Information sheet
PreNata® NIPT information for patients

The PreNata® NIPT (non-invasive prenatal test) is a prenatal test used to ascertain whether your child is affected by genetic changes that could impair its development without any risk to you or your child. All that is needed is a blood sample from you as the mother. The PreNata® NIPT is a diagnostic test in which foetal DNA in maternal blood is examined for chromosomal changes.

How does PreNata® NIPT work?

The detection of sufficient foetal DNA in maternal blood is possible from the 10th week of gestation. This cell-free DNA (cfDNA) of placental origin can be analysed using next generation sequencing (NGS). The VeriSeq NIPT v2 procedure used by illumina can perform a genome-wide examination of foetal cfDNA. These can be differentiated by the difference in the length of maternal and foetal DNA fragments. The foetal DNA sequences are analysed quantitatively, which makes it possible to detect additional (or missing) chromosomes or partial changes (≥ 7 Mb). A software-based probability for the presence of specific chromosome changes is then calculated.

Which chromosomal changes are examined?

PreNata® NIPT allows the selection of different options with different scopes of examination. Patients can choose freely between the services.

Option 1: Trisomies 13, 18 and 21

These three trisomies, whose frequency increases with maternal age, are the most common trisomies in live births:

- **Trisomy 21**
  (Down's syndrome, frequency approx. 1:700)
- **Trisomy 18**
  (Edwards syndrome, frequency approx. 1:3000)
- **Trisomy 13**
  (Pätau syndrome, frequency approx. 1:5000)

Option 2: Trisomies 13, 18 and 21 incl. sex determination

In addition, the child's sex can also be determined if desired. The notification in accordance with the provisions of the Gene Diagnostics Act is made by the attending physician after the 12th week of gestation (14+0 p.m.) if requested.

Option 3: Trisomies 13, 18 and 21, as well as the examination of the sex chromosomes incl. sex determination

In addition to the trisomies to be examined and sex determination, DNA sections of the sex chromosomes (gonosomes) can be examined for aneuploidies. This can provide indications of the presence of various syndromes:

- **Turner syndrome**
  (45, X0; monosomy X),
  frequency approx. 1:3000 in girls
- **Triple X syndrome**
  (47, XXX; trisomy X),
  frequency approx. 1:1000 in girls
- **Jacobs syndrome** (47, XYY),
  frequency approx. 1:1000 in boys
- **Klinefelter syndrome** (47, XXY),
  frequency approx. 1:1000 in boys

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Option 4: Trisomies 13, 18 and 21 as well as examination of the sex chromosomes incl. sex determination and examination for rare autosomal aneuploidies and copy number variations

Genome-wide examination of all chromosomes can detect both rare autosomal aneuploidies (RAAs) and copy number variations (CNVs). RAAs are very rare maldistributions of complete autosomal chromosomes. These are often so-called mosaics, which means that there are at least two different cell types with different sets of chromosomes. This can affect cells of the child (foetal mosaic) and/or only parts of the placenta (placental mosaic). In the case of placental mosaic, the child may be completely unaffected. However, this may result in placental insufficiency, which can lead to the child not being sufficiently supplied with nutrients in the womb. When parts of chromosomes are missing (deletions) or present several times (duplication) and thus the number of copies of the affected sections is altered, we speak of CNVs. CNVs occur with a frequency of less than 0.02% in births. They can lead to malformations of the organs and/or developmental disorders. They can be detected with PreNata® NIPT from a size of 7Mb.

As these additionally examined chromosomal changes occur very rarely, the number of false positive test results may increase as a result, possibly leading to an unnecessary invasive follow-up. Accordingly, this examination is currently not recommended by the professional medical associations.

How reliable is PreNata® NIPT?

The test detects the most common autosomal chromosomal changes (trisomy 13, 18 and 21) with a probability of over 99% and can also exclude them with the same probability. PreNata® NIPT also reliably detects changes in sex chromosomes and RAAs with a probability of 96%, and CNVs with a sensitivity of 74%.

