Noninvasive Prenatal Aneuploidy Screen by Cell-Free DNA Sequencing

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WHAT IS PRENATAL CELL-FREE DNA SCREENING?

Prenatal cell-free DNA (cfDNA) screening, previously referred to as noninvasive prenatal testing (NIPT) or noninvasive prenatal screening (NIPS), is a screening test that identifies pregnancies at increased risk for certain chromosomal abnormalities. Screening may be done as early as 10 weeks of gestation.

Prenatal cfDNA screening detects DNA that exists outside of cells (cell-free DNA). Fetal cfDNA comes from the placenta and crosses into the pregnant individual's bloodstream, where it can be measured by the laboratory. Maternal cfDNA is also in the individual's blood, in much higher quantities than fetal cfDNA. The portion of cfDNA that is from the fetus is called the fetal fraction (FF). Testing is most accurate when the fetal fraction is not too low (more than 4% FF is ideal).

WHICH DISORDERS CAN BE IDENTIFIED BY PRENATAL cfDNA SCREENING AT ARUP?

- Trisomy 21 (Down syndrome)
- Trisomy 18
- Trisomy 13
- Monosomy X (Turner syndrome)
- Sex chromosome trisomies (XXX, XXY, XYY)

For more information about these disorders, please refer to the "Disorders" section at the end of this brochure.

CAN PRENATAL cfDNA SCREENING IDENTIFY THE SEX OF THE FETUS?

Yes, this screen can help predict whether you are having a male or female. This is exciting news for most families. However, you may opt out if you do not want to know the sex of your baby; if you make that choice, sex will not be reported. Couples may have prenatal cfDNA screening performed because they want to know the sex of the baby, but they may not think about the other information they will

HOW RELIABLE IS cfDNA SCREENING AT DETECTING CHROMOSOMAL ABNORMALITIES?

DISORDER	DETECTION RATE[a,b]	POSITIVE PREDICTIVE VALUE[b,c]
DOWN SYNDROME (TRISOMY 21)	98.9%	20.9–95.1%
TRISOMY 18	>99%	6.2–94.1%
TRISOMY 13	>99%	1.6–76.8%
MONOSOMY X (TURNER SYNDROME)	>99%	

[a] Detection rate is the chance that if a fetus has the disorder, the test will detect it.

[b] Data are not sufficient to calculate detection rate and positive predictive value for every tested condition.

[c] Positive predictive value (PPV) is the chance that a fetus that has tested positive for a disorder will actually have that disorder. PPV is greatly affected by an individual's pretest risk for each of the screened conditions, which varies based on gestational age and maternal age. PPV ranges are calculated based on sensitivity and specificity, as reported by Borth et al[1] and the prevalence in a low-risk group (20 years of age, 30 weeks gestational age) through the prevalence in a high-risk group (44 years of age, 10 weeks gestational age) in Snijders.[2,3]

Sources: Borth, 2021[1]; Snijders, 1995[2]; Snijders, 1999[3]

NONINVASIVE PRENATAL ANEUPLOIDY SCREEN BY CELL-FREE DNA SEQUENCING

MY SCREEN CAME BACK AS "HIGH RISK." WHAT DOES THIS MEAN?

If a prenatal cfDNA screen result is reported as "High Risk," there is a significant chance the fetus is affected with that condition. However, prenatal cfDNA screen is a screening test and can incorrectly call unaffected pregnancies high risk (false positive) or call high-risk pregnancies low risk (false negative). For this reason, screening tests are **not** diagnostic. A positive screening test result does **NOT** mean that your baby has the condition—only that your baby has an **increased risk** for the condition.

Your healthcare provider will discuss options for follow-up testing. Most often, a detailed ultrasound is recommended. Genetic diagnostic testing by chorionic villus sampling (CVS) or amniocentesis may also be offered. CVS involves testing a small piece of the placenta. Amniocentesis involves testing a small amount of the fluid surrounding the baby. With both tests, the laboratory examines the baby's chromosomes to accurately determine whether the baby has a chromosome disorder predicted by the prenatal cfDNA screen screening. Because CVS and amniocentesis can introduce a small risk for miscarriage, the decision to have either test is completely yours.

However, *irreversible decisions regarding the pregnancy, such as pregnancy termination, should NOT be made based on prenatal cfDNA screen results alone.*

WHAT HAPPENS IF ADDITIONAL TESTING SHOWS THAT MY BABY HAS A CHROMOSOMAL ABNORMALITY?

