PRENATAL GENETIC TESTING

Information

A living document on the CMA website

With evidence-based medicine information required for informed consent

Respecting the value and dignity of the human person

AUSTRALIAN CATHOLIC MEDICAL ASSOCIATION

Note: This Information Document was produced by the Australian Catholic Medical Association upon request from the Australian Catholic Life, Family and Marriage Council, an advisory body to the Australian Catholic Bishops Conference. It is not a clinical guideline but provides information to be considered and discussed with obstetric and genetic health care providers.

1 July 2026

Cover Letter

Assembling information for parents about new testing offered of their unborn child has lagged behind the rapid technological developments in prenatal genetic investigations. It requires a sound knowledge of the subject matter, experience with obstetric management and parent consultations, carefully chosen words to provide reliable information without ambiguity, with technical language explained without jargon, and all while maintaining accuracy. Therein lies the challenge!

But as prenatal genetic testing gathers collegiate and societal momentum and acceptance, there are further challenges. Providing sufficient facts to parents and the public for application of values requires a level of genetic and medical literacy and understanding which most will not ordinarily have. For parental decisions about genetic testing and follow-up for their son or daughter, which all are now asked to do, they will need to be conversant with the topic and aware of the processes to engage in meaningful discussions with their health professionals.

It is important to keep in mind that the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) have openly stated that abortion is essential health care. Equally concerning, responsibility for the wellbeing of the baby was removed from the RANZCOG Code of Ethics in 2006.

Parents feel overshadowed by the magnitude of decisions they are asked to make regarding prenatal screening and testing – whether to engage, and when to exit the genetic testing process. They are hungry for information and rightly should be. As clinicians and members of RANZCOG while also often being these patients' General Practitioners, we are aware of the questions they ask, of the huge gaps in their knowledge and of the trust they place in their advisors. The duty they feel to do the 'right thing' for their unborn baby while lacking facility with the matters placed before them can favour 'flow-chart' expectations and the expectations of others rather than their own parental concerns and wisdom. Presented with decision-making, parents report concerns about inadequate information regarding the genetic screening and testing programme that has been set in train.[1] Others, expecting reassurance, are frightened by their baby's results and wholly unprepared ethically for the decision-making held out to them.[2]

Lacking the proficiency and confidence with both concepts and language, they are vulnerable to the influence of other decision-makers. Many times, parents phone for more discussion of their child's results. When information is given to the mother the father often wants to hear it again as soon as he gets home. Night calls from parents on speaker phone from home, with grandparents, within tertiary maternal-fetal medicine units or enroute to tertiary centres following atypical possibilities in their unborn are the experience of family doctors. The testing process has its own momentum and parents caught up in it at this critical time need more information and deeper conversations.

Added to their burden, the information parents and health professionals may have already absorbed carries an implicit expectation at odds with the Christian anthropology of the human person.

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[1] A. Cernat, C. De Freitas, U. Majid, F. et al. Facilitating informed choice about non-invasive prenatal testing (NIPT): A systematic review and qualitative meta-synthesis of women's experiences. *BMC Pregnancy and Childbirth*, 19 (1) (2019), p. 27, doi: 10.1186/s12884-018-2168-4.

[2] Mozersky, J. (2015). Hoping Someday Never Comes: Deferring Ethical Thinking About Non-invasive Prenatal Testing. *AJOB Empirical Bioethics*, *6*(1), 31–41. doi: 10.1080/23294515.2014.993097.

This booklet is designed for all who are involved with prenatal genetic testing. A Christian anthropology can re-emerge from within this technology, and it must. The need is to inform, reassure and empower parents to confidently assume the role of being the loving, informed, wise decision-makers for their child.

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Prenatal Testing Information for Families

Purpose

A major paediatric resource by Thomas Phaire in 1553 began with the promise:

> *'My purpose is here to do them good that have most need,*
> *that is to save children,*
> *And to share the remedies that God has created for the use of man'*

The purpose of modern medicine remains unchanged: to find the good and be ordered to it.

Foreword

Modern medicine and medical technology offer much to ensure the safety of mother and child as a pregnancy develops and to guide the safe passage of this new person into the world. They also hold much promise for future improvements in pregnancy health and birth. The technology of modern medicine, however, involves increasing complexity, with ramifications for the earliest days and weeks of human life requiring detailed explanation and clarity.

The Australian prenatal genetic screening and testing programme offers a separate function and goal to antenatal care. It aims to search the whole population of unborn babies to locate who is in the group more likely to have major chromosomal conditions. The diagnosis procedure itself then risks the lives of all babies in this group to identify and offer abortion of those few with the condition. The fetal mortality rate of up to 1 in 200 for amniocentesis, and up to 1 in 100 for Chorionic Villus Sampling, would be wholly unacceptable in adult medicine for a test on a well person. This population testing was not designed for therapy for the unborn. Its investment in the wellbeing of the child is evident from the combined peril in which diagnostic testing places the child, and the acceptance of an unfavourable risk-benefit ratio. Invasive testing may proceed without justified benefit for the child. Like any other medical intervention, diagnostic genetic testing would need to meet the simple standard: the benefit intended for the child by invasive testing would need to be greater than its risk of hazard and death to the child.

To enable parents to best understand the reasoning, purposes and the processes of the steps routinely offered them in prenatal genetic screening and testing, information must be readily available at the appropriate depth for the gravity of the discussions and decisions they are being asked to make. Ignorance of the genetic screening programme offered to all parents makes parents and pastors more susceptible to the approach of the prevailing culture. As Colleges of Health Professionals adopt the policy that 'abortion is health care'[3] standards and expectations gradually orient more to this philosophy.

To enable parental dialogue, for more meaningful engagement with health professionals, for the wellbeing of the baby at the centre of new testing protocols and for responsible decision-making of all parents being asked to make choices affecting their unborn child, very good life affirming and comprehensive information and discussion is needed. This is an appropriate time to enhance the relevant genetic literacy and understanding of parents and providers within their own conversations and in the context of a Christian anthropology. Not only can 'genomic' information acquired prenatally in screening programmes not reliably predict the physical and physiological effects, the 'phenotype,'

[3] RANZCOG Submission to the Senate Inquiry into Universal Access to Reproductive Healthcare, December 2022. Submission 65. Recommendation 2: 'RANZCOG regards abortion as essential healthcare'.

of the child, it cannot present the joy and love the child brings and the parents give and share. More especially, genetic information in the context of current testing protocols bears no attentiveness, commitment or responsibility to the intrinsic value of the human being. The concept of generous and unconditional love is not present to other sources of parent information. Love accepts all things in the process of new life.

Parents need access to fully appraised 'risk versus benefit' analysis for informed consent to all testing, extant from a purely genomic context. Where there is no known medical benefit for the child being tested and hence no therapeutic intent, the known procedural mortality and morbidity rates for the baby become unsupportable. This disproportion is a compelling factor. All invasive diagnostic testing is thereto accountable. Parents who have become distressed by anxiety about the possible genetic makeup of their child but do not intend abortion are best helped by support and counselling, and closer observation perhaps with further ultrasounds. For such parents, seeking to resolve anxiety or to find serenity from an invasive early pregnancy diagnosis procedure, whose baby may then suffer procedural harm, the grief and regret, sorrow and misgivings may be intensely distressing. Underlying anxiety conditions are not resolved by procedural tests. Meanwhile, all parents can be reassured that every assistance would be given them and their unborn child should an issue be present,

Pope Saint John Paul II taught, regarding prenatal investigations, that if some risk to the child must be undertaken it must be for the benefit of the child being tested.[4] Risks to the life of the tested child must be proportional to the benefit for the child:

> *[one] 'must first of all carefully assess the possible negative consequences that the necessary use of a particular examination technique may have on the conceived being and avoid recourse to diagnostic procedures whose honest purpose and substantial harmlessness are not sufficiently guaranteed. And if, as often happens in human decisions, a risk coefficient is involved, the doctor will take care to ensure that it is balanced by the real urgency of the diagnosis and by the importance of the results that can be achieved through it for the benefit of the unborn child.'* [5]

Our ever-increasing detection of genetic variability in the womb has no guard rails. The anxiety it generates undermines parental confidence and displaces the primary parental and therapeutic responsibility to prioritize the safety of the child. Parents are freed to embrace their child's development in the womb when given the reassurance that the intrinsic value of their child transcends all other persons' and protocol evaluations of their child, and cannot be diminished. It transcends this child's effect on their own lives and plans. Parents stand in advocacy, defence and fidelity to their child, and the Church stands with them.

Resources that are both reliable and imbued with the awareness that each human life is sacred and a gift which God the Father has entrusted to us, are best placed to give peace of mind to parents navigating genetic prenatal testing invitations. At the heart is placing the information within a Christian anthropology rather than a utilitarian philosophy.

Therefore, this resource seeks to outline the nature and purpose, outcomes and risks of different tests offered in modern screening protocols to detect chromosomal, genetic or structural abnormalities in

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[4] John Paul II, speech to the participants in the Convention of the "Movement for Life", 3 December 1982: Insegnamenti di Giovanni Paolo II, V, 3 [1982], 1512).

[5] John Paul II, speech to the participants in the Convention of the "Movement for Life", 3 December 1982: Insegnamenti di Giovanni Paolo II, V, 3 [1982], 1512).

the unborn child. It provides data for moral guidance based on a fundamental understanding of the human person and of human rights and responsibilities as developed within Catholic teaching. The assumptions of 21st century secular ethics are often presented as adequate in the decision-making context. However, these assumptions can be better weighed with a proper understanding of personhood applied to the prenatal investigative process and purpose. Similarly, the arguments proposed for procedurally endangering, and possibly ending, the lives of children in the womb to identify whether uncorrectable genetic abnormalities are present, can be evaluated with regard to proportionality.

In the light of ongoing medical progress this is a relevant moment to assess prenatal testing as distinct from routine antenatal care processes. Indeed, as Pope John Paul II previously observed

> *'the unprecedented and rapid progress of medical science carries with it the need for frequent reassessment of medical ethics...medical morality has always been defined, since the days of Hippocrates, by respect and protection of the human being.'* [6]

Venerable protection is owed each human person, since each bears 'the divine dignity of the human race' and carries the 'divine breath of life', sharing the oneness of our origin and destiny.[7]

Applying values to facts is the role of the Church and the need of every family journeying through the genetic screening protocols offered in modern pregnancy care. Responding to these issues, the Church has addressed the question as to which moral criteria must be applied in clarifying problems posed in the field of biomedicine.[8] The answer at the heart of any such question resides in the proper understanding and respect for the nature of the human person. By its union with a spiritual soul the human body cannot be considered merely as its physical attributes and functions, but as a constitutive part of the person. Respecting human dignity means safeguarding this authentic human identity.[9] Any intervention on the human body therefore involves a moral significance and responsibility. Herein rest foundations for decision-making in the case of diagnostic interventions for the unborn child - particularly for those embedded in routine screening programmes which confer no known benefit to mother or child.

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[6] Pope John Paul II, 'The Physician and the Rights of Mankind'. Discourse to the members of the 35th General Assembly of the World Medical Association, 29 October 1983: AAS 76 (1984) 393.
JAMA 1984 Feb 24;251(8):1037-8. doi: 10.1001/jama.251.8.1037.
Vatican version: https://www.vatican.va/content/john-paul-ii/en/speeches/1983/october/documents/hf_jp-ii_spe_19831029_ass-medica-mondiale.html.

[7] Joseph Cardinal Ratzinger Easter 1991 keynote address to the Extraordinary Consistory. Human Life Under Threat: 1. The biblical foundations. ISBN 0 85183 8375.

[8] Donum Vitae 3. Instruction on Respect for Human Life in its Origin and on the Dignity of Procreation Replies to Certain Questions of the Day. Congregation for the Doctrine of the Faith. February 22nd, 1987.

[9] Second Vatican Council, Gaudium et Spes [Pastoral Constitution on the Church in the Modern World], December 7, 1965, 14, Par1.

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Introduction to early pregnancy genetic screening and testing

Pregnancy and birth are exciting times. Joy and expectations for a new life entering the world and the family are accompanied by great hope. Even when there is insecurity and trepidation or fear on first realizing she is pregnant, a mother begins to think about the wellbeing of the child she is carrying. She becomes careful about what she does, where she goes, and what she eats. For parents and clinicians attentive to the health of mother and child, pregnancy is also a time of immense responsibility. As she plans to protect and provide for her new son or daughter she is taking the first steps of motherhood: welcoming the new life, and discerning what is safe from what is unsafe.

In protecting the health and security of the new person entrusted to her care she will visit doctors, midwives and other health professionals from early in her pregnancy. Good antenatal care includes various checks and investigations at different stages of pregnancy designed to safeguard mother and baby, or to determine any needed treatment. Blood tests and ultrasound imaging to assess the age, growth, development, or structural and anatomic changes in the baby that may affect the timing or place of delivery will be offered. Good antenatal care would never put at risk the health of her unborn child unless absolutely necessary for the therapeutic benefit proposed. Any interventions offered will need to have clearly explained therapeutic intent for the benefit of the child yet to be born. Its purpose is, and should always be, to place this baby in his or her mother's arms at the end of the pregnancy, with both enjoying the best possible health.

Amidst the loving anticipation and wonderment of pregnancy there are many unknowns. We all recognize that uncertainties are a part of living. As we develop in wisdom and maturity, we learn to manage changes and uncertainty, and to take on responsibilities. We learn how to adapt to new situations including those we may not have anticipated.

What is prenatal genetic screening of the baby?

