INFORMATION SHEET ON NON-INVASIVE PRENATAL SCREENING TEST (NIPT) FOR THE DETECTION OF ANEUPLOIDIES, CHROMOSOMAL REARRANGEMENTS, AND CERTAIN FETAL GENETIC DISEASES THROUGH THE ANALYSIS OF CELL-FREE FETAL DNA IN MATERNAL BLOOD.

TEST DETAILS:

The PrequelNIPT® test is performed on cell-free fetal DNA (cffDNA) isolated from maternal blood using massive parallel sequencing (MPS) through Next Generation Sequencing (NGS) technology (Illumina). The test is validated for pregnancies with a gestational age of at least 10 weeks. Additionally, conditions caused by other molecular mechanisms cannot be detected with this test. Limit of detection (LOD) of the method: fetal fraction equal to or greater than 2%. If the fetal fraction is insufficient or the obtained data do not meet other QC checks, a new sample will be requested to repeat the analysis.

THE PREQUELNIPT® TESTS:

PrequelNIPT® Basic is designed to detect common trisomies on chromosomes 21, 18, and 13.

PrequelNIPT® 5 is designed to detect common trisomies on chromosomes 21, 18, and 13, as well as sex chromosome abnormalities (trisomy X associated with Triple X syndrome, disomy Y associated with Jacobs syndrome, disomy X in a male fetus associated with Klinefelter syndrome, monosomy X associated with Turner syndrome).

PrequelNIPT® 5 Advance is designed to detect common trisomies on chromosomes 21, 18, 13, 9, and 16; sex chromosome abnormalities (trisomy X associated with Triple X syndrome, disomy Y associated with Jacobs syndrome, disomy X in a male fetus associated with Klinefelter syndrome, monosomy X associated with Turner syndrome); and microdeletions <7Mb including the following specific microdeletions: 1p36 (1p36 deletion syndrome), 4p- (Wolf-Hirschhorn syndrome), 5p- (Cri-du-Chat syndrome), 15q11.2 (Prader-Willi/Angelman syndrome) and, 22q11.2 (DiGeorge syndrome).

PrequelNIPT® 5 Di George is designed to detect common trisomies on chromosomes 21, 18, and 13; sex chromosome abnormalities (trisomy X associated with Triple X syndrome, disomy Y associated with Jacobs syndrome, disomy X in a male fetus associated with Klinefelter syndrome, monosomy X associated with Turner syndrome); and 22q11.2 microdeletion syndrome (DiGeorge syndrome).

PrequelNIPT® Karyo is designed to detect common trisomies on chromosomes 21, 18, and 13; sex chromosome abnormalities (trisomy X associated with Triple X syndrome, disomy Y associated with Jacobs syndrome, disomy X in a male fetus associated with Klinefelter syndrome, monosomy X associated with Turner syndrome); and rare autosomal aneuploidies: trisomies of all chromosomes other than those listed as common trisomies, deletions and duplications ≥7Mb, including all segmental chromosomal anomalies involving part of a chromosome.

PrequelNIPT® Karyo Advance is designed to detect common trisomies on chromosomes 21, 18, and 13; sex chromosome abnormalities (trisomy X associated with Triple X syndrome, disomy Y associated with Jacobs syndrome, disomy X in a male fetus associated with Klinefelter syndrome, monosomy X associated with Turner syndrome); rare autosomal aneuploidies (trisomies of all chromosomes other than those listed as common), deletions and duplications ≥7Mb including all segmental chromosomal anomalies involving part of a chromosome, and microdeletions <7Mb, including the following specific microdeletions: 1p36 (1p36 deletion syndrome), 4p- (Wolf-Hirschhorn syndrome), 5p- (Cri-du-Chat syndrome), 15q11.2 (Prader-Willi/Angelman syndrome), 22q11.2 (DiGeorge syndrome), 8q24 (Langer-Giedion syndrome), 11q23 (Jacobsen syndrome) and, 17p11.2 (Smith-Magenis syndrome).

The **PrequelNIPT® Risk 100 and PrequelNIPT® Risk 100 Advance tests,** which combine the capabilities of PrequelNIPT® Karyo and PrequelNIPT® Karyo Advance with the genetic analysis provided by **the Prequel 100 Gene Analysis test**, allow for the identification of the probability that the fetus is affected by 100 severe inherited genetic disorders (such as cystic fibrosis, beta-thalassemia, etc.). A complete list of the 100 monogenic diseases and the mutations analyzed in the parents is available at the following link**: https://bit.ly/VERAgeneMutations**

The **PrequelNIPT® MonoGene** and **PrequelNIPT® MonoGene Advance tests** combine the capabilities of **PrequelNIPT® Karyo** and **PrequelNIPT® Karyo Advance** with the ability to analyze **102 inherited monogenic disorders and De Novo** in the fetus. A complete list of the 102 monogenic diseases analyzed is available at the following link: https://drive.google.com/file/d/1IhSw68F0bNRC3w3a-8F-10pinfJj9spp/view?usp=sharing

The **PrequelNIPT® Total** and **PrequelNIPT® Total Advance tests** combine the capabilities of **PrequelNIPT® Karyo** and **PrequelNIPT® Karyo Advance** with the ability to analyze **102 inherited monogenic disorders and De Novo** in the fetus and to perform a **carrier screening test** on the mother. A complete list of the 102 monogenic diseases analyzed is available at the following link: https://drive.google.com/file/d/1IhSw68F0bNRC3w3a-8F-10pinfJj9spp/view?usp=sharing.The disorders analyzed in the maternal sample are: Cystic fibrosis (CFTR gene), congenital deafness (GJB2 gene), spinal muscular atrophy (SMN1 gene), Duchenne muscular dystrophy (DMD gene), and Fragile X syndrome (FMR1 gene).

