Prenatal Assessment of Chromosomal Abnormalities

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Highlights

- cfDNA (NIPT) is the preferred screen for fetal aneuploidy.
- Serum screening (i.e. QUAD or integrated screen) may be used if cfDNA is unavailable.
- Mid-trimester maternal-serum AFP screening for body-wall malformations (15-22 weeks) is optional as long as the patient receives a mid-trimester anatomy ultrasound.
- Diagnostic testing (i.e. amniocentesis or CVS) for aneuploidy and chromosomal copy-number variants should be offered to all pregnant patients.
- Obstetric providers should understand risks of aneuploidy and other chromosomal abnormalities, and be able to counsel regarding the benefits, risks and limitations of available diagnostic and screening methods.

Epidemiology of chromosomal abnormalities

Chromosome abnormalities are common, occurring in 1 in 150 live births[1,2]. include autosomal aneuploidies, sex-chromosome aneuploidies and pathogenic copy-number variants (CNVs). While the incidence of autosomal aneuploidy increases with maternal age, these can affect pregnancies at any age and are not related to race or ethnicity.[2] In contrast, sex-chromosome aneuploidies such as Turner syndrome (monosomy X) are generally not associated with maternal age. Finally, CNVs occur in approximately 0.4% of pregnancies and are also unrelated to maternal age.[2] **For patients under age 35, the risk of a pregnancy affected by a**

disease-causing CNV is higher than the risk of chromosomal aneuploidy (i.e. trisomies 13, 18, and 21).[2-4]

Screening for chromosomal aneuploidies

Assessment for chromosomal aneuploidy should be offered to every pregnant individual. While the risk of autosomal aneuploidy increases with age, all pregnancies are at risk. Patients may opt for screening, diagnostic testing, or no testing at all. Figure 1 provides information regarding differences in screening and diagnostic testing. Available aneuploidy screening methods include cell-free DNA based screening (cfDNA, also known as non-invasive prenatal testingalso known as non-invasive prenatal testing**,** or NIPT) and serum screening (including the Quad marker screen and integrated screens). **BCM OB/Gyn Perinatal Guidelines Committee recommends using cell-free DNA (cfDNA) screening as the preferred screening method** due to its superior sensitivity and specificity for detecting common aneuploidies such as trisom[5] Professional societies recommend cfDNA screening as an option for all pregnan[2,5,62,6,7] cfDNA screening can be collected as early as 9-10 weeks (depending on the laboratory).
Serum screening, including the Quad screen or integrated screen, can be utilized in cases where cfDNA is not covered by the patient's insurance or if the patient declines cfDNA screening for other reasons. While serum screening is less accurate than cfDNA, it still provides useful risk assessment for chromosomal abnormalities.

cfDNA screening for microdeletion/duplication syndromes, rare autosomal trisomies and single gene disorders is *not* currently recommended for routine use by ACOG.[2] In contrast, the American College of Medical Genetics (ACMG) recommends 22q11.2 deletion screening in the context of shared decision making.[7] **The BCM OB/Gyn Perinatal Guidelines currently recommends against offering cell-free DNA aneuploidy screening with microdeletion screening, and that this should be reserved for special situations after genetic counseling**.

Mid-trimester maternal-serum AFP screening

Mid-trimester maternal-serum alpha-fetoprotein (MSAFP) screening is used to detect body-wall anomalies such as neural-tube and ventral-wall defects. However, recent studies indicate that high quality anatomical ultrasounds performed in the first and early second trimesters have a higher sensitivity and specificity for detecting these anomalies compared to MSAFP screening.[8,9] Moreover, MSAFP has both low sensitivity and low specificity for body wall defects.[10-12]Per ACOG guidance and **BCM OB/Gyn Perinatal Guidelines Committee considers MSAFP screening optional** if the patient is undergoing a high-resolution anatomic survey at 20-24 weeks gestation.[2] If MSAFP screening is pursued, an elevation of ≥2.5 multiples of the median (MoM) should prompt referral for a comprehensive anatomy ultrasound and, in the absence of other findings, a third-trimester growth ultrasound.

