Screening for chromosomal and structural fetal anomalies: guidelines for South African private practice

L Pistorius[1], C Cluver[2], I Bhorat[3], C Hall [4], L Smit[5], C Scott[1], M Hoffman[6], B Goolab[7], J du Buisson[8], J Trusler[9] and L Geerts[2]

[1]Mediclic Panorama, Cape Town, South Africa
[2]Department of Obstetrics and Gynaecology, Faculty of medicine and health sciences, Stellenbosch University, Tygerberg Hospital, Stellenbosch, South Africa Cape Town, South Africa
[3]Department of Obstetrics and Gynaecology, Nelson R Mandela School of Medicine, University of KwaZulu Natal, South Africa
[4]Head of Legal, Natmed Medical Defence
[5]Department of Medical Genetics, Faculty of medicine and health sciences, Stellenbosch University, Tygerberg Hospital, Stellenbosch, South Africa Cape Town, South Africa
[6]Chemical Pathology, PathCare Laboratories, South Africa
[7]Lenmed Ahmed Kathrada Private Hospital, Lenasia , Johannesburg, South Africa
[8]CEO: Gynaecology Management Group, Mediclinic Panorama, Cape Town, South Africa
[9]Clinical Pathology and pathologists special biochemistry (Ampath Laboratories), South Africa

INTRODUCTION

Screening for Down syndrome and other common autosomal trisomies has been a part of obstetric care for half a century.[1] The development of ultrasound, biochemistry and genetic technology has complicated matters, so that patients and professionals are indeed "spoilt for choice."[2] Various options to screen for trisomies include different combinations of biochemistry and ultrasound in the first and second trimester as well as non-invasive prenatal testing (NIPT) of cell-free fetal and placental DNA in the maternal circulation. Despite access to the different screening tools,[3] a recent survey has shown that still only one in three cases of trisomy 21 is diagnosed prenatally in private practice in South Africa.[4] The same survey has confirmed that the different screening tests performed as well as would be expected from published literature. While it is possible that many patients opt against screening for trisomies, it is also possible that professionals do not offer screening to all pregnant women. Indeed, a number of medicolegal claims for missed diagnosis of Down syndrome relate to patients not having been offered screening or testing for Down syndrome.[5] Many of the options are too expensive or otherwise inaccessible to the average patient. The myriad of possibilities can make it more difficult to effectively counsel patient and for patients to make a well-informed choice.

To simplify matters for the practicing obstetrician and to improve equitable prenatal care and counselling we present these guidelines as a practical guide to guide screening for chromosomal and structural fetal anomalies in pregnancy. These guidelines should also help to guide the practitioner towards ethical and medicolegally safe practice.

GUIDELINES

1. Offer all patients screening for common autosomal trisomies (trisomy 21, 18 and 13) as appropriate to gestational age.

The possibility of screening should be discussed with all patients who present in the first half of pregnancy, regardless of the patient's age, socio-economic or religious background. The practitioner should inform patients that high risk results on screening tests would require further diagnostic tests before any further intervention is undertaken. Interventions might include pregnancy termination, but might also include fetal therapy, optimizing conditions for neonatal care at delivery, as well as parental preparation for possible future special needs. The patients should also know that they may change their minds at any point, but must be aware that some options are time sensitive and that screening and intervention options become more limited later in pregnancy.[6] They should also be aware that no screening test can completely rule out an anomaly.

If the patient opts against screening for common autosomal trisomies:

2. Make clinical notes of her decision, as well as her reason for the decision and whether her partner was present.

Include the patient's understanding and acceptance of the possible implications of her choice in writing. Give the patient material to access at home (such as the SASOG document on prenatal screening, which can be downloaded in several languages at https://www.sasuog.org.za/prenatal-tests-1). Medicolegally, the safest course of action might be to have the patient sign a document that she decided not to avail herself of screening. Retain all documentation and keep it accessible for future reference.