Genetic screening and testing look for changes in genes and chromosomes. Current Australian antenatal practice offers all mothers 'Prenatal Screening' for the most common chromosomal conditions, including Down Syndrome, during early pregnancy.[10] Current practice can also offer specific gene testing/screening. These screening tests cannot give a definite answer or a diagnosis. They can only suggest whether there may be an increased or a decreased possibility of a genetic condition. They can suggest whether the chance of a chromosome alteration is more or less than that which the clinical context would already suggest. Diagnosing such conditions before birth – finding out if they are actually present or not – is only possible by obtaining cells with baby's genetic material from inside the womb. This is called Diagnostic Testing, or sometimes 'Invasive Diagnostic Testing.' It is offered to parents if the screening tests and processes suggest an increased possibility of a genetic condition.

Knowing the actual chromosome count of the unborn child, however, does not enable any specific treatment at this time since these conditions cannot currently be corrected. Understanding the meaning, benefits, accuracy, context and implications of modern genetic screening tests is therefore important for parents, to prevent both undue anxieties and unhelpful, potentially lethal testing procedures. Some very rare conditions due to single gene changes may benefit from intrauterine

[10] Royal Australian and New Zealand College of Obstetricians and Gynaecologists Statement on Prenatal Screening and Diagnostic Testing for Fetal Chromosomal and Genetic Conditions. C-Obs 35 Version 3.0. Accessed May 5th 2025. https://ranzcog.edu.au/wp-content/uploads/Fetal-Anomalies-Clinical-Guideline.pdf.

treatments. Any such benefits have to be weighed against the hazard of the test procedure. These will be discussed separately below. While some chromosomal conditions may be associated with structural 'anatomic' effects in the baby, these are diagnosed by an ultrasound scan. They cannot be known from the chromosome count. Furthermore, understanding the safety hazard for the baby in obtaining cells during early to mid-pregnancy for chromosome diagnosis becomes vital for these parents. It must always be asked:

> 'what benefit for the baby is intended by obtaining a diagnostic sample of baby's cells from within the womb?' or simply: 'How is this test necessary for my baby?'

The Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) have stated to parents[11] that prenatal genetic screening is offered to all mothers to find Down Syndrome 'because of its frequency in the population (1:800) and its effects on health and learning'. The College offers no other testing purpose than to locate these babies, and no specific fetal treatment is proposed on the basis of the chromosome findings. The testing and its timing are designed to enable abortion of these children. Testing may not provide reassurance, preparation, or remove the uncertainties or worries[12] of parents before the baby is placed in his or her mother's arms. It may increase anxieties and worry, especially since the quality of life for genetic conditions is pre-determined by the biology.

The progression from genetic screening tests to the offering of diagnostic procedural tests in the womb is now a part of current obstetric practice. It is important to be sure amid new developments, however, that any prenatal diagnostic test is necessary. Research leading to future fetal therapy while still in the womb has commenced for some rare inherited conditions. A few experimental therapies for genetic disorders have also very recently entered the preliminary stage of clinical trials[13]. Treatment for the genetic condition spinal muscular atrophy has progressed into use and is discussed below. It will therefore become increasingly relevant, as technology advances, to ask the all-important question:

> *How will this prenatal diagnostic test change the management of my baby for his or her benefit?*

What are the modern genetic prenatal screening tests?

Modern genetic screening tests include the Combined First Trimester Screening Test, mid trimester Maternal Serum Screening and Non-Invasive Prenatal Testing. Questioning about family history may also be considered a 'screening' method, which may prompt further investigations, including those for specific gene alterations.

Combined First Trimester Screening (CFTS)

This screening test is carried out between eleven weeks of the pregnancy and the end of the thirteenth week of the pregnancy. CFTS uses ultrasound imaging of the baby, especially of baby's neck ('nuchal translucency') combined with results of pregnancy protein and hormone levels in the mother's blood. It will produce a 'risk' estimate of the chance number for the baby (such as eg one chance in three hundred or 1:300) having any of the three major chromosome alterations being sought. Chance ranges for 'low risk', 'intermediate risk' and 'high risk' are applied to each baby in the final result report. This

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[11] RANZCOG Patient Information Pamphlets 'Prenatal Screening for Chromosomal and Genetic Conditions' 09/2017.

[12] Michie M. Is preparation a good reason for prenatal genetic testing? Ethical and critical questions. Commentary. *Birth Defects Research* 2020;112:332-338. DOI: 10.1002/bdr2.1651.

[13] Lewis CJ, et al. AAV9 gene therapy in type II GM1 gangliosidosis - a phase 1-2 trial. *N Engl J Med*. 2026;394(12):1184-1194.

figure, and baby's classification level, are used to advise parents regarding future management. 'Low Risk' categorization is considered less than one chance in 1000. 'Intermediate risk' categorization is considered to be between one chance in 300 to one chance in 1000 of having a major chromosome alteration. 'High risk' category is applied to a baby with greater than a one in 300 chance of these conditions. These designations were originally drawn because diagnostic follow-up testing of the baby posed a greater risk of killing the baby than the child's chance of actually having Down syndrome. Such calculating devalues not only the child with Down Syndrome but all children. Respecting the personhood and life of a child would mean that – like any other medical intervention – the diagnostic test would need to meet this simple but important principle of having a therapeutic goal.

The current risk of the invasive test causing the death of the child is up to one in 200 for amniocentesis[14] and up to one in one 100 for placental biopsy[15]. No child is worth the risk to life to obtain a diagnosis, unless that diagnosis would give a greater than one in 200 chance of saving the life of the tested child. There is no evidence of chromosomal diagnostic testing saving the lives of children in this way.

If the CFTS result shows an increased chance of a major chromosome alteration, or if parents request it, the next step offered may be further screening from a blood test of the mother known as Non-Invasive Prenatal Testing (NIPT), discussed below. Sometimes this NIPT maternal blood test is done instead of the CFTS, since it is more reliable. The offer of proceeding straight to invasive diagnostic testing is also made at this time.

The CFTS test identifies which mothers are in the statistical 'high risk' percentage band for having a baby with an increased chance of a major chromosomal alteration. It screens for *'risk'* of Trisomy 21 (Down Syndrome), Trisomy 18 (Edwards Syndrome) and Trisomy 13 (Patau Syndrome), not for the actual chromosome change itself. Altered numbers of chromosomes are known as aneuploidies. These affected babies have three copies of a chromosome rather than two copies. For every 100 mothers whose babies have screened 'high risk' in Combined First Trimester Screening (eg for Down Syndrome), only approximately 7 to 10 babies will actually have Down Syndrome.[16] This figure varies a little over time and place depending on the population and in relation to increases in the average maternal age in the community.[17] For example, in 2009 only about three in every hundred babies screening 'high risk' for Trisomy 21 actually had Trisomy 21.[18]

CFTS testing acts as a net, designed to catch as many babies as possible with significant chromosomal alterations. The mother already knows her chance of Down Syndrome based on her age. The mother's age will significantly affect the final fetal software programme result assigned to this baby. A forty-year-old mother and a twenty-year old mother may have the same CFTS biomarker measurements on the screening test but the 40-year old's baby will be assigned a higher chance probability which may give a 'high risk' result. Another way of saying it is that the weighting given to maternal age in the Fetal Medicine Foundation formula skews the derived risk result significantly upwards to maintain this net's

[14] RANZCOG Patient Information Pamphlets. Amniocentesis. 02/2021.
[15] RANZCOG Patient Information Pamphlets. Chorionic Villus Sampling (CVS). 03/2021.
[16] Royal Australian and New Zealand College of Obstetricians and Gynaecologists Statement on Prenatal Screening and Diagnostic Testing for Fetal Chromosomal and Genetic Conditions. C-Obs 35 Version 3.0. Accessed May 5th 2025. https://ranzcog.edu.au/wp-content/uploads/Fetal-Anomalies-Clinical-Guideline.pdf.
[17] RANZCOG communication: Andrew McClelland spokesperson correspondence.
[18] RANZCOG Patient Information Pamphlets. A Decision Aid *testing in pregnancy for foetal abnormalities Edition 2, 15 Dec 2009.*

effectiveness. That is, at higher maternal ages there is an algorithmically increased false positive rate for this test

Advantages of modern CFTS include:

- Knowing whether the chance of a chromosome alteration in the baby is significantly more or less than the mother already knows from her age, while allowing for increased false positive rates in higher maternal age.
- Oher changes may be imaged at this time by the ultrasound and clarified on the subsequent anatomy ultrasound.
- Different measurements of pregnancy hormones and proteins in mother's blood, such as a decreased level of PAPP-A (<0.4 MoM)[19] and hCG (<0.5 MoM) may be associated with an increased chance of other obstetric problems such as pre-eclampsia and reduced fetal growth. Health care providers can then plan future observations and mothers can be aware of signs such as headaches or decreased fetal movements or signs of early labour. Health providers may introduce treatment such as low dose aspirin at this time depending on these results and medical history.

Disadvantages of CFTS include:

- Nuchal translucency measurements may vary in accuracy.
- CFTS can be costly and difficult to access in more remote areas.
- Prenatal screening has been associated with disruptive bonding between mother and child.[20]
- The high proportion of false positive results may cause undue anxieties and unnecessary further screening, or lead to invasive testing which may carry a greater chance of miscarriage, fetal death in the uterus and stillbirth than the condition tested.

Second trimester quadruple test (15-20 weeks) also known as Maternal Serum Screening

This test combines mother's age with mother's blood test measurements of biological markers such as alpha-fetoprotein (AFP), unconjugated oestriol, hCG and inhibin-A level. It is not routinely done since it is inferior to other screening tests.

Advantages include:

- It is available beyond the time window for CFTS.
- Unexplained increases of the biomarkers (AFP >2.5 MoM, hCG >4 MoM, inhibin-A >2 MoM), or decreased oestriol (<0.5 MoM) may be associated with an increased frequency of adverse obstetric outcomes. It may also suggest an open neural tube defect such as spina bifida or anencephaly. These can be clarified on an ultrasound routinely done around 18 weeks to 22 weeks gestation.

Disadvantages include increased false positive results for risk of Trisomy 21, resulting in heightened parental anxieties.

These genetic screening tests, CFTS and MSS, clearly have very many 'false positive' results in suggesting a possible chromosomal anomaly. They also have false negatives. They are only screening

[19] MoM is a statistical evaluation. It stands for ' Multiples of the Medium'.

[20] Lawson K L, Turriff-Jonasson S I, Maternal serum screening and psychosocial attachment to pregnancy *Journal of Psychosomatic Research* 60 (2006) 371-378. https://doi.org/10.1016/j.jpsychores.2006.01.010.

for the 'risk' of a genetic condition. There are ways of measuring the reliability of these screening tests.[21] The sensitivity of a test is how well the test detects the condition in all who truly have the condition. The sensitivity of CFTS is considered to be 85%. The specificity of a screening test describes how good the test is in reporting 'probably non-affected individuals' as truly not having the condition. The specificity of CFTS is 95%. The odds of being affected if positive range from only 7 per hundred to 10 per hundred of those babies who have been classified as 'high risk'.

The Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) now recommend health professionals discuss Non-Invasive Prenatal Testing (NIPT) with mothers who are interested in this genetic screening within the first 3 months of pregnancy. This maternal blood test is routinely looking for chromosome changes of trisomy 13, 18 and 21 in the baby. It may also be used as a screening test targeting specific single gene abnormalities, if requested. Because of this College recommendation, it is now offered either as the initial screen or as a subsequent screening test, depending on other test results - such as CFTS or ultrasound findings. The College also recommends that the CFTS (foetal ultrasound with maternal blood tests) be offered to those not accessing the NIPT as a prenatal screening test for major chromosome alterations.[22] This recommendation is due to the higher sensitivity and specificity of NIPT, compared with CFTS, in both single and twin pregnancies. NIPT also has the capacity to suggest the presence of sex chromosome aneuploidy such as Klinefelter syndrome and Turner syndrome. Rarer chromosome abnormalities may also be suggested. However, chromosomal alterations in themselves are not correctable. The options to maximise wellbeing and function in the presence of these changes do not require the chromosome diagnosis to be made before the birth. Diagnoses of altered chromosomal makeup can be made at any time after the birth, without the fetal hazard of invasive testing prenatally.

The ultrasounds of pregnancy recommended by RANZCOG in the first three months ('trimester') and at 20 weeks gestation (halfway through the pregnancy), give us the important information regarding structural changes in the baby's organs or anatomy that may need management at birth, or even before birth through surgery in the womb. These anatomic changes, sometimes called 'morphological' changes, may accompany some chromosome variants, or may be present in the absence of any chromosomal variation. Knowledge of these anatomical changes seen on ultrasound can determine the best location and timing of delivery for the safety of the baby.

Many parents choose NIPT to identify the gender of their child (as for the now popular 'gender reveal' opportunity) and are not prepared for unexpected findings NIPT might raise. Pre-test counselling and considerations are therefore important for parents, to help them understand the capabilities and significance of all these results before being confronted with any unexpected reports.

CFTS also provides for measurement of the Papp-A maternal pregnancy protein, which can flag the need for extra observation of the developing baby or of the mother's health. The College strongly recommends that mothers whose CFTS report suggests an increased chance of baby having a chromosomal abnormality be next offered an NIPT blood test of the mother.

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[21] Prenatal Screening for Chromosomal conditions including Down Syndrome. Practice Resource. January 2024: p12, Table 2. Author Elizabeth Callinan. Down Syndrome Queensland. Funded by Queensland Department of Health. https://prenatalscreening.org.au/resources/prenatal-screening-practice-resource/.

[22] Screening and Diagnosis of fetal structural anomalies and chromosome conditions (C-Obs 35) Version 3.0. (Last updated October 2024) p 12.

