GENESIS GENOMA LAB
Γενετική διάγνωση • Κλινική Γενετική • Έρευνα

GENOMA®
Molecular Genetics Laboratories Group

CONFIDENTIAL

MEDSANA

PATIENT'S DETAILS	
Name:	
Surname:	
Father's Name:	Husband's Surname:
Date of Birth:	Place:
Address:	P.C.:
Tel.:	email:
Date of blood withdraw:	
Doctor's Name:	
Address:	P.C.:
Tel.:	email:

REFERRING CLINICIAN/ LABORATORY

Name/ Stamp

MEDICAL HISTORY

PREGNANCY HISTORY

Patient current weight (kg): ..... Height:.....

Gestational age at draw: ..... weeks + ... days

Gestational age calculated by:

☐ ultrasound ☐ last menstrual cycle ☐ IVF treatment

Twin pregnancy ☐ YES ☐ NO IVF pregnancy ☐ YES ☐ NO

☐ Homologous Pregnancy ☐ Heterologous Pregnancy

☐ Embryo donation ☐ Egg donation ☐ Sperm donation

INDICATION FOR TESTING

☐ Advanced maternal age ☐ Parental anxiety (low-risk)

☐ Abnormal ultrasound (describe) .....

☐ Previous pregnancy with aneuploidy

☐ Abnormal maternal serum screening test

☐ Other :.....

☐ None

TYPE OF TEST

☐ For Singleton prengnancy: ☐ FAST Protocol[1]

☐ **PrenatalSAFE® 3** (chromosomes 21, 18, 13 only)[1]

☐ **PrenatalSAFE® 5** (chromosomes 21, 18, 13, X, Y)[1]

☐ **PrenatalSAFE® Plus** (chromosomes 21, 18, 13, X, Y) **+**

☐ panel 6 microdeletions* ☐ Trisomies 9 and 16 option

☐ **PrenatalSAFE® Karyo** (genome-wide NIPT that provides karyotype level insight)

☐ **PrenatalSAFE® Karyo Plus** (genome-wide NIPT that provides karyotype level insight + panel 9 microdeletions**

☐ **RhSAFE®**

Do you wish to know the fetal gender? ☐ YES ☐ NO

Is it a redraw? ☐ YES ☐ NO

☐ For Twin Pregnancy: ☐ FAST protocol[1]

☐ **PrenatalSAFE® 3** (chromosomes 21, 18, 13 only)[1]

☐ Presence of Y option

☐ **PrenatalSAFE® Karyo** (genome-wide NIPT that provides karyotype level insight)

* This option includes the following syndromes: 22q21 deletion (DiGeorge), 15q11 deletion (Angelman/ Prader-Willi), 1p36 deletion, 4p- (Wolf-Hirschhorn), 5p- (Cri-du-chat)

** The following syndromes are also included: 11q23 deletion (Jacobsen), 8q24 deletion (Langer-Giedion), 17p11.2 deletion (Smith-Magenis)

CHECK LIST

Please check if you provided the following information:

☐ Patient's details

☐ Pregnancy history

☐ If you wish to know the fetal gender

☐ If it is a redraw

REPORTING PREFERENCES

I ask and consent that the results of the test to be given to me by Medsana Laboratory through:

☐ **the referring clinician**

☐ e-mail ☐ FAX ☐ mail

I ask and consent for the above requested test to be performed:

Signature:. .....

☐ Reporting preferences

☐ Informed consent

Test Submission Instructions

IMPORTANT: Fill in all required Test Requisition Form information to avoid delays and ensure timely reporting.
To ensure acceptance of your patient's sample for testing, please verify that the informed consent has been signed by the patient and it has been enclosed with samples

Sample collection instructions

- Write the blood **collection date** in the specimen information section of the test requisition form
- Take the 10ml collection tube from the PrenatalSafe® Test Shiper Kit.
- Write the **patient's full name** and **date of birth** on the collection tube label.
- Fill the collection tube <u>almost completely</u> with whole blood.
- Invert the collection tube **10 times**.

Store collected blood at room temperature until ready for shipment.
Blood should never be frozen!
Medsana Laboratory must receive the sample on the withdraw day. The schedule of collection/receiving the samples for the test is from Monday to Thursday, 08.30-14.00.

Sample packaging and shipment

IMPORTANT: Always store kits at room temperature!

- Place the filled and properly labeled collection tube into the PrenatalSafe® shiper kit box
  Only one patient sample per box!
- Place the completed test requisition form and informed consent into the shipper kit box, at the side and close box
- Send or deliver the Shiper kit box to **Medsana Laboratory**
- **Medsana Laboratory MUST receive the sample on the collection day.**

PATIENT CONSENT FORM
PrenatalSafe® Non-Invasive Prenatal Test (NIPT)

This blood test is designed to measure the combined maternal and fetal DNA present in maternal blood, and is considered a genetic test. Your written consent is required to perform a genetic test. This consent form provides information about the PrenatalSafe® prenatal test, including what the
test is for, the testing process, and what results may mean. Before signing this document, you should ask your attending physician to answer any questions you may have about this test.

About the PrenatalSafe® prenatal test

The PrenatalSafe® Non-Invasive Prenatal Test (NIPT) looks at the DNA (genetic material) in your blood.

The **PrenatalSafe® 3** test can tell if there are too many or too few copies (also called an "aneuploidy") of certain chromosomes—21, 18, and 13—present in your fetus. This test is available for singleton and twin pregnancies.

The **PrenatalSafe® 5** test can tell if there are too many or too few copies (also called an "aneuploidy") of certain chromosomes—21, 18, and 13—present in your fetus. The test can also look at sex chromosomes (X and Y), and can determine if there are too many or too few copies of the sex chromosomes.

