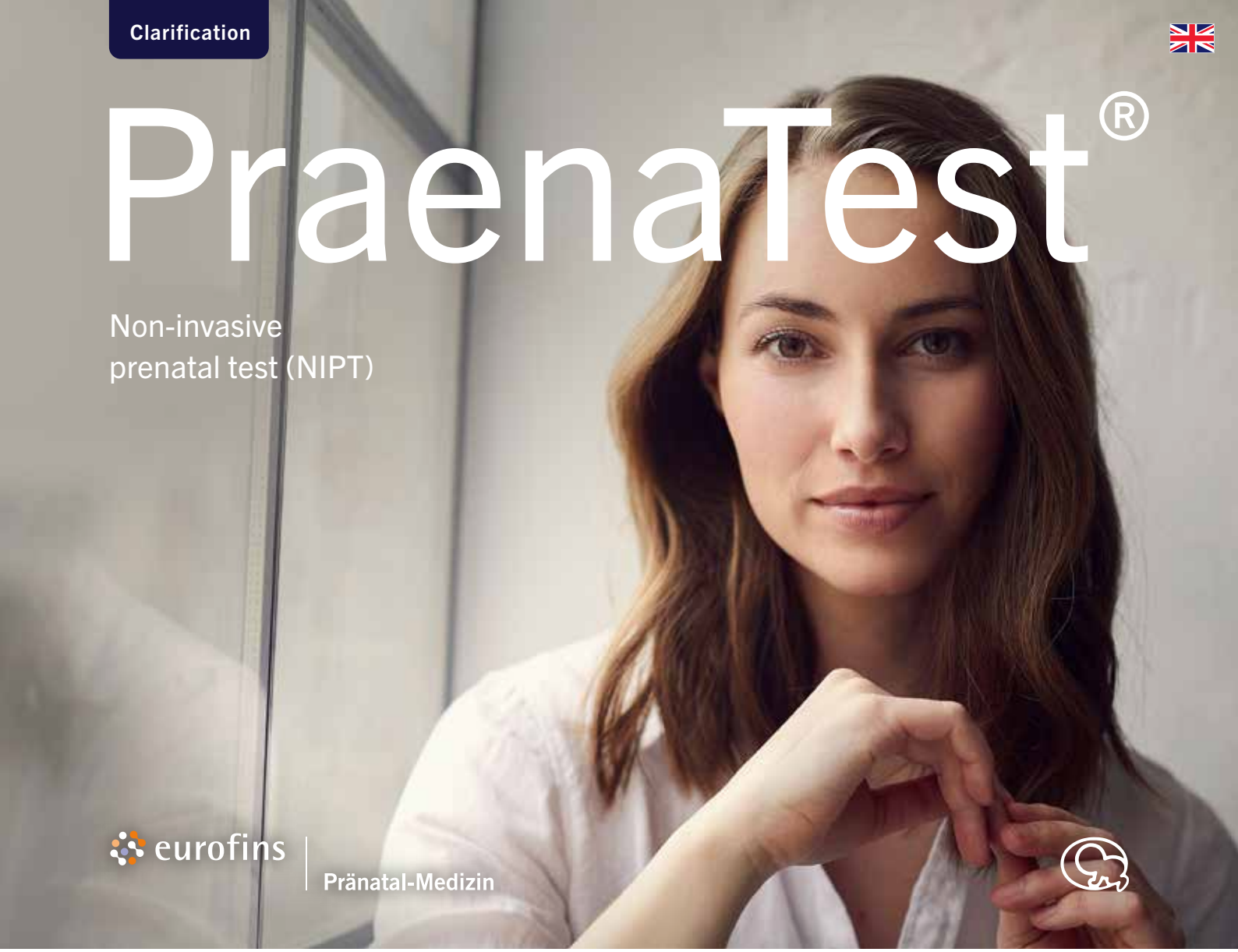
Clarification



To be kept at the medical practice

Clarification and Consent to Perform the PraenaTest®

Non-invasive, prenatal test for identifying chromosomal abnormalities in an unborn child

Dear patient,

A pregnancy comes with lots of joy and may well be the most exciting and important time of your life. Naturally, it can also come with mixed feelings and some uncertainty. Especially with your first child, it is often unclear what is in store in the months ahead, what might happen to you and how you can do the best for you and your unborn baby.

