

TEST REQUISITION FORM

PATIENT DETAILS

Protocol no. (internal use only): _____
 Name _____
 Surname _____
 Date of birth _____ Place of birth _____
 VAT no. _____
 Address: _____
 Date of blood withdraw _____
 Gynecologist name: _____
 Address: _____
 Phone no.: _____
 E-mail: _____



ORDERING LABORATORY / CLINICIAN

 Name / Stamp

PATIENT MEDICAL HISTORY

PREGNANCY HISTORY

Patient current weight Kg _____ Patient height _____
 Gestational age at draw _____ + days _____
 Gestational age calculated by:
 Ultrasound; last menstrual period; IVF treatment
Twin pregnancy? Yes; NO **IVF Pregnancy?** Yes; NO

INDICATION FOR TESTING

Advanced maternal age; Parental anxiety (low-risk)
 Abnormal ultrasound (describe): _____
 Previous pregnancy with aneuploidy;
 Abnormal maternal serum screening test;
 Other indication _____ None

TYPE OF TEST

For **Singleton** Pregnancy: FAST PROTOCOL option
 Prenatal**SAFE**® **3** test (for chromosomes 21, 18,13 only)
 Prenatal**SAFE**® **5** test (for chromosomes 21, 18, 13, X, Y)
 Prenatal**SAFE**® **Plus** test (for chr. 21, 18, 13, X, Y) +
 Panel 6 Microdeletion*; Trisomies 9 and 16 option
 Prenatal**SAFE**® **Karyo** test (genome-wide NIPT that provides karyotype-level insight)
 Prenatal**SAFE**® **Karyo Plus** test (genome-wide NIPT that provides karyotype-level insight + Panel 9 Microdeletions**)
 Do you wish to know the fetal gender? Yes; NO
 Is it a redraw? Yes; NO

For **Twin** Pregnancy: FAST PROTOCOL option
 Prenatal**SAFE**® **3** test (for chromosomes 21,13,18 only)
 Presence of Y option
 Prenatal**SAFE**® **Karyo** test (genome-wide NIPT that provides karyotype-level insight)
 Is it a redraw? Yes; NO
 *This option includes the following syndromes:
 22q11 deletion (DiGeorge); 15q11 deletion (Angelman/ Prader-Willi);
 1p36 deletion, 4p- (Wolf-Hirschhorn); 5p- (Cri-du-chat)
 ** This option includes in addition the following syndromes::
 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
 Pregnancy history
 If wish to know the fetal gender;
 If it is a redraw;
 Reporting preferences;
 Informed consent;

Please check if you performed the following procedures:
 Reading test submission instructions.
 Reading sample collection and packaging instructions.

REPORTING PREFERENCES

PHYSICIAN / LABORATORY

 Name / Stamp

E-mail; On-Line; Mail; Courier

PATIENT
 E-mail; address _____
 On-Line; By Phone, no.: _____

In order to activate the on-line reporting option, you need to provide us an user name and a password:
 Username: _____ Password: _____
 Signature _____



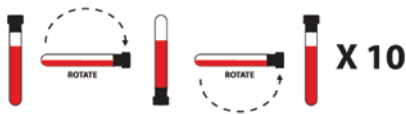
Test Submission Instructions

Informed consent and test requisition form

IMPORTANT: Fill in all required Test Requisition Form information to avoid delays and ensure timely reporting.

To ensure acceptance of your patient's specimen for testing, please verify that the **informed consent** has been signed from the patient and it has been enclosed with samples:

Sample collection instruction:



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

Store collected blood at **room temperature** until ready for shipment. **Blood should never be frozen!**

Sample Packaging:

IMPORTANT: Always store kits at **room temperature**.

- Place the filled and properly labeled collection tube into the **PrenatalSafe®** shipper 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.
- Close box.
- Place shipper kit box inside of **FedEx Clinical Pak** and seal.
- If you are shipping more than one sample, place as many as possible collection tubes into one shipper kit.
- If you are shipping more than one shipper kit, place as many as possible into one FedEx Clinical Pak.
- Adhere the **FedEx airbill** pouch to the outside of the FedEx Clinical Pak. Insert the airbill into the pouch.
- **Call FedEx** to arrange specimen pickup
- Ship specimens, preferably the **same day** as collected. Specimens must be received by Genoma **within 5 days** of collection date. Genoma receives specimens Monday through Saturday.

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 health care provider 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[®] 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. This test is available for singleton and twin pregnancies.

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 health care provider 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[®]:

<p>Trisomy 21</p>	<p>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.</p>
<p>Trisomy 18</p>	<p>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.</p>

Trisomy 13	<p>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.</p>
Sex Chromosome Aneuploidies	<p>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.</p>

(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.

Trisomies 9 and 16

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:

e 10 Mb, at every chromosome in the genome, with **PrenatalSafe® Karyo** test.

e 7 Mb, at every chromosome in the genome, with **PrenatalSafe® Karyo Plus** test.