3. Offer a basic scan to all patients who opt against screening for trisomies

An ultrasound examination should be offered to all pregnant women to assess fetal cardiac activity; the number of fetuses (and in case of a multiple pregnancy, the chorionicity and amnionicity), the gestational age or fetal size, basic fetal anatomy, amniotic fluid volume and placental location and appearance.[7] The patient should be aware that while some abnormalities may be detected on a basic scan, this is not its primary purpose and the majority of genetic or structural abnormalities would not be detected. Abnormal findings and appropriate referral should be documented and discussed with the patient.

If the patient opts for screening for common autosomal trisomies:

4. Perform a basic scan

See paragraph 3 for the contents of the basic scan.

5. If the pregnancy is in the first trimester, with a singleton fetus without obvious abnormalities, the options for

screening should be discussed, including first trimester biochemistry screening (PAPP-A and free β HCG), first trimester combination screening by a practitioner accredited with the Fetal Medicine Foundation (FMF-cFTS) and NIPT.

First trimester biochemistry screening is widely available at a cost of R1000 and has an acceptable detection rate in younger and older patients for an acceptable screen positive rate (table 1).[4] The gestational age has to be determined accurately by a crown rump length measurement prior to first trimester biochemistry screening.

The sensitivity of FMF-cFTS is superior to other forms of combined or biochemical screening, with good test performance in younger and older patients (table 1).[4] An up-to-date list of FMF accredited practitioners can be found at https://fetalmedicine.org/lists/map/certified/NT. For practical, logistical and financial reasons FMF-cFTS might not be available, feasible or affordable for all patients.

Combination screening with first trimester ɑlpha has a similar screen positive rate as FMF-cFTS, but a lower detection rate overall, and especially for patients younger than 35 (table 1).[4] Measuring the nuchal translucency without FMF accreditation can expose the practitioner to unnecessary medicolegal risk because of a higher risk of false negative findings.

NIPT is the most sensitive and specific screening test for common fetal aneuploidies,[8, 9] but remains expensive (R4500 to R6800 per test). Although currently many patients may not have the personal financial means or medical aid cover to fund NIPT, all patients who opt for screening for trisomies, regardless of maternal age or baseline risk should be made aware of the availability of NIPT, and make their own decision.[10]

First trimester biochemistry screening will probably be the first (or only) choice of many patients.

6. If the risk for common autosomal trisomies based on first trimester biochemistry screening is between 1:2 and 1:300 ("high risk"), the patient should be referred timeously for further screening: (before 14 weeks) for FMF-cFTS screening if possible or otherwise NIPT.

First trimester FMF-cFTS has a lower screen positive rate than biochemistry-only screening and offers more accurate triage into high, intermediate and low risk.[4]

If cFTS-FMF is not possible, NIPT should be offered as a superior screening test.

Parents should also be given the choice to opt for invasive testing, although this should not be first choice recommendation.

7. All patients who opt for NIPT should have both pre-test and post-test genetic counselling

A list of genetic counsellors can be found at https://sashg.org/genetic_services/. A patient's spouse or partner should be included in the counselling where appropriate.

There are different types of NIPT based on counting, single nucleotide polymorphism (SNP) or single gene technology. NIPT should be requested from a reputable laboratory that provides the fetal DNA fraction (and preferably other quality metrics).[11] In Rhesus negative patients or patients with Rhesus, Kell or Duffy iso-immunization, preference should be given to single-gene NIPT which can also determine the fetal Rh D, C, c, E, e, Kell or Fya antigen status.[13]

"All chromosomes NIPT" can provide information on the chromosomal status for all chromosomes and segmental deletions and duplications bigger than 7Mb. The use of "all chromosomes NIPT" is still debatable because of the risks of false positives, and should not be used without detailed prior genetic counselling. Screening for sex chromosome abnormalities should also not be done routinely.[10]

If NIPT demonstrates a high risk for aneuploidy, genetic counselling and confirmatory invasive testing should be offered. Pregnancy termination should not be offered without a confirmatory test.[11] NIPT cannot be performed on triplet and higher order multiple pregnancies, and results should be interpreted with caution in pregnancies complicated with vanishing twins.