During this time, your doctor is there to support you. Together with you, he/she will track your baby's development and advise you at all check-ups related to your pregnancy.

Modern medicine offers you lots of screening options – without any risk for you or your unborn baby – in order to detect the presence of health risks even during the early stages of pregnancy. This means that the non-invasive PraenaTest® can already determine whether your baby has any chromosomal abnormalities from the end of the ninth week of pregnancy.

Before your test and the blood test required for it, it is important that you are informed of the possibilities, limits and risks of this test method.

What can the PraenaTest® determine in my unborn baby?

The PraenaTest® is a modern screening test. It can be used to identify chromosomal abnormalities, i.e. certain changes in the genetic material of an unborn baby. Almost every human cell contains genetic material (in the form of DNA), which is organised in the nucleus in the chromosomes. Human body cells usually contain 46 chromosomes. Chromosomes 1–22 (autosomes) are all present twice. One chromosome each comes from the mother and the father respectively. In addition, human cells possess two sex chromosomes (gonosomes): Women have two X chromosomes, while men have one X and one Y chromosome. Here too, one sex chromosome each comes from the mother and one from the father.

In rare cases, it may occur that some of these chromosomes do not appear twice, but three times in the embryo's nucleus. The threefold presence of a chromosome is referred to as trisomy, while the next number specifies the chromosome affected, e.g. trisomy 21. While trisomies are rare, the risk increases as the mother (and sometimes also the father) gets older. Trisomies are usually associated with significant clinical findings or other health impairments of the embryo. The PraenaTest® is able to identify the following chromosomal abnormalities:

Trisomy 21 (Down syndrome)
The most common type of chromosomal abnormality is trisomy 21, which leads to Down syndrome. Children with Down syndrome experience physical and mental impairments in varying degrees.
Frequency: 1:700 to 1:800

Trisomy 18 (Edwards syndrome)
This very rare chromosomal abnormality greatly increases the risk of miscarriage. Due to the severity of this illness, around 90% of newborns die within the first few days of their lives. Those affected only reach adult age in rare cases and rely entirely on external assistance due to severe disability.
Frequency: 1:6000 to 1:8000

Trisomy 13 (Patau syndrome)
The rarest form of trisomy is Patau syndrome, where severe organ deformities occur and the risk of miscarriage is greatly elevated. Due to deformities in its organ systems, it is rare for the newborn to survive beyond its first year of life.
Frequency: 1:12,000

Monosomy X / (X0) (Ullrich-Turner's syndrome)
With Monosomy X, only one X chromosome is present, while the second sex chromosome is missing. It is the only survivable type of monosomy and only affects girls. Carriers typically experience infertility, dwarfism and an increased risk of cardiac defects. It does not usually come with any mental impairments.
Frequency: 1:2500

XXX (Triple X syndrome)
Triple X syndrome or Trisomy X is the most common chromosomal abnormality found in girls. In most cases, this syndrome remains undiscovered for the carrier's entire life, as it usually does not cause any clinically relevant abnormalities.
Frequency: 1:1000

XXY (Klinefelter syndrome)
Klinefelter syndrome occurs in male newborns, with those affected often being of above-average size, and usually leads to infertility.
Frequency: 1:600

XYY (Diplo Y syndrome/Jacobs syndrome)
With Diplo Y syndrome, an additional Y chromosome is present in the cells. In most cases, this syndrome remains undiscovered for the carrier's entire life. The boys are usually of normal intelligence, but have an above-average height.
Frequency: 1:1000

RAAs – Rare Autosomal Aneuploidies
RAAs are rare maldistributions in autosomes that affect entire chromosomes. The RAA analysis of the PraenaTest® also enables testing of chromosomes 1 to 12, 14 to 17, 19, 20 and 22 for monosomies and trisomies as well as chromosomes 13, 18 and 21 for monosomies. If a rare autosomal aneuploidy is determined in an existing pregnancy, this is often known as a mosaicism finding. In this case, not all cells of the unborn baby are affected (foetal mosaicism) and/or only parts of the placenta are affected (placental mosaicism). The clinical appearance of a mosaicism can vary greatly and depends on which chromosome is affected and which or how many cells carry the chromosomal abnormality. This means that a placental mosaicism may largely remain without any effect or even go hand in hand with placenta insufficiency. In some cases, the latter prevents the unborn baby from receiving a sufficient supply. Foetuses whose cells are affected by a rare autosomal aneuploidy in the form of mosaicism usually have physical deformities or mental developmental disorders. In some cases, however, their clinical presentation is normal.