The NIPT genetic screening test

The Non-Invasive Prenatal Test on maternal blood (NIPT)[23] does not harm the baby. It can be done after 10 weeks of pregnancy and offers more reliable genetic screening before any diagnostic testing, but it is very costly (currently $450Aus). It gives more reliable results for chromosome screening and is able to look for some specified gene changes in the baby.[24] NIPT[25] is not funded by Medicare in Australia. As with CFTS and MSS, NIPT cannot give a diagnosis without subsequent invasive prenatal testing.

The NIPT test in the general population has a positive predictive value of 91.78%.[26] This means that 91.78% of babies screened by NIPT who are reported at high chance of a major chromosome alteration such as Down Syndrome will actually have the chromosome alteration. The NIPT test has 99% sensitivity. This tells us the percentage of babies with the condition who have test results suggesting the condition is present. It has 99% specificity. This tells us how well the test suggests that babies who probably don't have the condition truly do not have it.

The range of genetic conditions that can be screened by NIPT can vary from the major chromosome changes of Trisomy 21, 13 and 18 to whole genome screening. There has been rapid uptake of NIPT in Australia since its RANZCOG 2016 endorsement.[27] NIPT, however, also detects less significant unanticipated genetic changes, as well as those of unknown and unknowable significance. This can cause much anxiety and distress to parents.

What happens next?

RANZCOG currently recommends that mothers with "increased chance" results of their baby having a chromosome change on CFTS be offered NIPT follow-up screening with counselling, compared with invasive diagnostic testing dangers.[28] Counselling is the domain of skilled clinicians and obstetricians, genetic counsellors, and maternal fetal medicine specialists. Having no further investigation is of course a very valid option.

For parents who have received an increased chance result from any form of screening, and who accept the offer of an invasive test to find out the actual diagnosis, there are two courses of action: abortion of an affected baby or continuation of the pregnancy. Parents should be aware that they will more likely feel pressured to abort their affected baby, since this option is the aim of embarking on genetic screening in current clinical practice. Specific, evidenced, therapeutic goals for genetic diagnostic testing before birth are comparatively rare and would need to be identified to parents, given the hazard to the baby of the testing process (the procedural risk, which is discussed below).

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[23] See Appendix.

[24] Jeppesen LD, Lildballe DL, Hatt L, et al. Noninvasive prenatal screening for cystic fibrosis using circulating trophoblasts: Detection of the 50 most common disease-causing variants. *Prenat Diagn*. 2023 Jan;43(1):3-13. doi: 10.1002/pd.6276.

[25] See Appendix.

[26] Lisa Hui, Katie Ellis, Dora Mayen, Mark D. Pertile, et al on behalf of the ISPD Board of Directors. *Prenatal Diagnosis* April 2023. https://doi.org/10.1002/pd.6357.

[27] Prenatal screening and diagnosis of chromosomal and genetic abnormalities in the fetus in pregnancy C-Obs 59 May 2016.

[28] Malan V, Bussieres L, Winer N. et al. Effect of Cell-Free DNA Screening vs Direct Invasive Diagnosis on Miscarriage Rates in Women with Pregnancies at High Risk of Trisomy 21: A Randomized Controlled Trial. *Jama.* 2018; 320(6) 557-565. doi: 10.1001/jama.2018.9396. https://pubmed.ncbi.nlm.nih.gov/30120476/.

Structural problems that may be associated with chromosomal abnormalities are detectable by ultrasound and not by the chromosomal count. This is a role of the routine 20-week gestation anatomy ultrasound scan, which can assist in determining the best place and time for delivery of the baby if a structural or other problem is found. Some rare anatomical changes seen on this scan can be treated by surgery performed on the baby while still in the womb. Diagnostic tests do not give this information but, in contrast, place every tested child's life at risk of harm and death from the procedure.

What does Diagnostic Testing of the baby involve?

There are two main methods to obtain a definitive genetic diagnosis in the unborn. They are 'chorionic villus sampling' and 'amniocentesis'. These are offered if screening (either prenatal screening, family history, parents' history or ultrasound) suggests an increased chance of chromosome or gene alteration. With the recent recommendation of carrier screening for Australian parents, invasive diagnostic testing may also be offered for these findings (see Carrier Screening below.)

Chorionic villus sampling

Chorionic villus sampling (CVS) is performed between 10 and 12 weeks of pregnancy. A needle, guided by ultrasound, is passed through the mother's abdomen or cervix to reach the baby's placenta. A sample of cells (biopsy) is then taken from the placenta, usually about 15 mg – 30 mg of tissue, which can then be analysed.

These placental cells usually contain the same chromosomes as the baby, but they may differ in about 2% of cases. Normal chromosomes may grow in one cell culture and affected chromosomes in another (see 'mosaicism' below). In mosaicism the result may not exactly reflect the genetic makeup of the child.

CVS results may be inaccurate or inconclusive. Sometimes the test fails and further invasive testing can be offered, which would entail further risk to the child.

Amniocentesis

Amniocentesis involves taking samples of amniotic fluid to obtain some of baby's cells from within it. This procedure is usually performed between 15 and 17 weeks but can also be done later. Under ultrasound guidance a needle is passed through the mother's abdomen, through the uterine wall and amniotic membranes and into the amniotic sac. Amniotic fluid is then drawn out and fetal cells within it can be used for chromosome and specific gene DNA analysis.

False positive results for chromosomal conditions from amniocentesis and CVS are rare but do happen in 0.06% of tested babies.[29]

Differing laboratory methods will return results rapidly, or within a couple of days and definitively within weeks if successful. Methods of diagnosis are described in the appendix and include terms parents may hear such as Quantitative Fluorescent polymerase chain reaction (QF-PCR) giving a rapid result; Fluorescence in situ hybridisation (FISH); G-band Karyotyping; and chromosomal microarray. This latter method is becoming more used, providing more genetic information and offering a whole genome study. It can also detect too much gene information of unknown relevance or importance and significantly add to parental anxiety, raising questions which have no answers.

[29] Alfirevic Z, Navaratnam K, Mujezinovic F. Amniocentesis and chorionic villus sampling for prenatal diagnosis. Cochrane Database. Syst. Rev. 2017;9(9): Cd003252. doi: 10.1002/14651858.CD003252.pub2.

What is the risk of harm and death to the unborn child from the diagnostic tests?

Mothers and fathers need accurate and reliable information about procedure-related risks to enable them to make an informed decision about invasive prenatal testing. Understanding the hazard risk to the unborn is vital for informed consent.

Different studies giving different results

Many studies report the increased miscarriage rate following invasive prenatal procedures.[30] Some have observed the unborn for only a few days after the procedure. Others have only counted miscarriages that occur within two weeks of the amniocentesis or CVS procedure. Still others only count the increased rate of fetal death occurring before 24 weeks gestation, or before 28 weeks gestation. Different studies also report different rates of tested babies 'lost to follow-up'. Procedural testing may have been carried out in highly specialized units, with mothers returning to their own locality and healthcare, with fetal outcomes unknown to the proceduralist. Different obstetric colleges in different countries report differing rates of fetal mortality. In addition to the reported 'miscarriage' risk is the total increased risk of pregnancy loss which would include stillbirth rates, deaths following premature births, or later complications arising from possible ongoing amniotic fluid loss or infection. Many studies – with shortened cut-off reporting - have observed only the early pregnancy increased miscarriage risk. However, when the invasive testing programme was first introduced, a significant study "Screening for Prevention of Down Syndrome" was published in the Lancet.[31] It advised that invasive prenatal testing:

> "*would require that every woman subjected to amniocentesis be followed at least until delivery. This is an ethical requirement and what is learned from it should enhance the informed quality of the consent given by participants in the screening procedure.*"

Randomized controlled trials[32] (RCTs) are considered the gold standard in modern medicine. However, such rigorous reporting of procedural outcomes for the unborn up until birth are scarce. More modern studies have been lower quality, short, observational studies. One original RCT study of the safety of genetic amniocentesis in low-risk women throughout the whole length of the pregnancy is an older one from 1986.[33] It reported an increased miscarriage rate of 1% (1 in 100) for tested babies. It also found that respiratory distress syndrome was diagnosed more often in the amniocentesis group after birth and more tested babies were treated for pneumonia. Although methods and experience have improved, such effects on the unborn which take longer to develop, or measure, indicate outcomes should be followed and reported throughout the entire pregnancy. RANZCOG advises parents that the increased miscarriage rate following chorionic villus sampling is less than 1% or up to one in 100,[34] and

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[30] Wilson RD, Gagnon A, Audibert F. et al. Prenatal Diagnostic Procedures and Techniques to Obtain a Diagnostic Fetal Specimen or Tissue: Maternal and Fetal Risks and Benefits. *J Obstet Gynecol Can* 2015;37(7): 656-668.

[31] Stein Z, Susser M, Guterman AV Screening programme for Prevention of Down Syndrome, The Lancet Feb 10, 1973.

[32] A study whose participants have been randomly assigned to a control group or an experimental group.

[33] Tabor A, Phillip J, Madsen M et al. Randomized controlled trial of genetic amniocentesis in 4606 low-risk women. *Lancet.* 1986;1:287-93. doi: 10.1016/s0140-6736(86)91218-3.

[34] RANZCOG Patient Information Pamphlets chorionic villus sampling (CVS) 03/2021.

that the increased fetal death rate following amniocentesis is less than 0.5% or up to one in 200.[35,36] Parents may only be informed of risks from the shorter pregnancy studies observing lower procedural deaths and complications rates of 0.22% for CVS and 0.11% for amniocentesis.[37]

There is also a risk of procedural complications to the mother such as introduced infection.

Is all procedural service risk the same?

Hazards of invasive tests are increased with less skilled operators and in smaller units. Trainee operators have previously demonstrated a six-fold increase in unborn death rates.[38] Fetal mortality remains related to the volume of skilled procedures performed.[39] Invasive procedures in Australia are not currently audited, so figures are uncertain. Hospital maternal morbidity and mortality review has recorded late stillbirth due to cord scarring following amniocentesis. Where a rare goal of altered fetal medical management is identified for a genetic diagnostic test, parents might consider RANZCOG guidelines: 'it is recommended that prenatal diagnostic testing be offered in a multidisciplinary fetal medicine team'[40]

There is much inconsistency in various guidelines, recommendations and research. The variation in studies[41,42] reflects not only the ambiguous definitions of pregnancy loss but also differences in study design, use of comparison groups and methods of data collection. Many recent observational studies have not used a comparison group (control group) of mothers who did not choose a diagnostic test with which to compare the pregnancy loss rates.

What other harms may be caused?

Complications of invasive testing include inflammation of the membranes (chorioamnionitis), ongoing amniotic fluid leak, lung under-development, umbilical cord damage, stillbirth and prematurity. The ongoing loss of amniotic fluid can result in feet abnormalities (talipes) due to constriction in an unusual position, and under-development of the lungs. Risk of haemolytic disease of the newborn is also known. Not all these complications will be evident within 2 weeks. As a direct result of the CVS procedure, arms legs and fingers may be damaged and deformed, particularly if CVS is conducted

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[35] Tabor A, Alfirevic Z. Update on procedure-related risks for prenatal diagnosis techniques. *Fetal Diagn Ther*. 2010;27(1):1-7. Tabor A, Alfirevic Z. doi: 10.1159/000271995.

[36] RANZCOG Patient Information Pamphlet. Amniocentesis 02/2021.

[37] Akolekar R, Beta J, Picciarelli G et al. Procedure-related risk of miscarriage following amniocentesis and chorionic villous sampling: a systematic review and meta-analysis. *Ultrasound Obstet Gynecol* 2015; 45(1):16-26. Doi: 10.1002/uog.14636.

[38] Guidelines and audit Committee of the Royal College of Obstetricians RCOG guideline no. 8 (revised) 2005 Jan. London UK Royal College of Obstetricians and Gynaecologists.

[39] L. Hui, A. Tabor, S. P. Walker, M. D. et al. How to safeguard competency and training in invasive prenatal diagnosis: 'the elephant in the room'. *Ultrasound in Obstetrics and Gynaecology* 2016. Vol47:1 pp8-13. doi: 10.1002/uog.15806.

[40] Screening and Diagnosis of fetal structural anomalies and chromosome conditions (C-Obs 35) Clinical Guideline version 3.0. last updated October 2024.

[41] Salomon LJ, Sotiriadis A, Wulff CB et al. Risk of miscarriage following amniocentesis or chorionic villus sampling: systematic review of literature and updated meta-analysis. *Ultrasound Obstet Gynecol*. 2019 Oct;54(4):442-451. doi: 10.1002/uog.20353.

[42] Akolekar R, Beta J, Picciarelli G et al. Procedure-related risk of miscarriage following amniocentesis and chorionic villous sampling: a systematic review and meta-analysis. *Ultrasound Obstet Gynecol* 2015; 45(1):16-26. Doi: 10.1002/uog.14636.

earlier than 10 weeks gestation. Some of the procedural effects on the developing baby may not be seen until later in the pregnancy.

Why is this population testing done?

The question: "is this test necessary for my child?" is vital to ask. It seeks to establish if there is a proportional benefit for the child from a diagnosis before birth, compared with the risk of death or harm from obtaining the diagnosis before birth. For example, if the chance of a treatable condition being present is 1 in 5000, but the death rate from the diagnosis itself is 25 times higher at 1 in 200, finding out is 1 in 200, this test would likely cause more harm than good. Diagnostic sampling for chromosome and gene identification by these procedures is usually done with the investigative intent of aborting the baby if diagnosis is unfavourable. Procedures for this purpose are always immoral.

The current routine genetic screening and diagnostic programmes were performed within protocols to facilitate abortion before 20 weeks gestation to avoid past legal and other jurisdictional processes arising after that time. These protocols are well known and approved by specialty colleges such as RANZCOG and the Royal Australian College of General Practitioners (RACGP). Practical bioethics application has been strongly influenced by this ideology, supporting the population genetic screening and diagnosis programme presuming a resultant but unevidenced benefit for the health of the mother and the health of the tested child.[43] Prevention of the lives of babies with Down Syndrome, however, has always been the functional objective of population screening.[44]

Can this testing give reassurance?