8. Discuss the possibility, risks and diagnostic advantage of invasive testing

If a patient opts for invasive testing, she should receive thorough pre- and posttest genetic counselling. Counselling should include the discussion of risks and complications of invasive testing. Practitioners performing less than 100 invasive procedures annually have higher fetal loss rates[14] and it would be misleading to quote a miscarriage rate (such as 1:200) derived from centers where practitioners perform more procedures. The discussion should also include other benefits of invasive testing, including as the use of more detailed tests such as chromosomal micro-array[15] or whole exome sequencing.[16]

9. If a multiple pregnancy is present, refer the patient for combination first trimester screening with an extended NT scan to a maternal fetal medicine specialist accredited with the FMF (Fetal Medicine Foundation) (Extended FMF screening).

In a multiple pregnancy, biochemical screening reflects the risk of the pregnancy rather than the individual fetus. Ultrasound markers are conversely more important.[17] Some laboratories would not use biochemistry for risk calculation in multiple pregnancies, and only use the ultrasound parameters.

The complexities of screening and diagnosis in multiple pregnancies are such that the input of a fetal specialist is invaluable.[18] NIPT is accurate in twin pregnancies,[19] but preference should also be given to NIPT based on single nucleotide polymorphism (SNP) testing. SNP based NIPT can determine the zygosity and calculates a fetal DNA fraction for each fetus separately.[12] Further diagnostic testing depends on determining which fetus (in case of dichorionic twins) is affected, for which advanced ultrasound and detailed counselling is required.[18]

10. If the pregnancy is in the second trimester, with a singleton fetus without obvious abnormalities and the patient opts against NIPT, offer second trimester screening for common autosomal trisomies by means of the triple test (maternal serum alpha-foetoprotein [MS-AFP], unconjugated estriol [uE3] and total human chorionic gonadotropin [HCG]) or the quadruple test (MS-AFP, uE3, HCG and dimeric inhibin A) (second trimester biochemistry screening).

Second trimester biochemistry screening has an lower detection of trisomy 21 than first trimester screening.[4] The quadruple test has a higher sensitivity for a similar screen positive rate compared to the triple test[20] and should be the test of preference, depending on availability, rather than the triple test.

11. If an intermediate risk for trisomies is found (between 1:301 and 1:1000 by first trimester screening or

between 1:271 and 1:1000 by second trimester biochemistry screening), the patient should be offered NIPT.

An alternative to NIPT would be an advanced ultrasound ("genetic sonogram") performed at mid gestation (18 – 22 weeks).[21] Although the detection of chromosomal anomalies using this approach is highly dependent on the expertise of the practitioner, it has been shown to be effective even in a low-cost setting.[22] If neither of these is a feasible option for the patient, this should be noted, and she should be managed as a patient at low risk of a common chromosomal anomaly.

12. If NIPT or FMF-cFTS demonstrates a high risk of a fetal chromosomal anomaly, the patient should be referred for genetic counselling and possible invasive testing.
13. If the risk for common autosomal trisomies based on second trimester biochemistry screening is between 1:2 and 1:270 ("high risk"), the patient should be referred for genetic counselling and offered invasive testing.
14. If a low risk for common autosomal trisomies is found on first or second trimester biochemistry or FMF-cFTS screening (between 1:1001 and 1:9999), or with NIPT, the patient should be offered or referred for a second trimester detailed ultrasound at mid-gestation (18 to 22 weeks) as screening for fetal structural anomalies.
15. If a patient declines a detailed anatomical fetal ultrasound evaluation because she does not want to know about any possible fetal anomalies, a basic ultrasound should be offered at mid gestation to obtain information of obstetric value only.

The patient should be aware that while some abnormalities may be detected on a basic scan, this is not its primary purpose and the majority of genetic or structural abnormalities would not be detected.

