www.prenatalgenome.it

GENOMICA
Next Generation Genetics

The first non-invasive prenatal test that screens the whole fetal exome

- Common and rare chromosomal aneuploidies
- Segmental chromosomal abnormalities
- Microdeletion / microduplication syndromes
- Inherited and *de novo* genetic disorders
- Fetal RhD
- Fetal gender
- Parental carrier screening

PRENATALGENOME
GENOMIC NON-INVASIVE PRENATAL TEST

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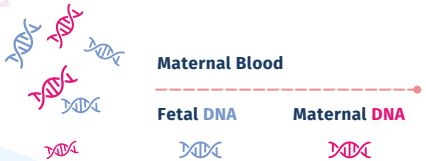
A REVOLUTIONARY NON-INVASIVE PRENATAL TEST

An advanced non-invasive prenatal test (NIPT) that offers an **in-depth screening** of the **entire fetal coding genome** (**exome**). By analyzing circulating cell-free fetal DNA (cfDNA) isolated from a maternal blood sample, **PrenatalGenome** provides a comprehensive evaluation of **genome-wide chromosomal abnormalities** and **severe genetic disorders** in the fetus. This cutting-edge approach delivers **unmatched accuracy and detection capabilities** compared to conventional NIPTs.

During pregnancy, the placenta releases DNA fragments into the maternal bloodstream via a physiological process known as "apoptosis", starting from the 5th week of gestation.

The quantity of this DNA, also named circulating cell-free fetal DNA, increases as the pregnancy progresses, reaching levels sufficient for reliable analysis by the 10th week, providing valuable insights into the fetus's health.



PRENATALGENOME
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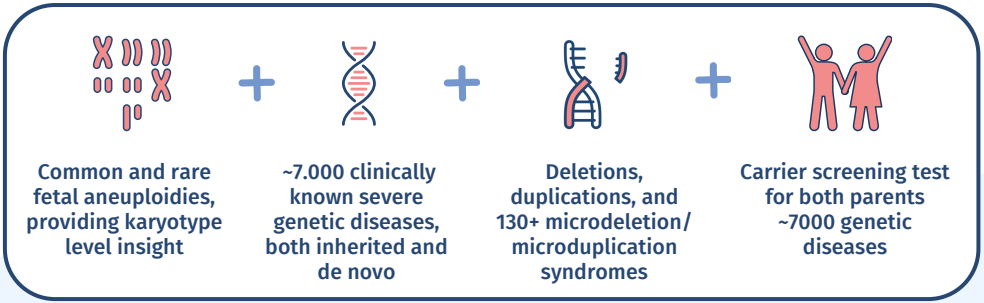
THE MOST ADVANCED AND COMPREHENSIVE NIPT

Traditional NIPT tests are limited by their low resolution to detecting fetal aneuploidies and structural chromosomal abnormalities. **PrenatalGenome** marks a significant technological advancement over conventional NIPT. In addition to identifying common and rare fetal aneuploidies, deletions, duplications, and microdeletion/ microduplication syndromes, it screens for approximately **7,000** clinically recognized **severe genetic diseases**, both **inherited** and ***de novo***. This is achieved through **high-resolution sequencing** of the entire protein-coding **fetal genome** (**exome**), covering over **20,000 genes**. The **PrenatalGenome Plus** screening option also includes a **carrier screening test** for both parents to assess the carrier status of gene mutations related to **~7000 genetic diseases**.

PrenatalGenome offers **unparalleled insight** into fetal genetic health.



PRENATALGENOME Plus

PRENATALGENOME
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THE NEXT LEVEL IN NON-INVASIVE PRENATAL TESTING

24 **CHROMOSOMES ANEUPLOIDY SCREENING**

Screening for common and rare fetal aneuploidies, segmental deletions and duplication§ across the whole fetal genome, providing **karyotype-level** insight.

§ Segmental detetions and duplications >7 Mb

Common chromosomal aneuploidies

Trisomy 21	Trisomy 18	Trisomy 13	
Monosomia X	XXX	XXY	XYY

Rare chromosomal aneuploidies

Trisomy 1	Trisomy 2	Trisomy 3	Trisomy 4
Trisomy 5	Trisomy 6	Trisomy 7	Trisomy 8
Trisomy 9*	Trisomy 10	Trisomy 11	Trisomy 12
Trisomy 14	Trisomy 15	Trisomy 16*	Trisomy 17
Trisomy 19	Trisomy 20	Trisomy 22*	

*With higher incidence among the less common fetal aneuploidies

>130 **MICRODELETION/MICRODUPLICATION SYNDROMES**

as low as 1 Mb

The complete list can be consulted by scanning the QR Code.