CNV (Copy Number Variations)
In a CNV, only a partial area within the chromosome is affected, meaning that it is present in an increased number of copies (duplication) or a reduced number of copies (deletion). How pronounced the illness' characteristics are depends on the location and size of the affected region. This can lead to deformities in the internal organs or disorders in mental development. In a PraenaTest®, tests are performed for the presence of a CNV ≥ 7 mB.
Frequency: 1:10,000

Microdeletion syndrome 22q11.2 (DiGeorge syndrome)
In this syndrome, a change is present in chromosome 22, which can impact the unborn baby's development. In 90% of cases, it occurs spontaneously and appears in one in around 4,000 newborns. This test can optionally be carried out and is especially sensible if your doctor identifies abnormalities e.g. with organ screening during the ultrasound, which could correlate with a DiGeorge or velocardiofacial syndrome.
Frequency: 1:4000

Please note
Most prenatal screenings do not find any abnormalities. However, in the event of an abnormal finding, it is more than understandable to feel uneasy at first. It is all the more important to obtain detailed information from your doctor. Psychological counselling can provide additional assistance in these situations.

More information on the PraenaTest®

Can the PraenaTest® also be carried out with a twin pregnancy?
The PraenaTest® may also be carried out with a twin pregnancy. No additional costs are incurred.

Does the PraenaTest® work after fertility treatment?
The PraenaTest® can be used without any restrictions following fertility treatment (egg donation, IVF or ICSI).

How does the PraenaTest® work?
Only a few steps are required until the result is passed on to your treating doctor within a few working days:

1. Comprehensive consultation and clarification carried out by your doctor
2. A simple blood test taken by your doctor
3. Blood analysis in Germany; the result is sent to your doctor within a few days
4. You discuss your result with your doctor.

How should a normal test result be assessed?
A normal (i.e. negative) test result means that the presence of the chromosomal abnormalities tested for in your unborn child is highly unlikely. Chromosomal abnormalities other than those requested in the test order are not recorded by the PraenaTest®, meaning that no statement is made on these. As a result, genetic aberrations beyond this cannot be captured. The PraenaTest® is also unable to identify special forms of chromosomal abnormalities. For more information, read the “Limits of testing” section and talk to your doctor.
Even if you have received a normal test result, you should consider the recommended preventive check-ups, in particular, the ultrasound tests.

How should an abnormal test result be assessed?
An abnormal (i.e. positive) test result provides a clear indication that your unborn baby carriers the chromosomal abnormality concerned.
According to medical recommendations, a positive test result must be further clarified through diagnostics measures by way of an invasive test. In very rare cases, the chromosomal abnormality found is even present in the cells of the placenta, but the unborn baby itself is not affected by it.

Costs
Discuss with your doctor which screening options are best for you and your personal situation. Since 1 July 2022, the non-invasive prenatal identification of the three trisomies 21, 18 and 13 is covered by the statutory health insurance funds. Beyond the spectrum of health fund services, every patient – in consultation with her doctor – can decide themselves on the identification of further chromosomal abnormalities on a self-paying basis. Current prices for self-paying patients can be found at www.praenatest.de/preise.

How conclusive is the PraenaTest®?

The PraenaTest®'s high accuracy has been proven in clinical studies. Here, the sensitivity indicates the probability of a chromosomal abnormality that is actually present being detected as positive ("abnormal") in the test. The specificity indicates the probability of a chromosomal abnormality that is not present being detected as negative ("normal").