The **PrenatalSafe® Plus** can also test for trisomies (too many copies) of chromosomes 9 and 16, as well as 6 microdeletions of certain chromosomes, which are listed below.

The **PrenatalSafe® Karyo** analyzes every chromosome in the genome, providing karyotype-level insight. Though not a fetal karyotype, it offers a level of information previously only available from a karyotype analysis. It provides information about gains or losses of chromosome material e 10 Mb across the genome.

The **PrenatalSafe® Karyo Plus** test analyzes every chromosome in the genome as well as 9 clinically significant microdeletion regions, which are listed below.

The PrenatalSafe® prenatal test is performed on a maternal blood sample which contains DNA (genetic material) from both the mother and fetus. It is available for women who are at least 10 weeks pregnant. This screening test can detect over 99% of the abnormalities evaluated for chromosomes 21, 18 and 13 and about 95% of cases of Monosomy X (see list below).

The PrenatalSafe® prenatal test has been studied in patients who have an increased risk for having a baby with an incorrect change in the number of certain chromosomes.

Your attending physician will determine if this test is appropriate for you and can provide you with more details about the chromosome abnormalities being evaluated.

Chromosome abnormalities evaluated with PrenatalSafe®:

Trisomy 21	This is caused by an extra copy of chromosome 21 and is also called Down syndrome. This is the most common genetic cause of intellectual disability. Individuals with Down syndrome have an average IQ of 50 and all have some degree of intellectual disability. Some children with Down syndrome have defects of the heart or other organs that may require surgery or medical treatment. Some have other medical conditions including hearing or vision loss.
Trisomy 18	This is caused by an extra copy of chromosome 18 and is also called Edwards syndrome. This causes severe intellectual disability. Most babies with Trisomy 18 have multiple severe birth defects of the brain, heart and other organs. Poor growth during pregnancy is common and many babies are miscarried or stillborn. Of those babies born alive, most die before one year of age. Babies who survive have profound intellectual disabilities and growth and development problems.
Trisomy 13	This is caused by an extra copy of chromosome 13 and is also called Patau syndrome. This causes severe intellectual disability. Most babies with trisomy 13 have multiple severe birth defects of the brain and other organs. Many babies are miscarried or stillborn. Of those babies born alive, most die before one year of age.
Sex Chromosome Aneuploidies	The PrenatalSafe® prenatal test also gives your healthcare provider the option to test for changes in the number of sex chromosomes. Sex chromosome aneuploidies are conditions in which there is a change from the usual 2 copies of sex chromosomes in males (XY) or females (XX). About 1 in 400 babies that are born will have a sex chromosome aneuploidy. The most common sex chromosome aneuploidies are caused by a missing sex chromosome in girls (45,X or monosomy X, also called Turner syndrome) or an extra chromosome in boys or girls (47,XXY (Klinefelter syndrome), 47,XYY, or 47,XXX). Children with a sex chromosome aneuploidy can have difficulties with language skills, motor skills, and learning, but can lead healthy and productive lives.

(Arthur Robinson & Mary G Linden, 1993, Clinical Genetics Handbook, Second Edition. Cambridge, Mass, Blackwell Scientific Publications)

Microdeletion syndromes and trisomies 9 and 16

All pregnancies have a risk for being affected with a chromosome disorder, whether a microdeletion or a trisomy. Collectively, microdeletion syndromes are common, affecting approximately 1 in 1,000 pregnancies, and have clinical features that can affect growth, intellectual ability, and development. Trisomy 9 or 16 often result in a first-trimester miscarriage. These microdeletion syndromes and trisomies usually occur spontaneously without any family history.

Trisomy 9: A rare chromosomal condition with the vast majority of instances resulting in miscarriage in the 1st trimester. While the majority of live births will not survive during early postnatal period, those that do will have serious health concerns, including intellectual disability and cardiac defects. It can also occur in mosaic form;

Trisomy 16: The most commonly occurring autosomal trisomy seen in first trimester miscarriages. Rare survivors with mosaic trisomy 16 are at increased risk for health concerns including intra-uterine growth restriction, intellectual disability, and cardiac defects. There is a small increased risk for a woman to have a pregnancy with a viable trisomy following a miscarriage with trisomies 9 or 16. The ability to identify these important chromosomal causes of miscarriage can help with risk assessment as well as monitoring and management of subsequent pregnancies.

GENOME-WIDE COPY NUMBER VARIANTS:

- ≥10 Mb, at every chromosome in the genome, with **PrenatalSafe® Karyo and PrenatalSafe® Karyo Plus** tests.

Microdeletion syndromes

Microdeletions are chromosomal disorders caused by small missing pieces of chromosome material. They are usually not visible by standard methods of chromosome analysis. Microdeletions can occur on any of the 23 pairs of chromosomes. Some occur more commonly in a specific area of a particular chromosome and have been linked to known genetic syndromes. Most occur by chance, rather than being inherited from a parent, and can occur with no prior family history and without other risk factors, such as advanced parental age. Results from routine pregnancy screening are usually normal.

Many microdeletion syndromes can cause serious health issues including both physical and intellectual impairment—the severity of which can vary from individual to individual. These conditions usually cannot be detected by traditional serum screening and may or may not be associated with ultrasound abnormalities. Until now, an invasive procedure, such as chorionic villus sampling (CVS) or amniocentesis, was the primary way to detect such conditions prenatally.

Routine prenatal serum screens cannot assess microdeletion syndromes. Additionally, microdeletion syndromes may not have abnormal ultrasound findings. Early information would aid patients and physicians greatly in pregnancy and newborn care. These expansions to the PrenatalSafe® test, the microdeletion panel and the test for trisomies 9 and 16, provide patients and physicians with additional non-invasive prenatal testing (NIPT) options based on clinical context.