Genetic testing results, whether screening tests or diagnostic tests, are confined to the genetic conditions tested for. They cannot give assurances about other conditions or other health indicators. The anxiety and questioning of parents who may have received 'increased chance' genetic screening reports – but who do not want abortion – also arise at this time. These parents are now anxious and wanting to understand more about the information they have been given. Some will have, or have already had, the NIPT screening test. Both screening measures, however, may have led to suggestions for invasive diagnostic testing. While anxiety is better managed by appropriate counselling and support, the desire for an immediate diagnosis may lead to a procedural test. The test itself however may not resolve anxieties. Distress may simply shift to another area of unknowns and assume another focus. Not all unknowns can be controlled. If foreknowledge is the objective, then the unborn is being exposed to significant risk of hazard to obtain this knowledge. The serenity of pregnancy is further disrupted by concerns of procedural complications and be tragically ended if miscarriage follows. Invasive testing giving a preferred result will still be followed by concerns the baby may have been harmed by the diagnostic test procedure.

We are not left alone to understand these issues. A careful consideration of the teachings of the Church and of the above-mentioned truths of reason provide a response to the numerous problems raised by options for technical interventions and procedures in the early phases of human life[4]. What is the intended therapeutic benefit to the tested child? Is there an evidenced benefit for the child? What is the effect on the parents? These are always the questions in good practice of medicine.

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[43] Catholic Health Australia *Health Matters* Autumn 2011.

[44] Coory MD, Roselli T, Carroll HJ. Antenatal care implications of population-based trends in Down Syndrome births by rurality and antenatal care provider. Queensland 1990-2004. *MJA* 186:5, March 2007; and subsequent discussion in *Australian Doctor* 9th March 2007.

The obligation to avoid disproportionate risks requires authentic respect for the human being and for the correctness of the therapeutic intention. This means that the doctor

> *"must first of all carefully assess the possible negative consequences that the necessary use of a particular examination technique may have on the conceived being and avoid recourse to diagnostic procedures whose honest purpose and substantial harmlessness are not sufficiently guaranteed. And if, as often happens in human decisions, a risk coefficient is involved, the doctor will take care to ensure that it is balanced by the real urgency of the diagnosis and by the importance of the results that can be achieved through it for the benefit of the unborn child.*" [45]

This clarification on "proportionate risks", ie risk versus benefit, should always be borne in mind.

There are many conditions that cannot be detected before a child is born. Even a normal result on a diagnostic test cannot identify the many possible genetic changes that can affect any one of us.

What are single gene disorders?

Single gene disorders are genetic conditions caused by an alteration in a single gene. Sometimes the family history, or perhaps an ultrasound of the baby, or perhaps the new 'Carrier Screening' publicly funded in Australia (discussed below) will raise the possibility of baby having a gene alteration. An NIPT screening test performed on the mother's blood can give an indication about whether the specified gene change suspected is likely to be present in the baby. As with other screening tests it cannot diagnose the condition. An invasive diagnostic test will be offered to the parents for clarification. (The commonest significant inherited gene conditions and NIPT are also discussed below). Some rare single gene changes in the baby such as congenital adrenal hyperplasia, inborn errors of metabolism (eg galactosaemia), and severe combined immunodeficiency (SCID), may benefit from treatment at birth, or in some cases before birth. If their presence is suggested by gene screening, the timing of the diagnostic tests should be discussed with parents to minimize testing hazards.

What is Reproductive Genetic Carrier Screening?

Screening of parents for the three more common gene alteration conditions has become available to all individuals of reproductive age in Australia. It is offered to all prospective parents or those already expecting a child, under Medicare. This screening routinely checks for the most common gene disorders (spinal muscular atrophy, cystic fibrosis and fragile X).

Carrier screening can also focus on conditions prevalent in family histories or in ethnic groups or be expanded to include rarer gene alterations and address concerns arising from parental consanguinity. The purpose of carrier screening is to identify parents with a high chance of bearing a child with a severe inherited genetic condition. The outcome is 'to reduce the chance of having an affected child',[46] or to 'optimize neonatal and postnatal care'. There is no cure for genetic conditions at present. Newborn umbilical cord blood can provide diagnosis of a suspected condition and guide subsequent care, avoiding invasive diagnostic procedures.

The case of spinal muscular atrophy is one of the rare examples of a therapeutic benefit provided by prenatal genetic diagnosis, enabling treatment to commence within hours of birth. (Reproductive

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[45] John Paul II, speech to the participants in the Convention of the "Movement for Life", 3 December 1982: Insegnamenti di Giovanni Paolo II, V, 3 [1982], 1512).

[46] Mina, Kym. Parenthood and the three-gene screen. *AusDoc* 20th June 2025 p44.

Genetic Carrier Screening [RGCS] is discussed below in the document under Further Information.) Once again, the diagnostic procedure could be timed to minimize hazard.

I have heard of couples selecting their children – What does that mean?

Pre-Implantation Genetic Diagnosis (PIGD or PGD) is a service available within the IVF industry and its processes. It involves biopsy of the embryo for genetic testing. These babies, by three to five days of age would normally be making their way down the fallopian tube to nestle or 'implant' in their mother's womb. In the IVF process however, they have only ever existed in the laboratory. The several tiny human sons and daughters of the couple, formed immediately when the IVF laboratory technician used the father's sperm to fertilize them all, are now biopsied (by removing one or more cells) to check for quality. Specified gene alterations may be investigated and chromosomal conditions identified. These and other characteristics will be offered to the parents. The most desired embryo is then chosen for inserting into the mother's womb. Usually only one is chosen but two embryos may be selected from among these babies. Those babies found to have an undesirable characteristic will usually be discarded. Other embryos may be frozen for an uncertain future. Babies who are carriers for a genetic change, perhaps having only one affected gene like their parents, but who do not have the gene condition which comes from having two genes, may be chosen, but also may be rejected or frozen. Specific gene and chromosome issues, as well as the sexes of the children can be identified. Sex linked genetic conditions may lead to sex selection of the desired child and rejection and discarding of the others.

This pre-implantation diagnosis IVF method is often promoted as preventing a 'termination' of the baby. However, the life of the baby bearing the unwanted features is still 'terminated' and ended along with other less desired siblings. PGD does not respect the humanity of these babies, nor even acknowledge their life.

PGD can also potentially endanger the mother since the high dose hormones used to stimulate production of multiple eggs from the ovary all at once can make some women seriously ill. There are also procedural risks to the mother in removing these eggs.

Concluding Discussion

The conclusion of diagnostic testing before birth will be to offer either an abortion or continuation of the pregnancy. The genetic diagnosis can also be made from baby's blood, often umbilical cord blood, after the birth. Courses of care available and decisions to be made at this time may involve palliative care[47,48,49] for the loved child or perhaps adoption. In the case of life limiting conditions present at birth, palliative care enables parents to hold, nurse and look into the eyes of their loved and living child, making the most of the short time they may have together. The child hears the loving voices of parents, experiences their touch and warmth. This also enriches the future with memories of the living

[47] R Limbo & C Wool, 'Perinatal Palliative Care' *J Obstet Gynecol Neonatal Nurs* (2016) 45(5): 611-613.
[48] Heidi Cope *et al.,* 'Pregnancy continuation and organizational religious activity following prenatal diagnosis of a lethal fetal defect are associated with improved psychological outcome', *Prenat Diagn (2015)* 35(8): 761-768.
[49] Balaguer A, Martín-Ancel A, Ortigoza-Escobar D, Escribano J, Argemi J. The model of Palliative Care in the perinatal setting: a review of the literature. BMC Pediatr. 2012 Mar 12;12:25. doi: 10.1186/1471-2431-12-25. PMID: 22409881; PMCID: PMC3320524.

child, other than those of death, and may prevent significant regret later. The parents will have experienced a relationship with the child even so briefly held.

Children with major genetic health conditions are infinitely valued and loved by God as all of us are. They enjoy being valued human beings and members of our families and communities as do we. We are all unique individuals with our own needs and personalities, and we are all called to different tasks, to something only we can do.

As one mother wrote:

> *'We believe that God chose us to be his parents and to be able to provide the most unconditional kind of love during his time on earth. He brought my husband and I closer to God and we are so grateful to have had our special moments with him.'*

And another parent observed on the SOFT (Support Organization for Trisomy) website in the UK:

> *'Trisomy children are like lightning bugs (fireflies): they shine bright and bring joy and wonder into this world'*

Our understanding of human life is informed by scripture and developed in tradition. 'The essential point of departure is, and remains, the biblical vision of man'.[50] Each human being is created in the image and likeness of God[51]. Each lives under the personal protection of God and is 'sacred'. Each person, from the first moment, carries in him or herself the divine breath of life. Human life is untouchable because it is of God[1].

It follows that the embryo then:

> *'must be treated from conception as a person...must be defended in its integrity, cared for, and healed, as far as possible like any other human being'*[52]

This is the foundation for understanding the morality of current prenatal testing and diagnosis. Prenatal diagnosis is morally licit if it respects the life and integrity of the embryo and the human fetus, *and* is directed toward its safeguarding or healing as an individual[53]. One is struck by the fact that, in any other area of medicine, ordinary professional ethics and the healthcare authorities themselves would not sanction a medical investigation which involved such a high proportion of failures and fatalities.[54]

'Human Biology and Medicine work together for the integral good of human life when they come to the aid of a person stricken by illness and infirmity and when they respect his or her dignity as a creature of God."[55]

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[50] Attributed to Jacques Maritain. Catholic Encyclopaedia.
[51] Gen 1:26.
[52] Catechism of the Catholic Church 2274; pub. June 1994.
[53] Donum Vitae 1,2.
[54] Dignitas Personae 15.
[55] Donum Vitae par. 3.

Parents' experience:

Individual stories from parents familiar with this journey can provide a valuable insight:

> *'The majority of women who choose to abort their babies likely do so out of fear: fear of the unknown, of what their child may face, or of being unable to handle the child's special needs. Many women tell stories of how their doctors pressure them to abort, calling their children "burdens" or scaring them into thinking that their family will be unable to handle a child with Down syndrome or even that this new miracle will "ruin" their family.'*[56]
>
> *'Medical professionals.. scare new parents by telling them all the things that can go wrong if you have DS, but the truth is that there's so much more that can and will go right. Will opens our eyes more every day to a beauty that I never realized existed. He's taught us to slow down and enjoy life's simple pleasures. He's taught us to rejoice in little and big accomplishments. He's taught us to love with reckless unconditional love, to see the humanity in others even when we don't agree, and to persevere through hard things with grace and hope.*
>
> *We were told he'd take longer to learn everything, and by the world's standards that's probably true. But truthfully, he's the teacher. We are the students, and we are the ones who took longer to learn what truly matters. I think people with Down syndrome hold the key to living a life of happiness. And we are thankful and humbled that God has allowed us the honour of raising Will and walking beside him through life.'*[57]

[56] "World Down Syndrome Day Shines Love on a Global Scale", published by *Celebrate Life Magazine*.
[57] Susan Cianio 'World Down Syndrome Day and the fight for love and life'. The Catholic World Report March 21st, 2025 (with permission).

Further Information

Non-invasive prenatal testing (NIPT)

The NIPT test is a screening test that can be performed using the mother's blood to look for some specific genetic alterations in the unborn baby. It can be done from 10 weeks gestation onwards and assesses the DNA (genetic material) fragments from the placenta that are present in the mother's blood. It cannot detect all chromosome differences, and it does not screen for single gene disorders in the general population.

NIPT is described by the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) as a highly accurate screening test for chromosome trisomies 21, 18, and 13 in both single and twin pregnancies. It identifies groups of pregnancies considered to be at increased risk of these chromosome differences, called aneuploidies. Its main role in Australia is to screen for these commonest chromosome variants – especially Down Syndrome – either in the general population as a first line screening test instead of CFTS, or contingent upon higher chance identification in prior screening processes.

Functions of NIPT can include:

1. Reducing the number of combined first trimester screen false positive results for these most common chromosomal syndromes. In doing this it also decreases the use of invasive testing with its potential harm for baby. It is a superior screen to the combined first trimester 12-week screen but still has false positives and negatives and cannot give a diagnosis.
2. Determining the blood RhD status of the baby in Rh negative women.
3. Targeting the screening for a single specific gene variation in 'higher chance' pregnancies.

It is not currently included on the Medical Benefits Scheme in Australia, and costs $400-$500. For those babies whose combined first trimester screening test reports a suggested 'high risk' of a chromosomal alteration, but the NIPT shows low probability, significant atypical abnormalities may be present in 1-2%[58].

Current Australian Guidelines from RANZCOG recommend an ultrasound of the baby be done before the NIPT test is done. This is to confirm the gestation of the baby and to identify if twins may be present or any other unexpected findings.

Chromosomal abnormalities have either extra genetic material or less genetic material. A chromosome abnormality can involve whole chromosomes. This is called 'aneuploidy'. Changes that only involve sections of chromosomes are called 'microduplications' or 'microdeletions'.

The NIPT test is based on the cell-free fetal DNA (cffDNA), which originates from the placenta and reflects the child's genetic make-up. Cell-free fetal DNA short fragments in the mother's blood comprise a proportion (usually 10% to 20%) of the total cell-free DNA in her bloodstream. The proportion increases during the pregnancy. The NIPT test is an assay (measurement) for the specific chromosomes indicated, to determine whether the proportions of those chromosomes differ from

[58] Norton M., Baer R., Wapner R. et al. Cell-free DNA vs sequential screening for the detection of fetal chromosome abnormalities. *Am J Obstet Gynecol.* 2016;214(6):727.e1-6.
doi: 10.1016/j.ajog.2015.12.018.

what is expected in the mother's blood. Further statistical analysis is then applied to determine whether these differences are significant.

