Prenatalis® Consortium

The Center for Human Genetics and Laboratory Diagnostics supports offering NIPT in an interdisciplinary network of prenatal medicine and human genetic institutions, and the **Prenatalis® Consortium** provides a platform for this purpose. The goals of the **Prenatalis® Consortium** are high medical quality standards, an improvement in clinical trials and to facilitate further development of NIPT methods. An annual meeting of prenatal medical specialists, gynecologists and human geneticists who use **Prenatalis®**, takes place in Martinsried to discuss the continued development of NIPT procedures.

Specification and Logistics

- Order form
- Signed declaration of consent
- 10 ml BCT blood (collection kits provided)
- Collection by prior arrangement +49 89 895578-0
- Transport box (provided)

Billing according to the German Fee Schedule (GOÄ)

As a medical led laboratory we charge our services in accordance with the German Fee Schedule for Physicians (Gebührenordnung für Ärzte, GOÄ). In certain cases, the costs may be reimbursed by statutory or private health insurances, however, it is advisable to contact health insurers prior to performing the test. A sample letter is available at **www.prenatalis.com**

Literature

[1] Futch et al., Prenat Diagn 33:569 (2013)
[2] Bhatt et al, 13th World Congress in Fetal Medicine (2014)
[3] Bianchi et al, J Med 370:799 (2014)

CENTER FOR HUMAN GENETICS AND LABORATORY DIAGNOSTICS
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Prenatalis®
Trusted medical Quality

Non-Invasive Prenatal Test (NIPT)

accredited according to DIN EN ISO 15189:2014

Prenatalis® – Trusted medical Quality

Non-Invasive Prenatal Test (NIPT) is a non-invasive genetic test which uses modern DNA sequence analysis (Next Generation Sequencing, NGS) for the analysis of aneuploidies, and is performed on cell-free fetal DNA (cffDNA) from the placenta that circulates in maternal blood. The NIPT enables the detection of the most common fetal chromosomal aberrations (trisomy 21, 18, 13 and optionally, gonosomal defects).

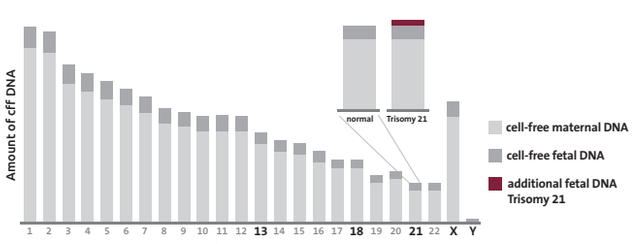
Since mid-2014 **Prenatalis®** NIPT is part of the diagnostics portfolio of the **Center for Human Genetics and Laboratory Diagnostics in Martinsried, Germany.**

- **Prenatalis® test method** is **accredited** according to DIN EN ISO 15189:2014 by **Germany's National Accreditation Body** (Deutsche Akkreditierungsstelle GmbH, DAkkS).
- The test is conducted and analyzed completely under **medical supervision** in the Center for Human Genetics and Laboratory Diagnostics, Martinsried, Germany.

Prenatalis® guarantees high quality medical advice and laboratory analytics and the high professional qualification of all personnel performing the test. A team of scientists and doctors can be consulted with questions at any time. The required genetic counseling can also be undertaken by us.

Test Principle

Cell-free fetal and maternal DNA is isolated from a maternal blood sample, and after enrichment is sequenced by NGS. The statistical evaluation yields an adjusted risk or Normalized Chromosome Value (NCV) with threshold value.

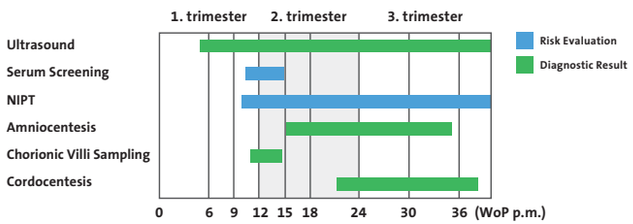


Massive Parallel Sequencing (MPS): Detection, counting and normalization of maternal and fetal chromosomes. Evaluation by means of special algorithm (e.g. SAFeR™, Verinata, Illumina).