16. If a patient declines a detailed anatomical fetal ultrasound evaluation for financial reasons, MS-AFP levels should be measured between 15 and 20 weeks (if not already done as part of second trimester biochemistry screening)

Second trimester MS-AFP screening can detect 95% of cases of anencephaly, and 80% of cases of open spina bifida.[23] If the MS-AFP is raised (more than 2 multiples of the median [MoM] or classified as "high risk"), the patient should be informed of the possible causes and referred for advanced ultrasound examination.

17. If a patient opts for a detailed anatomical fetal ultrasound evaluation, the risk of a fetal abnormality should be assessed. If there is an increased risk for a fetal anomaly, or if an anomaly is found on detailed or basic ultrasound, the patient should be referred for advanced ultrasound, including fetal echocardiography[24] or fetal neurosonography[25] as appropriate.(Table 2)

Conclusion

This document has been developed by interdisciplinary healthcare teams utilizing the best available evidence and resources believed to be accurate and current at the time of press. These guidelines are an attempt to standardize and improve the equality of the discussion and offering of prenatal screening in private practice in South Africa, while taking into account the disparity of resources available to different patients. The guidelines should not be solely relied on or used as a substitute for assessing the individual needs of each patient, and should be read with the attached flow charts (Figure 1 and 2) for singleton and multiple pregnancies.

Acknowledgements

We would like to thank dr Graham Howarth and dr Bettina Taylor for their critical review of the manuscript.

Table 1. Detection rate and screen positive rate of high risk results (> 1:300 in first trimester; >1:270 in second trimester)

	alpha software first trimester		FMF combined first trimester screening	alpha software second trimester biochemistry screeening
	biochemistry screening	combined screening		
Screen positive rate				
Overall	12 (11.3-12.2)	3.5 (3.4-3.7)	3.7 (3.5-3.9)	7.7 (7.5-7.8)
Maternal age < 35 years	6.9 (6.6-7.3)	1.7 (1.6-1.8)	2.4 (2.2-2.6)	3.7 (3.6-3.9)
Maternal age ≥ 35 years	35 (33.9-36.8)	12 (10.9-12.0)	7.2 (6.7-7.7)	28 (27.1-28.6)
Detection rate for high-risk result				
Overall	94 (69.7to>99.9)	79 (67.2–87.5)	94 (87.3-97.5)	75 (61.0–84.5)
Maternal age < 35 years	75 (28.9-96.6)	54 (35.5-71.3)	87 (71.6-94.6)	42 (23.1-63.8)
Maternal age ≥ 35 years	100 (71.8-100.0)	97 (84.6->99.9)	98 (90.7->99.9)	94 (78.8-99.3)

Numbers reflect percentages
(95% confidence intervals in brackets)
Simplified from reference (4)

Table 2. Indications for advanced fetal ultrasound examination

Family history of, or previous pregnancy with inheritable malformation
Maternal diabetes or other metabolic diseases (e.g. phenylketonuria)
Maternal exposure to teratogens (environmental, pharmaceutical or recreational)
Maternal antibodies (anti-Ro/SSA, anti-thyroid, anti-red cell, anti-platelet)
Conception by IVF, including ICSI
Monochorionic twins
Visibly enlarged nuchal translucency or cystic hygroma
Suspected or confirmed congenital intrauterine infection
Suspected or confirmed fetal structural anomaly or hydrops
Fetal cardiac rate or rhythm disturbances (Persistent bradycardia / tachycardia /irregular heart rhythm)Confirmed or suspected genetic abnormality (including whole exome sequence or microarray findings of uncertain significance)
(modified from references (24,25)