NIPT can also be used to screen for sex chromosome aneuploidies that are not included in the CFTS nuchal translucency and biomarker screening at 11 to 13 weeks gestation. However, some of the CFTS 11-13 week screening markers can now predict a possible increased chance of pregnancy complications to be managed, such as pre-eclampsia and fetal growth restriction, leading to extra watchfulness and assessment during pregnancy. These were not the screening test's original purpose but were subsequently identified in screened populations. NIPT cannot suggest the likelihood of these clinical conditions arising later in the pregnancy.

The NIPT screen is often chosen first as the most reliable screening test for the commonest chromosome abnormalities: Down Syndrome (Trisomy 21, with three copies of chromosome 21 instead of two copies), Edward Syndrome (Trisomy 18 with three copies of chromosome 18 instead of two), and Patou syndrome (Trisomy 13, with 3 copies of chromosome 13 instead of two). An unborn baby with Down Syndrome, for example, will produce more DNA fragments from Chromosome 21 due to the extra chromosome present in the trophoblast cells of the placenta. This excess amount will show up in the assay of the mother's blood.

Reliability of screening for trisomy detection

It is important to be aware of the limits of screening tests, and why they are not diagnostic. The complexities around positive predictive values, false positive rates, test failures and their causes and contexts make this testing less than straightforward. Many factors influence NIPT screening test results and their calculations. For example, the background prevalence of the condition in the population changes the ratio of true positive to false positive results. The odds of being affected if positive is the 'Positive Predictive Value' (PPV) of a screening test. A high PPV is associated with a low false positive rate. Therefore, a high PPV indicates a positive result is somewhat more likely to be correct.[59]

Expressed another way, PPV = true positive/(true positive + false positive) x100 will give the percentage of positive results that truly indicate the condition is present. For the same sensitivity and specificity of the testing technology, the PPV of NIPT will be lower for mothers who are already in a low-risk population (average age 30 years).

Similarly, for mothers who may have already had a Combined First Trimester Screening Test (fetal nuchal ultrasound and maternal biomarker measurement) suggesting a higher chance of their baby having a chromosomal condition, the NIPT test will have lower sensitivity at 89-100% vs 98.8%, and a high false positive rate (0.03-1.4% vs 0.04%) than for the general low risk population. Therefore, more of these mothers will be offered invasive testing.
The testing process itself engenders anxieties which affect parents and sometimes provoke hurried decisions. It is noted that in one study 6% of mothers aborted their son or daughter 'because of anxiety generated by a positive result' [60] on a screening test for Trisomy 21.

Even the more reliable NIPT maternal blood test screen provides only a statement of likelihood, or probability estimate, regarding whether a child has the chromosome changes looked for. Although more sensitive than other screening methods for narrowing in on a group of mothers more likely to have chromosomal issues in the unborn, it does not give a diagnosis. The odds of the NIPT test being

[59] Hui L., Bianchi D. Noninvasive prenatal DNA Testing: the Vanguard of Genomic Medicine. *Annu Rev Med* 2017; 68:459-472 doi: 10.1146/annurev-med-072115-033220.
[60] See Hui L., \Bianchi D.

correct in the presence of Down Syndrome is often cited as 80.9%[61] for an average maternal age of 30 years. The positive predictive value of the Combined Nuchal Translucency Screening test is only 3.4% for Down Syndrome. The positive predictive value decreases as the prevalence decreases. (These figures therefore vary in different studies and different demographics.)

It is also important to understand that NIPT may not reflect the baby's true chromosomal make-up, due to changes in the cells in the placenta (cellular rearrangements called 'mosaicism'), some maternal conditions such as being overweight (BMI> 30), and the possible effects left from a deceased twin in the pregnancy. If the chromosome variations known as 'aneuploid cells' are only in the placental tissue, and are not present in the baby, this is called 'confined placental mosaicism'. Because some of these abnormal chromosomes from the placenta will be circulating in the mother's blood, they can give a falsely elevated NIPT result from her blood test, known as a false positive result.

NIPT can also have false negative results if there is insufficient cell-free fetal DNA in the mother's blood sample, or due to laboratory issues.

There are several different types of technologies that can be used for NIPT testing (see appendix) They have differing applications. The treating obstetrician or genetic counsellor may advise further on these options in specific situations.

What is Trisomy 21?

Those among us with Down syndrome have an extra chromosome, that is, 3 copies of chromosome number 21 instead of having two copies: one from the mother and one from the father.

These children may possibly have a range of health-related problems. However, just knowing the chromosome count will not tell you which particular problems they have, nor how important they are. Heart conditions (40 to 50%) and gastro-intestinal malformations may be present; coeliac disease and hypothyroidism may develop; neck instability may need surgery. Intellectual disability is a feature of the condition, but children with Down Syndrome *learn and develop throughout life* albeit at a slower pace than usual.

Literacy rates of just over 40% have been noted and are improving. Early intervention programmes help to develop their potential. Symptoms of other problems can be treated. A wealth of information can be obtained from the Australian Down Syndrome Association. (Some associations are state based).

Children with this condition can become active members of the world around them with appropriate

[61] Norton M.E.. Jacobsson B., Swamy G.K. et al. Cell-free DNA analysis for non-invasive examination of trisomy. *New Eng J Med* 2015; 35(10): 1589-1597. doi: 10.1056/NEJMoa1407349.

attention to their specialized education needs, health development and employment opportunities. There are many resources to assist this journey:

- https://www.downsyndrome.org.au/
- https://www.downsyndrome.org.au/resources/life-stages/prenatal/

What is Trisomy 18?

Edwards Syndrome: is a serious chromosomal condition affecting several organs such as heart and kidneys and respiratory function. It is a spectrum type of condition wherein each child is different and may have differing challenges and concerns. Associated anatomic problems are identified on ultrasound examination and perhaps fetal echocardiograph. Anatomic problems are not identified by the chromosome count. One baby in 5000 is born with Edward Syndrome in Australia. Only half of these will survive the first two weeks and one to two out of twenty will live beyond their first birthday. There are three types of Edward Syndrome:

- Babies with full trisomy 18 have three copies of chromosome 18 in every cell of their body. This type is the most common. Some may die before or at birth or may live for some weeks or less commonly, years.
- Those with mosaic trisomy 18 have 85% or less cells containing the third copy of chromosome 18. Other cells are normal. They may have less severe and fewer problems.
- Some babies will have partial trisomy 18, in which a part of the extra chromosome 18 is in every cell.

They experience significant muscle strength and developmental delay and communication problems. Speech therapy is particularly helpful to optimize communication and safe swallowing. Speech Language Pathologists can assess, and devise programmes and strategies specifically tailored to the individual's context and needs. Learning other methods of communication can assist these children to reach their full potential to engage with others and interact with their environment.

The Edwards Syndrome Association suggests the following questions be asked if the diagnosis is suspected or known prenatally:

> *'have the doctors cared for and treated other babies with trisomy 18; how frequently will ultrasounds be done; how will the hospital handle early heart surgery if needed after the birth; will the hospital handle life-saving interventions that may be needed at birth such as intubation and ventilation; will the baby be taken to the neonatal intensive care nursery; will baby be observed before birth for issues which could require early delivery or caesarean section*?'

This knowledge will help to establish a prepared care and management plan.

In more severe cases needing palliative care this service optimizes every day of baby's life in the heart of a loving and welcoming family.

https://edwardssyndrome.org/get-to-know-us/

What is Trisomy 13?

Patau Syndrome: is a serious chromosomal condition wherein 3 copies of chromosome 13 are present in all or some of baby's cells. It is the third major chromosome abnormality test routinely offered in all first trimester pregnancies, the third commonest of the trisomies and the most severe. Many will not survive their first week. Affected babies may have a range of congenital heart defects, intellectual

disability, developmental delay, a cleft lip or palate, low muscle tone, extra fingers and toes, poor weight gain, and underdeveloped eyes, and increased risk of malignancy.

Trisomy 13 occurs in one in every ten thousand births and also has three forms. Full trisomy 13 has three copies of chromosome 13 in every cell and causes severe difficulties. There is a mosaic form in which some cells are unaffected, and a partial form wherein only sections of chromosome 13 are present in baby's cells.

Those babies with the mosaic form of trisomy 13, where not all baby's cells are affected, will usually have less severe genetic effects. Treatment varies from child to child depending on needs. Support groups for parents and families of children with trisomies 13 and 18 can offer further experience and input.[62] https://www.soft.org.uk/

From 2010 to 2020 chromosome abnormality was the reason given for 236 out of 305 late term abortions at the Centre for Advanced Prenatal Care, Royal Brisbane and Women's Hospital Queensland, a tertiary maternal and fetal medicine centre.[63] Injection of potassium chloride directly into baby's heart within the womb is the commonest method of feticide and sadly follows World Health Organization (WHO) and other protocols. Annual feticides in this study rose from 20 in 2010 to 54 in 2020.

Expanding NIPT screening to look for the chance of rarer trisomies is not currently recommended due to the low accuracy and reliability of this testing in the general population.

Palliative care is always a wonderful option available to these children, making the most of each precious day the family can experience together.

What are sex chromosome changes?

These are sometimes called 'Sex Chromosome Abnormalities' (SCAs). These changes form a group of chromosome disorders characterized by the loss or gain of one or more sex chromosomes. They include Turner Syndrome (designated XO or monosomy X instead of XX) affecting 4 babies in 10,000 live female births. These girls have 45 chromosomes instead of 46; and Klinefelter syndrome XXY affecting 1 in 500 live male births with 47 instead of 46 chromosomes, and others such as trisomy XXX, XYY and XXYY. Outcomes for an affected child vary widely. The NIPT test screening for these sex chromosome differences is offered to pregnant women alongside trisomy screening, in RANZCOG guidelines.

However, the clinical significance of these chromosome changes varies. Some may be asymptomatic, or possibly have hormonal effects, infertility, and cardiovascular issues. While the impact on cognitive, behavioural, social, and emotional development can sometimes be severe, they may also be very mild. Conclusions and outcomes vary widely, and the effects cannot be generalized to an individual child[64] from the chromosome count.

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[62] https://www.soft.org.uk/

[63] Rosser S., Sekar R., Laporte J. et al. Late Termination of Pregnancy at a Major Queensland Tertiary Hospital 2010-2020. *Med J Aust* 2022; 217 (8): 410-414. doi: 10.5694/mja2.51697.

[64] Skuse D., Printzlau F., Wolstencroft J. et al. *Handbook of Clinical Neurology*. Chapter 24 Sex Chromosome aneuploidies 2018:147:355-376. doi: 10.1016/B978-0-444-63233-3.00024-5.

Turner Syndrome

Women with this condition are missing either all or part of an X Chromosome. They therefore have 45 chromosomes, described a 'monosomy X' or 45,X' or sometimes designated as '45,XO'. The effects of this chromosomal change vary, and some people will have more features of the condition than others. Sometimes diagnosis is not made until puberty. The average cognitive ability is within normal range. While the tendency is to have a short stature, the height range is 133 to 162 cm. Other features to a varying degree include a short webbed neck, low-set ears, and underdeveloped ovaries. Of those with this syndrome 5% will menstruate for a time but pregnancy is rare. [65] Heart malformations may also occur.

NIPT has a higher false positive rate for detecting Turner syndrome. The odds of being affected if this screening test is positive are lower than for other chromosome changes. Mosaicism, wherein placental DNA is affected but not the baby's cells, creates significant discrepancies in the NIPT test results for this condition. An NIPT screen suggesting Turner Syndrome has a high chance of being false.

Klinefelter's Syndrome

Australian data reports "an unprecedented rise in the prenatal diagnosis of SCA since 2016, predominantly driven by detection of 47,XXY via NIPT".[66] Previously up to 75% of men remained undetected,[67] since only the more severe forms are evident in infancy. Most men are diagnosed when they present for infertility investigations.

Delays that may be present in speech and language (75%) and in motor skills (50%) of affected children are helped by early intervention with improved developmental outcomes. Tiredness and increased height are other manifestations. Timely interventions can also offset osteoporosis and small testes (hypogonadism) associated with lower testosterone levels. Although infertility due to absent sperm is an associated feature of Klinefelter's syndrome, sperm can be extracted from the testes tubules via a specialized surgical technique, for sperm banking, to assist the fertility of marital acts at a later time. Success and subsequent live birth is age dependent.

While NIPT remains a screening test prenatally, diagnosis can then be confirmed in the newborn period avoiding the hazard of invasive testing before birth.

NIPT testing for sex chromosome differences may also pick up previously unknown sex chromosome abnormalities in the mother.

What about screening for single gene problems?

NIPT and detection of a single gene

NIPT can now help in the early detection of a set of Single Gene Disorders (SGD) in the unborn baby. This is particularly so when there is either a specific ultrasound finding, or a family history concerning

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[65] Centre for Genetics Education Fact sheet 40 Turner Syndrome. NSW Government Health www.genetics.edu.au January 2018.

[66] Loughry et al. State-wide increase in prenatal diagnosis of klinefelter syndrome on amniocentesis and chorionic villus sampling: Impact of non-invasive prenatal testing for sex chromosome conditions. *Prenatal Diagnosis*. January 2022. https://doi.org/10.1002/pd.6103

[67] Nieschlag E. Klinefelter syndrome: the commonest form of hypogonadism, but often overlooked or untreated. Deutsches Ärzteblatt International. 2013 May 17;110(20):347. https://di.aerzteblatt.de/int/archive/article/138490.

a specific gene is present. Additional clinical studies are still needed to evaluate and identify babies who would most benefit from this. NIPT Single Gene Disorder screening offers a non-invasive prenatal screening option[68,69]. However, it is still only a screening test. NIPT testing cannot give a diagnosis. Definitive diagnosis still depends on an invasive test with all its attendant risks of harm to the baby.

