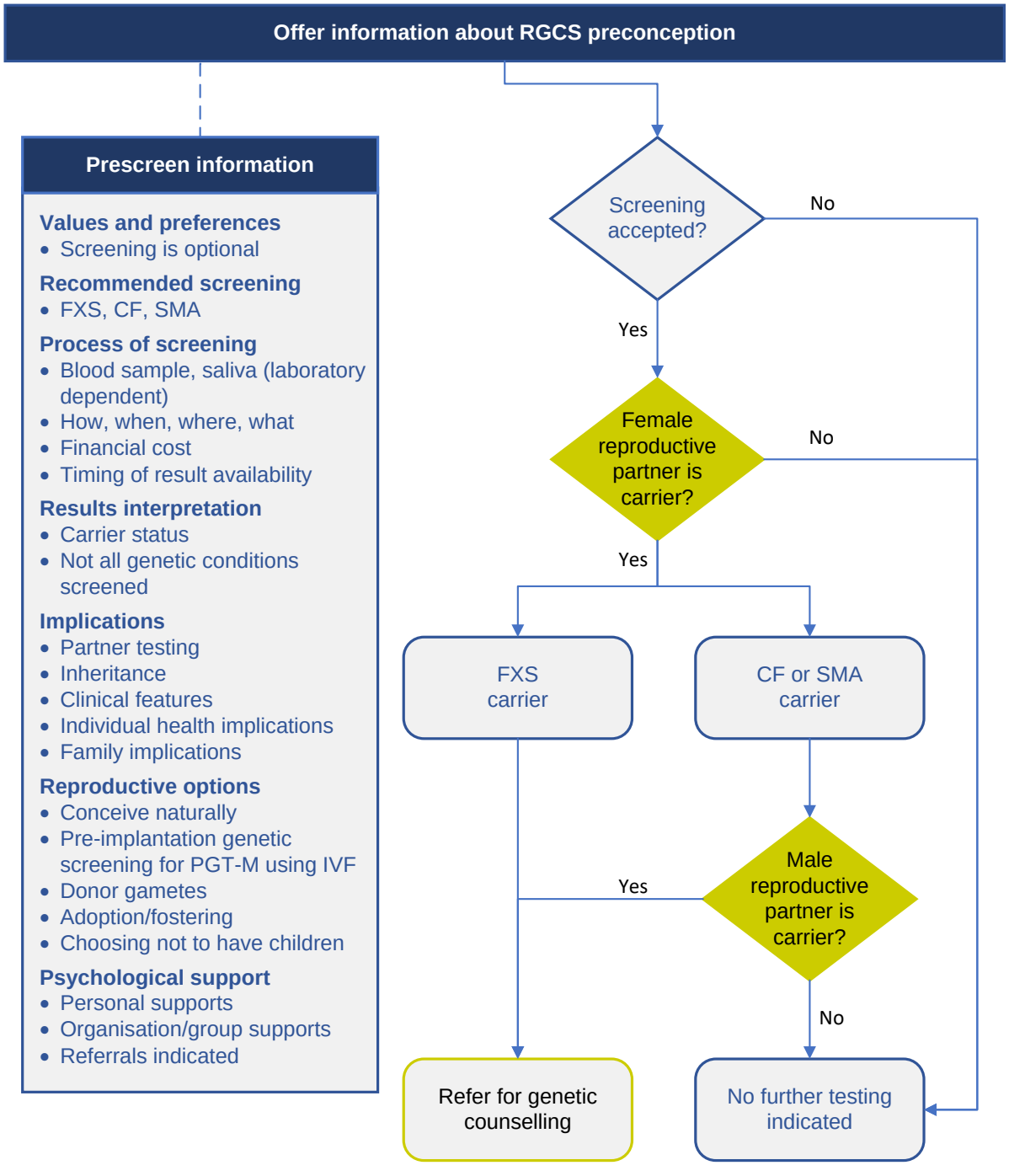
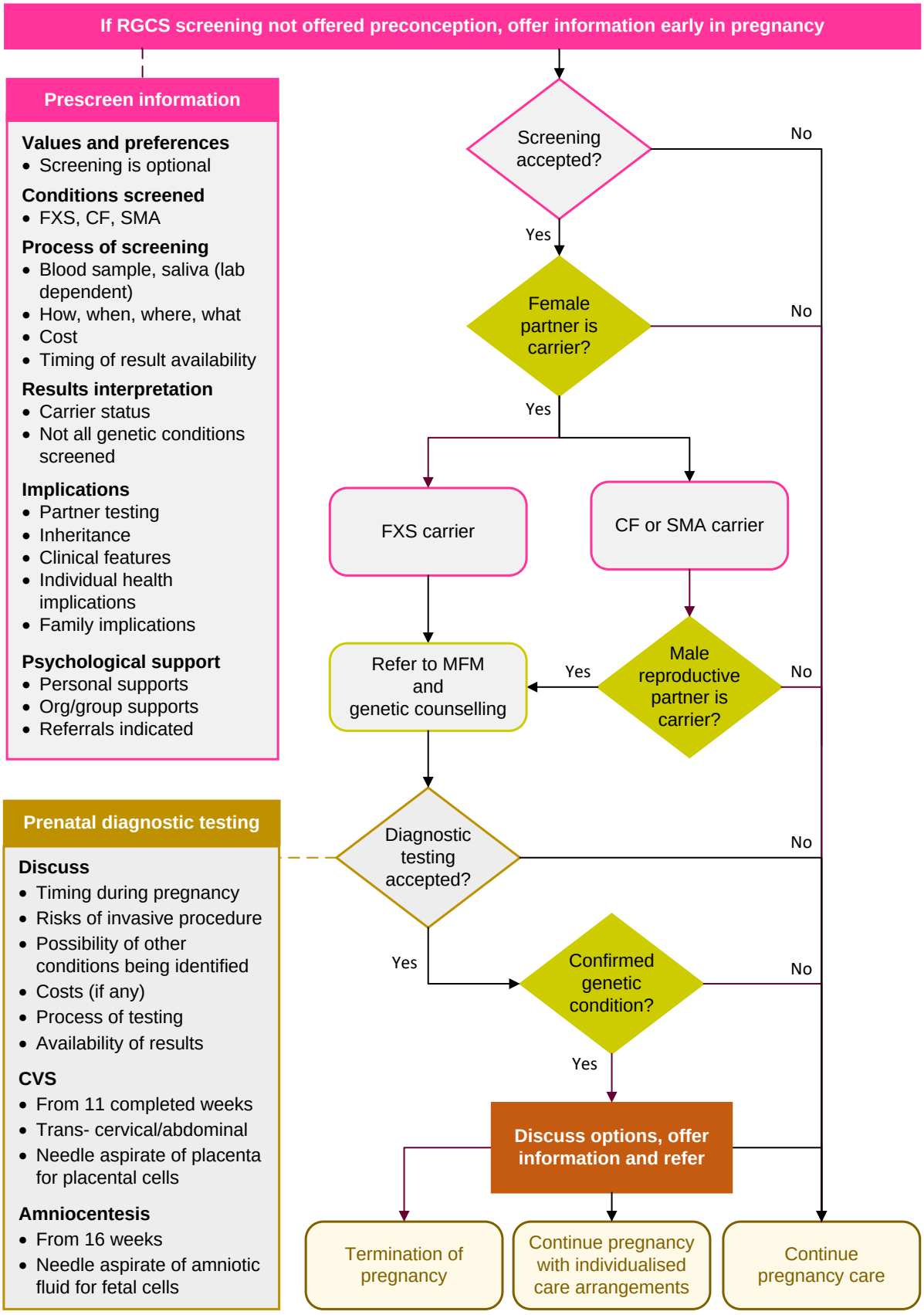
Flowchart: Preconception reproductive genetic carrier screening



CF: cystic fibrosis, **FXS:** fragile X syndrome, **IVF:** invitro fertilisation, **MFM:** maternal fetal medicine, **NPV:** negative predictive value, **Org:** organisation, **PGT-M:**:Pre-implantation genetic screening for monogenic conditions, **PPV:** positive predictive value, **RGCS:** reproductive genetic carrier screen, **SMA:** spinal muscular atrophy

