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Noninvasive Prenatal Testing for Fetal Aneuploidy

ABSTRACT: Noninvasive prenatal testing that uses cell free fetal DNA from the plasma of pregnant women offers tremendous potential as a screening tool for fetal aneuploidy. Cell free fetal DNA testing should be an informed patient choice after pretest counseling and should not be part of routine prenatal laboratory assessment. Cell free fetal DNA testing should not be offered to low-risk women or women with multiple gestations because it has not been sufficiently evaluated in these groups. A negative cell free fetal DNA test result does not ensure an unaffected pregnancy. A patient with a positive test result should be referred for genetic counseling and should be offered invasive prenatal diagnosis for confirmation of test results.

Noninvasive prenatal testing that uses cell free fetal DNA from the plasma of pregnant women offers tremendous potential as a screening tool for fetal aneuploidy. Circulating cell free fetal DNA, which comprises approximately 3–13% of the total cell free maternal DNA, is thought to be derived primarily from the placenta, and is cleared from the maternal blood within hours after childbirth (1). Recently, cell free fetal DNA analysis has become clinically available for women at increased risk of fetal aneuploidy.

Early attempts to detect trisomic fetuses using cell free fetal DNA required the use of multiple placental DNA or RNA markers, which made the screening test time consuming and expensive (2–4). Recently, a number of groups have validated a technology known as massively parallel genomic sequencing, which uses a highly sensitive assay to quantify millions of DNA fragments in biological samples in a span of days and has been reported to accurately detect trisomy 13, trisomy 18, and trisomy 21 (5–7) as early as the 10th week of pregnancy with results available approximately 1 week after maternal sampling. Another group has described a more targeted approach, using chromosome selective sequencing to detect trisomy 18 and trisomy 21 (8). Using archived blood samples from women who were undergoing prenatal diagnosis and were at increased risk of aneuploidy, several large-scale validation studies have demonstrated detection rates for fetal trisomy 13, trisomy 18, and trisomy 21 of greater than 98% with very low false-positive rates (less than 0.5%) (6–13). Although no prospective trials of this technology are available, cell free fetal DNA appears to be the most effective screening test for aneuploidy in high-risk women.

The American College of Obstetricians and Gynecologists has recommended that women, regardless of maternal age, be offered prenatal assessment for aneuploidy either by screening or invasive prenatal diagnosis regardless of maternal age; cell free fetal DNA is one option that can be used as a primary screening test in women at increased risk of aneuploidy (Box 1). This includes women aged 35 years or older, fetuses with ultrasonographic findings that indicate an increased risk of aneuploidy, women with a history of a child affected with a trisomy, or a parent carrying a balanced robertsonian translocation with increased risk of trisomy 13 or trisomy 21. It also can be used as a follow-up test for women with a positive first-trimester or second-trimester screening test result. Counseling regarding the limitations of cell free fetal DNA testing should include a discussion that the screening test provides information regarding only

Box 1. Indications for Considering the Use of Cell Free Fetal DNA ⇦

- Maternal age 35 years or older at delivery
- Fetal ultrasonographic findings indicating an increased risk of aneuploidy
- History of a prior pregnancy with a trisomy
- Positive test result for aneuploidy, including first trimester, sequential, or integrated screen, or a quadruple screen.
- Parental balanced robertsonian translocation with increased risk of fetal trisomy 13 or trisomy 21.

trisomy 21 and trisomy 18 and, in some laboratories, trisomy 13. It does not replace the precision obtained with diagnostic tests, such as chorionic villus sampling (CVS) or amniocentesis, and currently does not offer other genetic information. Other limitations of cell free fetal DNA include the lack of outcome data for low-risk populations; therefore, cell free fetal DNA testing is not currently recommended for low-risk women. Preliminary data available on twins demonstrate accuracy in a very small cohort, but more information is needed before use of this test can be recommended in multiple gestations (14). In a small percentage of cases, a cell free fetal DNA result will not be able to be obtained.

To offer a cell free fetal DNA test, pretest counseling regarding these limitations is recommended. The use of a cell free fetal DNA test should be an active, informed choice and not part of routine prenatal laboratory testing. The family history should be reviewed to determine if the patient should be offered other forms of screening or prenatal diagnosis for a particular disorder. A baseline ultrasound examination may be useful to confirm viability, a singleton gestation, gestational dating, as well as to rule out obvious anomalies. Referral for genetic counseling is suggested for pregnant women with positive test results. Because false-positive test results can occur, confirmation with amniocentesis or CVS is recommended. Patients also need to be aware that a negative test result does not ensure an unaffected pregnancy; false-negative test results can occur as well. In this high-risk population, a second-trimester ultrasound examination is suggested to evaluate pregnancies for structural anomalies. In patients in whom a structural fetal anomaly is identified, invasive diagnostic testing should be offered because a cell free fetal DNA test can only detect trisomy 13, trisomy 18, and trisomy 21. Maternal serum alpha-fetoprotein screening or ultrasonographic evaluation for open fetal defects should continue to be offered.

Conclusions

- Patients at increased risk of aneuploidy can be offered testing with cell free fetal DNA. This technology can be expected to identify approximately 98% of cases of Down syndrome with a false-positive rate of less than 0.5%.
- Cell free fetal DNA testing should not be part of routine prenatal laboratory assessment, but should be an informed patient choice after pretest counseling.
- Cell free fetal DNA testing should not be offered to low-risk women or women with multiple gestations because it has not been sufficiently evaluated in these groups.
- Pretest counseling should include a review that although the cell free fetal DNA test is not a diagnostic test, it has high sensitivity and specificity. The test will only screen for the common trisomies and, at the present time, gives no other genetic information about the pregnancy.
- A family history should be obtained before the use of this test to determine if the patient should be offered other forms of screening or prenatal diagnosis for familial genetic disease.
- If a fetal structural anomaly is identified on ultrasound examination, invasive prenatal diagnosis should be offered.
- A negative cell free fetal DNA test result does not ensure an unaffected pregnancy.
- A patient with a positive test result should be referred for genetic counseling and offered invasive prenatal diagnosis for confirmation of test results.
- Cell free fetal DNA does not replace the accuracy and diagnostic precision of prenatal diagnosis with CVS or amniocentesis, which remain an option for women.

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