I have heard the NIPT test sometimes doesn't work, why is that? Failure of NIPT, or 'No-Call' results

NIPT may not provide a result in up to 6%[70] of tests. This may be due to low fetal proportions or 'fractions' of cell free DNA in the mother's blood. Repeating the NIPT test later in the pregnancy may yield a result since the proportion of fetal cells, known as the 'fetal fraction', will increase as the pregnancy progresses. Increased maternal weight can cause a test failure because it decreases cell free fetal DNA in the mother's blood. In addition, the fetal fraction can be affected by some medications, fibroids, maternal ethnicity and multiple pregnancy. Low fetal fractions of cell free DNA can sometimes also be associated with chromosome abnormalities such as trisomy 13, 18, and others: monosomy X (45 XO) and triploidy (69 chromosomes). Such conditions can be associated with smaller placentas and therefore lower circulating levels of cell free fetal DNA. Detailed ultrasound may be helpful to check for structural abnormalities possibly associated with these chromosomal conditions that could be causing a 'no-call' test result. Repeat NIPT testing at a later time will give a result in 50%. The combined first trimester screening test (nuchal ultrasound and biomarkers) may also be offered. A specific diagnosis cannot be achieved without exposing the child to disproportionate dangers of invasive testing if treatment is not the goal.

What is expanded NIPT testing?

Testing for rare autosomal trisomies and 'copy number variants' of chromosomes is not deemed sufficiently accurate to be offered to all pregnant women at this time. Copy number variants are mutations that can include deletions, insertions, and duplications of segments of genetic material. Only one third of women who receive an NIPT result suggesting their baby has a chromosome 'copy number variant' will have an affected baby. This abundance of false positive results will increase parents' anxiety and may expose their babies to the procedural hazards of invasive testing. The false positive results for NIPT detection of rarer autosomal trisomies are also very high. Only 11% of these mothers who receive a positive NIPT result for rare trisomies have an affected baby. The remainder may have miscarried before diagnosis or have the suggested abnormality present only in some placental tissue.

What is mosaicism?

Mosaicism describes the phenomenon in which a person has a mixture of cells with different genetic information[71]. It can occur in the cells in part of the body or throughout all of a person's cells. Cells in the body usually have the same amount of DNA as each other. In mosaicism, however, there is a

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[68] Mohan P, Lemoine J, Trotter C, Rakova I, Billings P, Peacock S, Kao CY, Wang Y, Xia F, Eng CM, Benn P. Clinical experience with non-invasive prenatal screening for single-gene disorders. Ultrasound Obstet Gynecol. 2022 Jan;59(1):33-39. doi: 10.1002/uog.23756.

[69] Johnson, K, Eason J, Prenatal diagnosis of single-gene disorders. *Obstetrics, Gynaecology & Reproductive Medicine. V*olume 33: 6, 2023. pp 174-180. ISSN 1751-7214. https://doi.org/10.1016/j.ogrm.2023.03.004. (https://www.sciencedirect.com/science/article/pii/S1751721423000453).

[70] Cuckle H. cfDNA screening performance: Accounting for and reducing test failures. *Ultrasound obstet gynecol.* 2017;49(6): 689-692. doi: 10.1002/uog.17492.

[71] NSW Government Health Centre for Genetics Education.

difference in the DNA within different cells of the same person. If this mosaicism is in the egg or in the sperm it is called gonadal or germline mosaicism.

In pregnancy, 'true chromosome mosaicism' appears in both the fetal cells and placenta cells. This is different from 'confined placental mosaicism' which appears only in the placenta and is not present in the unborn baby. Mosaicism that is not confined to the placenta has other implications and can have a wide range of effects in the baby, often called phenotypic variation. Understanding the large range of possible effects requires genetic counselling for further detail.

Confined placental mosaicism has been detected in 2% of viable pregnancies at 10-12 weeks gestation[72]. It can cause false positive NIPT tests. Since placental chromosome abnormalities can impair the functioning of local areas of the placenta, they can contribute to slowed fetal growth and premature births.[73] It is suggested that such pregnancies be monitored more closely for these issues developing, and for fetal structural abnormalities. Confined placental mosaicism can cause conflicting NIPT results due to detection of extra chromosome doses circulating in the mother's blood.

Gonadal or germline mosaicism may be passed on directly from parent to offspring.

What are microdeletions and microduplications?

Microdeletions are small missing pieces of chromosomes. The genes contained on these pieces and the information they carry is lost. Microduplications are extra copies of small pieces of chromosomes, adding too much genetic material. Extra or 'expanded' NIPT screening for micro deletions and micro duplications of subsections of chromosomes is not considered sufficiently accurate and reliable to be routinely offered to pregnant mothers in Australia at this time. Ordinary karyotyping will not detect them and other technologies are used.

What follow-up testing may be offered?

Follow-up of a positive, inconclusive or failed screening test is commonly advised in antenatal care protocols. More diagnostic clarity may be offered and suggested. The question must still be asked: 'how will this test benefit my baby?' compared with testing after the birth. The number of chromosomes present in the cells cannot be changed. The number of chromosomes present within the cell does not enable specific treatment at this time. Anatomic and structural defects that may or may not be associated with the same genetic alteration in different individuals are identified on ultrasound. Sometimes imaging by more specialized ultrasound in maternal-fetal medicine units best used to identify structural issues that may alter the timing, the location or the manner of delivery. These monitoring ultrasounds can be implemented on clinical suspicion, or following screening test results, and are not dependent on chromosome verification. Chromosome identification cannot give us structural organ information. Determining the genetic fingerprint before birth predominantly leads clinicians to recommending abortion if there are genetic abnormalities.

As early as 2016 it was identified that the NIPT screening test availability was leading to less invasive testing procedures.[74] Since complication and miscarriage rates from CVS and amniocentesis relate to the experience of the proceduralist, quality assurance in both performing the test and correctly

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[72] Kalousek DK. Pathogenesis of chromosomal mosaicism and its effect on early human development. *Am J Med Genet* 2000; 91:39-45. doi: 10.1002/(sici)1096-8628(20000306)91:1<39::aid-ajmg7>3.0.co;2-l.

[73] Eggenhuizen GM, Go A, Koster MP et al. Confined placental mosaicism and the association with pregnancy outcome and fetal growth: a review of the literature. *Hum Reprod Update*. 2021;27(5):885-903. doi: 10.1093/humupd/dmab009.

[74] See Hui and Bianchi.

analysing results will become increasingly important. Proceduralist inexperience and skills maintenance is being offset by simulation training programmes. The effect of these on fetal mortality and morbidity complications has yet to be properly evaluated. Against this however, the increasing use of genetic screening of the unborn is broadening the numbers of children who will be categorized as possibly harbouring some gene change for which invasive testing is offered.

What are new areas of genetic research?

Testing such as NIPT, apart from reducing false positive test results and hazardous invasive testing, could in the future open up possibilities for personalized medicine for the unborn. At the same time, however, this technology raises potential ethical issues regarding accumulated data sets of genetic information, consent, data mining possibilities and intellectual property. Without future ethical regulation it could also be utilized for genetic interference and manipulations in the unborn which are wholly unrelated to cure or care. Comprehensive assessment of the fetal genome through NIPT technology could potentially provide for future treatment opportunities in the unborn and also provoke grave challenges and misuse. The same secular ethic which discards imperfect or excess embryos in the IVF industry could extend to any unborn in the womb who is lacking perfection or desirable traits.

Research has been developed, and has already entered into reproductive medicine, that leads further away from human care and morality. This is a growing concern and deserves our specific attention. The ethic which accepts unborn deaths as the cost of locating babies with Down Syndrome, and then approves their destruction as a good, now also approves the utilization of embryos and of cloning as a resource and a therapy. The cloning process has already been inserted to reproductive health care. When considering the ethical credibility of professional organisations in this regard, it should be recalled that RANZCOG actively promotes abortion as an essential part of health care, denies medical practitioners the right to exercise conscientious objection, and treats embryos as being without personhood.

What is mitochondrial disease?

Mitochondrial disease is a group of genetic conditions of which there are about 350 different types known. It is caused by changes or ‘mutations’ in either the mitochondrial DNA or the nuclear DNA. Mitochondria are very small organelles within the cell. They generate energy and are often called the ‘powerhouse’ of the cell but are important to other every-day cell functions. Mitochondrial diseases can present at any age and affect any organ, causing mild to severe disease. The majority of mitochondrial diseases are due to changes in the DNA in the nucleus of the cell, which affects products that end up in the mitochondria.

In Australia about 1 in 250 Australians are currently known to carry a mitochondrial mutation that may cause mitochondrial disease during their lifetime.[75] Although the DNA in the nucleus in human cells comes from both the father and mother, the child always receives its mitochondrial DNA from the mother. It can only be inherited from the mother, and it is passed from one generation to the next without very much change.

[75] Sue CM, Balasubramaniam S, Bratkovic, D. et al. (2022), Patient care standards for primary mitochondrial disease in Australia: an Australian adaptation of the Mitochondrial Medicine Society recommendations. Intern Med J, 52: 110-120 2022. doi: 10.1111/imj.15505.

Pre-conception genetic counselling is usually offered to those who have a mitochondrial disease, or whose family history includes diagnosed mitochondrial disease. Knowing what the chance is of passing on a mitochondrial disease mutation to the baby can help plan pregnancy care and suggest the best location for delivery. The genetic counsellor or a medical practitioner may also suggest invasive diagnostic testing of the baby for more definitive information. However, as always, one needs to know 'What is the goal of testing?' and 'Is early treatment the objective?' 'Can this test wait until the baby's cord blood can be tested at birth?'

Although research is underway, there is no current cure for mitochondrial disease.

Avoiding conception through the marital act may be offered by a genetic counsellor or doctor. Instead of natural conception through the intimacy of married love, the 'in vitro' fertilization of ova (eggs) producing multiple embryos at once is performed, to select an apparently unaffected embryo for implantation in the mother's womb. Other embryos produced will be destroyed or perhaps frozen for an indefinite time and future.

Mitochondrial donation from a third party may also be suggested by a genetic counsellor or doctor. 'Mitochondrial donation' refers to several specific techniques used in IVF-based assisted Reproductive Technology (ART):

> *In one technique the nucleus is removed from the donor egg of another woman. This is replaced with the nuclear DNA of the affected (prospective) mother. This donor egg, which now contains the nucleus of the affected mother but the mitochondria and other organelles of the donor woman's egg, is then fertilized by the prospective father's sperm in the laboratory. In short, it uses the egg of another woman to provide mitochondria with no known defect and the nucleus from the prospective mother and father. The recombined chromosomes of the mother and father are the DNA of the nucleus of baby's cells. Since it is only the egg which passes on mitochondria to the child, this method aims to minimize the risk of the child having mitochondrial disease. This process has made a 'three-parent child'. Use of a donor egg (using a third parent) cannot prevent the type of mitochondrial disease caused by mutation in the DNA of the nucleus.*[76]
>
> *In another technique the 'healthy' mitochondrial DNA can also be sourced from another embryo who is created for that purpose and then destroyed by the process. In this method the both the mother's egg and of the donor's egg are fertilized with the father's sperm. Two children are thus created. The nucleus is then removed from the fertilized donor egg child and replaced with the nuclear DNA of the parents' fertilized egg child. The other used child is discarded.*

The Catholic Bishops of Australia have outlined serious ethical concerns regarding mitochondrial donation technology. These include that the methods used do not respect the right to life and the human dignity of the individuals concerned and 'would create a child with three parents, confusing the biological parentage of any children born'.[77] They added that 'concerns emerge for the child who wishes to know their genetic history, including who the third parent is, and the impact this will have

[76] Australian Government National Health and Medical Research Council. https://www.nhmrc.gov.au/mitochondrial-donation.

[77] Australian Catholic Bishops Submission (no.11) to Mitochondrial Donation Law Reform (Maeve's Law) Bill 2021. https://www.aph.gov.au/Parliamentary_Business/Committees/Senate/Community_Affairs/MitochondrialLawReform/Submissions

on the development of their identity.' Use of pronuclear transfer (see appendix mitochondrial disease) is a form of human reproductive cloning which is unethical. Such courses of action are seen to also pose dangerous biological risks to the community "as these techniques can change the human germline, which means altered genes might be passed on to future generations". It is not known what affect this may have on persons in generations to come.

Both methods used in Australia involve the creation and destruction of human persons in the form of embryos.

Apart from being a grave injury to the sacrificed child, the Australian government department introducing this therapy has stated[78] 'Immediate and long-term risks for the child and longer-term implications for subsequent generations are not yet fully understood'.

These experimental techniques are being phased in under license in Australia.

What is 'Carrier screening'?

Screening of parents for their gene variations.

Although there are hundreds of genetic conditions that can affect us, they are mostly rare. It is thought, however, that each of us carries two or three clinically significant individual recessive gene changes[79] that we never know about and that never affect us.[80] Parents may be healthy and have no family history of a gene condition but still be carriers of the gene change for a genetic condition in one of their genes. Genes are usually present in pairs, of which one gene comes from the father and one gene comes from the mother. If only one of the pair of genes is altered, then we are said to be 'carriers' for that condition. The normal gene is compensating for the affected gene. Recessive genes usually only have their effect if they are paired with another affected, recessive gene.

