Prenatalsafe®

Patient Information Leaflet

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What is the Prenatalsafe® test?

Prenatalsafe® is a non-invasive prenatal test (NIPT) which evaluates if a fetus has an increased or decreased likelihood of certain chromosomal abnormalities e.g., three copies of chromosome 21, which causes Down's Syndrome.

Who can have the Prenatalsafe® test?

Pregnant women with a gestational age of at least 10 weeks determined by performing an ultrasound scan. Prenatalsafe® 3 can be offered to both single and twin pregnancies. Prenatalsafe® 5 can only be offered to singleton pregnancies. Both tests can be offered to pregnancies obtained either by natural conception or by assisted reproductive techniques, such as In vitro fertilization (IVF).

The Prenatalsafe® test will not be offered:

- If the expectant mother has not had an ultrasound scan (to determine gestational age and pregnancy type – singleton/twins/triplets/etc.,)
- To expectant mothers below 10 weeks gestation
- For pregnancies greater than twins (e.g., triplets)
- If the mother has the chromosomal abnormality being investigated (e.g. Down's Syndrome), or balanced translocation or mosaicism for 13, 18, 21, X or Y
- If the mother received an organ transplantation
- If the mother received a blood transfusion within a period of <4 months
- If the mother received allogeneic stem cell therapy
- If the mother has been diagnosed with a malignancy
- If the mother has received immunotherapy, sample will be rejected if taken less than 6 days after immunotherapy drug treatment

How does the Prenatalsafe® test work?

During pregnancy, the placenta sheds the baby's (fetal) DNA into the mother's blood.

A blood sample is taken from the expectant mother. Circulating free DNA is isolated from the plasma component of the maternal blood and is then evaluated to determine the chance of having a baby with a chromosomal abnormality (e.g., three copies, or trisomy for chromosome 21, which causes Down's Syndrome).

It is important to note, that the Prenatalsafe® test is a screening test and is not a diagnostic test. If a high-chance (detected) result is obtained, follow-up diagnostic testing is required.

What chromosomal disorders does Prenatalsafe® report?

- Prenatalsafe® 3 is a screening test for Trisomy 21 (Down's Syndrome), Trisomy 18 (Edwards' Syndrome) and Trisomy 13 (Patau's Syndrome).
- Prenatalsafe® 5 is a screening test for Trisomy 21, Trisomy 18, Trisomy 13 and aneuploidies (abnormal numbers) of the sex chromosomes e.g., Turner's Syndrome.
- Both tests have the option to report fetal sex.
- Both tests might detect abnormalities in other chromosomes, but this will not be reported.

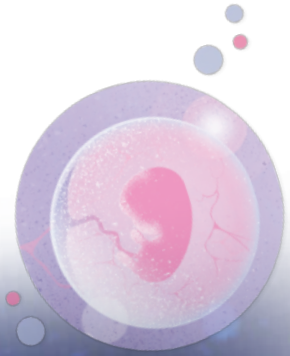
Does fetal biological sex have to be reported with the Prenatalsafe® test and how is it reported?

If a sex chromosome aneuploidy is tested and detected, the fetal biological sex will be disclosed when the abnormality is reported. If no sex chromosome aneuploidy is detected, biological fetal sex will not be reported unless requested.

In twin pregnancies and vanishing twin pregnancies, one result will be reported i.e., the presence or absence of the Y chromosome. The Y chromosome may be attributed to one or both fetuses.

In all other cases, the fetal biological sex is stated as male, or female based on the presence or absence of the Y chromosome.

	Prenatalsafe® 3	Prenatalsafe® 5
Fetal sex	●	●
Trisomy 21 *Down's Syndrome*	●	●
Trisomy 18 *Edwards' Syndrome*	●	●
Trisomy 13 *Patau's Syndrome*	●	●
Sex Chromosome *Aneuploidies*		●



What is Trisomy 21 (Down's Syndrome)?

Trisomy 21 is the presence of an extra copy of chromosome 21 and is also known as Down's Syndrome. It is the most common genetic cause of learning disability and is estimated to be present in 1/700 births. However, the chance that a fetus has Down's Syndrome increases as maternal age increases.

What is Trisomy 18 (Edwards' Syndrome)?

Trisomy 18 is caused by the presence of an extra copy of chromosome 18 and is also known as Edwards' Syndrome. It is linked to a high risk of miscarriage and causes severe mental disability. Newborns with trisomy 18 often have congenital heart defects, as well as other pathological conditions that reduce their life expectancy. It is estimated that trisomy 18 is present in 1/5,000 births. However, the chance increases as maternal age increases.

What is Trisomy 13 (Patau's Syndrome)?

Trisomy 13 is caused by the presence of an extra copy of chromosome 13 and is also known as Patau's Syndrome. It is linked to a high risk of miscarriage. Newborns with trisomy 13 may have heart defects and other pathological conditions, which means that survival beyond the age of one year is rare. It is estimated that trisomy 13 is present in 1/16,000 births. However, the chance increases as maternal age increases.

What are Sex Chromosome Aneuploidies?