Flowchart: F24.36-1-V1-R29

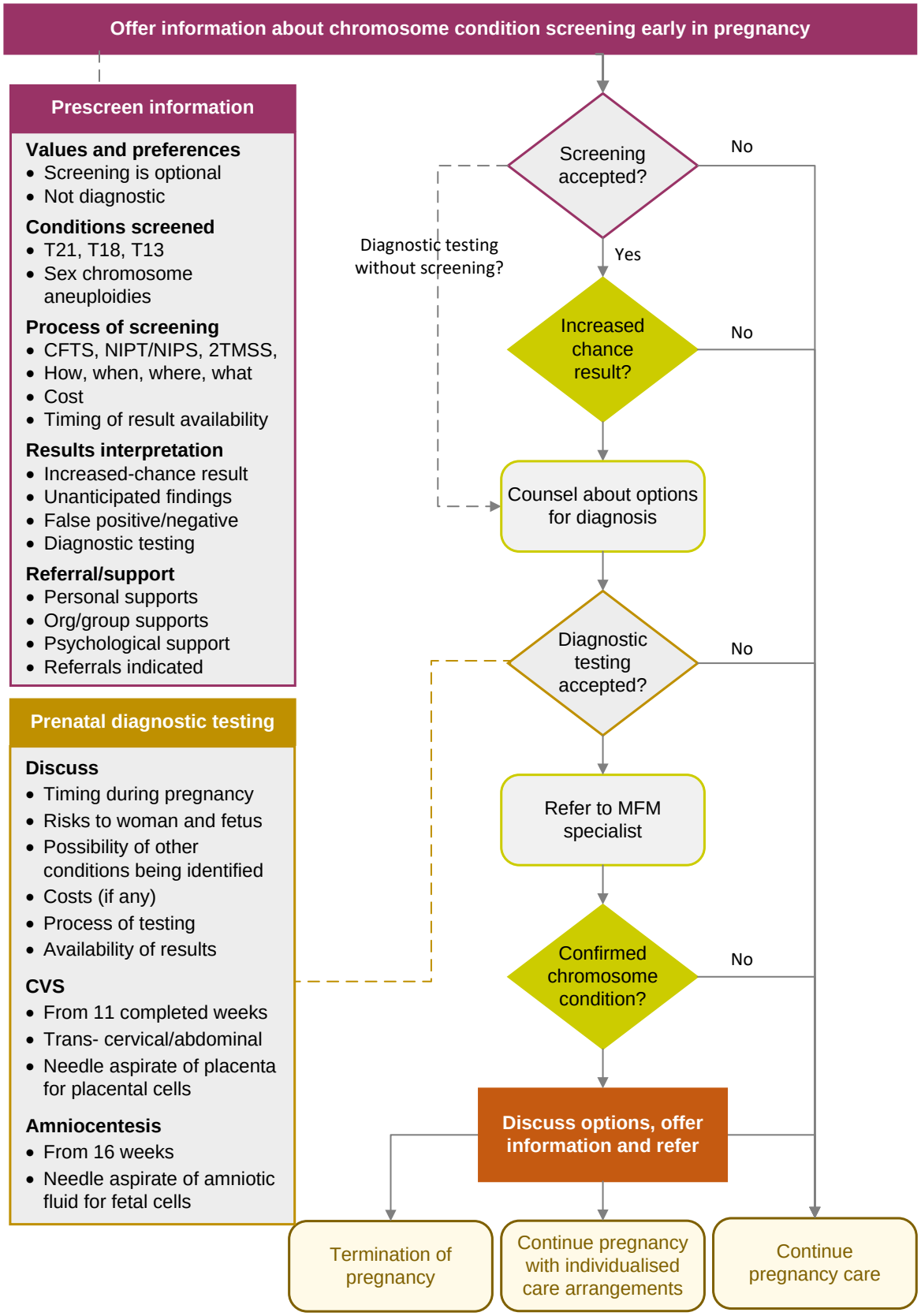
Flowchart: Reproductive genetic carrier screening during pregnancy



CF: cystic fibrosis, **FXS:** fragile X syndrome, **MFM:** maternal fetal medicine, **NPV:** negative predictive value, **Org:** organisation, **PPV:** positive predictive value, **RGCS:** reproductive genetic carrier screen, **SMA:** spinal muscular atrophy
Individualised care arrangements: may include (as relevant to individual circumstances) increased antenatal surveillance, increased ultrasound surveillance, preparation for palliative care, or kinship or formal adoption, or foster care arrangements

Flowchart: F24.36-2-V1-R29

Flowchart: Chromosome condition screening during pregnancy



2TMSS: second trimester maternal serum screening, **CF:** cystic fibrosis, CFTS: combined first trimester screening, **CVS:** chorionic villus sampling, **FXS:** fragile X syndrome, **MFM:** maternal fetal medicine, NIPT/NIPS: non-invasive prenatal screening test, **NPV:** negative predictive value, **Org:** organisation, **PPV:** positive predictive value, **RGCS:** reproductive genetic carrier screen, **SMA:** spinal muscular atrophy, **T13:** Trisomy 13 (Patau syndrome) **T18:** Trisomy 18 (Edwards syndrome) **T21:** Trisomy 21 (Down syndrome)
Individualised care arrangements: may include (as relevant to individual circumstances) increased antenatal surveillance, increased ultrasound surveillance, preparation for palliative care, kinship or formal adoption, or foster care

Flowchart: F24.36-3-V1-R29

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Abbreviations

2TMSS	Second trimester maternal serum screening
AGG	adenine guanine guanine
cfDNA	Cell-free DNA
CF	Cystic fibrosis
CFTS	Combined first trimester screening
CGG	cytosine guanine guanine
CPM	Confined placental mosaicism
CVS	Chorionic villus sampling
DNA	Deoxyribonucleic acid
FISH	Fluorescence in situ hybridisation
FXPOI	Primary ovarian insufficiency
FXS	Fragile X syndrome
IQ	Intelligence quotient
MBS	Medicare Benefits Schedule
NIPT/NIPS	Non-invasive prenatal screening test
NBST	Newborn bloodspot screening test
NT	Nuchal translucency
PAPP-A	Pregnancy associated plasma protein A
PGT-M	Pre-implantation genetic screening for monogenic conditions
SMA	Spinal muscular atrophy
RGCS	Reproductive genetic carrier screening
T13	Trisomy 13 (Patau syndrome)
T18	Trisomy 18 (Edwards syndrome)
T21	Trisomy 21 (Down syndrome)
USS	Ultrasound scan

Definitions

Aneuploidy	A chromosome number that deviates from a multiple of the haploid set.[1] May include three copies (trisomy) or a single copy (monosomy).
Carrier	Used to refer to individuals who are heterozygous for a clinically significant variant in a gene associated with an autosomal recessive or X linked condition.[2]
Chromosome condition	A phenotype associated with a change in the number or structure of chromosomes. [3]
Clinically significant variants	In this guideline used to refer to class 4 (likely pathogenic) and class 5 (pathogenic) variants in genes.
Genetic condition	A phenotype associated with[3]: • 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.[4]
Healthcare professional	Any healthcare provider involved in the care of a person making decisions about prenatal screening (i.e. includes medical practitioner, registered nurse or midwife, sonographer, genetic counsellor, as well as social worker, counsellor/psychologist hospital liaison officer).
Mosaicism	The occurrence of two or more genetically different sets of cells within an individual.[5]
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.[4]
Reproductive partner	In this guideline used to mean the biological male or female person (as relevant to the context) whose genetic material contributes to the actual or potential development of offspring.
Segmental imbalance	A large section of a chromosome that is either deleted or duplicated resulting in an imbalance in chromosome material.
Single gene condition[3]	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.[6]
Specialist service	In this guideline, refers to a maternal fetal medicine service, genetic counselling service, or clinical geneticist. Individual Hospital and Health Services may assign the roles and functions of specialist services to other organisations, groups or individuals as appropriate to their service delivery. Use clinical judgment when determining the most appropriate specialist service for referral.
Woman/women	QCG recognise that individuals have diverse gender identities. In QCG documents, the terms *woman* and *women* are used in an inclusive sense. The terms are not meant to exclude individuals who are pregnant or give birth and who do not identify as female.[7,8] Additionally, in this guideline • *Male* and *female* are used where biological and physiological characteristics are relevant to the context. • *Person/people* is used where the context is relevant to any sex or gender (e.g. *male, female, woman, partner, other)*

1 Introduction

Every child has a chance of having a chromosomal or genetic condition. These are suspected in approximately 3–5% of liveborn babies although only 15–25% of these will have a confirmed genetic condition.[9] In Australia, it is estimated that 1 in every 1,158 babies born will have trisomy 21 (Down syndrome), the most commonly occurring chromosomal condition.[10]

There are two common types of genetic screening offered preconception and in the prenatal period.

- Prenatal chromosome screening
  - Is offered during pregnancy
  - Provides information about the chance of chromosomal conditions in the developing baby
- Reproductive genetic carrier screening (RGCS)
  - Is ideally offered preconception but may also be offered early in pregnancy.
  - Provides information about the chance of having children with an inherited autosomal or X linked genetic condition

Genetic screening can be considered by anyone planning a pregnancy or early in pregnancy regardless of family history. Refer people with a strong family history of a known or possible genetic condition directly to a specialist clinical genetics service for further discussion about genetic testing.[6]

An understanding of the screening options, how results are interpreted and all the available options following an increased-chance screening result, are appropriate for discussion. This can support informed decision-making consistent with the person's values and preferences.[11,12] The choices and decisions people make about preconception and prenatal genetic screening are individual and varied.

Some people may decline all screening before or during pregnancy. After a screening result that identifies an increased chance of a chromosome or genetic condition, some may decline further diagnostic testing, preferring to wait until conception or birth to confirm diagnosis. Other people will choose to proceed with prenatal diagnostic testing and consider all options before birth.