There are two main ways healthy parents can pass on a genetic condition to their children:

1. Through autosomal recessive genes. If both parents carry the same gene change and both pass on this altered gene to the child, the child will have both genes and develop the medical condition. Cystic fibrosis and Thalassaemia are the most common autosomal recessive conditions in Australia.
2. Through X-linked recessive genes. For some conditions, the gene that is affected is only present on the X chromosome. There is no corresponding gene present on the Y chromosome. A male (XY chromosomes) with a faulty such gene present on the X chromosome has no other gene to offset its effect. He will have the genetic condition in some way from the altered gene

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[78] Australian Government Department of Health. Legalizing Mitochondrial donation in Australia. Public Consultation Paper. 2021.

[79] *For most genes, except those on parts of the X-chromosome in men, we have two copies, one from our mother and one from our father. For any specific gene, one or both copies can have changes that result in the gene not working properly. For many genes, the body can tolerate a problem with one copy that is not working, but not both. In other words, as long as you have at least one working copy, you have enough for your cells to work normally. However, if both copies are damaged, the cell can't function normally.*
Carriers have one gene copy with a problem but have enough leftover function from the other copy for normal cell function. People with two altered genes are missing whatever cell function is associated with the gene.
David Adams. National Human Genome Research Institute.
https://www.genome.gov/genetics-glossary/Recessive-Traits-Alleles.

[80] Bell CJ, Dinwiddie DL, Miller NA et al. Carrier testing for severe childhood recessive diseases by next generation sequencing. *Sci. Transl Med.* 2011;3(65):65ra4. doi: 10.1126/scitranslmed.3001756.

present on his X chromosome. The most common X-linked gene condition is Fragile X syndrome.

It is now a RANZCOG recommendation in Australia that all pregnant women in the first trimester, and those planning pregnancy be offered 'Carrier Screening' for the three commonest genetic conditions. Carrier screening informs parents on the chance of their child having one of the genetic conditions: cystic fibrosis, Fragile X syndrome and spinal muscular atrophy. A sample can be collected from the mother first, and then from the father, or collected simultaneously.

What are the clinical conditions that may be suggested by the '3-gene' carrier screening?

Cystic Fibrosis

Cystic Fibrosis can affect lung, digestion, pancreas, sweat glands and reproductive organs. Symptoms will vary in their nature and severity. Some persons may have more severe problems than others[81], however the condition tends to be progressive in its effects. Although life expectancy is reduced, it is increasing with improved treatments and care. Cystic Fibrosis CFTR gene defects now have some therapies available. Introduction of next generation triple therapy CFTR modulators target the underlying cause of Cystic fibrosis morbidity by assisting the faulty protein to function, thinning mucus and reducing respiratory infections. This and other treatments delay development of lung scarring. Cystic fibrosis affects one in two thousand five hundred persons in Australia. One in twenty-five persons are gene carriers. It is already routinely screened for in the Australia-wide newborns' heel-prick test, enabling commencement of early clinical management strategies.

If both parents are found to be carriers for Cystic fibrosis there is a one in four chance of the baby being affected by the condition.

Spinal Muscular Atrophy

Spinal Muscular Atrophy, in summary, is a degenerative neurological condition. It does not affect intellect or cognitive function, but causes respiratory, orthopaedic and nutritional problems. Recently, however, the clinical approach to spinal muscular atrophy has involved treatments which can give gains in motor function and increased life expectancy,[82] particularly if implemented early.[83] Disease-modifying therapies are changing the clinical course of the disease enabling some stabilization and small gains. There are four types of spinal muscular atrophy reflecting four levels of severity of the disease. Early diagnosis and intervention improve clinical outcomes and attainment of milestones, with contribution from neurologists, physiotherapy, orthopaedic and respiratory specialists.

Spinal Muscular Atrophy (SMA) causes deterioration of lower motor neurons (nerves) controlling muscle movement. The muscles supplied by these nerves begin to waste or 'atrophy' when the nerves die. Spinal Muscular Atrophy is due to an alteration or deletion of the recessive gene that codes for 'survival motor neuron 1' (SMN1). If not enough of this protein can be produced, motor neurons start to die. We each have two copies of this gene, inheriting one from each parent. If one copy of the gene is deficient, we are carriers for SMA. If we inherit a deficient copy from each parent and have two deficient genes we have Spinal Muscular Atrophy. If both parents are carriers for this gene loss there is a 1 in 4 chance their baby will be affected by the condition since both the genes are non-functional.

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[81] https://www.mayoclinic.org/diseases-conditions/cystic-fibrosis/symptoms-causes/syc-20353700.

[82] Davidson JE and Farrar, MA. The changing therapeutic landscape of spinal muscular atrophy. *AJGP* Vol 51 1. Jan-Feb 2022 doi: 10.31128/AJGP-03-21-5924.

[83] Ramdas S, Servais L. New treatments in spinal Muscular atrophy: an overview of currently available data. *Expert Opin Pharmacother* 2020;21(3):307-15. doi: 10.1080/14656566.2019.1704732.

Treatment for these affected newborns can now transform the outcome. The earlier the treatment is started after birth the more effective it is, since it is best given before motor neuron loss and symptoms occur.[84,85,86,87] Neuron loss can potentially start within days. Treatments are available on the Pharmaceutical Benefits Scheme (including a single lifetime gene therapy dose).

Carrier screening for SMA is offered to parents and prospective parents under Medicare in Australia since November 2023 (together with carrier screening for cystic fibrosis and fragile X). If the woman is found to be a carrier, her partner is also tested. All newborns in Australia are themselves also now screened for this condition within 36 to 72 hours of birth with a heel prick blood test. The result may take two weeks to be returned after it is received in the laboratory. A targeted cord blood test is also available. Routine newborn screening for SMA will detect 95% of cases. (The measurement assay techniques used will not detect 'point mutations', however, which are single changes within a gene's DNA sequence. While most point mutations tend to be benign, they can affect function). The SM1 gene primarily affected in SMA is on chromosome 5 ('5qSMA'). There are some other very rare gene changes on other chromosomes that may also cause SMA effects.

Spinal Muscular atrophy is a relatively rare condition, affecting from 1 in 6000 to 1 in 10,000 babies born. Approximately 1 in 50 adults are carriers of an alteration to the SMN1 gene causing SMA[88].

Untreated, spinal muscular atrophy in the child will lead to progressive weakness affecting trunk and limbs and may progress to swallowing and breathing. Brain and intellect are not affected and sensation is normal.

SMA is classified into four types, based on the physical milestones achieved. SMA1 is the most severe form with onset from birth to 6 months of age, and a short life expectancy if untreated. Type 4 is adult-onset SMA and is more mild. The severity of SMA is offset by the presence of small amounts of SMN protein produced by another gene known as the SMN2 gene. The more copies of SMN2 a person has the more 'Survival Motor Neuron 2 protein' will be produced. Other disease modifiers also exist that are less well understood.

Therapy for SMA

Early treatment is especially crucial for children with lower SMN2 gene copy numbers as they will produce less survival motor neuron protein. Obstetricians and other health practitioners in Australia

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[84] Govoni A, Gagliardi D, Comi GP et al. Time Is Motor Neuron: Therapeutic Window and Its Correlation with Pathogenetic Mechanisms in Spinal Muscular Atrophy. *Mol Neurobiol*. 2018 Aug;55(8):6307-6318. doi: 10.1007/s12035-017-0831-9. Epub 2018 Jan 2. PMID: 29294245.

[85] Crawford TO, Swoboda KJ, De Vivo DC. et al. NURTURE Study Group. Continued benefit of nusinersen initiated in the presymptomatic stage of spinal muscular atrophy: 5-year update of the NURTURE study. *Muscle Nerve*. 2023 Aug;68(2):157-170. doi: 10.1002/mus.27853. Epub 2023 Jul 6. PMID: 37409780.

[86] Dangouloff T, Servais L. Clinical Evidence Supporting Early Treatment Of Patients With Spinal Muscular Atrophy: Current Perspectives. Ther Clin Risk Manag. 2019 Oct 2;15:1153-1161. doi: 10.2147/TCRM.S172291. PMID: 31632042; PMCID: PMC6778729.

[87] Strauss KA, Farrar MA, Muntoni F. et al. Onasemnogene abeparvovec for presymptomatic infants with three copies of SMN2 at risk for spinal muscular atrophy: the Phase III SPR1NT trial. Nat Med. 2022 Jul;28(7):1390-1397. doi: 10.1038/s41591-022-01867-3. Epub 2022 Jun 17. PMID: 35715567; PMCID: PMC9205287.

[88] Estimates of carrier rates vary. Muscular Dystrophy Australia suggests a 1:40 carriage rate (Spinal Muscular Atrophy Overview). https://www.mda.org.au/spinalmuscularatrophyoverview.
Verhaart et al. *Orphanet Journal of Rare Diseases* (2017) 12:124. DOI 10.1186/s13023-017-0671-8 suggest a carrier rate of 1:50, in Caucasian and Asian populations, possibly lower in Hispanic and Black populations.

are advised that 'a baby treated at 5 days will have better outcomes than a baby treated at two weeks of age'.[89]

Gene Therapy[90]aims to increase SMN protein production by providing a synthetic copy of the SMN1 gene to the motor neurons. Treatment is a single lifetime dose given intravenously. Other treatments developed and available in Australia aim to increase the production of functional Survival Motor Neuron Protein from the SMN2 gene with administration via lumbar puncture, or by oral doses increasing Survival Motor Neuron Protein throughout the body. These very effective treatments have progressively become available in the last decade for SMA affected children. They are commenced as soon as possible in the early newborn period to maximize effectiveness before the infant develops any symptoms of SMA - which can potentially develop within days or weeks of birth.

These recent developments in the treatments available for Spinal Muscular Atrophy have highlighted the need to distinguish non-therapy prenatal genetic diagnoses from those which do propose specific therapy, such as SMA diagnostic testing. The mortality rate of the testing process requires this distinction. The benefit that can be obtained for the baby from invasive fetal testing always has to be balanced against the fetal death rate of the tests. That which confers benefit to the newborn due to prior prenatal genetic awareness must always be differentiated from prenatal genetic testing that imposes more risk of death than of any demonstrable proportional medical benefit. Where both parents are SMA carriers, prenatal diagnostic testing of their baby for SMA enables the setting up of earliest possible disease modifying treatment with life-long benefit to the child to be commenced within days of birth. Counselling and involvement of a paediatric neurologist prenatally can provide for treatment before the loss of motor neurons has occurred[91]. Treatment has been commenced in some cases within hours of birth

Most carrier screening and prenatal genetic diagnosis cannot offer specific genetic condition therapy. Most modern health institutions follow carrier screening to the abortion outcome option: *'What we want are at risk couples to be provided with information about diagnosis, prognosis and treatment before they make a decision to continue or to terminate their treatment.'*[92] This approach reflects Australia's legal and ethical frameworks where the fetus does not have recognition of personhood, and abortion is considered healthcare by professional bodies such as RANZCOG.

SMA testing and treatment availability is encompassed by Pope Saint John Paul II's teaching regarding prenatal investigations, that if some risk to the child must be undertaken it must be for the benefit of the child being tested. Risks to the life of the tested child must be proportional to the benefit for the child.

Fragile X syndrome

Fragile X syndrome is the most common inherited form of intellectual disability. One in two hundred and fifty persons are Fragile X carriers and one in four thousand persons are affected by it. It is also

[89] Anita Cairns Paediatric Neurologist Queensland Children's Hospital; Senior Lecturer University of Queensland.

[90] Mendell JR, Al-Zaidy R et al.Single-dose Gene-replacement therapy for Spinal Muscular Atrophy *NEJM* Nov 2017 Vol 377 18 DOI: 10.1056/NEJMoa1706198 https://www.nejm.org/doi/full/10.1056/NEJMoa1706198.

[91] Farrar MA, Mandarakas M, Briggs N, Cairns AG. Gestational Age at Birth and Clinical Manifestations of Spinal Muscular Atrophy. *Neurology*. 2025 Jul 22;105(2):e213799. doi: 10.1212/WNL.0000000000213799. Epub 2025 Jun 27. PMID: 40577675.

[92] Senior Genetics Counsellor Pauline McGrath Queensland Children's Hospital.

associated with developmental delay, speech delay, behavioural and emotional problems and may be associated with autism features and epilepsy.

Fragile X syndrome is caused by changes in the genetic information in the FMR-1 gene on the X chromosome. This gene codes for a protein required for usual brain development and function. Within the FMR-1 gene a series of three bases called CGG (cytosine guanine guanine) can be repeated many times over. If there are too many repeat sequences the gene becomes too long and faulty to produce the right quantities of the protein needed for usual brain development. Because males only have one copy of this gene to make the brain development protein (called 'FMRP') they tend to be more affected by the faulty gene. While females have two copies of this gene, one copy will be switched off, but some body cells will be using the unaffected gene copy and some will draw on the affected copy. The FMPR protein may be present in reduced but adequate amounts. If not enough of the faulty gene is turned off the female carrying this gene will have Fragile X syndrome symptoms. The inheritance pattern is complex. Fathers as unaffected carriers cannot pass the faulty gene to their sons, but their daughters will be carriers. Maternal transmission is related to the number of CGG repeats that are ultimately passed on to the son or daughter.

Both men and women with medium length repeats of the CGG base, known as permutations of the FMR-1 gene, may develop Fragile X tremor/ataxia syndrome after age 60 and women have a 20% chance of early menopause.