Usually, females have two copies of the X chromosome (XX) and males have one X and one Y chromosome (XY). A sex chromosome aneuploidy is an abnormal number of sex chromosomes. The most frequent sex chromosome aneuploidy is **Monosomy X**, which is clinically known as **Turner Syndrome (XO)**. Females with Turner Syndrome have a short stature and reproductive difficulties in association with other possible clinical manifestations such as congenital heart disease, neurosensory hypoacusis, renal abnormalities such as horseshoe kidney and predisposition to some autoimmune diseases (thyroiditis, diabetes, coeliac diseases, etc.). Other sex chromosome aneuploidies that can be found with the test are **Klinefelter Syndrome (XXY)**, **Jacobs' Syndrome (XYY)** and **Triple X (XXX).**

What type of results are expected from Prenatalsafe®?

DETECTED (High Probability/Chance)

Aneuploidy detected: indicates that the test has produced a result consistent with an aneuploidy of one (or more) of the chromosomes investigated. However, this result is not diagnostic and therefore does not guarantee that the fetus has the condition. The recommended follow-up is an invasive prenatal diagnosis test, such as chorionic villus sampling (CVS) or amniocentesis.

NOT-DETECTED (Low Probability/Chance)

Aneuploidy not detected: indicates that the test did not detect any aneuploidies for the chromosomes investigated. However, this result does not guarantee that the fetus does not carry these abnormalities. See test limitations.

INCONCLUSIVE RESULT (approximately 1%)

In certain cases where the sample did not pass the quality parameter thresholds, an inconclusive result is issued. In such cases, the expectant mother will likely be asked for a new blood sample in order to repeat the test. The re-test might still produce an “Inconclusive result” and a discussion with a health care professional is needed to determine the next steps.

How reliable is the Prenatalsafe® test?

The sensitivity and specificity and the limitations of the test are described by Pertile et al., 2021. Concordance of the test for trisomy 13, trisomy 18 and trisomy 21 is 99.9% for singleton pregnancies. For fetal sex, concordance was 100% for both 'female' and 'male' (based on newborn physical exam) and for XX and XY (based on cytogenetic results). For sex chromosome aneuploidies, concordance was 90.5% for monosomy X (19/21), 100% for XXY (23/23), and 91.7% for XYY (11/12) *Pertile et al. 2021 – DOI: 10.1093/clinchem/hvab067.*

What are the limitations of the Prenatalsafe® test?

Non-invasive prenatal testing of circulating cell-free fetal DNA isolated from a sample of maternal blood is a screening test and although this test is very accurate, the results are not diagnostic and need to be evaluated in the context of the patient's clinical and family history. In addition, the test is not a substitute for invasive prenatal diagnosis (CVS or amniocentesis). The Prenatalsafe® 3 test has been validated on single and twin pregnancies, monozygotic or dizygotic. The Prenatalsafe® 5 test has been validated on singleton pregnancies. Both tests validated from week 10 of gestation onwards.

The test cannot rule out the presence of all fetal chromosomal abnormalities. Prenatalsafe® 3 will only report the aneuploidies of chromosomes 13, 18, 21. Prenatalsafe® 5 will only report the aneuploidies of chromosomes 13, 18, 21 and the sex chromosomes (X and Y). Prenatalsafe® cannot detect balanced chromosomal rearrangements, fetal and/or placental chromosomal mosaicism (i.e., the presence of two cell lines with a different chromosomal arrangement).
In non-identical twin pregnancies and vanishing twin pregnancies, the presence/absence of the Y chromosome can be detected. If the Y chromosome is detected, it is not possible to discern whether only one or both fetuses are male.

In pregnancies that have started as twins or multiples, followed by the loss of one or more fetuses with reabsorption of the gestational chamber (vanishing twin), cell-free fetal DNA of the lost fetus may also be present in the maternal blood. This could interfere with the accuracy of the test leading to potential false positive results. Similarly, there may be a mismatch in sex results (e.g., presence of the Y chromosome originates from the DNA of the lost fetus).

What are the limitations of the Prenatalsafe® test?
(continued)

Malignancy/tumour, organ transplant, recent blood transfusion, allogeneic stem cell therapy in the expectant mother could produce false positive test results.
The test is based on the quantification of cell-free fetal DNA fragments circulating in maternal blood, which are placental in origin. Placental chromosomal mosaicism (frequency: 1-2%), a condition where the chromosomal composition of the placenta differs from that of the actual fetus, may lead to false positive or false negative results, hence sensitivity and specificity of <100%. A false positive result can occur when the test detects a chromosomal aneuploidy (confined to the placenta) but the invasive diagnostic test does not. A false negative result occurs when the test does not detect a chromosomal aneuploidy but the invasive diagnostic test (e.g., performed after an abnormality is detected in a late-gestation ultrasound scan) does or a child is born with the chromosomal disorder.

If the expectant mother has a chromosomal abnormality in a homogeneous or mosaic form, the test might lead to a false positive result and cannot give any information about the presence of the abnormality in the fetus.

A "**NOT-DETECTED**" result significantly reduces the chances that the fetus has an aneuploidy at the level of the examined chromosomes, but it cannot guarantee that the chromosomes are actually normal or that the fetus is healthy. Due to the above limitations, in the event of a "**DETECTED**" result, it is recommended to have a referral for genetic counselling and confirm the result by invasive testing. Pregnancies with abnormal ultrasound findings suggestive of fetal disease should undergo invasive prenatal diagnosis, such as molecular fetal karyotype on chorionic villi or amniotic fluid.

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