1.1 Guideline purpose

There are many RGCS and prenatal screening options for a wide range of chromosomal and genetic conditions (e.g. RGCS for large panels of genes and genome wide non-invasive prenatal screening tests (NIPT/NIPS) conditions).[13] The focus of this guideline is on the most broadly accessible screening options as follows:

- Three-condition RGCS (of the male and female reproductive partners) preconception or during pregnancy which screens for:
  - Spinal muscular atrophy (SMA)
  - Fragile X syndrome (FXS)
  - Cystic fibrosis (CF)
- Prenatal screening (of the fetus during pregnancy) for the chromosome conditions:
  - Trisomy 21 (T21) (Down syndrome)
  - Trisomy 18 (T18) (Edwards syndrome)
  - Trisomy 13 (T13) (Patau syndrome)
  - Sex chromosome conditions

1.2 Decision and referral points

There are three key decision and referral points during preconception and prenatal genetic screening.

1. At the time screening is offered (either preconception or in the current pregnancy)
2. Following an increased-chance result for a genetic condition arising from either
   - Identification of the female (for FXS) or the female and the male reproductive partner (for CF and SMA) as a carrier for a single gene condition
   - Screening of the fetus for a chromosome condition in the current pregnancy
3. Following diagnosis of a single gene or chromosome condition in the fetus of the current pregnancy

1.3 Result reporting terminology

Table 1. Screening result terminology

<table>
<tr><th>Aspect</th><th>Consideration</th></tr>
<tr><td>‘Chance’ versus ‘risk’</td><td>
• In this guideline the term ‘chance’ (low-chance, increased-chance) is used to refer to the possibility or probability of a genetic or chromosome condition
o Is an emotionally neutral term that supports unbiased information sharing[14]
o Reduces value-laden negative assumptions as ‘risk’ is generally used in the context of a negative outcome[15]
o Is supported by multiple professional, consumer groups/individuals[14]
• Terminology used in laboratory reported results may vary (e.g. high or low risk, high- or low-chance, increased decreased or low probability)
</td></tr>
<tr><td>True/false positive/negative</td><td>
• 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)
<table>
<tr><th>Term</th><th>Screening result is</th><th>True status is</th></tr>
<tr><td>True positive</td><td>Increased-chance</td><td>Condition present</td></tr>
<tr><td>True negative</td><td>Low-chance</td><td>Condition not present</td></tr>
<tr><td>False positive</td><td>Increased-chance</td><td>Condition not present</td></tr>
<tr><td>False negative</td><td>Low-chance</td><td>Condition present</td></tr>
</table>
</td></tr>
<tr><td>Predictive value</td><td>
• A measure (%) of the instances that the result (increased or low-chance) is the true result
• Varies with pre-test probability (e.g. for chromosomal aneuploidies depends on age) and prevalence
o Positive predictive value: the percent (%) of all increased-chance results that accurately reflect the outcome are true positives (i.e. person has increased-chance result and the condition is present)
o Negative predictive value: the percent (%) of all low-chance results that accurately reflect the outcome are true negatives (i.e. person has a low-chance result and the condition is not present)
</td></tr>
<tr><td>Sensitivity</td><td>
• Sensitivity is also referred to as detection rate
• The more sensitive a test:
o The less likely an individual with a low-chance screening result will have the condition
o The greater the negative predictive value
• Example: If the test sensitivity is 90%—the test:
o Correctly identifies 90 out of 100 people who have the condition (true positive)
o Incorrectly identifies 10 out of 100 people as being free of the condition when they do have the condition (false negative)
</td></tr>
<tr><td>Specificity</td><td>
• The more specific the test:
o The less likely an individual with an increased-chance screening result will be free from the condition
o The greater the positive predictive value
• Example: If the test specificity is 80%—the test:
o Correctly identifies 80 out of 100 people who do not have the condition (true negative)
o Incorrectly identifies 20 out of 100 people as having the condition when they do not have the condition (false positive)
</td></tr>
<tr><td>Desirable test characteristics</td><td>
• A test has robust clinical validity when both the negative and positive predictive values are high[2]
• Higher false positive rate than for a diagnostic test is usually accepted
• A high true positive rate and a low false positive rate decreases[16]:
o Procedure-related miscarriages per condition identified
o Psychosocial impacts due to false positive result
o Post-test genetic counselling sessions required
o Additional follow up laboratory tests, imaging specialist consultation and other reproductive interventions (e.g. Invitro fertilisation (IVF) with pre-implantation genetic screening for monogenic conditions (PGT-M))
</td></tr>
</table>

1.4 Clinical standards

Table 2. Clinical standards

Aspect	Consideration
Standard care	• Refer to Queensland Clinical Guideline: *Standard care*[17] for care considered 'usual' or 'standard' o Includes for example: privacy, consent, decision-making, sensitive communication, medication administration, staff education and support, culturally appropriate care (e.g. translator services, information in a language other than English), family and women centred care
Equity of access	• As relevant to the local service, develop pathways and protocols that support access to preconception and prenatal screening, counselling and diagnostic testing (e.g. Patient Travel Subsidy Scheme, telehealth consultation, referral to higher level service) • Support investment in outreach screening services (e.g. mobile imaging machines and visiting sonographer) to support women and families impacted by geographical isolation • Consider the barriers/access needs of women from culturally and linguistically diverse populations (e.g. information in a language other than English, interpreters, cultural supports)
Clinician education	• Prenatal ultrasound scan (USS) requires staff trained, accredited and credentialled for fetal screening[18] • Support healthcare providers engaged in counselling about prenatal screening, to access and maintain contemporary knowledge about screening tests, conditions for which screening is offered, result interpretation and sensitive communication[2] o Treatment advances and rapidly evolving changes in outcomes may affect pre-screening counselling for some people
Support for healthcare providers	• Supporting families through counselling, screening and decision-making before and during pregnancy can take an emotional toll on the healthcare provider o Utilise reflective practice and supervision[19] o Practice self-care o Seek out additional supports as required
Preconception folate	• Recommend folate 400 microgram for at least one month prior to conception and then for three months after conception[20] o Reduces chance of neural tube defects[21]
First trimester USS (anatomy)	• Offer pregnant women a first-trimester USS (11–13 weeks) regardless of whether they have had or intend to have other screening (e.g. cell-free DNA (cfDNA) testing)[22]
Second trimester USS (morphology)	• Not considered a screening test for chromosome conditions due to poor sensitivity and specificity[23] • May provide additional clinical information relevant to decision-making • Offer pregnant women a second trimester USS (18–20 weeks) regardless of their intentions to have other screening
Ethical concerns	• The implications of prenatal and preconception screening are considerable for individuals and for society more broadly[14,24,25] • 'Routinisation' or 'standardisation' as part of suite of antenatal blood tests may limit opportunity for informed decision-making[26], decrease deliberation about decision and/or increase pressure to accept screening[26] • Inequitable access to screening related to financial out of pocket expense • As many pregnancies with genetic conditions are terminated, an increase in screening/diagnosis of genetic conditions may increase the number of terminations and the social stigma associated with having a child with a genetic condition[14] • Potential loss of support structures for people with genetic conditions[27] • Commercialisation of NIPS/NIPT specifically targeting general practitioners (GP to encourage offering of screening, has occurred without sufficient accompanying education to enable appropriate information transfer and counselling[28]) • Future and expanded use of technology for non-medical use[25]

2 Support and communication

A person's socio-demographics, individual characteristics and preferences inform their choices about preconception and prenatal screening. The manner in which support and information is offered and discussed, can also have significant and lasting impacts on the emotional and social wellbeing of individuals.[20] Where lower health literacy is evident, adapt communication accordingly.
People with intellectual disability may need additional support to make their own decisions (supported decision-making).[29]

2.1 Psychosocial support and wellbeing

Psychosocial support during pre- and post-screening counselling can be an opportunity to gather information, make meaning of a high chance or diagnostic result, and adjust and prepare for birth or termination. It can mitigate the potentially negative psychosocial impacts of preconception and prenatal genetic screening decision-making.[25,28]

Table 3. Psychosocial support and wellbeing

Aspect	Consideration
When screening offered	• Counselling supports informed access to genetic information before and throughout the pregnancy[30] • Include cultural, social and emotional considerations as well as the technical aspects of the screening technology and process[31] • Offer culturally appropriate information and resources to support and empower decision-making • Support the values and preferences of the pregnant person[30,32]
Increased-chance result or diagnosis	• People respond differently; there is no right or wrong way to feel or think • Consider a person's ability to absorb information or ask questions following unexpected results o Additional appointments or repetition of information may be required • The waiting interval from screening to result, and from an increased-chance result to diagnostic result (where this is sought) can be distressing • A trauma response may lead to significant emotional and psychological impacts that may also carry into subsequent pregnancies[19] • Consider if professional mental health support is indicated • Refer to Section 7 Diagnostic testing
Following diagnosis	• Acknowledge the opportunity for information gathering, meaning making, adjustment, and preparation for birth or termination • Provide access to relevant, accurate and current information about the suspected or diagnosed condition • Offer the opportunity to connect with people living with the condition and their families, and a clinician specialising in the condition • Offer people support for the emotional and psychosocial impacts of the genetic information received • Acknowledge: o Challenge of high-stakes decision-making under conditions of uncertainty[33] o Complex range of individual, social and cultural factors impacting decision-making[19] • Communicate clearly where there may be clinical implications related to the timing of decisions (e.g. mode of termination) • Refer to Section 8 Confirmed genetic condition
Following a decision	• Offer empathic care and support regardless of the person's decision (to continue or terminate the pregnancy) • Normalise the range of emotions experienced following decisions • Where a choice is made to terminate the pregnancy: o Recognise termination of pregnancy following a prenatal diagnosis as a unique loss with potential additional complexities for adjustment[34] o Where possible provide consistency of care and plan for follow-up[19] • Where a choice is made to continue the pregnancy: o Support parents as they adjust to the diagnosis (or possibility of a diagnosis where diagnostic testing has not occurred), and plan for the birth of their baby • Offer the opportunity to connect with condition specific support groups

