Understanding Non-Invasive Prenatal Screening with Cell-free fetal DNA.

The purpose of the cell-free fetal DNA test is to screen pregnancies to determine which ones are at high risk for the fetus to have extra or missing copies of the specific chromosomes 21, 18, 13, X and Y. Cell-free fetal DNA is performed on a maternal blood sample which contains DNA (genetic material) from both the mother and the fetus. Fetal DNA is separated from maternal DNA and analyzed for representative material from chromosomes 21, 18, 13, X and Y.

The cell-free fetal DNA test is available for women who are at least 10 weeks pregnant. This screening test can detect over 99% of the abnormalities evaluated for chromosomes 21, 18, and 13, and about 92% of cases of Monosomy X. The cell-free fetal DNA test only provides information about the risk of these abnormalities in your current pregnancy.

Chromosome Abnormalities Evaluated with Cell-free Fetal DNA:

Trisomy 21	Trisomy 21 (T21) is caused by an extra copy of chromosome 21 and is also called Down Syndrome. This is the most common cause of genetic intellectual disability; individuals with T21 have an average IQ of 50. Some children with T21 have defects of the heart or other organs that may require surgery or medical treatment. Some have other medical conditions including hearing or vision loss. T21 affects approximately 1 in 700 live births and the risk of conceiving a child with T21 increases with a woman's age.
Trisomy 18	Trisomy 18 (T18) is caused by an extra copy of chromosome 18 and is also called Edwards syndrome. T18 causes severe intellectual disability, and most babies with T18 have multiple severe birth defects of the brain, heart, and other organs. Poor growth during pregnancy is common and many babies are miscarried or stillborn. Of those babies born alive, most die before one year of age. Babies who survive have profound intellectual disabilities and growth and development problems. T18 occurs in approximately 1 in 6,000 live births, but more conceptions are affected by the syndrome because the majority of those diagnosed with the condition prenatally will not survive the prenatal period. Although women in their 20s and early 30s may conceive babies with T18, the risk of conceiving a child with T 18 increases with a woman's age.
Trisomy 13	Trisomy 13 is caused by an extra copy of chromosome 13 and is also called Patau syndrome. This causes severe intellectual disability. Most babies with T13 have multiple severe birth defects of the brain and other organs. Many babies are miscarried or stillborn. Of those babies born alive, most die before one year of age. T13 affects somewhere between 1 in 10,000 and 1 in 21,700 live births and the risk of conceiving a child with T13 increases with a woman's age.
Monosomy X	Monosomy X is caused by a missing copy of the X chromosome and is also called Turner syndrome. Monosomy X only affects girls. Girls with Monosomy X are shorter than average. Some girls have heart or kidney defects and hearing problems, and some have minor learning disabilities. Girls with Monosomy X may need growth hormone treatments in early childhood and usually need sex hormone treatments at the time of puberty. As adults, they often have infertility. The incidence of Monosomy X in live female births is believed to be around 1 in 2000.

Methods and Test Results

To perform the cell-free fetal DNA test, two tubes of blood are required from the mother. The only test performed with this blood is to evaluate the number of copies of chromosomes 21, 18, 13, X and Y in the fetus.

Results are sent back to our office in 7 to 10 days, and can include:

- A **"High Risk"** result indicates that the test has detected a very high chance for the fetus to have an abnormal number of one or more of the following chromosomes: 21, 18, 13, X and Y. The specific risk will be listed on the report. A "High Risk" result does not confirm that your baby has one of the chromosomal conditions tested. The recommended follow up to a high risk result is a prenatal diagnostic test such as chorionic villus sampling (CVS) or amniocentesis. Referral to a genetic counselor may also be indicated.

- A **"Low Risk"** results means that the test detected a very low chance for the fetus to have an abnormal number of the following chromosomes: 21, 18, 13, X and Y.

There is also a chance that the sample submitted will not return any results. In this case, a second sample may be required to repeat the test (at no charge to you). In rare cases, a second sample will not meet testing requirements and be unable to yield any results.

Because cell-free fetal DNA tests for material from the Y chromosome, it is able to identify the sex of the fetus. (Normal males have one X and one Y chromosome, while normal females have two X chromosomes.) We will ask you whether or not you would like know the sex of your baby at the time of testing.

Test Limitations

Although this screening test will detect the vast majority of extra or missing copies of chromosomes 21, 18, 13, X and Y, it cannot detect 100% of the extra or missing copies. A "Low Risk" result greatly reduces the chances that your fetus has an extra or missing copy of one of the tested chromosomes, but it cannot guarantee normal chromosomes or a healthy baby. The result of this test does not eliminate the possibility of other abnormalities of the tested chromosomes, and it does not detect abnormalities of untested chromosomes, other genetic disorders, birth defects, or other complications in your fetus or pregnancy.

While results of cell-free fetal DNA are highly accurate, infrequent errors may be due to unusual DNA sequences in the DNA analyzed or other causes.

Test Alternatives

The cell-free fetal DNA test is not the only non-invasive option for detecting pregnancies at high risk for fetal chromosome abnormalities. Other non-invasive screening options are the Sequential Screen and the Quad Screen.