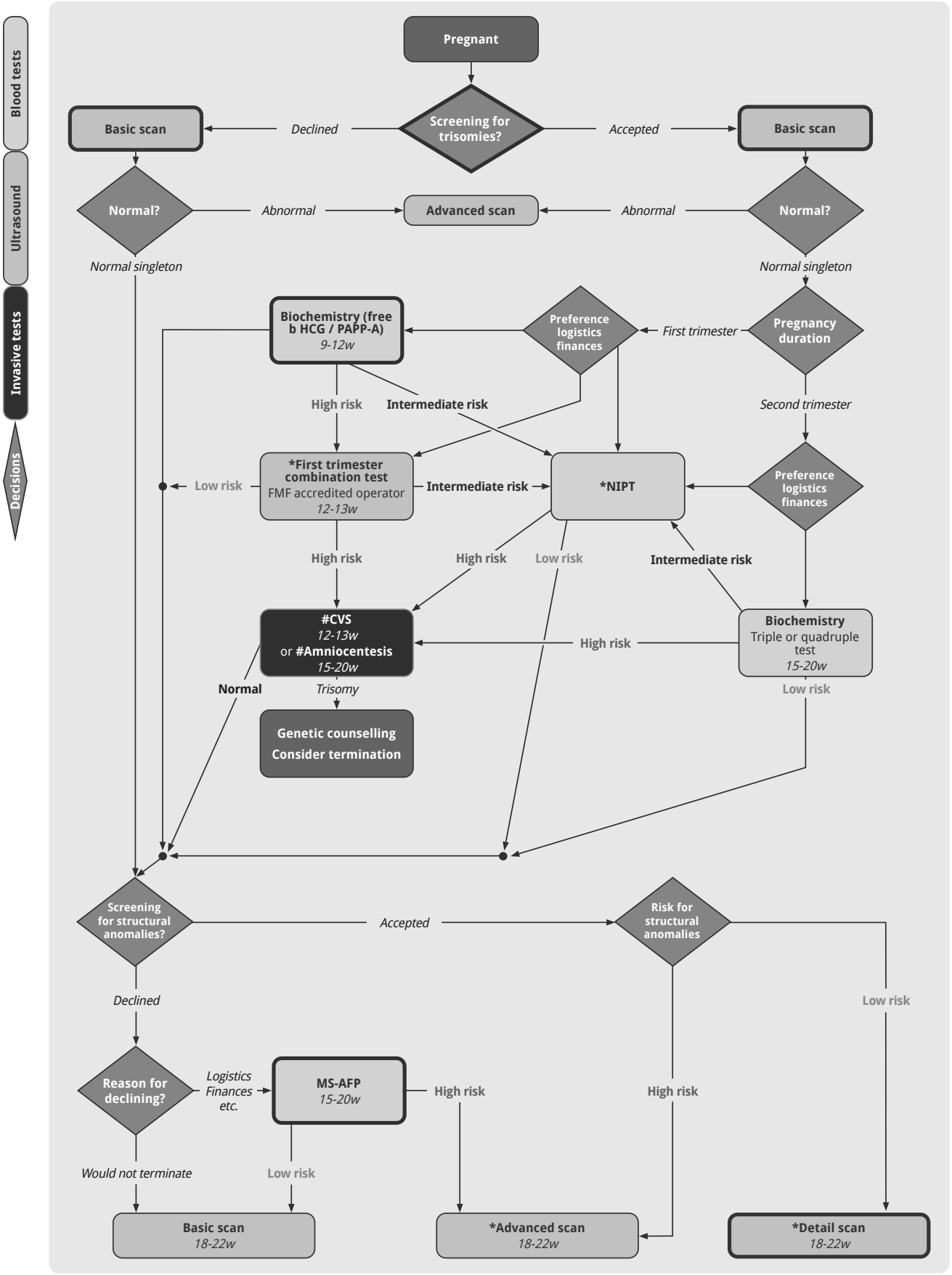
REFERENCES

1. *Nicolaides KH. Screening for fetal aneuploidies at 11 to 13 weeks. Prenat Diagn [Internet]. 2011 Jan 1 [cited 2017 Nov 26];31(1):7–15. Available from: http://doi.wiley.com/10.1002/pd.2637*
2. *Geerts L. Spoilt for choice? How to approach the subject of Down's syndrome screening with expecting parents | Obstetrics and Gynaecology Forum. O&G Forum [Internet].*

2014 [cited 2023 Oct 24];1–5. Available from: https://journals.co.za/doi/10.10520/EJC149110