Most common microdeletion/microduplication syndromes	Cytogenetic region
22q11 deletion syndrome (Velocardiofacial / DiGeorge syndrome)	22q11.2
Cri du Chat Syndrome (5p deletion)	5p15.3
Prader-Willi syndrome (Type 1)	15q11.2-q13.1
Angelman syndrome (Type 1)	15q11.2-q13.1
rader-Willi Syndrome (Type 2)	15q11.2-q13.1
Angelman syndrome (Type 2)	15q11.2-q13.1
1p36 microdeletion syndrome	1p36
Wolf-Hirschhorn syndrome (4p16.3 deletion syndrome)	4p16.3
Jacobsen syndrome (11q deletion syndrome)	11q23.3-q24.3
Smith-Magenis Syndrome	17p11.2
16p11.2-p12.2 microdeletion syndrome	16p11.2-p12.2
2q33.1 deletion syndrome	2q33.1

Most common microdeletion/microduplication syndromes	Cytogenetic region
8p23.1 deletion syndrome	8p23.1
12q14 microdeletion syndrome	12q14
Miller-Dieker microdeletion syndrome (MDS)	17p13.3
2p15-16.1 microdeletion syndrome	2p15-p16.1
Potocki-Shaffer microdeletion syndrome	11p11.2
18q deletion syndrome	18q22.3-q23
Witteveen-Kolk syndrome (15q24 Deletion)	15q24.2
Glass syndrome (2q32-q33 deletion syndrome)	2q32-q33
17q23.1-q23.2 deletion syndrome	17q23.1-q23.2
6q25 microdeletion syndrome	6q25.2-q25.3
Phelan-McDermid syndrome (22q13.3 deletion syndrome)	22q13
2q37 deletion syndrome	2q37.2

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~ 7.000
Genetic disorders

~20.000
Genes

Over **20,000** protein-coding genes make up the exome. Mutations in approximately 5,000 of these genes are associated with about **7,000** genetic diseases with known phenotypes.

By analyzing the entire coding fetal genome (exome), the **PrenatalGenome** test enables screening of thousands of clinically recognized genetic diseases in the fetus.

The complete list can be consulted by scanning the QR Code.

GENETIC DISEASES OF DE NOVO ORIGIN

***De novo* genetic diseases** arise from random mutations in the fetal exome that are absent in the parents, making them undetectable through pre-conception carrier screening tests. These mutations can lead to conditions such as skeletal dysplasias, congenital heart defects, multiple congenital anomalies, autism, epilepsy, and/or intellectual disabilities. Many of these conditions are often not detectable by ultrasound, especially in early pregnancy.

PrenatalGenome effectively detects *de novo* genetic diseases, which have a cumulative incidence of approximately 1 in 600, increasing to 1 in 300 for conditions linked to developmental delays[1-2].

INHERITED GENETIC DISEASES

Inherited genetic diseases result from mutations in the fetal exome passed down from carrier parents, often unaware of their status. **PrenatalGenome** enables the detection of mutations responsible for thousands of inherited genetic conditions.

The analysis of the fetal exome increases the detection rate by approximately 30% compared to other prenatal diagnostic techniques. It is especially recommended for pregnancies involving fetal structural anomalies.[3-4]

1. Zhang J, et al. Non-invasive prenatal sequencing for multiple Mendelian monogenic disorders using circulating cell-free fetal DNA. Nat Med. 2019;25:439-447.
2. McRae J, et al. Prevalence and architecture of de novo mutatians in develapmental disarders. Nature 2017: 542:433-438.
3. Van den Veyver IB, et al. International Society for Prenatal Diagnosis updated position statement on the use of genome-wide sequencing for prenatal diagnosis. Prenat Diagn. 2022;42:796-803.
4. Mellis R, et al.. Diagnostic yield of exome sequencing for prenatal diagnosis of fetal structural anomalies: a systematic review and meta-analysis. Prenat Diagn. 2022;42:662-685.

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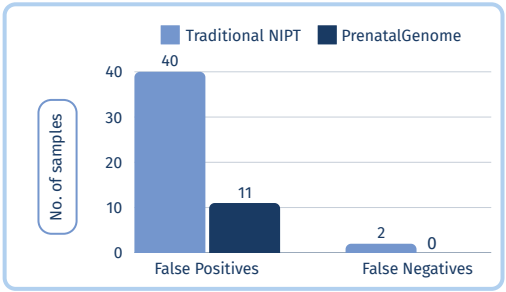
TEST PERFORMANCE

Chromosomal abnormalities

Performance parameters	Traditional NIPTs*	PrenatalGenome Preformance
True Negatives	85	114
False Negatives	2	0
True Positives	123	125
False Positives	40	11
Sensitivity	98.4%	100%
Specificity	68.0%	91.2%
Positive predictive value	75.5%	91.9%
Negative predictive value	97.7%	100%

*Low resolution NIPT (~9.6M reads)



SUPERIOR SENSITIVITY AND SPECIFICITY COMPARED TO TRADITIONAL NIPT

A pre-clinical validation study assessed the performance of **PrenatalGenome** in detecting chromosomal abnormalities, including common and rare aneuploidies, as well as structural chromosomal alterations (e.g. deletions/duplications and microdeletion/microduplication syndromes). This study included 250 plasma samples from pregnant women previously tested with low-resolution traditional NIPT, with results confirmed by invasive prenatal diagnostic techniques such as amniocentesis or chorionic villus sampling.

