Cell-free DNA Screening

Society for Maternal•Fetal Medicine
High-risk pregnancy experts

Patient Education Series

Quick Facts

- Cell-free DNA (cfDNA) screening is a prenatal test that analyzes genetic material fragments circulating in the pregnant person's bloodstream. It is used to screen for abnormalities in chromosomes 13, 18, and 21 and sex chromosome beginning at 10 weeks of pregnancy.
- A positive cfDNA result means there is a higher chance that the fetus has a chromosomal disorder compared with the general population. A negative cfDNA result means there is a lower chance that the fetus has a chromosome disorder compared with the general population.
- cfDNA screening is highly accurate, but it cannot tell for certain that the fetus has a disorder. Diagnostic testing is necessary to confirm a positive test result. Diagnostic testing is also an option for all pregnant people regardless of their age or risk factors.
- cfDNA screening doesn't detect structural birth defects and does not evaluate accurately for genetic disorders outside of trisomy 21, 18, 13, and sex chromosome abnormalities.

Cell-free DNA (cfDNA) screening is a prenatal test that uses a sample of the pregnant person's blood to assess the risk of genetic conditions in the fetus caused by an abnormal number of **chromosomes**. You may also hear cfDNA screening referred to as noninvasive prenatal testing (NIPT). It's important to understand how cfDNA screening works, what it can and cannot screen for, and what the results mean.

What is cfDNA?

cfDNA are fragments of **DNA** that circulate in a pregnant person's blood. Some of these fragments come from the pregnancy, and some from the pregnant person. In cfDNA screening, the fragments from the pregnancy are analyzed to find out whether the fetus has a low risk or high risk of having certain chromosome disorders.

What chromosome disorders does cfDNA screening screen for?

cfDNA assesses the risk for several common chromosome disorders in which there are extra or missing chromosomes. This type of chromosome disorder is called **aneuploidy**.

Normally, there are 2 copies of each chromosome. In Down syndrome, also called **trisomy 21**, there is an extra copy of chromosome 21. cfDNA checks for trisomy 21 as well as **trisomy 13** and **trisomy 18**. It also can screen for missing or extra copies of the X and Y **sex chromosomes**, if requested. Most of the time, these disorders are not inherited from the parents but rather occur by chance. The chances of having a child with trisomy 13, 18, and 21 increase with maternal age.

When during pregnancy is cfDNA screening performed?

cfDNA screening can be performed beginning at 10 weeks of pregnancy.

What do the results of cfDNA screening mean?

cfDNA is a **screening test.** It cannot tell for certain whether the fetus has a chromosome disorder. It only reports the risk that a fetus is affected:

- A positive cfDNA screening test result means there is a higher chance that the fetus has a chromosome disorder compared with the general population.
- A negative cfDNA screening test result means there is a lower chance that the fetus has a chromosome disorder compared with the general population.

The most accurate way to prenatally test for chromosome and other genetic conditions is with a **diagnostic test**, such as **chorionic villus sampling (CVS)** or **amniocentesis**. A diagnostic test can tell with certainty whether the fetus has a chromosome disorder. It can also diagnose other genetic disorders like cystic fibrosis and sickle cell disease if specific genetic testing for the condition is requested. CVS is an option starting at 11 weeks of pregnancy, and amniocentesis is an option at 15 to 16 weeks of pregnancy.

What does it mean if cfDNA screening doesn't give a test result?

Sometimes, cfDNA screening will not be able to provide a test result. This can happen because there isn't enough pregnancy-derived DNA available in the blood sample or because there is a problem interpreting the test result in the laboratory. The most common reasons are that the test was done before 10 weeks of pregnancy, increasing maternal weight, large **fibroids**, or because the fetus has a chromosome abnormality.

Your healthcare professional may suggest additional testing based on your results and other risk factors.

How accurate is cfDNA screening?

cfDNA is highly accurate in screening for Down syndrome and is slightly less accurate for trisomy 13 and 18. However, **false-positive** and **false-negative** results can occur. A false negative cfDNA screening result is a negative result when the fetus has the disorder being screened for. A false positive cfDNA screening result is a positive result when the fetus does not have the disorder being screened for.

Does a pregnant person's age affect cfDNA screening results?

Yes. A person's age affects cfDNA screening's **positive predictive value (PPV)**. A test's PPV is the likelihood that a person with a positive test result actually has the condition being tested for.

PPV varies based on how common the condition is in a certain group of people at a given time. The rarer the condition, the lower the PPV.