3. *Bhorat I, Chauke L, Coetzee E, Geerts L, Lombaard H, Nicolaou E, et al. Challenges and controversies in prenatal genetic screening in the South African context. Obstet Gynaecol Forum. 2018;28(1).*
4. *Pistorius LR, Cluver C, Bhorat I, Geerts L. Trisomy 21 screening with alpha software and Fetal Medicine Foundation algorithm. South African Med J. 2023;113(11):27–34.*
5. *Taylor B. Claims: Ethiqal experience (congress talk). In: SASUOG 2023. 2023.*
6. *SASUOG. SASUOG POSITION STATEMENT ON THE LATE TERMINATION OF PREGNANCY FOR FETAL ANOMALIES [Internet]. 2021. Available from: https://www.sasuog.org.za/downloads/SASUOG Position statement on late TOP for fetal anomalies.pdf*
7. *Salomon LJ, Alfirevic Z, Berghella V, Bilardo CM, Chalouhi GE, Da Silva Costa F, et al. ISUOG Practice Guidelines (updated): performance of the routine mid-trimester fetal ultrasound scan. Ultrasound Obstet Gynecol [Internet]. 2022 Jun 1 [cited 2023 Oct 24];59(6):840–56. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/uog.24888*
8. *Dungan JS, Klugman S, Darilek S, Malinowski J, Akkari YMN, Monaghan KG, et al. Noninvasive prenatal screening (NIPS) for fetal chromosome abnormalities in a general-risk population: An evidence-based clinical guideline of the American College of Medical Genetics and Genomics (ACMG). Genet Med [Internet]. 2023 Feb 1 [cited 2023 Nov 2];25(2). Available from: http://www.gimjournal.org/article/S1098360022010048/fulltext*
9. *Taylor-Phillips S, Freeman K, Geppert J, Agbebiyi A, Uthman OA, Madan J, et al. Open accuracy of non-invasive prenatal testing using cell-free DNA for detection of Down, Edwards and Patau syndromes: A systematic review and meta-analysis. BMJ Open. 2016.*
10. *Hui L, Ellis K, Mayen D, Pertile MD, Reimers R, Sun L, et al. Position statement from the International Society for Prenatal Diagnosis on the use of non-invasive prenatal testing for the detection of fetal chromosomal conditions in singleton pregnancies. Prenat Diagn [Internet]. 2023 Jun 1 [cited 2023 Oct 30];43(7):814–28. Available from: https://pubmed.ncbi.nlm.nih.gov/37076973/*
11. *Salomon LJ, Alfirevic Z, Audibert F, Kagan KO, Paladini D, Yeo G, et al. ISUOG updated consensus statement on the impact of cfDNA aneuploidy testing on screening policies and prenatal ultrasound practice. Ultrasound Obstet Gynecol [Internet]. 2017 Jun 1 [cited 2021 Aug 28];49(6):815–6. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/uog.17483*
12. *Benn P, Rebarber A. Non-invasive prenatal testing in the management of twin pregnancies. Prenat Diagn [Internet]. 2021 Sep 1 [cited 2023 Oct 28];41(10):1233–40. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/pd.5989*
13. *Alford B, Landry BP, Hou S, Bower X, Bueno AM, Chen D, et al. Validation of a non-invasive prenatal test for fetal RhD, C, c, E, K and Fya antigens. Sci Reports 2023 131 [Internet]. 2023 Aug 7 [cited 2023 Oct 28];13(1):1–12. Available from: https://www.nature.com/articles/s41598-023-39283-3*
14. *Ghi T, Sotiriadis A, Calda P, Da Silva Costa F, Raine-Fenning N, Alfirevic Z, et al. ISUOG Practice Guidelines: invasive procedures for prenatal diagnosis. Ultrasound Obstet Gynecol [Internet]. 2016 Aug 1 [cited 2019 Dec 10];48(2):256–68. Available from: http://doi.wiley.com/10.1002/uog.15945*