2.2 Communicating screening and diagnostic results

Table 4. Communicating screening and diagnostic results

Aspect	Consideration
Context	• The way information is presented and received can have impacts on immediate and longer-term psychological wellbeing[35]
Sharing results	• Plan for result disclosure (e.g. time to result availability, mode of communication)[2] • Provide factual information about the chromosome or genetic condition, and avoid negative commentary or personal opinions[19] • If sharing results over the phone, consider supports available to the person and the possibility of in-person follow up or referral to a clinician with experience in the relevant condition • Use a non-directive approach and allow sufficient time to: o Consider information o Ask questions o Decline or accept screening or diagnostic testing o Make meaning of the news they have received • Maximise opportunities to incorporate culturally appropriate supports (e.g. support person)
Terminology[36]	• Avoid prefacing comments with 'I'm sorry' or 'I have some bad news' • When discussing results use neutral terminology such as, 'difference' and 'variation' • In the case of variations avoid use of stigmatising terms like 'abnormality', 'malformation', 'problem', 'mistake', 'wrong', 'defect' and 'adverse finding'
Examples of lead-in phrases[37]	• 'We've just received your screening results and there have been some unexpected findings. Are you able to come into the clinic so we could talk about the results? Would you like to bring in a support person?' • 'I am here to make sure you have all the information and the care you need. I will support you and give you the time you need to make decisions that are right for you and your family' • 'The results of these screening tests suggest that there is a chance of a chromosomal condition(s)' • 'I can give you information from a clinical perspective about a particular condition but my understanding of the experience of people with this condition and their families is limited' • 'Talking with a clinician who has specialist knowledge of the condition can be helpful' • 'It can be useful to connect with people who have personal experience of a particular condition. If this is something you are interested in, I can refer you (to a diagnosis specific group)'

2.3 Cost of screening

Table 5. Costs of screening

Aspect	Consideration
Medicare Benefits Schedule (MBS)	• Not all preconception and prenatal screening is eligible for Medicare Benefits Schedule (MBS) rebate o Refer to MBS online for listed services subsidised by the Australian Government[38]
Financial implications	• Cost of screening can be a factor in a person's decision to accept or decline screening including: o Medicare eligibility (e.g. some visa recipients are ineligible[39]) o Cost of travel to access screening (e.g. due to geographical isolation or limited local resources)
Recommendation	• Discuss the financial implications of screening options including: o Out-of-pocket costs associated with individual screening tests o Genetic counselling [refer to Table 6. Other psychosocial considerations] o Potential for further investigations (e.g. invasive diagnostic testing) o Medicare eligibility status

2.4 Other considerations

Screening can give rise to or exacerbate other concerns related to a person's health, and/or emotional and social wellbeing.

Table 6. Other psychosocial considerations

Aspect	Considerations
Current and future pregnancy care	• Identification of chromosomal variations in the female reproductive partner may have implications for their health in the current pregnancy and for future pregnancies, including increased pregnancy surveillance, testing or birth planning o If confined placental mosaicism (CPM) is suspected after an increased-chance NIPT/NIPS result, increased surveillance during pregnancy may be indicated depending on the chromosome involved (e.g. CPM for trisomy 16)
Paternity	• Discuss implications for paternity identification prior to partner testing (e.g. following high chance result for CF in the female partner) • Paternity testing not available with RGCS
Information overload	• During pregnancy, people receive a large amount of information in a relatively short span of time and this can be overwhelming for some • In relation to screening information, consider (as appropriate to the circumstances) o Staging and spacing of information o Exploring perspectives and level of detail that the person would like to know
Incidental and secondary findings[40]	• May include: o Vanishing twin pregnancy o Maternal malignancy o Clinically significant variants (unrelated to the phenotype being investigated) identified by chance during the analysis
Uncertainty	• False negative or false positive results have a psychological impact that may be long lasting for the person and their family[41,42] • Inherent uncertainty associated with screening including phenotypic variability and 'chance' results may affect mental health and emotional wellbeing
Support and referral options	• Clinician awareness of the role and function of support organisations can be important for longer term wellbeing • Explore availability of informal supports (e.g. family and friends) • Can include genetic counselling, relevant medical specialists, condition-specific support groups, abortion services, perinatal palliative care, and psychological and psychosocial support services • Neonatologist, general or subspeciality paediatricians or surgeons may also be considered • Include partners and family and consider grief and support counselling as appropriate to the circumstances • Refer to Queensland Clinical Guidelines: *Resource list for preconception and prenatal genetic screening*[43]
Genetic counselling	• Genetic Health Queensland–referral generally: o Not indicated following an increased-chance result for chromosome screening during pregnancy o Accepted following a diagnosed chromosome condition during pregnancy o Accepted following RGCS with an increased-chance result of an affected baby o Accepted following RGCS performed during pregnancy where the male reproductive partner is not available/not willing to be screened • Private genetic screening test providers o May include genetic counselling (online or telehealth) as a component of a paid screening service

3 When screening is offered

Provide information about the decisions to be made at each point, consequences and support available. Offer, irrespective of family history, age or ethnicity[2]:

- RGCS to people who are planning a pregnancy
- If RGCS has not been offered preconception, offer as early as possible in pregnancy
- Prenatal screening for fetal chromosome conditions early in pregnancy[6] (from 10 weeks gestation)

Table 7. Offering screening

Aspect	Consideration
Rationale for screening	• Genetic information can inform preconception and pregnancy decisions relevant to conception and continuing or terminating a pregnancy[6] • RGCS when performed preconception o Supports people to understand their chance of conceiving a child with a single gene condition[2] o Informs preconception decisions and increases reproductive choices[2] o Provides information (if pregnancy ongoing) for pregnancy and neonatal care • Prenatal screening o Provides pregnant women with information about the development and/or genetic makeup of the fetus in the current pregnancy[6]
Screening declined	• Preconception and prenatal screening are optional[2] • There may be many reasons for why screening is declined[32] • If screening is declined o Respect and record the choice o Advise that the decision can be reviewed/revised at any time o Offer counselling (if relevant to the circumstances) o Continue to offer usual/routine care
Reproductive genetic carrier screening (RGCS)	• Genetic tests for carrier status of CF, SMA and fragile X syndrome (FXS) (also known as three-condition RGCS) • Ideally, offered preconception[2] o If not offered before conception, offer at the first opportunity during pregnancy (preferably first trimester) • Other options include single-condition and expanded carrier screening[2] (beyond the scope of this guideline)
Chromosome condition screening	• Screens for chromosome conditions present in the fetus during the current pregnancy including: o T21 (Down syndrome) o T18 (Edwards syndrome) o T13 (Patau syndrome) o Sex chromosome conditions • Some genome wide NIPT/NIPS provide information about a wider range of chromosomal conditions
Pre-screen information	• For each relevant screening option, routinely offer information and counselling about[44]: o Conditions being screened o Differences between screening and diagnostic tests, and their limitations o Pathway and process of screening (how, when, where, what) o Result interpretation (including false positive, false negative results and possibility of test failure)[2] o Predictive values of the screening test relevant to the person's characteristics o Cost [refer to Table 5. Costs of screening] • Discuss the potential for and implications of: o An increased-chance screening result and indications for diagnostic testing[20] o Unanticipated findings of relevance to a person's health (e.g. female FXS carrier)[20] o Future conception and/or pregnancy options

4 Reproductive genetic carrier screening

Offer RGCS to all prospective parents as almost 90% of carriers have no known family history of the genetic condition they carry.[45] From November 2023 an MBS item is available for three-condition RGCS. The MBS items form a sequential approach where the female reproductive partner is initially offered screening (Medicare item 73451), and the male reproductive partner is offered screening only if the female receives a carrier result for CF or SMA (Medicare item 73452).[46]

