Cell-free DNA Screening

PATIENT EDUCATION SERIES

Society for Maternal•Fetal Medicine
High-risk pregnancy experts

Cell-free DNA (cfDNA) screening, also known as **noninvasive prenatal testing (NIPT),** 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**.

It's important to understand how cfDNA screening works, what conditions it can screen for, and what the results mean.

What is cfDNA?

Cell-free DNA (cfDNA) refers to tiny fragments of **DNA** that are found in a pregnant person's bloodstream. Some of these DNA fragments come from the pregnant person, and some come from the placenta, which can reflect the fetus's genetic makeup.

In cfDNA screening, these DNA fragments 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 during pregnancy?

cfDNA helps identify the risk of several common **chromosome** disorders where there are extra or missing chromosomes. This type of chromosome disorder is called **aneuploidy**.

Normally, there are 2 copies of each chromosome (one is inherited from each parent). 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**. 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.

cfDNA screening can also look for missing or extra copies of the **sex chromosomes**. Sex chromosomes determine the genetic sex of a fetus (typically XX for female and XY for male). This part of cfDNA screening is optional.

When is cfDNA screening performed during pregnancy?

cfDNA screening can be performed beginning at 9 to 10 weeks of pregnancy. Some people choose to have cfDNA screening as early in the pregnancy as possible. cfDNA screening can also be done later in pregnancy if an ultrasound exam shows a concern or other issues arise.

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 chances that a fetus is affected:

- A positive cfDNA screening test result means there is a high chance that the fetus has a chromosome disorder.
- A negative cfDNA screening test result means there is a low chance that the fetus has a chromosome disorder.

The most accurate way to test for aneuploidy 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 these conditions is requested.

CVS is an option starting at 11 weeks of pregnancy, and amniocentesis is an option starting at 15 to 16 weeks of pregnancy. Both have a very low risk of pregnancy loss of less than 0.5%.

Diagnostic testing is an option for all pregnant people, regardless of their age or risk factors.

Who should consider cfDNA screening?

cfDNA screening is an option for any pregnant person who wants more information on their risks of having a child with the most common chromosomal conditions. It's often chosen by people who:

- Want to know more about their pregnancy
- Are over age 35
- Have had abnormal ultrasound findings
- Have a personal or family history of genetic conditions

Are other prenatal screening tests available for aneuploidy?

Yes. Maternal serum screening is a blood test that measures certain substances in the mother's blood. Test results can be combined with ultrasound results. cfDNA is the most accurate screening test currently available for trisomy 13, 18, and 21. However, no screening test is as accurate as a diagnostic test.

What if cfDNA screening doesn't give a result?

In some cases, cfDNA screening may not provide a result. This is called a "no-call" or test failure. It may happen if:

- The test was done too early (before 10 weeks)
- There wasn't enough pregnancy DNA in the blood sample
- There are large fibroids or a higher body weight
- The fetus has a chromosome condition

If this happens, your healthcare professional may suggest:

- Repeating the cfDNA test
- Using a different cfDNA test
- Going directly to diagnostic testing

Any pregnant person can request diagnostic testing, which will provide the most definitive information about your pregnancy.

How accurate is cfDNA screening?

cfDNA is highly accurate in screening for Down syndrome and is slightly less accurate for trisomy 13 and 18.

Screening for sex chromosome conditions is less accurate than screening for trisomies 13, 18, and 21. Results can be harder to interpret and may lead to additional testing. Before deciding to have sex chromosome screening, talk with your healthcare professional about what the results could mean and whether this part of the test makes sense for you.

Screening test results can sometimes be wrong. With any screening test, there is a chance of:

- A **false-positive** result (the test shows a higher risk, but the fetus does not have the disorder)
- A **false-negative** result (the test shows a lower risk, but the fetus does have the disorder)

Does 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 pregnant person with a positive test result actually has a fetus with the condition being tested for. Thus, the pregnant person's age itself does not impact the way the blood test is run, but, rather, the likelihood of disease in a high-risk result.