15. *Levy B, Wapner R. Prenatal Diagnosis by Chromosomal Microarray Analysis. Fertil Steril [Internet]. 2018 Feb 1 [cited 2023 Nov 2];109(2):201. Available from: /pmc/articles/PMC5856154/*
16. *16. Mellis R, Oprych K, Scotchman E, Hill M, Chitty LS. Diagnostic yield of exome sequencing for prenatal diagnosis of fetal structural anomalies: A systematic review and meta-analysis. Prenat Diagn [Internet]. 2022 May 1 [cited 2023 Nov 2];42(6):662–85. Available from: https://pubmed.ncbi.nlm.nih.gov/35170059/*
17. *Spencer K. Screening for Down syndrome. Scand J Clin Lab Invest [Internet]. 2014 [cited 2023 Oct 28];74(SUPPL. 244):41–7. Available from: https://www.tandfonline.com/doi/abs/10.3109/00365513.2014.936680*
18. *18. Khalil A, Rodgers M, Baschat A, Bhide A, Gratacos E, Hecher K, et al. ISUOG Practice Guidelines: role of ultrasound in twin pregnancy. Ultrasound Obstet Gynecol [Internet]. 2016 Feb [cited 2019 Dec 10];47(2):247–63. Available from: http://doi.wiley.com/10.1002/uog.15821*
19. *Gil MM, Galeva S, Jani J, Konstantinidou L, Akolekar R, Plana MN, et al. Screening for trisomies by cfDNA testing of maternal blood in twin pregnancy: update of The Fetal Medicine Foundation results and meta-analysis. Ultrasound Obstet Gynecol [Internet]. 2019 Jun 1 [cited 2023 Oct 24];53(6):734–42. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/uog.20284*
20. *Wald NJ, Bestwick JP, Huttly WJ. Improvements in antenatal screening for Down's syndrome. J Med Screen. 2013 Mar 1;20(1):7–14.*
21. *Agathokleous M, Chaveeva P, Poon LCY, Kosinski P, Nicolaides KH. Meta-analysis of second-trimester markers for trisomy 21. Ultrasound Obstet Gynecol [Internet]. 2013 Mar [cited 2023 Nov 2];41(3):247–61. Available from: https://pubmed.ncbi.nlm.nih.gov/23208748/*
22. *Geerts L. Prenatal diagnosis of chromosomal abnormalities in a resource-poor setting. Int J Gynecol Obstet. 2008 Oct 1;103(1):16–21.*
23. *Palomaki GE, Bupp C, Gregg AR, Norton ME, Oglesbee D, Best RG. Laboratory screening and diagnosis of open neural tube defects, 2019 revision: a technical standard of the American College of Medical Genetics and Genomics (ACMG). Genet Med 2019 223 [Internet]. 2019 Nov 8 [cited 2023 Oct 30];22(3):462–74. Available from: https://www.nature.com/articles/s41436-019-0681-0*
24. *Carvalho JS, Axt-Fliedner R, Chaoui R, Copel JA, Cuneo BF, Goff D, et al. ISUOG Practice Guidelines (updated): fetal cardiac screening. Ultrasound Obstet Gynecol [Internet]. 2023 Jun 1 [cited 2023 Oct 30];61(6):788–803. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/uog.26224*
25. *Malinger G, Paladini D, Haratz KK, Monteagudo A, Pilu GL, Timor-Tritsch IE. ISUOG Practice Guidelines (updated): sonographic examination of the fetal central nervous system. Part 1: performance of screening examination and indications for targeted neurosonography. Ultrasound Obstet Gynecol [Internet]. 2020 Sep 1 [cited 2023 Oct 29];56(3):476–84. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/uog.22145*