Table 8. Three-condition carrier screening

Aspect	Consideration
Conditions screened	• Identifies most individuals who are carriers of CF, SMA and FXS • People who are carriers have a greater chance of having children with that condition
Description	• Identifies known commonly clinically significant variants based on Australian population cohorts
Timing	• Ideally preconception o Where this has not occurred, offer at the first opportunity in pregnancy • Sequential screening is covered by MBS while simultaneous screening is not[2]
Sample type	• Blood • Saliva (lab dependent)
Result reporting	• Reported as: o Carrier (clinically significant variant identified) or o Negative (clinically significant variant not identified) • Result availability varies and is laboratory dependent o May take up to 4–6 weeks
Test performance	• Dependent on individual laboratory services
Advantages	• Supports people to avoid or prepare for having children with an inherited genetic condition • Pre-conception screening increases reproductive options compared to screening during pregnancy (e.g. preimplantation genetic testing, use of donor gamete/embryo, adoption, prenatal diagnosis to prepare for care at birth or terminate the pregnancy, decision not to conceive)[2]
Limitations	• Will not identify de-novo variants in the fetus[2] • Screens a limited number of genes • Does not screen for all genetic variants that cause each condition screened[2] • If clinically significant variants are not identified, the possibility the person is a carrier for the condition is reduced but not eliminated (i.e. they have a residual risk)[2] • Assumes person(s) tested is/are biological parent(s)
Comment	• Additional carrier screening for larger panels of genes is available beyond MBS funded items • RGCS does not replace the o Newborn bloodspot screening test[2] (NBST) or o Prenatal screening for chromosome conditions • Carrier testing may identify relatives at risk of carrying the same variant[2] • Consanguineous reproductive partners have a greater likelihood of receiving an increased-chance result[2] (i.e. both being carriers for the same condition) • If family history of genetic condition, refer to clinical genetic services for specialist assessment, as a tailored approach to testing may be more appropriate

4.1 CF and SMA carrier screening results

Refer to Section 9.5 Cystic fibrosis and Section 9.6 Spinal muscular atrophy for condition details.

Table 9. CF or SMA carrier

Aspect	Consideration
Inheritance	• CF and SMA are autosomal recessive conditions[47] o For a child to have CF or SMA, both reproductive partners are carriers for that condition • If the female reproductive partner is a carrier, the status of the male reproductive partner is required to estimate the chance of having children with the condition[47]
Reproductive partner result	• If the male reproductive partner is a carrier for the same condition (CF or SMA) as the female reproductive partner, there is a 1 in 4 (25%) chance for each pregnancy that a child will have the condition[47]
Preconception result	• If both reproductive partners are identified as carriers of CF or SMA preconception o Recommend genetic counselling to discuss reproductive options, and to inform and support decision-making[48] o Reproductive options may include PGT-M using IVF[47], donor gametes, adoption, fostering, or choosing not to have children • Reproductive partners may choose to conceive without further testing
Prenatal result	• If both reproductive partners are identified as carriers of CF or SMA during the current pregnancy: o Recommend genetic counselling to inform and support decision-making including the option of invasive and diagnostic testing (CVS or amniocentesis)[49] • If the male reproductive partner declines or is unavailable for screening, discuss: o Options for diagnostic testing[2] o Referral for genetic counselling • Refer to Section 7.3 Prenatal diagnostic tests
Implications for blood relatives	• Advise carriers that blood relatives also have an increased-chance of being carriers[50] • Providing information about potential carrier status to relatives can allow the relatives to also consider and access screening (known as 'cascade testing')[50]
Limitations	• Not all people who are carriers will be detected (i.e. is a risk reduction not a risk elimination screening test) • CF and SMA may arise de novo (rare and complex)

4.2 FXS carrier screening results

Refer to Section 9.7 Fragile X syndrome for condition details

Table 10. FXS carrier

Aspect	Consideration
Inheritance	• FXS is inherited in an X linked pattern[47] • The result may have potential health implications for the person being screened[47] o Premutation associated with primary ovarian insufficiency, (FXPOI) and fragile X associated tremor/ataxia syndrome (FXTAS)
Female carrier	• Premutation and full mutation carriers have an increased-chance of having children with FXS[47] o Dependent on the cytosine guanine guanine (CGG) repeat size, with larger repeat sizes more likely to expand to the full mutation in children o If premutation results are between 55 and 69 CGG repeats, recommend adenine guanine guanine (AGG) analysis to assist with result interpretation
Male partner screening	• Male reproductive partner screening is not required (only the female reproductive partner can pass on the condition)
Preconception result	• Recommend genetic counselling to discuss, further screening options, (e.g. AGG interruptions if not provided by the laboratory for premutation carriers), reproductive options, support decision-making and understand implications for the person's own health[49] o Referral to an endocrinologist and/or fertility specialist may assist assessment of FXPOI symptoms o Reproductive options may include PGT-M using IVF[47], donor gametes, adoption, fostering, or choosing not to have children • People may choose to conceive without further testing[2]
Prenatal result	• Recommend genetic counselling to discuss options for the pregnancy and support decision-making including the option of invasive diagnostic testing (CVS or amniocentesis)[49]

4.3 Low-chance result for CF, SMA or FXS

Table 11. Low-chance result for CF, SMA or FXS

Aspect	Consideration
Result reporting	• When the variants screened for each gene have not been identified, the result indicates the person screened has a low-chance of being a carrier • RGCS o Not able to detect every genetic variant for CF, and SMA[45] o Will not identify carriers of other genetic conditions[2]
Implications	• A low-chance result: o Indicates a clinically significant variant was not detected and the possibility that the person screened is a carrier, although low, cannot be completely excluded[2] o Does not eliminate the chance that a person will have children with a genetic condition[2]
Preconception result	• Continue routine care and screening
Prenatal result	• Continue routine care and screening • Advise that the NBST is still indicated and is recommended

5 Chromosome condition screening in pregnancy

The following screening tests do not detect all chromosome conditions. Invasive diagnostic testing (CVS or amniocentesis) detects the widest range of chromosome conditions prenatally.

5.1 Combined first trimester screening (CFTS)

Table 12. Combined first trimester screening

Aspect	Consideration
Conditions screened	• T21 (Down syndrome) (most common chromosome condition), T18 (Edwards syndrome) and T13 (Patau syndrome)
Description	• Algorithm that incorporates: o Fetal nuchal translucency (NT) and crown rump length (CRL) USS measurement in late first trimester o Pregnancy-associated plasma protein A (PAPP-A) and free β subunit of human chorionic gonadotrophin (free/total β-hCG/) at 9–13+6 weeks o Maternal and fetal characteristics[6]
Timing	• Between 11–13+6 weeks gestation[35]
Sample types	• Maternal blood sample • NT screening USS[20] o Transvaginal and transabdominal may be performed • Maternal demographic information o Increasing maternal age increases the chance of pregnancy with some (but not all) chromosome conditions • Fetal characteristics o Variations in nasal bone, structural anomalies, tricuspid value flow and ductus venosus waveform may indicate increased-chance of a pregnancy with a chromosome condition
Result reporting[51]	• Reported relative to 1:300 o Low chance: less than 1 in 300 (e.g. 1 in 1,500) o Intermediate chance: 1 in 300 up to 1 in 1,000 (e.g. 1 in 450) o Increased chance: more than 1 in 300 (e.g. 1 in 100) • Example result for T21 is 1 in (n) o Means that among a group of (n) pregnant women with this result, one pregnancy will have T21, while the remaining (n-1) will not • Review individual results and refer to specialist services if: o NT greater than 3.5 mm o PAPP-A less than 0.4 multiples of median (MoM) o Nasal bone is absent/structural anomaly demonstrated o If chance of aneuploidy intermediate or increased (i.e. more than 1:300)
Pattern of result	• Refer to Appendix A: Pattern of screening results by condition
Test performance	• CFTS performs better than any single component (e.g. NT alone) • Detects approximately 85% of T21 with a false positive rate of 5%[52-54] • Limited data for T13 and T18 • Refer to Appendix B: Test performance
Advantages	• Provides early detection and maximises time for decision-making • USS confirms fetal number, gestation, viability and structural development • Pre-eclampsia and fetal growth restriction screening can be performed at the same time (adding uterine artery Doppler)
Limitations	• Not as accurate as cell free DNA (cfDNA) screening (NIPT/NIPS)
Comment	• If CFTS declined, consider offering other screening (e.g. NIPT/NIPS and PAPP-A as separate investigation for placental function[16]) • May identify fetus with T21 that would have been a spontaneous miscarriage (approximately 15% of all pregnancies with T21 miscarried between 11 and 16 weeks compared with less than 2% euploid pregnancies)[55] • Individual results outside of normal parameters can be associated with increased-chance of other chromosome conditions

5.2 Non-invasive prenatal screening test (NIPT/NIPS)

Table 13. Non-invasive prenatal screening test (NIPT/NIPS)