The **PrequelNIPT® Total Family test** combines the capabilities of **PrequelNIPT® Karyo Advance** with the ability to analyze **50 De Novo monogenic disorders** in the fetus and to perform **carrier screening on both parents**, involving the analysis of **over 900 genes related to more than 1300 genetic disorders**. A complete list of the 50 De Novo monogenic disorders analyzed in the fetus is available at the following link: https://drive.google.com/file/d/1seRF4Mf8yl0AXhLpD1eygYTCy5knE075/view?usp=sharing. A complete list of the 900+ genes and 1300+ monogenic diseases analyzed in the parents is available at the following link: https://drive.google.com/file/d/1k6Junw7hGL3Bk2mnci-hfJb9dBAy0w9m/view?usp=drive_link

This test represents the most comprehensive level of information currently available during pregnancy through non-invasive prenatal screening.

A copy of the original report has been retained by the laboratory and is available upon request.

TEST LIMITATIONS

NIPT is a screening test with a residual risk of false positive and false negative results (<0.1%) and is neither intended nor validated for diagnosis. This test is not validated for pregnancies with more than two fetuses and is not designed to detect chromosomal mosaicisms and triploidies. This test is not intended to identify pregnancies at risk for open neural tube defects. The result of this test does not exclude the possibility that the chromosomes harbour abnormalities other than those included in the test, and it does not detect abnormalities of untested chromosomes, genetic disorders, birth defects or congenital complications of other origin. A low-chance result does not completely exclude the presence of one of the chromosomal abnormalities investigated. The test result may not reflect the real state of the fetus, as it can detect chromosomal abnormalities arising from confined placental mosaicisms, vanishing twin or maternal condition. When an aneuploidy result is detected in a twin pregnancy, the status of each individual fetus cannot be determined. Although the presence or absence of Y chromosome material can be reported in a twin pregnancy, the detection of sex chromosome aneuploidies such as Monosomy X, XXX, XXY, and XYY is not possible. The results of the test can be confounded by certain maternal and fetal factors including but not limited to: recent maternal blood transfusion; maternal organ transplant; maternal surgical procedure; maternal immunotherapy, stem cell therapy; maternal malignancy; maternal mosaicism; fetal placental mosaicism; fetal demise; nonviable twin.

SENSITIVITY AND SPECIFICITY

The concordance of the test for trisomy 13, trisomy 18, and trisomy 21 is 99.9% for singleton pregnancies (Pertile et al., 2021). For fetal sex determination, the concordance was 100% for both “female” and “male” (based on the physical examination of the newborn) and for XX and XY (based on cytogenetic results). Sequencing data were generated using the Illumina NextSeq 550Dx platform. Bioinformatics and data analysis were performed using the VeriSeq NIPT Assay v2.0 software (Illumina).

PREQUEL GENETICS®

INFORMATION SHEET AND CONSENT FORM

PLEASE WRITE CLEARLY USING CAPITAL LETTERS

PATIENT CONSENT PERFORMING GENETIC ANALYSIS

The undersigned _____

Date of birth_____ Place of birth_____

Resident in _____ Address _____ Zip code _____

ID: _____ No. _____

Issued on _____ by

_____

Telephone: _____ e-mail: _____

I DECLARE

That I understood the test limitations described below:

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I confirm that, during the meeting with Dr.or Healthcare Professional _____ on the date _____, I was provided with detailed information regarding the genetic analysis I am about to undergo. I have understood and considered all aspects of the exam, as well as the benefits and purpose of the genetic test, including its potential limitations. I had the opportunity to ask any questions I deemed necessary and received answers I consider to be comprehensive. In particular:

- I consent to the test I have chosen, understand where my test will be processed and confirm that I have been informed about the purpose, scope and limitations of the test by my healthcare provider.
- I understand this is a screening test for selected abnormalities and that results do not exclude the possibility of other abnormalities that have not specifically been screened for.
- I understand that the results should be reviewed by my healthcare provider.
- I have had the opportunity to ask questions, I have received the patient information leaflet and understand I can request further information and genetic counselling.
- I agree that my personal data may be used for auditing and quality control purposes and understand I can withdraw my consent at any point.
- I consent to the use of leftover specimen and for anonymised health information to be stored and used for the development or enhancement of future non-invasive testing.

Date_____/_____/_____ Patient signature: _____

THEREFORE I AUTHORISE

Take note that the processing of my personal data and details are processed pursuant to art. 7 and 9, par. 2, lett. a) of Reg. EU 2016-679. The data **will not be disclosed or transferred to third parties** and used only for the purposes of diagnosis and treatment as described in the information.

Date_____/_____/_____ Patient signature: _____

I **RELEASE MY CONSENT** to the processing of data pursuant to Article 7 of GDPR 2016/679 and **AUTHORIZE** to provide news related the genetic investigations to:

- Relatives (first and last name)
  _____
- Physician (first and last name)
  _____