Because the risk of having a child with trisomy 13, 18, or 21 increases with the age of the pregnant person, the cfDNA screening PPV for these conditions differs by age. For example:

- A 40-year-old pregnant person has a higher risk of having a baby with Down syndrome (1 in 50). The PPV is higher in this group of people.
- A 20-year-old pregnant person has a lower risk (about 1 in 800). The PPV is lower in this group of people.

Let's say that both have cfDNA screening at 10 weeks of pregnancy and receive a positive result for Down syndrome.

- For the 40-year-old pregnant person, the PPV is 95%. This means there is a 95% chance that the

positive result is a true positive, ie, that the fetus has Down syndrome. There is a 5% chance that the result is a false positive.

- For the 20-year-old pregnant person, the PPV is 55%, meaning there is a 55% chance that the positive result is a true positive and a 45% chance the result is a false positive.

PPV may be reported with some cfDNA screening results. If it is not, a healthcare professional or genetic counselor will be able to calculate the PPV.

What are the next steps if a cfDNA screening test result is positive?

If you have a positive cfDNA screening result, it's recommended that you meet with a **maternal-fetal medicine subspecialist**, geneticist, or **genetic counselor** to review your results and discuss follow-up testing options. Patients with positive results are usually offered an **ultrasound** evaluation and diagnostic testing.

What are the other limitations of cfDNA screening?

cfDNA screening does not screen for genetic disorders caused by changes in a single gene. Although some companies offer testing for additional chromosome disorders, such as trisomy 16 and trisomy 22, there is not much information about the accuracy of these tests. For this reason, cfDNA screening for genetic conditions other than the common trisomies is not recommended.

It is important to know that cfDNA screening doesn't screen for structural birth defects. All pregnant people are offered a second-trimester ultrasound exam to check for these types of disorders.

cfDNA screening is less accurate in people pregnant with twins if one twin stops developing early in the pregnancy. No information is available on the test's accuracy in people carrying three or more fetuses. cfDNA screening can also be less accurate in patients with a history of a transplanted organ.

Glossary

Amniocentesis: A procedure in which a sample of amniotic fluid is removed from the uterus during pregnancy and tested to look for genetic problems in the fetus.

Cell-free DNA (cfDNA): Small pieces of DNA (genetic material) from the pregnancy that circulate in the blood of a pregnant person.

Cell-free DNA (cfDNA) screening: A prenatal screening test that looks for certain chromosomal disorders in the fetus. It analyzes small pieces of DNA (genetic material) from the pregnancy that circulate in a pregnant person's blood.

Chorionic villus sampling (CVS): A procedure in which a small sample of the villi, a part of the placenta, is removed and tested to look for genetic problems in the fetus.

Chromosomes: The structures inside cells that carry genes, the pieces of hereditary material passed down from parents to offspring. Every normal human cell (except for eggs and sperm) has 46 chromosomes.

Diagnostic test: A test that determines with a high degree of accuracy whether a disease or other problem is present.

DNA: Deoxyribonucleic acid; the material in the cell's chromosomes that carry all the genetic instructions for an individual's growth, functioning, and development.

False-negative result: A test result that indicates a person does not have a disorder being tested for when they do actually have it.

False-positive result: A test result that indicates a person has a disorder being tested for when they do not actually have it.

Fetus: The unborn offspring of a human that develops in the uterus; the fetal stage lasts from nine weeks to birth.

Fibroid: A noncancerous growth that develops in the muscular wall of the uterus.

Genetic counselor: A healthcare professional who specializes in helping individuals and families understand how genetic conditions might affect them.

Maternal-fetal medicine subspecialist: An obstetrician with specialized training in caring for people with high-risk pregnancies.

Positive predictive value (PPV): The likelihood that a person who has a positive test result actually has the condition being tested for.

Sex chromosomes: The chromosomes that determine a person's biological sex. There are two sex chromosomes: X and Y. A person with two X chromosomes is biologically female (XX). A person with an X and a Y chromosome is biologically male (XY).

Trisomy: A genetic condition where there is an extra chromosome, resulting in three copies of a chromosome instead of the usual two.

Trisomy 13: A condition in which there are three copies of chromosome 13 instead of the usual two. It often causes severe anomalies affecting many of the body's organs and structures. Also known as Patau syndrome.

Trisomy 18: A condition in which there are three copies of chromosome 18 instead of the usual two. It can cause serious medical conditions affecting the heart, spine, abdomen, and brain. Also known as Edwards syndrome.

Trisomy 21: A condition in which there are three copies of chromosome 21 instead of the usual two. It can cause a wide range of developmental delays and physical disabilities. Also known as Down syndrome.

Ultrasound: Use of sound waves to create images of internal organs or the fetus during pregnancy.

To find a maternal-fetal medicine subspecialist in your area, go to https://www.smfm.org/members/search

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