Niptify®
Non-Invasive Prenatal screening Test (NIPT)

13 18 21 XO XXX XXY XYY Mito

Sample ID (*example AA000N*)

Celvia CC AS
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INFORMED CONSENT

NIPTIFY Focus Plus is a CE-IVD marked screening test assessing fetal chromosomal disease risk from 10+ weeks of gestation. For the analysis, up to two tubes of venous blood are taken from the pregnant woman. The test evaluates the risk of trisomy of chromosomes 13 (**Patau syndrome**), 18 (**Edwards syndrome**), 21 (**Down syndrome**), absence of one X chromosome in a female fetus (**Turner syndrome** or monosomy X), and microdeletion 22q11 (**DiGeorge syndrome**) in the fetus. If desired, the **chromosomal sex of the fetus** is determined.

The sensitivity of the NIPTIFY test is greater than 99.9% for trisomies 21, 18, and 13, monosomy X, and 22q11 microdeletion*. The test's specificity is more than 99.9% for trisomies 21 and 18 and microdeletion 22q11. The test's specificity is 99.2% for monosomy X and trisomy 13.

GENOME-WIDE STUDY and INCIDENTAL FINDINGS

NIPTIFY performs a genome-wide study and has the power to identify copy-number variances in entire chromosomes (trisomies or monosomies), deletions and duplications in clinically significant regions (microdeletions or microduplications), and point mutations in mitochondrial DNA. There are five types of conditions under analysis:

1) **trisomy or monosomy** in autosomal chromosomes other than 13, 18, 21.
2) **sex chromosome aneuploidies** like Klinefelter (XXY), Jacobs (XYY), or triple X (XXX) syndromes.
3) **segmental aneuploidies** in chromosomes 13, 18, 21, i.e. partial trisomy or monosomy of a chromosome.
4) **microdeletions and microduplications** larger than 1 Mb. The 18 most clinically relevant and frequent regions are analyzed.
5) **DNA point mutations in mitochondrial DNA**. With some mitochondrial DNA mutations (1095T>C, 1494C>T, and 1555A>G), the patient may develop hearing loss and deafness when treated with antibiotics of the aminoglycoside class. Alternative antibiotics can be used if the mutation is present.

NIPTIFY reports such cases as **incidental findings ONLY IF** a high risk of the condition or mutation is detected. More information about regions, conditions and risks can be found at **NIPTIFY.com/results.**

RESULTS

NIPTIFY results are sent to the clinician no later than 10 working days after the blood sample arrives at the Celvia medical laboratory. The test result and the need for subsequent analysis must be explained to the patient by a doctor, midwife, or medical geneticist. The test can give the following results:

Low risk. The result shows that no trisomy 13, 18, 21, monosomy X, or 22q11 microdeletion was detected in the sample. The probability that the fetus will have the chromosomal disorder is very low. The pregnancy will be monitored as usual.

High risk. The result shows that the fetus has a high probability of trisomy 13, 18, 21, monosomy X, or 22q11 microdeletion. Patients with a high-risk result should be counseled by a doctor or medical geneticist, who will make decisions with the patient about the additional tests needed. Decisions about the subsequent course of the pregnancy should not be made based on the NIPTIFY results alone. An invasive diagnostic test (amniocentesis) should confirm high-risk chromosomal disease results.

Incidental findings. The fetus has been identified as being at high risk for a clinically significant incidental finding. In this case, the patient must be advised by a doctor or medical geneticist, who will make decisions with the patient about the additional tests needed. Decisions about the subsequent course of the pregnancy should not be made based on the NIPTIFY results alone, as the high risk should be confirmed by an ultrasound or an invasive diagnostic test (amniocentesis). Identifying the aforementioned three point mutations in mitochondrial DNA helps to avoid the use of antibiotics of the aminoglycoside class, which can cause hearing loss or deafness in the mutation carrier. Mitochondrial DNA mutations are inherited by children only from the mother. Thus, the information is useful for the mother and her children to avoid possible hearing loss or deafness caused by aminoglycoside antibiotics.

Unable to determine. Based on the blood sample, it was not possible to reliably assess the risk of chromosomal diseases (less than 0.5% of cases). The patient can give a new blood sample for NIPTIFY retesting. One retest is free for the patient. More information at **NIPTIFY.com**

METHODS

During the NIPTIFY test, cell-free DNA isolated from a pregnant woman's blood sample is analyzed with the Focus Plus method (*Fragmented DNA Compact Sequencing Assay for enriched fetal material*) and sequenced with Illumina technology. The risk estimates for fetal chromosomal diseases are calculated based on whole genome data.

RISKS AND LIMITATIONS ARISING FROM THE METHODOLOGY

NIPTIFY does not substitute ultrasound, or serum screening and is not a diagnostic test. Therefore, the possibility of false-negative or false-positive results remains. The test can give false results for various clinical reasons such as placental or maternal mosaicism, chromosomal abnormalities if the mother has a tumor, the mother is a carrier of a studied aneuploidy or other biological and technical reasons. A test result with a low risk of chromosomal disease does not exclude other abnormalities of fetal development detected by ultrasound examination. NIPTIFY does not provide information about fetal developmental disorders such as brain or heart developmental disorders, spine developmental disorders, fetal growth disorders, etc. NIPTIFY cannot detect mosaicism, balanced translocations, and monogenic point mutation diseases, except for three point mutations in mitochondrial DNA. The NIPTIFY test cannot be performed in multiple pregnancies or if the patient has been diagnosed with a malignancy during the current pregnancy. More information at **NIPTIFY.com**

* The sensitivity of determining the DiGeorge microdeletion (22q11) has been validated based on a limited number of control samples. Based on the scientific literature, the expected sensitivity of the NIPT test for 22q11 determination is 75-100%.

I confirm that I have read the information on the consent form and I agree to give a blood sample for the NIPTIFY test.

.....
Patient's signature

TEST ORDERING FORM

Fill it in only if you didn't order electronically

First name and surname of the patient

Patient personal ID or date of birth

Single pregnancy? ☐ YES

Do we report the sex of the fetus? ☐ YES ☐ NO

Pregnancy week (*example 10+4*)

Date of blood sampling (*dd/mm/yyyy*)

Clinician's name

Clinician's phone number

Clinician's e-mail

I confirm that I am ordering the NIPTIFY Focus Plus test at the patient's request. I confirm that the patient has been informed about the possible results, risks, and limitations of the NIPTIFY test. I confirm that the presented data is correct.

☐ If a high risk is detected, I confirm the patient's request to report **incidental findings** under the terms described in the informed consent.

.....
Clinician's signature

.....
Date

The document is in **three copies**. One is sent to the Celvia medical laboratory, clinician keeps another, and the third is for the patient.