Aspect	Consideration
Conditions screened	• T21 (Down syndrome), T18 (Edwards syndrome) and T13 (Patau syndrome) • Sex chromosome conditions (e.g. monosomy X) • Some NIPT/NIPS may also screen (upon request) for other less common chromosomal variances (at additional cost)
Timing	• From 10 weeks gestation (fetal fraction increases with gestation)
Description	• Molecular targeted screening test that analyses short fragments of cell free DNA (cfDNA) released into the maternal circulation from the placenta through a natural process of cell death o Both maternal and fetal cfDNA are present in the maternal serum o Analysis estimates the chance of trisomy based on deviation from the expected percentage contribution from each chromosome, adjusted for the percentage of fetal DNA fragments in the maternal blood (fetal fraction)
Sample type	• Maternal blood (plasma)
Result reporting	• Reported as increased-chance or low-chance, or no-result
Pattern of result	• Refer to Appendix A: Pattern of screening results by condition
Test performance	• Higher performance (sensitivity/specificity) compared to CFTS as a screening test for T21, T18 and T13[13] o Similar results reported across multiple systematic review and meta-analysis[56-60] • If 'no result' test (no-call result), recommend referral to specialist care as associated with an increased risk of aneuploidy[12] • Refer to Appendix B: Test performance
Advantages	• Higher test performance characteristics than alternatives (e.g. CFTS) may mean fewer women require invasive diagnostic procedures[44] • False positive rate (specificity) is age independent (unlike CFTS)
Limitations	• Requires enough fetal cfDNA in the maternal blood for analysis, (typically reached after 10 weeks gestation)[44] o If fetal fraction is low, may return a false negative or no result[44] • Proportion of pregnancies with low fetal fraction (less than 4%) increases with increasing maternal weight[61] • Unreliable if maternal transplantation/recent whole blood transfusion • False positive results may occur due to placental mosaicism, co-twin demise and maternal chromosomal variations[44] • Offer diagnostic testing after an increased-chance NIPT/NIPS result to confirm the chromosome condition is present in the fetus • Incurs a financial cost as no MBS rebate
Multiple pregnancy	• In multiple pregnancy, the overall fetal fraction is higher but the individual contribution for each fetus is lower, making analysis more complex[64] • In non-identical multiple pregnancy, result unable to report if a fetal sex or a chromosome condition applies to one or more fetus • Additional chromosome condition screening may not be available
Comment	• cfDNA has displaced CFTS as the most common screening test preceding a confirmed prenatal diagnosis of T21[62] • In Queensland, an estimated 25–50% of the pregnant population use cfDNA as a first line screening test[63] • Can be used as a second-tier screening test before progressing to CVS or amniocentesis[20] in some clinical circumstances • Discuss implications for fetal sex identification during screening[20] • RHD genotype may also be performed via the NIPT/NIPS but is not currently offered by commercial laboratories with aneuploidy screening o Refer to Queensland Clinical Guideline: *Rh D negative woman and pregnancy*[65]

5.3 Second trimester serum screening (triple test)

Table 14. Second trimester serum screening

Aspect	Consideration
Conditions screened	• T21 (Down syndrome), T18 (Edwards syndrome) and T13 (Patau syndrome) • Does not report individual chance for T18 or T13
Timing	• 15–20 weeks gestation
Description	• Maternal serum testing (triple test) o Alpha-fetoprotein (AFP) o Free beta (β) human chorionic gonadotrophin(β-hCG) o Unconjugated oestriol (uE3)
Pattern of results	• Refer to Appendix A: Pattern of screening results by condition
Result reporting	• Reported as increased or low-chance (risk) number
Test performance	• Lowest detection rate of any chromosome screen • Combination of individual serum screening tests perform better than any single individual serum screening test[66] • Detection rate varies by laboratory and is approximately74.6% with false positive rate 7%[67]
Comment	• If first trimester NT and PAPP-A performed, second trimester maternal serum screening (2TMSS) is not recommended • If no prior screening, 2TMSS may be considered • Confirm gestational age by USS prior to screening • Individual results outside of normal parameters may also suggest other conditions[68] (e.g. increased AFP may suggest neural tube defect)

6 Increased-chance results

May arise as a result of RGCS before or during pregnancy, or following chromosome condition screening during pregnancy.

6.1 Increased-chance result for chromosome condition

Table 15. Increased-chance screening result for chromosome condition

Aspect	Consideration
Referral	• Recommend referral to a MFM service • Discuss psychosocial support referrals
Information sharing	• Discuss and offer information about the difference between increased-chance result and a diagnosis • Offer accurate and balanced information about the condition identified, including supports available o Refer to Queensland Clinical Guidelines: *Resource list for preconception and prenatal genetic screening*[43] • Refer to Section 2 Support and communication • Refer to Section 7. Diagnostic testing
Care pathways and support	• Discuss and offer information about care pathways available relevant to the circumstances, including: o Diagnostic testing (i.e. CVS or amniocentesis) and prenatal versus neonatal diagnosis o Continuation of pregnancy without further investigation o Preparation for birth of a child with a suspected or confirmed condition (including ongoing pregnancy care/birth planning and neonatal management) o Termination of pregnancy (including implications for method in relation to timing of diagnostic testing) • Refer to Section 2 Support and communication
Comment	• Depending on concurrent clinical findings (e.g. with a hydropic fetus) some women may choose not to have a diagnostic test and have genetic testing of the fetus at the time of termination of pregnancy or after birth • If further investigation is declined or deferred, document decision and plan (e.g. for birth or postnatal testing) in the health record

6.2 Increased-chance result for single gene condition

Table 16. Increased-chance screening result for single gene condition

Aspect	Consideration
Referral	• Refer to specialist clinical genetics counselling/service if: o Both reproductive partners are carriers of the same single gene condition (e.g. CF or SMA) o Female partner is a carrier of an X linked condition (e.g. FXS)
Preconception	• Offer information about reproductive options • Refer to Section 4 Reproductive genetic carrier screening
During pregnancy	• Discuss the care pathways available during this pregnancy including (as relevant to the circumstances) o Diagnostic testing (i.e. CVS or amniocentesis) and prenatal versus neonatal diagnosis o Continuation of pregnancy without further investigation o Preparation for birth of a child with a suspected or confirmed condition (including ongoing pregnancy care/birth planning and neonatal management) o Termination of pregnancy (including implications for method in relation to timing of diagnostic testing) • Refer to Section 7 Diagnostic testing
Support	• Offer psychosocial counselling and support • Refer to Section 2 Support and communication

7 Diagnostic testing

7.1 Preimplantation genetic testing

Table 17. Preimplantation diagnostic tests

Aspect	Consideration
Relevant to	• Reproductive partners who are both carriers of an autosomal recessive condition • Females who are carriers of an X-linked condition
Pre-implantation genetic diagnosis	• Conception occurs by IVF and embryos are tested before implantation • Unaffected embryos are selected for the implantation

7.2 Prior to prenatal diagnostic testing

Relevant when an increased-chance result is identified in the current pregnancy following RGCS or for a chromosome condition.

Table 18. Prior to diagnostic testing

<table>
<tr><th>Aspect</th><th>Consideration</th></tr>
<tr><td>Informed decision-making</td><td>• Before definitive management decisions, offer information about diagnostic tests (CVS or amniocentesis)
• Offer in a non-directional manner that allows personal decision-making (i.e. diagnostic testing is optional)
• Offer counselling or referral to promote and facilitate informed decision-making
• Refer to Section 2 Support and communication</td></tr>
<tr><td>Information sharing</td><td>• Offer information about the:
o Available diagnostic tests and their timing relevant to gestation
o Contribution of the test to ongoing management decisions (e.g. is pregnancy or neonatal care informed by fetal diagnosis)
o Possibility that other conditions not identified by the screening result may be identified
o Procedural risks of the test (to the woman and fetus)
o Costs involved and how they are to be met[20]
o Process/procedure of the test
• Timeframe for receiving results and for making further decisions about the desired care pathway (e.g. if termination of pregnancy is requested, the timing of diagnostic procedure may impact options for method of termination (i.e. medical versus surgical termination of pregnancy)
o Refer to Queensland Clinical Guideline: Termination of pregnancy[69]</td></tr>
<tr><td>Pregnancy loss risk</td><td>• Reported rates vary (due to limitations in study design, methodology, quality, technological advances since older studies conducted, operator related variables)[70,71]
o Estimated rate of subsequent pregnancy loss after CVS and amniocentesis when performed by skilled operators range from[72]: 0.1 to 0.5%</td></tr>
<tr><td>Other risks[72]</td><td><table><tr><th>Risk</th><th>Amniocentesis</th><th>CVS</th></tr><tr><td>Second/repeat sample required</td><td>Up to 6%</td><td>Up to 6%</td></tr><tr><td>Blood-stained sample</td><td>0.8%</td><td>N/A</td></tr><tr><td>Confined placental mosaicism</td><td>N/A</td><td>Less than 2%</td></tr><tr><td>Maternal cell contamination</td><td>1–2%</td><td>1–2%</td></tr><tr><td>Rapid test failure</td><td>2%</td><td>2%</td></tr><tr><td>Severe infection</td><td>rare</td><td>rare</td></tr><tr><td>Fetal injury</td><td>rare</td><td>rare</td></tr><tr><td>Maternal visceral injury</td><td>rare</td><td>rare</td></tr></table></td></tr>
<tr><td>If multiple pregnancy[72]</td><td>• Requires skilled and experienced operator (for performance, pregnancy mapping, ultrasound scanning)
• Increased risk of miscarriage in twin pregnancy of approximately 1%</td></tr>
</table>

7.3 Prenatal diagnostic tests

In some clinical circumstances a diagnostic test may be an alternative to prenatal screening. Counsel reproductive partners and refer for specialist services (e.g. maternal fetal medicine, genetic counselling, clinical geneticists) according to individual circumstances.[6]