Prenatal Screening Flowchart

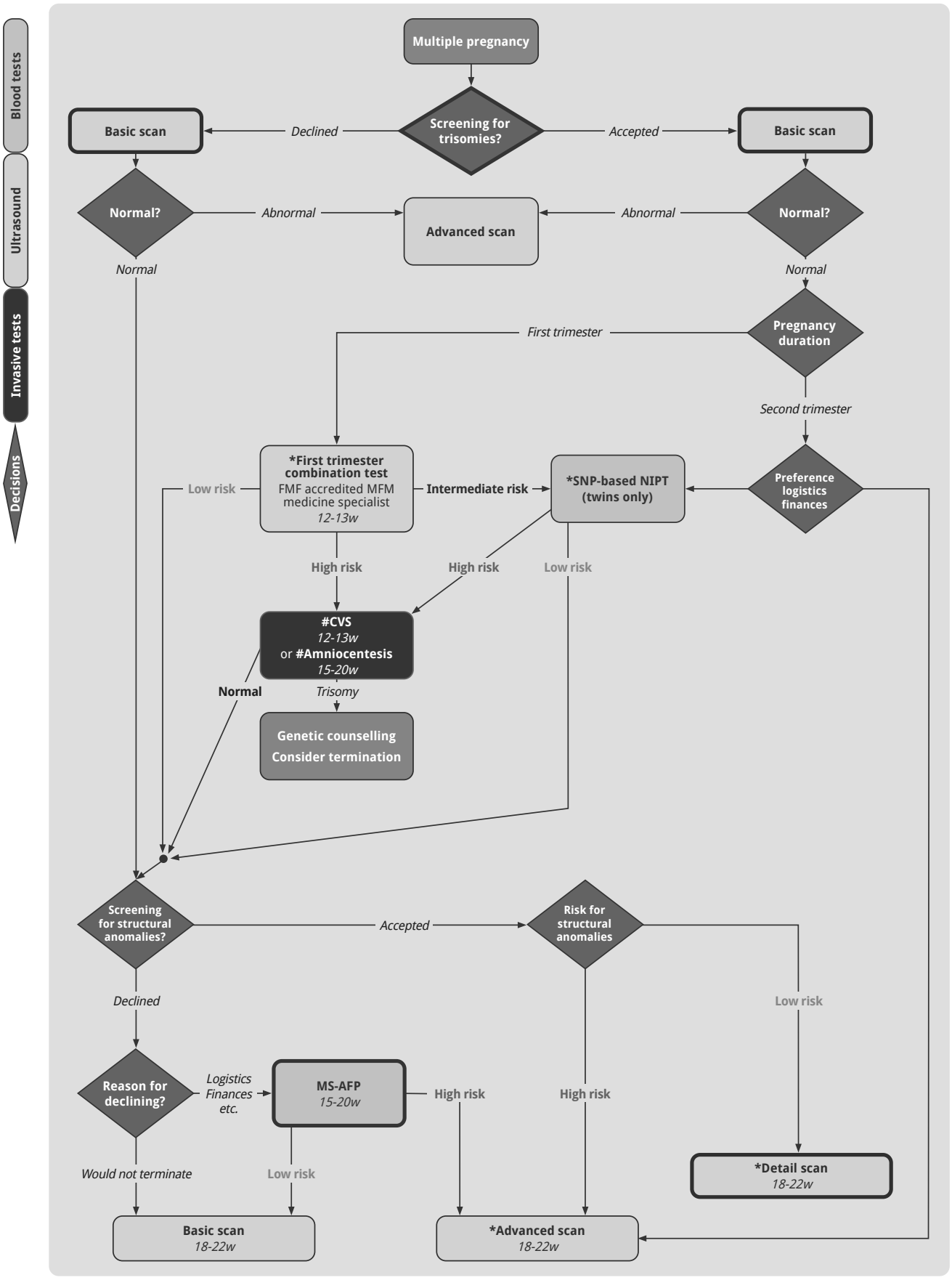


Always done when patients opt in for screening

* Available to all patients if requested / accessible

\# Genetic screening available to all patients if requested / accessible and after genetic counselling

Prenatal Screening Flowchart



Always done when patients opt in for screening

* Available to all patients if requested / accessible

Genetic screening available to all patients if requested / accessible and after genetic counselling