If a chromosomal abnormality is confirmed by chromosomal analysis using CVS or amniocentesis procedures, your healthcare provider or genetic counselor will give you the most current information about that condition. They will also explain your options to you, which may include more ultrasounds, arrangements for special care at delivery, or termination of pregnancy.

DOES A NEGATIVE TEST RESULT GUARANTEE MY BABY DOES NOT HAVE A BIRTH DEFECT?

No. Prenatal cfDNA screening is not a diagnostic test. Although it detects most pregnancies affected with the most common chromosomal disorders, it does not detect all types of disorders. A small percentage of babies with one of the listed disorders will not be identified by this screen. Other kinds of birth defects and chromosomal abnormalities, including other rare chromosome aneuploidies and chromosomal deletions or duplications outside the scope of this screen, will not be detected.

If you would like to learn more about any of these tests, please talk to your healthcare provider.

Disorders

TRISOMY 21 (T21)—Commonly known as Down syndrome, T21 caused by an extra copy of chromosome 21. Children with T21 have intellectual disabilities ranging from mild to severe and may have various health problems, including heart defects, gastrointestinal problems, and an increased risk for certain childhood leukemias that can affect lifespan. However, most individuals with T21 will live into their 60s. About 25–30% of pregnancies with T21 will result in miscarriage, and about one in 700 babies are born with T21.

TRISOMY 18 (T18)—Caused by an extra copy of chromosome 18. T18 is sometimes referred to as Edwards syndrome. Babies with T18 have severe intellectual disabilities, tend to be small at birth, and may have birth defects that affect the heart, kidneys, and brain. Most infants born with T18 will pass away within the first few weeks of life, but reports have shown a small number of infants survive beyond the first year. Most pregnancies with T18 will result in miscarriage, and about one in 3,000 babies are born with T18.

TRISOMY 13 (T13)—Occasionally called Patau syndrome, T13 is caused by an extra copy of chromosome 13. Babies with T13 will have severe intellectual disabilities and may have birth defects that affect the heart, brain, and kidneys. They may have extra fingers and toes, as well as cleft lip and/or palate. Most pregnancies with T13 will result in miscarriage, and the majority of those who are born alive will pass away within a few weeks of birth. As in T18, reports have shown a small number of infants with T13 survive beyond the first year. T13 occurs in about one in 5,000 live births.

TURNER SYNDROME (45,X)—Also known as monosomy X, Turner syndrome is usually caused by a missing sex chromosome (either X or Y) in females, although some females with Turner syndrome have an abnormal second sex chromosome instead. The majority of pregnancies with Turner syndrome are miscarried. Most females with Turner syndrome have normal intelligence, although they do have an increased risk of learning difficulties. The most common physical problems in females with Turner syndrome are heart defects, short stature, and infertility. Approximately one in 2,500 females are born with Turner syndrome.

KLINEFELTER SYNDROME (XXY)—Caused by the presence of an extra X chromosome in males, Klinefelter syndrome does not increase risk for any birth defects. Children with Klinefelter syndrome may have learning difficulties and/or behavioral problems, and males with this syndrome are usually not fertile. About one in 500 males are born with Klinefelter syndrome.

TRIPLE X SYNDROME (XXX)—Triple X syndrome, also known as trisomy X syndrome, is caused by the presence of an extra X chromosome in females. Females with this syndrome generally do not have any birth defects but may have some learning difficulties or behavioral problems and can be taller than average. Females with triple X syndrome are generally fertile. About one in 800 females are born with triple X syndrome.

XYY SYNDROME—XYY Syndrome is caused by an extra Y chromosome in males. Although most males born with XYY syndrome do not have any birth defects, they may be taller than average and have an increased risk for learning and behavioral problems. Approximately one in 650 males are born with an extra Y chromosome.

Sources: Jones, 2013[4]; Meyer, 2016[5]; Otter, 2010[6]; Unique[7]; Bardsle, 2013[8]; Groth, 2013[9]

Patient Resources

1) National Down Syndrome Society (https://ndss.org/)

2) National Down Syndrome Congress (https://ndsccenter.org/)

3) Lettercase (https://lettercase.org/)

4) Down Syndrome Diagnosis Network (https://www.dsdiagnosisnetwork.org/)

5) Support Organization for Trisomy (SOFT) (https://trisomy.org/)

6) Turner Syndrome Society of the United States (https://www.turnersyndrome.org/)

7) Turner Syndrome Foundation (https://turnersyndromefoundation.org/)

8) AXYS - Association for X and Y Chromosome Variations (https://genetic.org/)

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