Table 19. Prenatal diagnostic tests

Aspect	Consideration
Conditions tested	• Chromosome and single gene conditions • Confirms an increased-chance screening result (if performed)
Test description	• Performed on cells collected from the amniotic fluid or placenta • Rapid technological advances in testing occurring (e.g. next generation sequencing)[73]: • Traditionally[73]: o Fluorescence in situ hybridisation (FISH) o Chromosome microarray analysis o Karyotyping (if indicated) o Single gene testing (where indicated) o Genomic testing (where indicated)
Test type	• CVS o Needle aspirate of placental villi for placental cells o Transcervical or transabdominal • Amniocentesis o Needle aspirate of amniotic fluid for membrane cells (amniocytes)
Timing	• CVS: from 11 completed weeks[72] o Prior to 11 completed weeks, associated with increased chance of transverse limb reduction[6] • Amniocentesis: 16 weeks or more[72,74] o Compared to second trimester amniocentesis, first trimester amniocentesis increases pregnancy loss and spontaneous miscarriages and occurrence of anomalies (particularly talipes)[75]
Test performance	• Procedure related complication rate inversely associated with operator skill and experience[6]
Laboratory	• Pre-notify laboratory prior to collection of CVS/amniocentesis, especially for single gene or genomic testing o If possible, two or more weeks in advance as pre-planning and bespoke test set-up may be required o Maternal blood sample also required for exclusion of maternal cell contamination testing (MCC) of sample • Provide sufficient information for the genetic variant to be tested (e.g. copy of parental/proband genetic test report/s) • Paternal blood sample may also be required on rare occasions
Comments	• Results usually available within 2–3 weeks (laboratory dependent) o FISH usually within 48 hours to five days o Small sample size may delay result • CPM from CVS may require confirmation by amniocentesis[73] • Placental location not always favourable for performing CVS • If the increased-chance result is for a chromosome that has a higher likelihood of CPM, amniocentesis may be the preferred diagnostic procedure • Risk of mother to child transmission[72] o Human immunodeficiency virus (HIV)—low with optimised antiretroviral treatment) o Hepatitis B—increases with higher viral load o Hepatitis C—no evidence of risk

8 Confirmed genetic condition

Table 20. Confirmation of a chromosome or genetic condition

Aspect	Consideration
Context	• A rapidly evolving area of new information, technology and treatments that affect outcomes o Maintain currency of knowledge, training and expertise to facilitate accurate and impartial information transfer
Referral	• If has not already occurred, following confirmation of a genetic condition in the fetus, refer to specialist services (e.g. maternal fetal medicine, genetic counselling, clinical geneticists, neonatologist, paediatrician or other clinician or service specialising in the single gene condition)[20]
Information sharing	• Facilitate opportunities for information sharing and decision-making within the timeframes required by the reproductive partners and family o Subsequent appointments may be required, information repeated or provided in written or takeaway formats for later review/access • Provide information about health and developmental outcomes for children with the condition • Offer details of diagnosis specific support groups where connections with people with relevant lived experience can be made o Refer to Queensland Clinical Guidelines: *Resource list for preconception and prenatal genetic screening*[43] • Discuss options for the pregnancy o Continuing the pregnancy o Termination of pregnancy
Decision to continue pregnancy	• Discuss as relevant to the individual circumstances o Ongoing specialist pregnancy management o Adoption or alternative care arrangements o If diagnosis is life-limiting or life-threatening, perinatal palliative care • If there are new/revised clinical findings during the pregnancy, discuss in a manner that supports the woman's choice to continue or change the decision • Refer to paediatric services to facilitate early development of a post-birth management plan
Decision to terminate pregnancy	• Refer to termination of pregnancy service • Refer to Queensland Clinical Guideline: *Termination of pregnancy*[69]
Psychological support	• Refer to Table 3. Psychosocial support and wellbeing

9 Common chromosome and single gene conditions

T21, T18 and T13 make up approximately 73% of the total prenatally diagnosed aneuploidies.[62] T21 accounts for approximately half (52%) followed by T18 (11%). Sex chromosome aneuploidies account for approximately 7% and T13, approximately 4%.[62]

One in 20 people carry a gene variant for one of CF, FXS or SMA.[45] Approximately 1 in 240 reproductive partners will both be carriers and have an increased chance of having a child with the condition.[45]

There is wide variation in the phenotype of many recognised genetic conditions. The functional and/or health related issues that may eventuate for a child diagnosed with a genetic condition are difficult to predict. Communicate clearly about what is currently known, the uncertainties, and the potential for new technologies and treatments in relation to chromosome and single gene conditions. For referral and support options refer to Queensland Clinical Guidelines: *Resource list for preconception and prenatal genetic screening.*[43]

9.1 Trisomy 21 (Down syndrome)

Table 21. Trisomy 21 (Down syndrome)

Aspect	Consideration
Genotype	• Additional copy of chromosome 21 • Approximately 3% of people with Down syndrome have an unbalanced chromosome translocation rather than a complete extra chromosome 21 • Approximately 1–2% of people with Down syndrome have a mosaic form where some but not all cells have an additional chromosome 21[13]
Incidence	• Approximately 1 in 1,158 babies are born with T21 in Australia[10] • Incidence increases with the age of the woman from 1 in 1,400 for a woman 20 years of age to 1 in 30 at age 45 years • Because younger women have more babies, the majority of babies born with T21 are born to women under 35 years of age[11]
Phenotype traits	• May include hypotonia (single most consistent feature), short stature, brachycephaly, up-slanting palpebral fissures, epicanthus, Brushfield spots on the iris, protruding tongue, smaller ears, short, broad hands, fifth finger clinodactyly and single transverse palmar crease[76] • Intellectual disability • Increased frequency of anomalies of the cardiac, gastrointestinal, urinary, endocrine, musculoskeletal and respiratory systems, leukemia and early onset of Alzheimer's disease[76]
Life and health	• Early intervention supports developmental outcomes • Regular health screening important

9.2 Trisomy 18 (Edwards syndrome)

Table 22. Trisomy 18 (Edwards syndrome)

Aspect	Consideration
Genotype	• Additional copy of chromosome 18[77]
Incidence	• In Victoria Australia, reported as[78]: o Overall prevalence of 0.87 per 1000 pregnancies o Live birth prevalence of less than 0.01 per 1000 live births • High chance of fetal loss and stillbirth[79]
Phenotype traits	• Multiple anomalies including cardiovascular, nervous and musculoskeletal system[77] • Developmental and intellectual disability[77]
Life and health	• Considered a life-limiting condition • Most babies with T18 require specialist care[79] • Sex specific differences in survival with females more likely to be born alive[77] • Increased intervention may account for better survival and outcomes[80] • Improved survival for children with mosaic T18[79]

9.3 Trisomy 13 (Patau syndrome)

Table 23. Trisomy 13 (Patau syndrome)

Aspect	Consideration
Genotype	• Additional copy of chromosome 13
Incidence	• In Victoria Australia reported as[78]: o Overall prevalence of 0.66 per 1000 pregnancies o Live birth prevalence of 0.02 per 1000 live births • High chance of fetal loss, stillbirth or neonatal death
Phenotype traits	• Multiple congenital anomalies including orofacial clefts, microphthalmia/anophthalmia, cardiovascular and postaxial polydactyly of the limbs[81] • Developmental and intellectual disability[81]
Life and health	• Considered a life-limiting condition • Most babies born with T13 require specialist care[79] • Increased intervention may account for better survival and outcomes[82] • Improved survival for children with mosaic T13[79]

9.4 Common sex chromosome conditions

Prior to the inclusion of sex chromosome aneuploidy (SCA) in NIPT/NIPS, most cases of prenatally diagnosed SCAs were incidental findings following diagnostic testing for an unrelated indication. Many individuals remained undiagnosed in the general population.

Table 24. Sex chromosome conditions

Aspect	Consideration
Genotype	• A missing X chromosome, an extra copy of the X chromosome, or one or more extra copies of the Y chromosome
Turner syndrome	• Also called monosomy X or 45, X • Only females affected • Usually associated with having one copy of the X chromosome • Mosaicism is frequent • Estimated to occur in 1 in 2,000 females[83] • There are many Turner syndrome variant arrangements[2]
Klinefelter syndrome	• Associated with having an additional copy of the X chromosome (47, XXY) • Only males affected • Estimated to occur in 1 in 500 to 1 in 1000 males born in Australia[84] • In Victoria Australia, most common prenatally diagnosed SCA[85] • Early intervention improves neurodevelopmental outcomes[85]
Triple X	• Associated with an additional copy of the X chromosome (47, XXX) • Only females affected • Estimated to occur in1 in 1000 females[86]
Jacob syndrome	• Associated with an additional copy of the Y chromosome (47, XYY) • Only males affected • Estimated to occur in 1 in 1000 males[87]
Life and health	• Wide phenotypic variation • Many remain undiagnosed in the general population
Considerations	• cfDNA has led to a significant increase in the rate of prenatal detection of sex chromosome aneuploidies[85]