PrenatalGenome demonstrated **superior sensitivity and specificity**, significantly reducing false positives (40 vs. 11) and false negatives (2 vs. 0) compared to traditional NIPT. Overall, the test achieved **100% sensitivity** (versus 98.4% for traditional NIPT, $p < 0.001$) and significantly **improved specificity at 91.2%** (compared to 68.0% for traditional NIPT, $p < 0.001$).*

*Results obtained from the preclinical validation study of the test

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TEST PERFORMANCE

Genetic Disorders

Performance parameters	Targeted NIPT SGD	95% CI	PrenatalGenome	95% CI
True Negatives	122		125	
False Negatives	0		0	
True Positives	125		125	
False Positives	3		0	
Sensitivity	100%	97.09% - 100%	100%	97.09% - 100%
Specificity	96.0%	93.15% - 99.50%	100%	97.09% - 100%
Positive predictive value	96.2%	93.15% - 99.50%	100%	97.09% - 100%
Negative predictive value	100%	97.02- 100%	100%	97.09% - 100%

HIGH SENSITIVITY AND SPECIFICITY IN DETECTING SEVERE GENETIC DISEASES IN THE FETUS

PrenatalGenome 's ability to identify mutations responsible for severe genetic diseases, both inherited and *de novo*, was confirmed through a retrospective analysis of 250 plasma samples. These samples were obtained from pregnant women who had previously undergone non-invasive prenatal screening for a panel of 79 genetic diseases (targeted SGD NIPT). Results were confirmed using invasive prenatal diagnostic techniques.
PrenatalGenome achieved **100% sensitivity** (95% CI: 97.1–100%) and **100% specificity** (95% CI: 97.1–100%) in detecting pathogenic *de novo* and paternally inherited mutations.*

*Results obtained from the preclinical validation study of the test

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A GROUNDBREAKING TECHNOLOGY FOR REVOLUTIONARY SCREENING

Utilizing the advanced **deep whole exome sequencing technology**[5-6], combined with **sophisticated bioinformatic analysis** using a proprietary algorithm, enables **PrenatalGenome** enables a comprehensive study of the fetal karyotype and the screening of thousands of severe inherited or *de novo* genetic diseases in a single analysis. This level of detail was previously achievable only through invasive prenatal diagnostic methods.

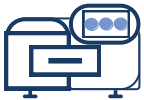
1

CfDNA extraction

2

Library prep and exome capture

3



Deep fetal exome sequencing by *Next Generation Sequencing* (>500X)

5. Brand H, Whelan CW, Duyzend M, et al. High-resolution and noninvasive fetal exome screening. N Engl J Med. 2023;389:2014-2016.
6. Miceikaitė I, Hao Q, Brasch-Andersen C, et al. Comprehensive Noninvasive Fetal Screening by Deep Trio-Exome Sequencing. N Engl J Med. 2023;389:2017-2019.

4 **Screening for chromosomal aneuploidies and structural aberrations**

5 **CfDNA mutation analysis**

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The high resolution of the test allows for a low limit of detection (LOD)

highly accurate at 1% of **Fetal Fraction**

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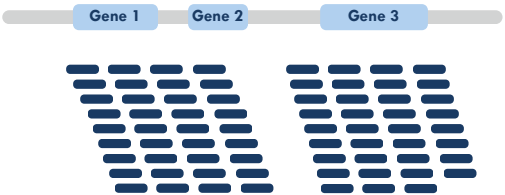
HIGH RESOLUTION FOR SUPERIOR PERFORMANCE

Traditional NIPTs

PrenatalGenome



Traditional NIPTs use **low-depth sequencing** (coverage **0.1X**), which limits their detection capabilities to chromosomal abnormalities, because of the **limited coverage** of the gene regions.

PrenatalGenome employs **ultra-high-resolution sequencing** with a read depth exceeding **500X—**more than **5,000 times greater** than traditional NIPTs. This ensures comprehensive coverage of the fetal genome, enabling also the detection of **~7,000** clinically recognized **severe genetic diseases**, both **inherited** or ***de novo***, with greater reliability and improved performance.