Accuracy of the PraenaTest® in identifying autosomal aneuploidies

PraenaTest® [1]	Trisomy 21	Trisomy 18	Trisomy 13	RAAs	CNVs
Sensitivity	>99.9% (130/130)	>99.9% (41/41)	>99.9% (26/26)	96.4% (27/28)	74.1% (20/27)
Specificity	99.9% (1982/1984)	99.9% (1995/1997)	99.9% (2000/2002)	99.8% (2001/2005)	99.8% (2000/2004)

Accuracy in identifying gonosomes or gonosomal aneuploidies

Out of 1,963 newborns examined, 100% were correctly recognised as male or female.[1]
Matches with known gonosomal aneuploidy are shown in the following table.

Matches in foetal sex classification in clinical studies with cytogenically confirmed gonosomal aneuploidy[1]

	X0	XXX	XXY	XYY
Match with NIPT result	90.5% (19/21)	100% (17/17)	100% (23/23)	91.7% (11/12)

[1] VeriSeq NIPT Solution v2 Packaging Enclosure 1000000078751 v06 August 2021

Accuracy in identifying 22q11.2 microdeletion

During the validation process, an internal blind study that included positive sample material was carried out. Every sample analysed that met the quality criteria was classified correctly. The expected sensitivity is 85%, while the specificity is 99.65%.

The NIPT is a non-invasive screening test that is able to quickly – and without risk for mother or child – determine the risk of one of the chromosomal abnormalities mentioned here being present in the unborn baby. In very rare cases, it is possible to obtain false-positive or false-negative test results.

Limits of testing

The PraenaTest® is unable to identify chromosomal deletions/duplications smaller than 7 Mb (excluding 22q11.2 microdeletion). Triploidies and polyploidies cannot be identified with the PraenaTest®. Mosaicisms are also unable to be detected with certainty. In mosaicisms, tissue cells or the entire organism carry different genetic information. The presence of a vanishing twin can – if this is affected by a chromosomal abnormality – result in an abnormal PraenaTest® result that is not representative of the intact pregnancy situation. A vanishing twin may also lead to a sex discrepancy between the foetal sex observed and the sex determined by the PraenaTest®.
Further information regarding the limitations of the PraenaTest® may be obtained from your doctor.

Vanishing twin

A vanishing twin refers to a foetus from a multiple pregnancy. During the first weeks of pregnancy, one of the twins dies, but instead of a miscarriage including bleeding, it is absorbed by the mother's body. However, parts of the genetic material of the vanishing twin may still be present in the mother's bloodstream, which can influence the result of the PraenaTest®.

Polyploidy/triploidy

With a polyploidy, the entire chromosome set occurs more than twice (Greek: "poly" = many times). With a triploidy for example, the chromosomes are present three times (Latin: "tri"). Instead of the usual 46 chromosomes, the physical cells in the event of a triploidy thus contain 69 chromosomes.

Genetic consultation

In accordance with the German Gene Diagnostics Act (GenDG), a genetic consultation will be offered before further testing as well as after the test results, in addition to this clarification. A consultation before genetic testing in accordance with the GenDG includes:

- clarification of any questions you may have
- evaluation of existing medical findings or reports
- a testing-related collection of significant findings in your personal and family medical history (anamnesis)
- information on the necessity of genetic testing based on your questions or prior history
- information on the possibilities, limits and risks connected to material sample removal for the testing method under consideration
- assessment of the genetic risks, including discussion of what all the information means for your life and family planning, and if applicable, for your health
- support options for physical and mental stress due to the testing and its result
- assessment of the need for an in-depth genetic consultation by a specialist doctor for human genetics

The genetic consultation is provided by your doctor following the clarification and your consent to the genetic testing.

Declaration of Consent to Perform the PraenaTest® in accordance with GenDG §9

I have received, read and understood the general written declaration (and any additional special written declarations) on genetic analyses in accordance with GenDG.
With my signature, I give my consent for the PraenaTest® and the required blood test to be carried out.

I have had sufficient opportunity to discuss any unanswered questions. I have been informed that I can withdraw my consent in whole or in part at any time without specifying reasons, without this resulting in disadvantages to me, and that I have the right not to find out test results.

Further notes on clarification and consulting (to be filled out by doctor)

Place/date

Last name and first name of patient (in print letters)

Patient's signature

✗

I am aware that I can stop the test procedure at any time once it has started up until the results are notified and that I can request the destruction of the test material, including all components obtained from it and all results collected until that point. This revocation must be made in writing.

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