Test Procedure

NIPT requires an adequate fraction of fetal DNA against the background of maternal DNA. The NIPT **Prenatalis®** is **possible with a fetal fraction of approximately 2.7 %**. Despite this low detection limit, it is currently recommended **not to take a blood sample** for NIPT **before the 10th week of gestation**.

Use of the NIPT **Prenatalis®** avoids the **procedural risks of invasive prenatal tests** used to detect aneuploidies trisomy 21, 18 and 13 and gonosomal aberrations. A **positive result should always be confirmed by invasive prenatal diagnostics (preferably amniocentesis)**.



Prenatal diagnostics: Invasive and non-invasive testing methods according to the week of gestation.

Benefits and Limitations

Prenatalis® data recorded

Autosomal aneuploidies:	Gonosomal aneuploidies:
Trisomy 21 (Down Syndrome)	45,X (Ullrich-Turner Syndrome)
Trisomy 18 (Edwards Syndrome)	47,XXX (Triple X Syndrome)
Trisomy 13 (Patau Syndrome)	47,XYY (Double Y Syndrome)
	47,XXY (Klinefelter Syndrome)

Prenatalis® NIPT is applicable for single and twin pregnancies as well as pregnancies resulting from in-vitro fertilization (IVF) and can be carried out after the 10th week of gestation.

The established and validated method used by the Center for Human Genetics and Laboratory Diagnostics is based on the Illumina verify® method. **Prenatalis®** does not use enrichment procedures susceptible to faults and instead allows a greater sequencing depth whereby a higher degree of analytical quality is achieved.

CHROMOSOME	SENSITIVITY	SPECIFITY
Trisomy 21	99,14 %	99,94 %
Trisomy 18	98,31 %	99,90 %
Trisomy 13	98,15 %	99,95 %
Monosomy X	95,00 %	99,00 %
Gender classification XX	97,60 %	99,20 %
Gender classification XY	99,10 %	98,90 %

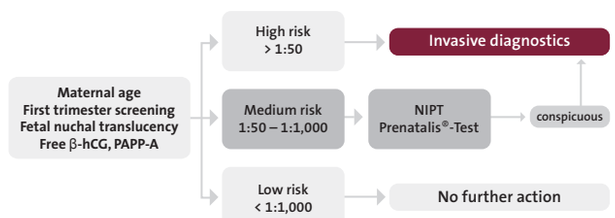
Sensitivity and specificity modified from www.illumina.com

All commercial NIPTs have been validated in high risk cohorts (e.g. women with increased maternal age, abnormal first-trimester screening results). There is also evidence demonstrating the validity of NIPT in low-risk pregnancies. Due to the significantly lower false-positive rate (0.2 % with NIPT vs. 5 % with first trimester screening, FTS), the positive predictive value for trisomy 21 accounts for 45 % with NIPT compared to approximately 4 % with FTS [1, 2, 3].

Despite high sensitivity and specificity, false-positive and false-negative results may occur, which is why the test result cannot be used as a diagnosis at this time.

Currently, **Prenatalis®** can be used to detect only chromosomal trisomies 21, 18, 13 as well as gonosomal aneuploidies. The procedure is not validated for the detection of chromosomal mosaics, translocations, triploidies or other sub-chromosomal changes. Invasive prenatal diagnostics are recommended for all conspicuous NIPT results.

Indication Criteria



Modified from Kagan et al, Ultraschall Med. – Eur. J. Ultrasound 35:229 (2014)

Genetic counseling

According to the German Gene Diagnostics Act (GenDG), genetic counseling is a prerequisite for the performance of a NIPT. As well as patient information, GenDG requires that genetic counseling is performed by a qualified genetic counselor prior to taking the test, and before the results are provided. A transitional arrangement is valid up to July 10, 2016 (see also training courses of the State Medical Council under www.blaek.de). From July 11, 2016, a further 72 hours of training will be required to qualify as a genetic counselor (see also 8th announcement of the German Genetic Diagnostics Commission (GEKO), www.rki.de).

Brochures, forms and further information on Prenatalis® can be found under www.prenatalis.com