9.5 Cystic fibrosis (CF)

Table 25. Cystic fibrosis

Aspect	Consideration
Inheritance mode	• Autosomal recessive (occurs equally in males and females)[88]
Genotype[89]	• Two copies of *Cystic Fibrosis Transmembrane Conductance Regulator* (*CFTR*) gene with clinically significant variants • Over 2,000 known CFTR variants, not all of which cause CF o Different variants and variant combinations associated with varying symptoms o Although a variant by itself does not predict the course of the disease, knowing which variant(s) people have, may assist in identifying how others with the same variant(s) have been affected o In Australia estimated 90% of people with CF have the variant C.1521_1523del (p.Phe508del) (47% of whom are homozygotes)
Incidence and carrier frequency[90]	• Carrier frequency and therefore prevalence varies across populations and ethnicities but screening is recommended for all ethnicities (pan-ethnic) o People of East Asian ancestry are less likely to have CF than people of European ancestry, but are more likely to have variants that are missed by screening tests that target a limited set of high frequency CF variants • Incidence in Australia estimated at 1 in 3,000 live births with wide variation worldwide (1 in 3000–6000 in Europe, 1 in 1350 in Ireland and 1 in 25,000 in Finland) • Carrier frequency estimated at 1 in 34 in Australia
Phenotype traits	• Classic CF chronic suppurative lung disease, pancreatic exocrine insufficiency, blocked biliary ducts, elevated sweat electrolytes, poor weight gain, and infertility in males[45] • Other more variable phenotypes include pancreatic sufficient CF and *CFTR-RD* • Some *CFTR* genes associated with a broad phenotype including with minimal disease • Early commencement of disease-modifying therapies that can be aided by prenatal diagnosis
Life and health	• Rapidly evolving area affected by medical advances • The most common life-limiting autosomal recessive condition affecting Australian children[88] • Meticulous daily management of lung disease and prompt aggressive treatment of exacerbations is required to preserve lung function[91] • Management by multidisciplinary teams with expertise in respiratory medicine, gastroenterology, endocrinology, physiotherapy, nutrition, psychology and social work[92] • Median life expectancy has significantly improved to 53 years[88] • Potential for disease-modifying therapies to dramatically reduce symptoms and further increase survival[93] • Depending on *CFTR* variant, some people are eligible to receive *CFTR* modulators o A class of drugs that act by improving production, intracellular processing, and/or function of the variant CFTR protein (e.g. ivacaftor, lumacaftor/ivacaftor, tezacaftor/ivacaftor, elexacaftor/tezacaftor/ivacaftor)[93]

9.6 Spinal muscular atrophy (SMA)

Table 26. Spinal muscular atrophy

Aspect	Consideration
Inheritance mode	• Autosomal recessive[94]
Genotype	• 95% have homozygous deletions of the survival motor neuron gene (*SMN1*)[94]
Prevalence and carrier frequency	• Prevalence[45]: 1 in 10,000 • Carrier frequency[45,95]: 1 in 35 to 1:40
Phenotype traits	• Characterised by progressive muscle weakness and atrophy[96] • Classified according to maximal functional status achieved (descriptions based on presentation without treatment)[45] o Type 1: never sit unsupported, onset before 6 months, marked weakness and hypotonia, areflexia, tongue fasciculations, life expectancy less than two years due to respiratory failure o Type 2: sit independently but never stand or walk, onset between 6 and 18 months, proximal weakness, hand tremor, scoliosis, life expectancy more than 2 years to 3rd/4th decade o Type 3: stand and walk independently, onset after 18 months, may ultimately require wheelchair, life expectancy similar to normal population
Life and health	• Most frequent genetic cause of infant mortality[40] • Treatment landscape is rapidly changing the clinical presentation[97] • Greater clinical benefit with early (pre-symptom onset) initiation of treatment (e.g. nusinersen, risdiplam and onasemnogene abeparvovec)[96,97] • Requires multidisciplinary management of pulmonary, gastrointestinal, nutritional, neurological and orthopaedic issues[45]

9.7 Fragile X syndrome

Table 27. Fragile X syndrome

Aspect	Consideration
Inheritance mode	• X-linked[98]
Genotype	• The expansion of the CGG triplet repeat region of the *Fragile X messenger ribonucleoprotein* (*FMR1*) gene[98,99] o Full mutation defined as 200+ CGG repeats[45] o Premutation defined as 55–200 CGG repeats[98]
Prevalence/ carrier frequency	• Prevalence[45]: 1 in 4,000 to 1 in 6,000 • Carrier frequency[45]: 1 in 250
Phenotype traits	• Most common cause of inherited intellectual disability[98] with males more severely affected than females[98] • Features vary depending on mutation state (full versus premutation) o Full mutation male: intellectual disability profound (intelligence quotient (IQ) less than 20) to moderate (IQ 40–54)[98] o Full mutation females: 30–50% have IQ less than 70, and 50–70% have IQ less than 85[98] • Commonly developmental and speech delay, autistic-like behaviours, anxiety, hyperactivity, epilepsy, macrocephaly, large ears, long face[98] • Individuals with premutation do not have FXS but o Female premutation carriers have an increased chance of primary ovarian insufficiency[98] o Male and female premutation have an increased chance of fragile X-associated tremor/ataxia syndrome (usually developing after age 50 years)[45] • Female full and premutation carriers have an increased chance of having a child with FXS
Life and health	• Early intervention including occupational and speech therapy, supports developmental outcomes[100] • Pharmacological treatments available for hyperactivity, anxiety, aggression and mood instability[45] • Promising results from targeted treatment pharmacological therapy aimed at improving symptoms and increasing independent functioning in everyday life[101]

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Appendix A: Pattern of screening results by condition

Condition	AFP	uE3	hCG	NT	PAPP-A	Fetal fraction
T21 (Down syndrome)	↓	↓	↑	↑↑	↓↓	↑
T18 (Edwards syndrome)	↓	↓↓	↓↓	↑↑	↓↓	↓
T13 (Patau syndrome)	↔	↔	↔	↑	↓↓	↓
45X with hydrops	↓	↓	↑	↑	↑↓	
45X without hydrops	↓	↓	↓	↑	↑↓	
Sex chromosome aneuploidy	↔	↔	↔	↔	↔	
Triploidy (maternal)	↔	↓	↓	↑	↑↓	
Triploidy (paternal)	↔	↓	↓	↑	↑↓	

↑: Increased, ↓: decreased, ↔: unchanged, ↑↓: variable, **AFP**: alpha fetoprotein, **hCG**: human chorionic gonadotrophin, **NT**: nuchal translucency, **PAPP-A**: pregnancy associated plasma protein, **uE3**: unconjugated estriol

Adapted from: Messerlian G, Farina A, Palomaki G. Maternal serum marker pattern in selected fetal syndromes 2022. UpToDate Inc. Waltham MA. Internet [cited 2023 April 02]. Available from: https://www.uptodate.com

Appendix B: Test performance

Take into account that test performance varies by laboratory, underlying population prevalence and individual person characteristics.

NIPT/NIPS test performance for trisomies and sex chromosome aneuploidies (SCA)

Condition	Sensitivity	95% CI	Specificity (%)	95% CI	PPV (%)	95% CI	NPV	95% CI
T21 (Down syndrome)	98.80	97.81 to 99.34	99.96	99.92 to 99.98	91.78	88.43 to 94.23	100	99.99 to 100
T18 (Edwards syndrome)	98.83	95.45 to.99.71	99.93	99.83 to 99.97	65.77	45.29 to 81.68	100	100 to 100
T13 (Patau syndrome)	100	0 to 100	99.96	99.92 to 99.98	37.23	26.08 to 49.93	100	100 to 100
Monosomy X	97.68	84.25 to 99.70	99.84	99.67 to 99.92	29.52	22.72 to 37.36	100	99.98 to 100
47,XXX	100	0 to 100	99.97	99.96 to 99.98	53.95	40.58 to 66.77	100	0 to 100
47,XXY	99.25	78.13 to 99.98	99.99	99.98 to 99.99	74.05	59.47 to 84.73	100	99.98 to 100
47,XYY	100	0.0 to 100	99.99	99.99 to 100	74.45	58.40 to 85.81	100	0 to 100
Overall SCA	99.63	94.83 to 99.98	99.80	99.69 to 99.88	43.13	37.92 to 48.50	100	99.99 to 100

Source: Rose NC, Barrie ES, Malinowski J, Jenkins GP, McClain MR, LaGrave D, et al. Systematic evidence-based review: The application of noninvasive prenatal screening using cell-free DNA in general-risk pregnancies. Genetics in Medicine 2022;24(9):1992.

NIPT/NIPS: non-invasive prenatal screening test

CFTS test performance for T21

Condition	Sensitivity	95% CI	Specificity	95% CI
T21 (Down syndrome)	87.95	79.22 to 93.32	99.97	99.95 to 100
Combined T21/18/13	89.57	82.64 to 93.93	97.25	97.10 to 97.40

Source: Lindquist A, Hui L, Poulton A, Kluckow E, Hutchinson B, Pertile MD, et al. State-wide utilization and performance of traditional and cell-free DNA-based prenatal testing pathways: the Victorian Perinatal Record Linkage (PeRL) study. Ultrasound in Obstetrics & Gynecology 2020;56(2):215-24.

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