The microdeletion panel and trisomies 9 and 16 testing, offered as options to the **PrenatalSafe® Plus** prenatal test, use the same proven whole-genome massively parallel sequencing technology as the original test. The microdeletion panel included in the **PrenatalSafe® Plus** prenatal test covers 5 of the more commonly seen and clinically relevant microdeletion regions:

	Incidence	Clinical Features (may include but not limited to)	Life Expectancy
22q11.2 syndrome (**Di George syndrome**, Velocardialfacial syndrome)	1 in 4,000	Learning problems, congenital heart defects, palatal abnormalities	Usually normal, can be reduced for Di George syndrome
1p36 deletion syndrome	1 in 4,000 to 1 in 10,000	Characteristic craniofacial features, intellectual disability, seizures, brain and heart defects	Depends on the severity of features, but can be normal
Angelman syndrome (15q11.2 deletion syndrome)	1 in 12,000	Intellectual disability, speech impairment, seizures	Normal
Prader-Willi syndrome (15q11.2 deletion syndrome)	1 in 10,000 to 1 in 25,000	Hypotonia, morbid obesity, delayed motor and language skills, intellectual disability, hypogonadism	Normal, may be reduced depending on the severity of symptoms
Cri du Chat syndrome (5p-syndrome)	1 in 20,000 to 1 in 50,000	Intellectual disability, speech delay, cat-like cry	10% mortality in the first year; otherwise usually normal, but will depend on the severity of features
Wolf-Hirschhorn syndrome (4p-syndrome)	1 in 50,000	Growth deficiency, hypotonia, craniofacial features, intellectual disability, heart and brain abnormalities	Depends on severity of features

The microdeletion panel included in the **PrenatalSafe® Karyo Plus** prenatal test covers the 5 clinically relevant microdeletion regions included in the **PrenatalSafe® Plus** test, adding 3 further regions:

Microdeletion syndrome	Chromosomal Region	Prevalence (at birth)
Jacobsen syndrome	11q23-q24.3 deletion	1/100.000
Langer-Giedion syndrome	8q24.11-q24.13 deletion	1/200.000
Smith-Magenis syndrome	17p11.2 deletion	1/15.000 - 1/25.000

Individually, microdeletion syndromes are rare, with a low prevalence in the general population. False positive NIPT results may lead to unnecessary invasive testing. To this end, Genoma understands that not everyone is an appropriate candidate for additional microdeletion testing as part of their pregnancy care. For this reason, Genoma provides this testing as an elective option. This test should be used in the context of the patient's history, including information about family history and pregnancy information such as an abnormal ultrasound.

Your attending physician or genetic counselor can also give you more information about these conditions. If your healthcare provider chooses the sex chromosome option, and no sex chromosome aneuploidies are found, then the test report will state whether your baby is expected to be a girl or boy. If you do not wish to know the gender of your baby, please let your attending physician know in advance to not disclose this information to you.

The Testing Process

To analyze the DNA from your blood, your health care provider will take a blood sample from you (between 7 and 10mL, in a standard blood draw). The physical risk to you of obtaining the blood sample is usually minimal. This test uses a technology called "massively parallel DNA sequencing" to count the number of copies of these chromosomes, and then uses a calculation method to determine if there are too many or too few copies of these chromosomes present in your fetus.
Some important points about the testing and reporting process:

- **Your sample is worked by Genoma Laboratory of „EUROFINS Genoma Group Srl" („GENOMA srl"), Via di Castel Giubileo 11, Rome, 00138 Italy**
- Your test results are confidential and are kept according to the security requirements as per applicable laws and guidelines. The GENOMA srl Notices of Privacy Practices are available on the company websites at http://www.laboratoriogenoma.eu.
- **Only tests authorized by you will be performed on your identified blood sample.**
- Collecting information on your pregnancy after prenatal diagnosis is part of a laboratory's standard practice for quality purposes. As such, GENOMA srl may contact your healthcare provider to obtain this information.
- The test is performed after at least 10 weeks, 0 days of pregnancy. Adequate DNA in the blood sample is required to complete the test. Additional samples may be needed if the sample is damaged in shipment or incorrectly submitted, or if a test repetition is needed. After analysis in GENOMA srl laboratory, the test results will be returned to your healthcare provider, who will discuss them with you.

Obtaining and Interpreting Test Results

After the sample has been worked by GENOMA srl, the results will be reported only to the qualified health care provider(s) indicated in this form or to the genetic counselor (where allowed). Additionally, the test results could be released to authority entities, institutions or persons who, by applicable law, may have access to such data. Your results will tell your attending physician whether too few or too many copies of the chromosomes being tested for are present. It is the responsibility of the attending physician ordering this test to understand the specific uses and limitations of this test, and to make sure you understand them as well. If a genetic disorder is detected, follow up testing (such as amniocentesis or chorionic villus sampling) may be recommended to confirm the result.
Your test report will include one of three possible results for chromosomes 21, 18, and 13: No Aneuploidy Detected, Aneuploidy Detected, or Aneuploidy Suspected (Borderline Value). Sex chromosomes will be reported as No Aneuploidy Detected, or Aneuploidy Detected, or XX or XY, as appropriate. In the case of a twin pregnancy, Y chromosome presence will be reported as Detected or Not Detected.

A **No Aneuploidy Detected** test result means that this test identified the expected number of copies of chromosomes reported.

An **Aneuploidy Detected** test result means that this test identified too many or too few copies of one of the chromosomes as seen on the report. This can indicate either a trisomy or a sex chromosome aneuploidy

An **Aneuploidy Suspected** test result means that this test identified more copies than expected of the chromosomes reported. This means that your attending physician should follow up on this result to obtain more information.