Genetic counselling

Genetic Counselling provides technical information for enriched understanding and fully informed decision-making around these three tested gene carrier states and their issues for the child conceived. Background knowledge and familiarization with terms and issues is important for the conversations which will follow and the understanding behind what is now offered to parents. The presence and infinite value of the life of the son or daughter conceived will not ordinarily be contained within the technical information delivered during genetic counselling

Carrier screening cannot identify all the mutations (changes) in the genes being sought. Therefore, it is possible that a couple's child may still unexpectedly have one of the genetic conditions screened for. It is also possible that carrier screening of parents may pick up a genetic condition in a parent. While there is no cure for these genetic conditions there are now treatments for children which can weaken their impact. In utero diagnosis is only possible with invasive techniques and its attendant risks to the fetus. Testing the child with a simple blood test after birth, often from umbilical cord blood, would equally enable these early treatments. Counselled goals, however, may be to offer parents invasive diagnostic procedures with an option for abortion, or in vitro fertilization (IVF) selecting unaffected embryos, and rejecting or destroying others, or using IVF with sperm, egg or embryo donors. Adoption or avoiding a pregnancy are other options.

What is Expanded Carrier Screening?

Modern new gene sequencing techniques have made 'expanded carrier screening' possible, with rarer genetic variations discoverable in parents with no relevant medical or family history. Many adults in this context will be carriers for at least one detectable gene disorder of unclear significance. Of the many genes which can currently be screened for either separately, or as a merged couple report, the results may be difficult to interpret. Processing the meaning of findings can be problematic and

complex, engendering anxieties and undermining parental confidence and joy in their ability to be loving, caring and competent parents meeting the needs of the children God gives them.

For all genetic conditions suspected or possible, genetic screening is becoming available. It may be arranged by the test provider or be available in some public and private hospitals.

21st Century Purpose

It is important to always bear in mind the infinite worth of every baby and every human being. No amount of testing should reduce or overshadow the life that is given in the form of this new son or daughter. Medical science is steadily growing and what may not have been possible in one decade is opened up in the next. Although modern medicine cannot at present alter chromosome or genes in the womb, intrauterine correction of anatomic problems is possible for some of the structural problems that can be diagnosed on ultrasound and has been achieved for some needing cardiac surgery[93] and spina bifida correction.[94]

Informed parental and medical wisdom, however, is the best safeguard for the new son or daughter who has entered the womb and the world. Genetic testing does not alter our mutual calling and responsibility to love and protect.

> *'My purpose is here to do them good that have most need,*
> *that is to save children,*
> *And to share the remedies that God has created for the use of man'*

It is a promise we can all look to and uphold. We can do no less.

[93] Crystal MA, Freud LR. Fetal aortic valvuloplasty to prevent progression to hypoplastic left heart syndrome in utero. *Birth Defects Research* March 2019. Vol 11(8):363-399. doi: 10.1002/bdr2.1478.

[94] Moehrlen U, Ochsenbein N, Vonzun L. *et al.* Fetal surgery for spina bifida in Zurich: results from 150 cases. *Pediatr Surg Int* 37, 311–316 (2021) doi: 10.1007/s00383-020-04824-8.

Appendix

Aneuploidy: is a type of chromosome abnormality. It is the inaccurate inheritance of haploid cells (see 'haploid cells' in the Appendix) cells resulting in more or fewer chromosomes than the expected 46 chromosomes**.** The common cause is non-disjunction of chromosomes during stages of meiosis, or mitosis. Aneuploidy is associated with a wide range of possible fetal abnormalities and may cause miscarriage and stillbirth. Chromosome abnormalities are thought to affect 1:150 conceptions and to be associated with 50% of early pregnancy losses.

Cell-free DNA (cfDNA): Cell-free DNA is found in the mother's blood and is mostly from the mother. However, in pregnancy, 10 to 12% derives from the baby's placenta (from the outer layer of the cytotrophoblast) and is called cell-free fetal DNA (cffDNA). It is useful because it reflects on the fetal genetic make-up. The maternal blood test's analysis of cell-free fetal DNA may not always reflect the true fetal chromosomal make-up. This is due to the effects of some maternal conditions, placental cell variations (known as confined placental 'mosaicism') or even the effect of a now-deceased twin.

Analysis of cell-free DNA in maternal blood is the basis of non-invasive prenatal testing (NIPT). If the unborn baby has an extra chromosome 21, for example, more chromosome 21-specific DNA will be found in the maternal bloodstream. Non-invasive prenatal testing analyses the cell-free DNA content, and can now detect small changes in the sequences on the specific chromosome of interest.

Embryo: A woman's ovum (egg) has a nucleus with 23 chromosomes (half the number of chromosomes in all other human cells). A man's sperm also has 23 chromosomes. When the sperm fertilises the ovum, the female and male chromosomes recombine creating a new person, with half the nucleus DNA having come from the mother and half from the father. The life of the new person has begun. The first fused cell is sometimes called a Zygote or may be called an embryo.

Changing use of the term 'Embryo': In Australia, the Research Involving Human Embryos Act (RIHE) of 2002 chose to define a human embryo as an entity existing after the first cell division of the fertilized egg, since this is a measurable, or 'verifiable' event. However, fertilization of the egg to produce a new human being has occurred almost a day prior to this first cell division. [National Health and Medical Research Council (2017). Ethical guidelines on the use of assisted reproductive technology in clinical practice and research 2017 (updated 2023). Canberra: National Health and Medical Research Council].

Euploid cells: humans have two sets of cells: euploid and haploid. One set comes from the father and one from the mother, and together they form cells with the complete complement of chromosomes known as euploid cells

Haploid cells: are cells with half the complement of chromosomes of other body cells. They are the sperm and ova, known as gametes, and they contain 23 chromosomes. Persons have two sets of haploid cells, one inherited from the father and the other inherited from the mother. These two sets together form what are called euploid cells, containing 46 chromosomes.

Laboratory testing techniques of fetal cells

- Quantitative Fluorescent Polymerase Chain Reaction (QF-PCR) needs only a small amount of fetal DNA. It amplifies markers on the tested chromosomes to test the number of copies of chromosomes 21, 13 and 18 as well as sex chromosomes. It usually provides a result in 24 hours. It can identify maternal cell contamination and mosaicism.
- Fluorescence in situ hybridization (FISH) can detect extra copies of chromosomes 13, 18 and 21 as well as sex chromosomes. It can also detect mosaicism and microdeletions such as 22q11 deletion.

- G-Band karyotyping cultures the cells and then harvests the chromosomes for analysis over two weeks. It can examine all of the chromosomes and identify whole or partial aneuploidy. It can detect balanced translocations.
- Chromosomal microarray analysis is replacing other karyotyping. It is particularly used in the context of structural fetal anomalies. This has higher resolution than previous methods, picking up chromosome copy numbers as well as changes in specified genes. It does not detect balanced translocations. It can detect too much genetic information posing unanswerable questions and increasing parental anxieties.

Mitochondria: are organelles within cells which generate the energy of the cell from the food we eat.

Mitochondrial DNA is derived only from the mother and is therefore helpful in tracing genetic lines. Study of mitochondrial DNA suggest that humans may have originated in Africa, possibly around 200,000 years ago, from a common ancestor evolutionary biologists call 'Mitochondrial Eve'.

Mitochondrial Donation: There are different techniques currently used for 'mitochondrial donation' in Assisted Reproductive Technology. More techniques are being investigated and developed. The main methods are:

- *Maternal Spindle Transfer*. In this method the nucleus is removed from the donor egg of another woman. This is replaced with the nuclear DNA of the affected (prospective) mother. This donor egg, which now contains the nucleus of the affected mother but the mitochondria and other organelles of the donor woman's egg, is then fertilized by the prospective father's sperm in the laboratory, aiming to produce an embryo without affected mitochondria.
- *Pronuclear transfer*. This method involves the fertilization of both the mother's egg and of the donor's egg with the father's sperm. Two children are thus created. The nucleus is then removed from the fertilized donor egg child and replaced with the nuclear DNA of the parents' fertilized egg child. The other used child is discarded.

NIPT testing methods:

- 'Next Generation Sequencing' detects smaller chromosome imbalances, and can be used in genome-wide NIPT;
- Chromosome selective NIPT employs a statistical method using the mother's prior chance of aneuploidy and will not usually detect unsought chromosomal changes but can detect eg diGeorge Syndrome, a chromosome microdeletion (22q11.2 deletion);
- 'Single Nucleotide Polymorphisms-based chromosome-selective NIPT' uses an allele ratio to obtain other information and may also detect specific recurrent microdeletions and microduplications of chromosome segments. Uses targeted amplification of specific chromosomes or specific sections of chromosomes.

Recessive Gene: a recessive gene refers to a gene (allele) that only expresses its associated effect, known as a trait or phenotype, when a person carries two copies of it (one from each parent)

'Sensitivity' and 'specificity' of a screening test: Are measures of reliability of a screening test. Sensitivity describes how well the test detects the condition in all who truly have the condition. It tells us the percentage of affected individuals who have positive test results. Specificity of a screening test describes how well the test is detecting 'probably non-affected individuals' as truly not having the condition. It tells us the percentage of non-affected individual who have negative test results.

Trimester: this term literally means three months. The normal duration of a pregnancy is 40 weeks but is often described as being nine months. The first trimester therefore refers to the first third of a

pregnancy usually up to thirteen weeks. The second trimester describes the next third of the pregnancy, and the third trimester refers to the final third of the pregnancy from twenty seven weeks onwards.

Glossary of Terms[95,96,97]

Amniocentesis: A procedure in which amniotic fluid and cells are taken from the uterus for testing. The procedure uses a needle to withdraw fluid and cells from the sac that holds the fetus.

Amniotic Fluid: Fluid in the sac that holds the fetus.

Aneuploidy: Having an abnormal number of chromosomes. The total number does not equal 46.

Cells: The smallest units of a structure in the body. Cells are the building blocks for all parts of the body.

Chorionic Villus Sampling (CVS): A procedure in which a small sample of cells is taken from the placenta and tested.

Chromosomes: Threadlike structures found in the nucleus of cells. They contain the genes that determine a person's physical makeup. There are 46 chromosomes in each cell which come in 23 pairs. One of each pair is passed on to us from our mother and one from our father. Twenty two of these pairs are numbered and known as autosomal chromosomes. The 23rd pair is made up of sex chromosomes called X and Y. Males have an X and a Y chromosome, and females have two copies of the X Chromosome. Since the chromosomes are in a pair, there are also two copies of each of the genes. Genes carried on the sex chromosomes are an exception to this rule.

Cystic Fibrosis: An inherited disorder that causes problems with breathing and digestion.

Diagnostic Tests: Tests that look for a disease or cause of a disease.

DNA: DNA is our genetic information. Each cell contains a complete copy of our DNA *a double stranded helical structure which contains the genetic material passed down from parent to child. DNA is contained in chromosomes in the nucleus. The genetic information is stored in the sequence of four chemical bases: adenine (A), guanine (G), cytosine (C), and thymine (T).*

Embryo: The stage of development that starts at fertilization (joining of an egg and sperm) and lasts up to 8 weeks. Note the slightly differing definition given by the National Health and Medical research Council provided in the appendix.

Fetus: The stage of human development beyond 8 completed weeks after fertilization.

Fluorescence In Situ Hybridization (FISH): A screening test for common chromosome problems. The test is done using a tissue sample from an amniocentesis or chorionic villus test.

Gametes: Gametes: eggs and sperm. They contain half the number of chromosomes as other body cells, ie they are therefore called haploid cells

Genes: Genes are segments of DNA that contain instructions for the development of a person's physical traits and control of the processes in the body. The gene is the basic unit of heredity and can be passed from parent to child. We have many thousands of genes. Our chromosomes located in our cells contain our genes.

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[95] American College of Obstetricians and Gynecologists (ACOG) definitions.
[96] NSW Government Health Centre for Genetics Education accessed https://www.genetics.edu.au/SitePages/Mosaicism.aspx May 2025.
[97] RANZCOG. Screening and Diagnosis of fetal structural anomalies and chromosome conditions. (C-Obs35). Version 3.0.

Genetic Counsellor: A health care professional with special training in genetics who can provide expert advice about genetic disorders and prenatal testing and results.

Genetic Disorders: Disorders caused by a change in genes or chromosomes.

Haploid Cells: are eggs and sperm, which contain half the number of chromosomes of other body cells

In Vitro Fertilization (IVF): A procedure in which an egg is removed from a woman's ovary, fertilized in a laboratory with the man's sperm, and then transferred to the woman's uterus to achieve a pregnancy. (Most embryos conceived by IVF die.)

Karyotype: An image of a person's chromosomes, arranged in order of size.

Microarray: A technology that examines all of a person's genes to look for certain genetic disorders or abnormalities. Microarray technology can find very small genetic changes that can be missed by the routine genetic tests.

Mitochondria are tiny organelles within cells. They generate the organic chemical adenosine triphosphate (ATP) which powers metabolic processes. They convert the energy from food into a usable form.

Monosomy: A condition in which there is a missing chromosome.

Mutations: Changes in a gene that can be passed on from parent to child.

Placenta: An organ that provides nutrients to and takes waste away from the fetus. It has a fetal component and a maternal component. The fetal component arises from the morula, which is a cluster of cells from which the embryo also develops.

Preimplantation Genetic Diagnosis: A type of genetic testing done during in vitro fertilization (IVF). Tests are done on the embryos created before transferring one or two to the womb.

Screening Tests: Tests that look for possible signs of a condition in people who do not have signs or symptoms.

Sensitivity of a screening test: Describes how well the test detects the condition in all who truly have the condition. It tells us the percentage of affected individuals who have positive test results.

Specificity of a screening test: Describes how well the test is detecting non-affected individuals as truly not having the condition. It tells us the percentage of non-affected individual who have negative test results.

Trisomy: A condition in which there is an extra chromosome.

Ultrasound Examination: An investigation using sound waves to image and examine inner areas and organs of the body.

Uterus: A muscular organ in the female pelvis. During pregnancy, this organ holds and nourishes the fetus. Also called the womb.