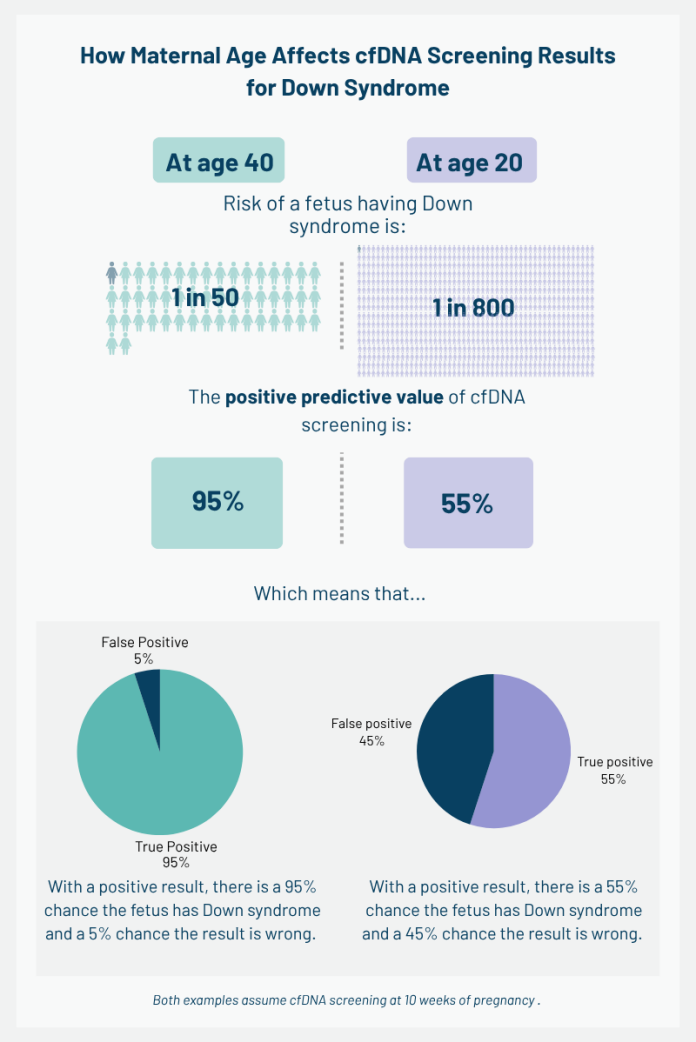
PPV varies based on how common the condition is in a certain group of people at a given time. The rarer the condition, the lower the PPV.

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 pregnant persons 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 (in other words, the fetus has Down syndrome). There is a 5% chance that the result is a false positive (the result is wrong).
- 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?

While cfDNA screening is a useful tool, it has limitations. This test does not screen for:

- **Single-gene conditions** (at this time): cfDNA screening cannot detect genetic conditions caused by changes in a single gene, such as cystic fibrosis. While some labs may offer testing for certain single-gene conditions, there isn't enough reliable data on the accuracy of these results.
- **Copy number variants (CNVs)**: These are small missing or extra pieces of a chromosome. cfDNA is very limited in its ability to detect these changes. Some labs offer screening for a few of the more common CNVs, but these results are more likely to be false positives or false negatives. If there's a concern about CNVs, diagnostic testing is recommended for more accurate information.
- **Rare chromosome conditions:** cfDNA is most accurate for the three most common chromosome conditions: trisomy 21 (Down syndrome), trisomy 18, and trisomy 13. Some labs offer screening for other rare conditions (like trisomy 16 or 22), but the accuracy of these results has not been well studied. . For this reason, cfDNA screening for these rare conditions is not generally recommended.
- **Structural birth defects**: cfDNA does not detect physical abnormalities such as heart defects, spina bifida, or brain malformations. A second-trimester ultrasound is recommended for all pregnancies to check for these types of structural conditions. Diagnostic testing (such as amniocentesis or CVS) may also be offered.

Special Situations:

What if I have twins or triplets?

In twins, cfDNA is a highly effective method of screening trisomies 13, 18 and 21. Some testing companies can also confirm if the twins are fraternal, though there is still a need for early ultrasound assessment of twin pregnancies. 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.

What if I had IVF with preimplantation genetic testing?

Aneuploidy screening can still be beneficial even if you had genetic screening prior to embryo transfer. There is the possibility of a false negative result with preimplantation genetic testing, and it does not replace routine screening with cfDNA.

What if I've had an organ transplant?
cfDNA screening can be less accurate in patients with a transplanted organ. Be sure to talk with your doctor about whether the test is right for you.

What questions should I ask myself before deciding whether to have cfDNA screening?
Before choosing cfDNA screening, it's helpful to think about how you might feel if the results give you unexpected information, either about the pregnancy or your own health. Some people find this information reassuring, while others may find it stressful or overwhelming.

Ask yourself:

- Would I want to know if there's a higher chance of a chromosome condition?
- What would I do with that information?
- Am I okay with the possibility of needing more testing?
- How might the results affect my pregnancy decisions?
- Does my insurance cover this test? What will the cost be?

Remember, genetic testing is completely optional. You get to decide what information you want to know during your pregnancy and what feels right for you.

If you feel unsure or have questions, reach out to your healthcare professional for more information. They can explain your options, offer support and resources, and help you make a decision that feels right for you.

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 chromosomes beginning as early as 9 weeks of pregnancy.
- A positive cfDNA result means there is a high chance that the fetus has a chromosomal disorder A negative cfDNA result means there is a low chance that the fetus has a chromosome disorder.
- 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.
- The role of cfDNA in screening for other, less common, conditions is not broadly established at this time.

Glossary

Aneuploidy: A genetic disorder in which there are missing or extra chromosomes.

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.

Copy Number Variant (CNV): An addition or deletion of a small segment of a chromosome resulting in an additional or missing portion of genetic material

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.

Noninvasive prenatal testing (NIPT): Prenatal blood tests that measure certain substances in a pregnant person's blood or analyze fragments of placental DNA from the pregnancy to screen for chromosome disorders.

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.

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