In the case of microdeletions testing, negative results will be classified as "**No abnormality detected**" and positive results classified as "**abnormality detected**" with additional comment indicating that interpretation is consistent with a loss in the genomic region that is associated with a particular syndrome.

There is a chance that the sample submitted will not return any results; in this case a second sample may be requested to repeat the test.

Genetic counseling before and after testing is recommended. Results of "Aneuploidy Detected" or "Aneuploidy Suspected" are considered positive and patients should be offered invasive prenatal procedures for confirmation. A negative test does not ensure an unaffected pregnancy. Chorionic villus sampling and amniocentesis provide definitive diagnostic information, but may pose harm to the fetus.

The PrenatalSafe® prenatal test does not test for all health problems. Normal results do not eliminate the possibility that your pregnancy may have other chromosomal/genetic conditions, birth defects, or other complications. A 'No Aneuploidy Detected' result on this test does not completely rule out the presence of the conditions being tested for, and does not guarantee the health of your baby.

Your attending physician may decide to order additional genetic testing (e.g., amniocentesis, or chorionic villus sampling) after receiving the results from this test. Before signing this form, you should ask your attending physician if you have any questions about this test, or have questions about what its results could mean.

This test represents the newest service currently available for prenatal testing. However, as with any complex genetic test, there is always a chance of failure or error in sample analysis. Extensive measures are taken to avoid these errors. The PrenatalSafe® prenatal test was tested in a multi-center clinical study, in a population of high risk patients, and the test performance is indicated in the tables below.

Performance **PrenatalSAFE® (FAST Protocol): follow-up December 2017**

	Trisomy 21 (n=78.542)	Trisomy 18 (n=78.542)	Trisomy 13 (n=78.542)	Monosomy X (n=78.542)	XXX (n=78.542)	XXY (n=78.542)	XYY (n=78.542)	SCA (n=78.542)
True Positive	628	136	101	86	40	79	14	219
False Positive	5	4	7	34	4	10	0	48
True Negative	77912	78402	78434	78422	78498	78453	78528	78275
False Negative	0	0	0	0	0	0	0	0
Sensitivity (95% CI)	100% (99.41% - 100.00%)	100% (97.32% - 100.00%)	100% (96.41% - 100.00%)	100% (95.80% - 100.00%)	100% (91.19% - 100.00%)	100% (95.44% - 100.00%)	100% (76.84% - 100%)	100,00% (98.33% - 100.00%)
Specificity (95% CI)	99.99% (99.99% - 100.00%)	99.99% (99.99% - 100.00%)	99.9% (99.98% - 100.00%)	99.96% (99.94% - 99.97%)	99.99% (99.99% - 100.00%)	99.99% (99.98% - 100.00%)	100% (99.99% - 100%)	99,94% (99.92% - 99.95%)
PPV (95% CI)	99.21% (98.12% - 99.67%)	97.14% (92.73% - 98.91%)	93.52% (87.30% - 96.80%)	71.67%% 64.38% - 77.97%	90.91% (78.96% - 96.38%)	88.76% (80.96% - 93.62%)	100% (73.23% - 100%)	82,02% (77.47% - 85.22%)
NPV (95% CI)	100% (99.98% to 100%)	100% (99.98% to 100%)	100% (99.98% to 100%)	100% (99.98% - 100%)	100% (99.98% - 100%)	100% (99.98% - 100%)	100% (99.99% - 100%)	100,00% (99.98% - 100.00%)

PPV: Positive Predictive Value; NPV: Negative Predictive Value; SCA: Sex Chromosomes Aneuploidy (cases with maternal mosaicism have been excluded). * Since September 2014. Updated data from Fiorentino et al., Prenat Diagn 2016 Apr;36(4):304-11

PrenatalSAFE® Karyo test validation data(Fiorentino et al., EJHG conference 2016)

	Trisomy 21 (n=1419)	Trisomy 18 (n=1419)	Trisomy 13 (n=1419)	SCA (n=1419)	CNV (n=1419)
True positive	100	31	14	36	37
False positive	0	0	0	0	0
True negative	1319	1388	1405	1383	1382
False negativi	0	0	0	0	0
Sensitivity (95% CI)	100,00% (96.38% - 100.00%)	100,00% (88.78% - 100.00%)	100,00% (76.84% - 100.00%)	100,00% (90.26% to 100.00%)	100,00% (90.51% to 100.00%)
Specificity (95% CI)	100,00% (99.72% - 100.00%)	100,00% (99.73% - 100.00%)	100,00% (99.74% - 100.00%)	100,00% (99.73% to 100.00%)	100,00% (99.73% to 100.00%)
PPV (95% CI)	100,00% (96.38% - 100.00%)	100,00% (88.78% - 100.00%)	100,00% (76.84% - 100.00%)	100,00% (90.26% to 100.00%)	100,00% (90.51% to 100.00%)
NPV (95% CI)	100,00% (99.72% - 100.00%)	100,00% (99.73% - 100.00%)	100,00% (99.74% - 100.00%)	100,00% (99.73% to 100.00%)	100,00% (99.73% to 100.00%)

PPV: Positive Predictive Value; NPV: Negative Predictive Value; SCA: Sex Chromosome aneuploidy; CNV: Copy Number Variation

Performance **PrenatalSAFE® Karyo: Clinical Cases with Follow-up (update May 2016)**