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THE ADVANTAGES OF HIGH-RESOLUTION NIPT

HIGH SENSITIVITY

- Improved detection rate
- Reduced incidence of false negatives

HIGH SPECIFICITY

- Reduced incidence of false positives
- Fewer invasive prenatal follow-ups (amniocentesis or CVS)

RELIABLE RESULTS AT LOW FETAL FRACTION (FF)

- Improved detection rate for samples with low FF
- Reduced need for retesting
- Better option for patients with high BMI

MOSAICISM

- Identifies placental/ fetal mosaicism
- Lower incidence of false positives

IMPROVED DATA QUALITY

- Lower incidence of inconclusive results
- Fewer retests required
- Better option for cases involving medications that affect data quality (e.g., high background noise)

GENETIC DISEASES DETECTION

- Comprehensive coverage of coding regions of the fetal exome
- Detects mutations causing genetic diseases, both inherited or *de novo*

SEGMENTAL CHROMOSOMAL IMBALANCES

- Superior performance in detecting segmental anomalies
- Increased sensitivity and specificity
- Lower incidence of false negatives and positives

MICRODELETIONS/ MICRODUPLICATIONS

- Detects microdeletions as small as 1 Mb
- Improved detection rate
- Reduced incidence of false negatives and positives

Higher sequencing coverage enhances the reliability of test results, improving overall test performance. **PrenatalGenome** offers **unmatched resolution**, providing a more detailed and accurate assessment of fetal genetic health.

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THE TEST REPORT

The test result may be **negative**, indicating that no chromosomal anomalies or genetic diseases were detected in the fetus, within the limits of the methodology used. In this case, the pregnancy can proceed without futher follow-up.

In some cases, the test result may be **positive**, indicating an **higher risk** for a chromosomal abnormality or a genetic disease in the fetus. Such instances require follow-up with invasive prenatal diagnostic techniques (amniocentesis or chorionic villus sampling) to confirm the findings.

Follow-Up for Positive Results

Amniocentesis or chorionic villus sampling to confirm the detected chromosomal anomaly or genetic disease.

Complimentary services

- Refund in cases of entirely inconclusive test results
- Free Pre- and Post-test genetic counseling

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A TEST THAT MEETS THE HIGHEST QUALITY STANDARDS

SIMPLE
A simple blood sample (8-10 ml) collected at 10^ weeks of gestation is required

RELIABLE
Sensitivity and specificity >99%

SENSITIVE
Low limit of detection: highly accurate at low cfDNA quantity (FF:1%)

COMPLETE
Detection of both genome-wide chromosomal abnormalities and single gene disorders, providing the most comprehensive information available from a noninvasive prenatal test to date

ADVANCED
Groundbreaking technologies and advanced bioinformatic analysis

VALIDATED
Pre-clinical validation studies performed on a wide cohort of pregnant women

INDICATION FOR TESTING

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SUITABLE FOR ANY PREGNANCY

PrenatalGenome is suitable for a wide range of pregnancies, including:

- Pregnant women under and over 35 years of age
- Situations where invasive prenatal testing is contraindicated
- Singleton and twin pregnancies, whether naturally conceived or through assisted reproductive technologies
- Pregnancies with abnormal ultrasound findings
- Pregnancies requiring risk assessment for genetic diseases
- Family history of chromosomal aneuploidy or genetic conditions
- Couples where one partner is a balanced chromosomal translocation carrier
- Couples who are genetic disease carriers

PrenatalGenome is recommended for all types of pregnancies, providing tailored solutions for various needs, from singleton or twin pregnancies to those conceived naturally or through IVF. It is particularly valuable for couples with a history of genetic diseases and is also indicated for pregnancies without specific a priori risks.

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How to perform the test

1. Request the shipping kit
2. Fill in the test requisition form
3. Collect blood samples
4. Ship the samples to Genomica
5. Receive results

Samples required

Maternal blood sample
(Streck tube)

+

Paternal blood sample
(EDTA tube)
or
Buccal swab

Turnaround Times

15 working days

GENOMICA
Next Generation Genetics

Leading diagnostic laboratory and research center of excellence specializing in genetics and molecular diagnostics.

GENOMICA is a highly innovative company with extensive technical and scientific expertise, active in both clinical applications and research. Supported by a team with over 20 years of experience in molecular diagnostics, GENOMICA combines cutting-edge technology with a strong commitment to innovation, delivering increasingly accurate and accessible diagnostic services.

Over **100.000 genetic tests/year**

Laboratories with **groundbreaking technologies** and high quality standards

Dedicated **R&D Team**

International **Partnerships**

Personalized genetic counseling with genetic counselors experts in discussing genetic test results and familial risks

20+ years experience in prenatal molecular diagnostics

PrenatalGenome ENG M rev.00

LABORATORIES

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Visit the website dedicated to the test