When are the results available?

The results should be sent to the attending physician within about 9 working days.

What do the results mean?

An inconspicuous result means that a chromosome change can be almost excluded. If there is a conspicuous result, there is a high probability of a chromosomal change. As this is a screening test and the result is not a diagnosis, a conspicuous result must be confirmed by further invasive diagnostic procedures. Your doctor will tell you about the options, which are usually an amniocentesis or a chorionic villus sampling.

Limitations of the test

The changes examined represent only some of the possible prenatal chromosomal changes. It is not possible to identify other abnormalities and malformations and to make statements about the child's state of health. This does not replace the need for regular screening examinations or the obstetric ultrasound examination. Furthermore, mosaics cannot be detected with certainty. The presence of a so-called "vanishing twin" may result in a false positive. This can also lead to a discrepancy in sex determination. In general, no deletions or duplications smaller than 7 Mb can be detected.

Test failure

Only very rarely does PreNata® NIPT fail to produce a reliable result. If this does occur, a common cause is that the proportion of foetal DNA in the maternal blood (foetal fraction, FF) is too low. Thus, the examined changes can neither be excluded nor confirmed. It is possible to repeat the test free of charge with a new blood sample.

Genetic counselling

According to the Genetic Diagnostics Act, genetic counselling is mandatory before carrying out a genetic examination and after the result is available. Such counselling includes clarification and the explanation of the following points:

- What is the individual question?
- Are there findings or reports available, and how are they to be evaluated?
- Are there any abnormalities in terms of personal and family health history (anamnesis)?
- Does the need for a genetic examination arise from the question or a person's previous history?
- How high are the genetic risks to be assessed, and what significance can they have for life and family planning and for health?
- What are the possibilities, limits and risks associated with the examination under consideration for the purposes of clarification?
- What support options are there for the physical and psychological stress that may be associated with the examination and the result?
- Is detailed genetic counselling by a specialist in human genetics necessary?

Consent under the Gene Diagnostics Act

PreNata® NIPT cannot be performed without your consent. Therefore, after having consulted your doctor, please sign the following section on the laboratory request form:

Consent under the Gene Diagnostics Act

With this declaration of consent, and having been informed and given sufficient time to consider the matter in accordance with the Genetic Diagnostics Act, I confirm my agreement to the requested genetic analysis/analyses and the necessary sample collection. I agree to the forwarding of the examination order to a specialised laboratory. I have been fully informed about the purpose of the examination, the disease(s) to be examined and their genetic basis, as well as the possible outcomes and limits associated with the tests to be carried out. It was explained to me that the PreNata® NIPT test is not a diagnostic procedure, and an inconspicuous result does not completely rule out a foetal chromosomal disorder. I agree that the findings can be transmitted to the requesting doctor. I agree to:

the **storage and use of the collected results,** anonymised for the purpose of quality assurance and for scientific purposes ☐ no

the **storage and use of the examination material** for possible subsequent investigations and anonymised for quality assurance and for scientific purposes ☐ no

Clarification of additional findings: In rare cases, medical findings can be obtained that are not related to the question at hand, but that are clinically relevant according to the current state of knowledge. In extremely rare cases, this also includes maternal tumour diseases. I would like to be informed about these findings (if no selection is made, "no" is assumed).

☐ **yes** ☐ **no**

This declaration of consent pursuant to the Gene Diagnostics Act may be revoked in whole or in part at any time.

Please sign the original document "Declaration of consent to request a prenatal genetic examination according to the Gene Diagnostics Act".

Last name, first name of the responsible doctor(s)	Place, date	Signature of responsible doctor*	Signature of the patient/ legal representative

Further notes on information and advice (to be completed by the doctor)

Place/Date

Patient's last and first names (in block letters)

Signature of the patient or legal representative