	Trisomy 21 (n=11.932)	Trisomy 18 (n=11.932)	Trisomy 13 (n=11.932)	SCA (n=11.932)	Rare Trisomies (n=11.932)	CNV (n=11.932)
True Positive	88	15	12	36	10	8
False Positive	1	1	1	12	7	5
True Negative	11.843	11.916	11.919	11.884	11.915	11.919
False Negative	0	0	0	0	0	0
Sensitivity (95% CI)	100.00% (95.89% - 100.00%)	100.00% (78.20% - 100.00%)	100.00% (73.54% - 100.00%)	100.00% (90.26% - 100.00%)	100.00% (69.15% - 100.00%)	100.00% (63.06% - 100.00%)
Specificity (95% CI)	99.99% (99.95% - 100.00%)	99.99% (99.95% - 100.00%)	99.99% (99.95% - 100.00%)	99.90% (99.82% - 99.95%)	99.94% (99.88% - 99.98%)	99.96% (99.90% - 99.99%)
PPV (95% CI)	98.88% (92.54% to 99.84%)	93.75% (67.88% - 99.07%)	92.31% (62.83% - 98.84%)	75.00% (63.02% - 84.08%)	58.82% (40.52% - 74.97%)	61.54% (39.98% - 79.35%)
NPV (95% CI)	100.00% (99.95% - 100.00%)	100.00% (99.95% - 100.00%)	100.00% (99.95% - 100.00%)	100,00% (99.95% - 100.00%)	100.00% (99.95% - 100.00%)	100.00% (99.95% - 100.00%)

PPV: Positive Predictive Value; NPV: Negative Predictive Value; SCA: Sex Chromosomes Aneuploidy. CNV: Copy Number Variation

PrenatalSAFE® Karyo test validation data (Fiorentino et al., EJHG conference 2016)

	risomy 21 (n=1419)	risomy 18 (n=1419)	risomy 13 (n=1419)	SCA (n=1419)	CNV (n=1419)
True positive	100	31	14	36	37
False positive	0	0	0	0	0
True negative	1319	1388	1405	1383	1382
False negative	0	0	0	0	0
Sensitivity (95% CI)	100,00% (96.38% - 100.00%)	100,00% (88.78% - 100.00%)	100,00% (76.84% - 100.00%)	100,00% (90.26% to 100.00%)	100,00% (90.51% to 100.00%)
Specificity (95% CI)	100,00% (99.72% - 100.00%)	100,00% (99.73% - 100.00%)	100,00% (99.74% - 100.00%)	100,00% (99.73% to 100.00%)	100,00% (99.73% to 100.00%)
PPV (95% CI)	100,00% (96.38% - 100.00%)	100,00% (88.78% - 100.00%)	100,00% (76.84% - 100.00%)	100,00% (90.26% to 100.00%)	100,00% (90.51% to 100.00%)
NPV (95% CI)	100,00% (99.72% - 100.00%)	100,00% (99.73% - 100.00%)	100,00% (99.74% - 100.00%)	100,00% (99.73% to 100.00%)	100,00% (99.73% to 100.00%)

PPV: Positive Predictive Value; NPV: Negative Predictive Value; SCA: Sex Chromosome aneuploidy; CNV: Copy Number Variation

Test limitations

While the results of the PrenatalSafe® test are highly accurate, discordant results, including inaccurate fetal sex prediction, may occur. Cell-free DNA (cfDNA) testing does not replace the accuracy and precision of prenatal diagnosis with CVS or amniocentesis.

The **PrenatalSafe®** prenatal test does not test for all health problems. Normal results do not eliminate the possibility that your pregnancy may have other chromosomal/genetic conditions, birth defects, or other complications. A '**No Aneuploidy Detected**' result greatly reduces the chances that your fetus has an extra or missing copy of one of the tested chromosomes but it cannot guarantee normal chromosomes or a healthy baby. The result of this test does not eliminate the possibility of other abnormalities of the tested chromosomes, and it does not detect abnormalities of untested chromosomes, other genetic disorders, birth defects, or other complications in your fetus or pregnancy.

The **PrenatalSafe® 3** and **5** prenatal tests are designed to look at full chromosome aneuploidies only, and has been validated for chromosomes 21, 18, 13 and chromosomes 21, 18, 13, X and Y only, respectively. The **PrenatalSafe® Karyo** analyzes every chromosome in the genome, providing karyotype-level insight. It provides information about gains or losses of chromosome material e 10 Mb across the genome.

A patient with a **positive** PrenatalSafe® test result should be referred for genetic counseling and offered invasive prenatal diagnosis for confirmation of test results.

An **uninformative result** may be reported, the causes of which may include, but are not limited to, insufficient sequencing coverage, noise or artifacts in the region, amplification or sequencing bias, or insufficient fetal fraction.

There is a small possibility that the test results might not reflect the chromosomes of the baby, but instead might reflect chromosomal changes to the placenta (confined placental mosaicism), or in the mother (chromosomal mosaicism).

Inaccurate test results or a failure to obtain test results may occur due to one or more of the following rare occurrences: biological factors such as but not limited to too little DNA from the fetus in the maternal blood sample, placental, maternal, or fetal mosaicism (a mixture of cells with normal and abnormal chromosomes) or neoplasm; vanishing twin; prior maternal organ transplant; or an unrecognized twin pregnancy; other circumstances beyond our control; or unforeseen problems that may arise, or other causes.

The PrenatalSafe® test is not intended to identify pregnancies at risk for neural tube defects or ventral wall defects. cfDNA testing for whole chromosome abnormalities (including sex chromosomes) and for subchromosomal abnormalities could lead to the potential discovery of both fetal and maternal genomic abnormalities that could have minor, or no, clinical significance. Evaluating the significance of a positive or a non-reportable test result may involve both invasive prenatal testing and additional studies on the mother. Such investigations may lead to detection of maternal chromosomal or subchromosomal abnormalities, which on occasion may be associated with benign or malignant maternal neoplasms. cfDNA testing may not accurately identify fetal triploidy, balanced rearrangements, or the precise location of subchromosomal duplications or deletions; these may be detected by prenatal diagnosis with CVS or amniocentesis. The ability to report results may be impacted by maternal body mass index (BMI), maternal weight, and/or maternal systemic lupus erythematosus (SLE).