The **Sequential Screen** is a test with two stages. The first stage happens at 12 weeks and includes an ultrasound and a maternal blood sample. Preliminary results are available one week later, at which time the test detects 70% of cases of Trisomy 21 and 80% of cases of Trisomy 18. The second stage happens at 15-22 weeks and includes only a maternal blood sample. Final results that combine the information gained from both stages are available one week later (16-23 weeks). At this point, the Sequential Screen detects 90% of Trisomy 21 cases, 90% of Trisomy 18 cases, and 80% of cases of open neural tube defects (like Spina bifida). The Sequential Screen does not screen for Trisomy 13 or missing copies of the X chromosome. No information about the sex of your baby can be gained from the Sequential Screen.

The **Quad Screen** is a single maternal blood test that is done between 15 and 21 weeks of pregnancy. It measures the same proteins and hormones in a mother's blood as are measured in the second stage of the Sequential Screen. The Quad screen detects 81% of Trisomy 21 cases, 80% of Trisomy 18 cases, and 80% of cases of open neural tube defects (like Spina bifida).

For women who want or need more conclusive information about their fetus' chromosomes, commonly used invasive diagnostic tests such as chorionic villus sampling (CVS) or amniocentesis are available and will detect greater than 99% of all chromosome abnormalities, including rare abnormalities on chromosomes not evaluated with cell-free fetal DNA or the Sequential Screen or Quad Screen. While invasive diagnostic tests are the most accurate, they do come with a small risk of pregnancy loss.

CVS is performed between 10 and 13 weeks. A small sample of placental tissue (which has the same genetic composition as the fetus) is taken using a catheter threaded through the mother's cervix or a needle inserted into the mother's abdomen. Fetal chromosomes are analyzed in the lab. Preliminary results are available in 24-48 hours and final results are available in a week. Risk of miscarriage from CVS is estimated at 1 in 100-200 procedures.

Amniocentesis is performed as early as 16 weeks and involves the withdrawal of a small amount of amniotic fluid from the uterus. A very thin needle is inserted through the mother's abdomen and into the uterus under ultrasound guidance to obtain the fluid. Fetal chromosomes from skin cells found in amniotic fluid are analyzed in the lab. Risk of miscarriage from amniocentesis is estimated at 1 in 200-600 procedures. Preliminary results are available in 24-48 hours, and final results are available in 2 weeks.

Maternal Age	Risk of Trisomy 21 (Down Syndrome)
20	1 in 1,667
21-23	1 in 1,429
24-25	1 in 1,250
26	1 in 1,176
27	1 in 1,111
28	1 in 1,053
29	1 in 1,000
30	1 in 952
31	1 in 909
32	1 in 769
33	1 in 625
34	1 in 500
35	1 in 385
36	1 in 294
37	1 in 227
38	1 in 175
39	1 in 137
40	1 in 106
41	1 in 82
42	1 in 64
43	1 in 50
44	1 in 38
45	1 in 30
46	1 in 23
47	1 in 18
48	1 in 14
49	1 in 11

Maternal Age	Risk of Any Chromosomal Disorder
15-24	1 in 500
25-29	1 in 450
30	1 in 385
31	1 in 370
32	1 in 340
33	1 in 320
34	1 in 270
35	1 in 200
36	1 in 170
37	1 in 130
38	1 in 100
39	1 in 80
40	1 in 65
41	1 in 50
42	1 in 40
43	1 in 30
44	1 in 24
45	1 in 20
46	1 in 15
47	1 in 12
48	1 in 9
49	1 in 7

Options for Prenatal Testing for Chromosomal Abnormalities

	Non-Invasive		Invasive	
	Sequential Screen	**Cell-free fetal DNA**	**Amniocentesis**	**CVS**
Purpose and Detection Rate	90% Trisomy 21 90% Trisomy 18	99.7% Trisomy 21 97.9% Trisomy 18 99.0% Trisomy 13 95.8% Monosomy X	All chromosomal abnormalities. >99%	All chromosomal abnormalities. >99%
Timing of Testing	First stage at 12 weeks. Second stage 15-22 weeks.	As early as 10 weeks.	As early as 16 weeks.	10-13 weeks.
Timing of Results	Preliminary results at 13 weeks. Final results one week after second blood draw (as early as 16 weeks).	7 days after blood draw (as early as 11-12 weeks).	Preliminary results in 24-48 hrs. Final results 2 weeks after procedure (as early as 18 weeks).	Preliminary results in 24-48 hrs. Final results 1 week after procedure (11-14 weeks).
Risks to pregnancy	None.	None.	Risk of miscarriage is 1:200-600.	Risk of miscarriage 1:100-200. Very small risk of limb reduction defects.
Cost	Generally covered by insurance for women of all ages.	Usually covered by insurance for women 35 yrs or older at delivery. Max out-of-pocket cost is $99.	Generally covered by insurance.	Generally covered by insurance.
Other		Results can reveal fetal sex.	Results can reveal fetal sex.	Results can reveal fetal sex.