Diagnostic testing for chromosomal abnormalities

The American College of Obstetricians and Gynecologists (ACOG) recommends that diagnostic testing for chromosomal abnormalities be offered to all pregnant individuals, regardless of age or *a priori* risk.[2] Diagnostic testing is the only method to accurately and comprehensively evaluate for chromosomal abnormalities, including aneuploidy as well as over 100 sub-chromosomal copy-number conditions. Diagnostic testing requires either chorionic villus sampling (CVS; 10-13 weeks gestation) or amniocentesis (15+ weeks gestation). These procedures enable advanced testing with a chromosomal microarray, with or without a karyotype.[4,13]. While insurance coverage for these procedures may be limited to specific indications such as advanced maternal age or the presence of fetal anomalies, it is appropriate to offer diagnostic testing for chromosomal conditions to all pregnant patients. While testing for single-gene disorders with exome or genome sequencing is not recommended for structurally normal fetuses with low *a priori* risk, these tests available for information-seeking families. The risks associated with CVS and amniocentesis are low. The procedure-related risk of pregnancy loss after amniocentesis is approximately 0.1% to 0.3%, and 0.2% to 0.5% after CVS. **Amniocentesis is appropriate and safe in the late-second and third trimesters**, as the risk of preterm birth or other pregnancy complication is low.[14] In general, the risks of diagnostic testing are minimal

compared to the significant benefits of obtaining early and accurate genetic information.[3,4,14,15] Offering diagnostic screening to all pregnant patients ensures that they have the opportunity to make informed decisions based on comprehensive genetic information.

Pretest counseling

All prenatal care providers should be comfortable providing basic genetic counseling and arranging for standard genetic testing. Table 1 summarizes key points in pre-test counseling for pregnancies with a known or presumed structurally normal fetus. If a patient opts for diagnostic genetic testing, they should be referred to genetic counseling for coordination. Every patient has the right to pursue or decline prenatal genetic screening and diagnostic testing, and a patient's decision should be documented. **Table 2** provides a sample script when discussing genetic screening options.

Table 1. Pretest counseling for chromosomal screening and testing.

Critical information to discuss
• Review family history, medical history, medications, and exposures. • Age-related aneuploidy risk and the 1:250 age-independent copy-number variant risk. • A diagnostic test is most accurate and comprehensive, screening for over 100 additional chromosomal conditions. • All screening tests have a risk of false positives and false negatives. • cfDNA is the preferred screening test if the patients declines diagnostic testing. • Avoid irreversible pregnancy decisions based on a screening test result alone. • An abnormal screen warrants a detailed anatomy scan, genetic counseling, and diagnostic testing.
Additional topics to discuss
• Screening tests may identify maternal health problems (e.g. malignancy or mosaic Turner). • Screening tests are most sensitive for Down syndrome and less accurate for other aneuploidies. Most screens do not detect CNVs. • Use of cfDNA as follow-up for a positive serum screening is an option, but there is a residual risk of adverse outcome.

At minimum, providers should discuss the patient's history, review the age-related aneuploidy risk, discuss the limitations of aneuploidy screening to detect aneuploidy, sub-chromosomal (i.e. copy-number) variants, and single-gene disorders. Patients should be aware that screening tests are limited and that false positives and false negatives are a possibility. Patients should be aware that pregnancy termination is not recommended on the basis of a screening test result alone, and that an abnormal screen warrants detailed ultrasound, genetic counseling, and diagnostic testing.

In addition, providers can consider discussing with patients that both screening and diagnostic options have the potential for secondary findings with maternal health implications. These may include malignancy, mosaic Turner syndrome, and 22q11.2 deletion syndrome.

Table 2. Sample script for genetic testing options.

Some babies are born with genetic conditions that can affect their health. This is possible even if nobody else in the family has a genetic problem or birth defect. While some of these conditions, like Down Syndrome, are easy to recognize at birth, many others are not obvious and only cause problems later in childhood. Recognizing a genetic change early gives parents and doctors the chance to begin early treatment, which can help children perform their best in school and in some cases even save their life. *There are two types of genetic testing to help identify potential genetic conditions in pregnancy. Some families choose to begin with a screening test, which is more convenient but less accurate. This test uses a blood sample to estimate the risk for a few chromosomal conditions such as Down syndrome. Screening*

tests can be helpful but are not definitive—they can miss conditions and can produce false positives or false negatives. Any positive screening result should be confirmed with a more accurate follow-up test.

Some families instead choose to begin with a diagnostic test, which is more comprehensive and more accurate. This test uses a small sample of the placenta or the fluid around the baby to check for over 100 genetic conditions. This test is quick, safe, and performed in the office. Typically, we have results for families in about two weeks. Do you want more information about either of these tests?