Microdeletions testing: limitations of the Test

This test is designed to detect subchromosomal deletions and is validated for common deletions in chromosomal regions 15q11.2, 5p15.2, 22q11.2, 1p36, and 4p16.3. The test is validated for singleton pregnancies with gestational age of at least 10 weeks as estimated by last menstrual period. These results do not eliminate the possibility that this pregnancy may be associated with other chromosomal or subchromosomal abnormalities, birth defects, and other conditions. This test is not intended to identify pregnancies at risk for open neural tube defects. A negative test result does not eliminate the possibility of Angelman syndrome, Prader-Willi syndrome, 5p-/Cri-du-Chat syndrome, 22q11.2 deletion syndrome, Williams syndrome, 1p36 deletion syndrome, or 4p-/Wolf-Hirschhorn syndrome. In addition, conditions caused by other molecular mechanisms cannot be detected with this assay. There is a small possibility that the test results might not reflect the chromosome status of the fetus, but may reflect subchromosomal changes of the placenta (confined placental mosaicism), or of the mother.

Alternatives

This non-invasive prenatal screening test is only one option for detecting pregnancies at high risk for fetal chromosome abnormalities. There are multiple other screening options available during pregnancy and, if you want more details on your other options, you should ask your health care provider. You also have the option to decline all chromosome screening tests during your pregnancy. For women who want or need more conclusive information about the fetal chromosomes, commonly used invasive diagnostic tests such as CVS or amniocentesis are available and will detect >99% of all chromosome abnormalities, including rare abnormalities on chromosomes not evaluated with this or other screening tests.

Pregnancy Outcome Information. Collecting information on your pregnancy after testing is part of a laboratory's standard practice for quality purposes, and is required in several states. As such, Genoma or its designee may contact your healthcare provider to obtain this information.

Incidental Findings. In the course of performing the analysis for the indicated tests, information regarding other chromosomal alterations may become evident (called Incidental Findings). Our policy is to NOT REPORT or comment on any Incidental Findings that may be noted in the course of analyzing the test data.

Genetic Counseling:

If you have remaining questions about non-invasive prenatal testing after talking with your attending physician, we recommend that you make an appointment with a local genetic counselor who can give you more information about your testing options.

Use of Information and Leftover Specimens

Pursuant to best practices and clinical laboratory standards, ONLY BASED ON YOUR EXPRESS CONSENT (according to the para. **Research and Retention of samples in the end of this form**), leftover de-identified specimens (unless prohibited by law) as well de-identified genetic and other information learned from your testing may be used by Genoma srl or others on its behalf for purposes of quality control, laboratory operations, laboratory test development, and laboratory improvement. All such uses will be in compliance with applicable law.

NOTIFICATION REGARDING THE PROCESSING OF PERSONAL DATA

A. The company under the name "MEDSANA BUCHAREST MEDICAL CENTER S.R.L." and registered seat in Romania, the municipality of Bucharest, district 5 (12 Dr. Nanu Muscel street, Postal Code 050521) ("Medsana"), pursuant to the General Data Protection Regulation (EU) 2016/679 (the "GDPR"), informs you about the following: The biological sample necessary for testing is drawn in Romania, at Medsana, in proper conditions, in compliance with the Romanian legal requirements as well as with the instructions sent by Genesis Genoma Lab. As your sample to be worked, your sample and related medical information are submitted to Genesis Genoma Lab, Greece which sends them to GENOMA srl, Italy. The containers and transport medium for samples are provided by Genesis Genoma Lab.

The price of testing shall be entirely paid in Romania, after the drawing procedure.

OTHER INFORMATION PROVIDED TO THE PATIENT AT MEDSANA CLINIC	YES	NO
INFORMATION REGARDING AVAILABLE MEDICAL SERVICES		
INFORMATION REGARDING IDENTITY AND PROFESSIONAL STATUS OF MEDICAL STAFF WHO TREATING HER		
THE PACIENT HAS BEEN INFORMED ABOUT HER RIGHT TO THE SECOND OPINION		
INFORMATION REGARDING THE RULES/PRACTICES/CUSTOMS OF THE CLINIC WHICH MUST BE OBSERVED		
ARE YOU SUFFERING FROM A MENTAL ILLNESS THAT AFFECTS YOUR DISCERNMENT?	YES	NO
DOES THE PATIENT WISH TO BE FURTHER INFORMED ABOUT HIS HEALTH?	YES	NO
DO YOU AGREE WITH THE RETRIEVING AND USING OF YOUR BIOLOGICAL SAMPLES WITH THE PURPOSE OF PERFORMING THE ANALYSIS AS MARKED ABOVE BY GENESIS GENOMA LAB?	YES	NO

Medsana complies with the Romanian legislation on medical data protection. To this way, transmission of your personal data and of your sample to be processed outside the country shall be made only on the basis of your agreement. As your sample will be processed at the laboratory GENOMA srl, Italy through the laboratory Genesis Genoma Lab (Leoforos Kifisias Avenue 302, Chalandri, 152 32 Attiki-Greece), the Form shall be filled and signed both Romanian and English version. In Italy/Greece, the English version shall be evaluated. Therefore, you are asked to make sure that the form is entirely filled / marked and you sign it on every page.

Only by your written request, the bulletin of results received from Genesis Genoma Lab in English is translated into Romanian. The translation is done by a translator authorized by the Ministry of Justice, with whom Medsana has a privacy agreement, at no extra cost on your side.

Your personal data are processed by Medsana in accordance with its Personal Data Privacy Policy. Compliance with the legislation on personal data protection and good practice in the field, as well as ensuring a climate of transparency, safety and trust for patients are important for Medsana. By signing the Informed Patient Agreement, you agree to adhere to the Medsana Privacy Policy. You can get more information about your rights [meaning (a) the right of access to processed personal data (the "Data"); (b) the right to request the rectification or deletion of the Data; (c) the right to request restriction of processing; (d) the right to oppose processing; (e) the right not to be subject to an automatic decision, including profiling; (f) the right to data portability; (g) the right to lodge a complaint with the National Supervisory Authority for Personal Data Processing and to refer the matter to the competent courts] by consulting the document "PRIVACY NOTICE ON PROCESSING PERSONAL DATA BY MEDSANA BUCHAREST MEDICAL CENTER S.R.L." available on the Medsana website at https://www.medsana.ro/despre-noi/gdpr or on paper support at the waiting room of each Medsana' clincs. At any time you may exert the rights mentioned at let. (a) – (f) above using one of following communication channels: e-mail address dpo@medsana.ro or submit a written request at the Medsana Clinic's offices or by mail to the address Medsana Bucharest Medical Center S.R.L., Bucharest, 5th district, ZIP 050521, 12 Dr. Nanu Muscel street.

B. The company under the name "GENESIS - GENOMA PRIVATE DIAGNOSTIC LAD – GENETIC ANALYSIS GENETIC CLINIC AND RESEARCH PRIVATE LIMITED COMPANY" and registered seat in the municipality of Chalandri, Attiki (Leoforos Kifisias, number. 302, Postal Code 152 32) (the "Genesis Genoma Lab"), pursuant to the General Data Protection Regulation (EE) 2016/679 (the "GDPR"), informs you about the following:

1. Types of personal data processed: The Company processes personal data, in particular and as the case may be, of the following persons ("data subjects"): (a) adults, (b) infants which are being represented by the holders of the parental responsibility or the guardianship over them, (c) unborn or embryo, subject to the legislation and (d) persons which are incapacitated and they are represented by their judicial supporter. The personal data which are being processed by the Company are inter alia and as the case may be: (a) their contact details (e.g. last name, first name, telephone (home phone number or cell phone number), address, town, Postal Code, country, email address), date of visit, ID or passport, date of birth, profession, insurance fund, details of private insurance, husband's/ partner's details (as per above where relevant), details of the person making the recommendation etc.), (b) data of special category, meaning, where relevant, genetic data, health data (medical history, relevant medication, etc.)

and (c) payout information, including bank card/ account information, invoice and payment information etc. The disclosure of the above data constitutes a legal or contractual obligation of the data subject or a precondition for the conclusion of the contract. In case the data subject does not provide the above personal data, wholly or partly, Genesis Genoma Lab may not be able to provide its services.

2. Source of personal data: The source of these data is, as the case may be, the natural person that discloses personal data of himself and/ or any third party, the holders of the parental responsibility, the guardian, where relevant, the judicial supporter, doctors, medical companies, health service providers, irrespective of their legal form, other professionals in the health sector, laboratories, andrology centres, medically assisted reproduction units, cryopreservation banks etc. In so far as the above persons disclose to the Company personal data of third parties, they are responsible for complying with the applicable data protection legislation. In this context, they may need to ensure that the data subjects have given their consent prior to the transmission of their personal data to the Company.

3. Purposes of the processing of personal data: The purposes of the processing of personal data held by the Company are, as appropriate, the following: (a) the preventive or professional medicine, the medical diagnosis and the fulfilment of the Company's obligations in general (e.g. arrangement of appointment etc.)[1], (b) the protection of the fundamental rights and freedoms of the data subjects or of any natural person, in case the data subject is legally or physically incapable of giving its consent[2], (c) to ensure the Company's legitimate interests[3], (d) to assist public, administrative and Independent Authorities and for reasons which are deemed to be material for the public interest[4], (e) the scientific survey and statistics purposes, which are not considered to be incompatible with the above initial purposes[5], (f) for direct marketing purposes (e.g. brochure or newsletter) via email. It is to be clarified that email contact details (email address or phone number for sms) which were legally obtained, in the context of the service provision or other transaction with the Company may under the law be used for direct marketing purpose only on the basis of written prior consent[6].

4. Recipients of personal data: The personal data may be transmitted, depending on the purpose of the processing and as the case may be, to authorised employees of the Company by department/ by service, medical staff, associate doctors and other partners, doctors/ companies involved in any way in the provision of these services and professionals in the health sector in general, collaborating laboratories (including the laboratory GENOMA srl, Italy), the Supervisory Authority, other Independent Authorities, Judicial Authorities, Public Services which have to be informed for purposes of public interest, private or public insurance companies, any representatives of the data subjects, provided that they are relevantly authorised, credit institutions, collaborating companies that the Company has contracted with and which process personal data on behalf of the Company (e.g. IT companies, operators of medical machinery, IT service providers etc.) and to their employees, in the context of their responsibilities and all being committed to confidentiality, to professional/ medical confidentiality and to the data protection legislation.

5. Retention of personal data: The retention period of the above data is the time allowed or required by the applicable law according to the legal framework, depending on the nature of the service provided, taking into account the limitation period provided.