Formal genetic counseling

Genetic counseling services[16] are available at both Texas Children's Hospital and Ben Taub General Hospital. There are several circumstances in which a referral for dedicated genetic counseling should be considered. These include:

- An abnormal screening or diagnostic test result
- A fetal structural anomaly detected on ultrasound
- A family history of a known or suspected genetic disorder
- The patient is a known carrier of a genetic condition
- The pregnancy has a teratogenic exposure
- Consanguinity (parents are first-cousins or closer)
- Recurrent pregnancy loss
- History of stillbirth or fetal/neonatal loss with structural anomalies
- Patient request for additional information regarding testing options
- Patient desires expanded carrier screening
- Patient desires diagnostic testing
- Discordant fetal sex on screening and ultrasound

Table 3. Genetic Counseling Referral Process at Each Baylor Hospital

Hospital	Genetic Counseling Referral Process
Ben Taub Hospital	1. Place Order: REFERRAL TO OB/PRENATAL GENETIC COUNSELING 2. Send Message: to Wanda Dosal and Adriana Del Rio, attach patient chart
Pavilion for Women	1. Place Order: REFERRAL TO MATERNAL FETAL MEDICINE SERVICES 2. After indicating that patient is pregnant, select "Genetic Counseling"

Limitations of cfDNA screening

While cfDNA is considered a high-quality screening test, it does have false positive and false negative results, as well as the possibility of a "no call" result. Some of the many causes for false positive and false negative cfDNA results are detailed in **Table 4**.

The success of cfDNA screening is dependent on adequate fetal (i.e. placental) free DNA in the maternal circulation, called the fetal fraction. The fetal fraction is a function of several factors. Advancing gestational age and multiple pregnancy increases the fetal fraction, while mosaicism, trisomy 13, trisomy 18, triploidy, artificial reproductive technology, parity, maternal age, low molecular-weight heparin, active autoimmune disease and obesity lower the fetal fraction and increase the chance of a test failure.[17-20]

No-call result due to a low fetal fraction are associated risk for an increased risk of adverse outcomes including growth restriction, aneuploidy, preeclampsia, and preterm birth.[17,21] **Therefore, increased vigilance for these outcomes and consideration for a third-trimester growth ultrasound in cases of no-call results**.

Table 4. Potential causes for false positive or false negative cfDNA results

False Positive Results	False Negative Results
Leiomyoma Maternal Cancer Maternal 45,X or 47,XXX Confined placental mosaicism Fetal or maternal copy-number variants Death of a twin *in utero* (vanishing twin)[30,31] Organ or bone marrow transplant from male donor Medical condition/treatment affecting cfDNA quality Intrahepatic cholestasis of pregnancy Autoimmune disease B12 deficiency	Maternal obesity Low fetal fraction Multiple gestation Confined placental mosaicism Rare fetal aneuploidies (e.g. triploidy) Medical condition/treatment affecting cfDNA quality

Appendix

Table S1. Differences between Available cfDNA Screening Tests (as of 9/15/2025)

Lab	Trisomy 13, 18, 21	Sex-chr aneuploidy	22q11.2 micro-deletion	Other micro-deletions	Additionally validated for	Rh antigen	Other RBC Antigens	Twins	Zygosity	Triplets	Donor & Surrogate Pregnancies	Fetal Fraction Enrichment[a]
BillionToOne (Unity)	Yes	Yes	Opt in	--	--	Opt in	Big C, Little C, Duffy, E, Kell	Yes	Yes	--	Yes	--
LabCorp (MaterniT21)[b]	Yes	Opt in	Opt in	Opt in	T16, T22	--	--	Yes	--	Yes	Yes	--
Myriad (Prequel)	Yes	Opt in	Opt in	Opt in	All autosomal aneuploidies	--	--	Yes	--	--	Yes	Yes
Natera[c] (Panorama)	Yes	Yes	Opt in	Opt in	Triploidy, Vanishing twin	Opt in	--	Yes	Yes	--	--	--
Quest (Qnatal)	Yes	Yes	Opt in	Opt in	--	--	--	Yes	--	--	Yes	--

[a]Fetal fraction enrichment may be useful at earlier gestation or in cases of no-calls due to low fetal fraction.
[b]MaterniT GENOME is not suitable for multiple gestation.
[c]This lab utilizes SNP-based (rather than counting-based) method / analysis, offering unique advantages and drawbacks.

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