6. Data subjects' rights: The data subject has the following rights according to the GDPR: (a) to receive a copy of his personal data held by the Company, including information about the way of processing. (b) to request the correction of inaccurate personal data and, where applicable, to request the erasure or the restriction of processing, or otherwise to object to the processing of his personal data. (c) to object to the processing of his personal data. (d) to request the modification of his personal data. (e) to request the erasure of his personal data. (f) To request to receive a copy or to have a copy of his personal data transmitted to another company (data portability) (in a machine-readable format), when the processing is essential for the performance of the contract. (g) To lodge a complaint with the competent supervisory authority regarding the way that his personal data are being processed by the Company. If the data subject wishes to receive more information/ to be notified relating to the processing of his personal data or to exercise any of his aforementioned rights, he needs to send an email to the Data Protection Officer (DPO) solely and exclusively at the email address: dpo@genlab.gr, or to send a letter to the address of correspondence mentioned above, being explicitly excluded any other means of communication (e.g. fax, phone number).

For more information on the Genesis Genome Lab's personal data protection policy, please visit: https://www.genlab.gr/eng/notification-to-counterparties-and-third-parties-regarding-the-processing-of-their-personal-data/.

CONSENT – DECLARATION

By signing this form, I, the patient, consent and authorize the Genetic Diagnostic Laboratory Genesis Genoma Lab to access my medical information and my biological sample in order to transfer them to GENOMA srl, Italy and, subsequently, to communicate the test results to Medsana Laboratory.

I understand that:

- genetic analyses are complex and sensitive and there is a chance of false results due to problems in quality and/or identity of the sample, the presence of polymorphisms and other technical issues.
- all results are confidential and covered by medical confidentiality.
- if the sample is considered unsuitable for one or more of the selected tests, it will be destroyed and a new sample will be requested at no extra charge
- the genetic material is to be analyzed only for the above requested genetic tests and this does not exclude the presence of mutations related to

[1] Legal basis: article 6, para. 1 subpara. (b), (c), (d), (e) and (f) and for the data of special categories article 9, para. 2 (h) of GDPR
[2] Legal basis: article 6, para. 1 subpara. (d) and for the data of special categories article 9, para. 2 (c) of GDPR
[3] Legal basis: article 6, para. 1, subpara. (b) and (f) of GDPR and for the data of special categories article 9 para. 2 (f) of GDPR
[4] Legal basis: article 6, para. 1, subpara. (c), (e) and (f) of GDPR and for the data of special categories article 9 para. 2 (f), (g) and (i) of GDPR
[5] Legal basis: article 6, para. 1, subpara. (f) of GDPR and for the data of special categories article 9 para. 2 (j) of GDPR
[6] Legal basis: article 6, para. 1, subpara. (a) of GDPR

another genetic disease.

Genesis Genoma Lab intends to use my genetic material, clinical data and / or results, when the analysis and interpretation of my results is completed, de-identified and coded, for research, educational and quality control purposes. In the event of my refusal of my sample and / or results to participate in research, educational and quality control activities, this will not influence the completion of genetic analyses. (To this aspect, please see below para. **Research Activities and Retention of samples**).

I declare that:

- I have received and read or have had read to me the above informed consent information about the PrenatalSafe® Non-Invasive Prenatal Test (NIPT) in its entirety and realize I may retain a copy for my records;
- I have had the opportunity to ask questions of my health care provider regarding this test, including the reliability of test results, the risks, and the alternatives prior to my informed consent;
- I have discussed with the attending physician ordering this test the reliability of positive or negative test results and the level of certainty that a positive test result for a given disease or condition serves as a predictor of that disease or condition; I have been informed about the availability and importance of genetic counseling and have been provided with information identifying an appropriate healthcare provider from whom I might obtain such counseling;
- I consent to having this test performed and I will discuss the results and appropriate medical management with my attending physician.
- the clinical information and the family medical history that I provide are true and accurate.
- I have read and been informed about the management policy of my personal data and genetic material, as well as my rights in relation to them.

I have been informed and I understood completely that: (a) all the above tests are carried out in the laboratory GENOMA srl, Italy, to which the sample is going to be shipped. The laboratory GENOMA srl, Italy holds the full liability for the validity of the result. (b) Genoma laboratory is the Italian company "EUROFINS Genoma Group Srl", which is different and independent from the Greek company "Genesis Genoma Lab".

Research Activities and Retention of samples

Remaining samples of genetic material/ and analyses ☐ **I Consent** ☐ **I DO Not consent**

to the retention and usage by GENOMA srl / Genesis Genoma Lab of any remaining samples from the biological/ genetic sample analyses of our material, for the purposes of prospective medical and scientific researches, by genetic analyses. We have been informed, we have understood and we declare that: (a) our above decision is based on a voluntary basis and without any financial trade-off for myself or my successors, and any non-consent of mine will have no impact on working my sample in the context of the present paper, (b) taking into account the rapid evolution of the bio-medical sciences, it may not predict the researches which are going to be held on the basis of the collected samples of biological/ genetic material, (c) the results of prospective researches that may be held on the samples of my biological/ genetic material that have been kept will be not communicated to me. However, the results of the prospective analyses aim at contributing to the amelioration of the population's health and they may be published on scientific magazine, being always the data in an anonymous or a codified form, (d) any of the samples will be kept, anonymous or codified, in the premises of laboratory performing the research or of a third person which acts on behalf of that laboratory, with restricted access, and there will not be labelling based on which we will be identifiable, (e) any of the sample of biological/ genetic material will never be sold or used

Name/Surname:	Date:	Signature	**Select one of the following:** ☐ **The person himself** ☐ **The holder of the parental responsibility** ☐ **The guardian** ☐ **The judicial supporter**

in order for products of commercial exploitation to be produced and (f) in case we consent, as per above, we have (any of the examinees separately) the right to withdraw our consent at any time provided that a prior written notification is given to Medsana Laboratory which will send it to Genesis Genoma Lab and GENOMA srl, whereby any of the remaining samples of biological/ genetic material will be destroyed.