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 (DiGeorge syndrome, Velocardialfacial syndrome)	1 in 4,000	Learning problems, congenital heart defects, palatal abnormalities	Usually normal, can be reduced for DiGeorge 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)
Sindrome di Jacobsen	11q23-q24.3 deletion	1/100.000
Sindrome di Langer-Giedion	8q24.11-q24.13 deletion	1/200.000
Sindrome di Smith-Magenis	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 healthcare provider 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 healthcare provider 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 test results are confidential to the extent required by law. The GENOMA srl Notices of Privacy Practices set forth the companies' privacy policies and are available on the company websites at <http://www.laboratorioigenoma.eu>.
- Only GENOMA srl personnel will have access to your blood sample and testing information and results. All results will be kept confidential as per applicable laws and guidelines. Results will only be disclosed to your ordering healthcare provider(s).
- Only authorized tests will be performed on your identified blood sample.
- Your sample will be destroyed at the end of the testing process, in accordance with your state's requirements.
- Collecting information on your pregnancy after prenatal diagnosis is part of a laboratory's standard practice for quality purposes, and is required in several states. As such, GENOMA srl may contact your healthcare provider to obtain this information.
- The test is performed after 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

Your test results will be returned to your healthcare provider after analysis by GENOMA srl. The results will be reported by GENOMA srl only to the qualified health care provider(s) indicated on the front of this form. Your results will tell your healthcare provider whether too few or too many copies of the chromosomes being tested for are present. It is the responsibility of the healthcare provider 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 provider 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 also 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 health care provider 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 health care provider 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[®] (Standard Protocol): follow-up March 2016

	Trisomy 21 (n=31.800)	Trisomy 18 (n=31.800)	Trisomy 13 (n=31.800)	Monosomy X (n=31.800)	SCA (n=31.800)
True Positive	257	47	32	77	160
False Positive	6	6	7	48	58
True Negative	31536	31746	31746	31675	31582
False Negative	1	1	0	0	0
Sensitivity (95% CI)	99,61% (97.86% - 99.99%)	97,92% (88.93% - 99.95%)	100,00% (89.11% - 100.00%)	100,00% (95.32% - 100.00%)	100,00% (99.72% - 100.00%)
• % False Negative	0,39%	2,08%	0,00%	0,00%	0,00%
Specificity (95% CI)	99,98% (99.96% - 99.99%)	99,98% (99.96% - 99.99%)	99,98% (99.95% - 99.99%)	99,85% (99.80% - 99.89%)	99,82% (99.76% - 99.86%)
• % False Positive	0,02%	0,02%	0,02%	0,15%	0,18%
PPV (95% CI)	97,72% (95.10% - 99.16%)	88,68% (76.97% - 95.73%)	82,05% (66.47% - 92.46%)	61,60% (52.48% - 70.16%)	73,39% (67.01% - 79.13%)
NPV (95% CI)	100,00% (99.98% - 100.00%)	100,00% (99.98% - 100.00%)	100,00% (99.99% - 100.00%)	100,00% (99.99% - 100.00%)	100,00% (99.99% - 100.00%)

PPV: Positive Predictive Value; NPV: Negative Predictive Value; SCA: Sex Chromosomes Aneuploidy.

Performance PrenatalSAFE[®] (FAST Protocol): follow-up March 2016

	Trisomy 21 (n=15.258)	Trisomy 18 (n=15.258)	Trisomy 13 (n=15.258)	Monosomy X (n=15.258)	SCA (n=15.258)
True Positive	156	30	20	57	91
False Positive	2	1	1	18	22
True Negative	15100	15227	15279	15183	15145
False Negative	0	0	0	0	0
Sensitivity (95% CI)	100,00% (88.43% - 100.00%)	100,00% (88.43% - 100.00%)	100,00% (83.16% - 100.00%)	100,00% (93.73% - 100.00%)	100,00% (96.03% - 100.00%)
• % False Negative	0,0%	0,0%	0,0%	0,0%	0,0%
Specificity (95% CI)	99,99% (99.96% - 100.00%)	99,99% (99.96% - 100.00%)	99,99% (99.96% - 100.00%)	99,88% (99.81% - 99.93%)	99,85% (99.78% - 99.91%)
• % False Positive	0,01%	0,01%	0,01%	0,12%	0,15%
PPV (95% CI)	98,73% (83.30% - 99.92%)	96,77% (83.30% - 99.92%)	95,24% (76.18% - 99.88%)	76,00% (64.75% - 85.11%)	80,53% (72.02% - 87.38%)
NPV (95% CI)	100,00% (99.98% - 100.00%)	100,00% (99.98% - 100.00%)	100,00% (99.98% - 100.00%)	100,00% (99.98% - 100.00%)	100,00% (99.98% - 100.00%)

PPV: Positive Predictive Value; NPV: Negative Predictive Value; SCA: Sex Chromosomes Aneuploidy.

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

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 test 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.

Confidential Reporting Practices

Genoma complies with the Italian confidentiality laws. Test results will be reported only to the ordering health care providers(s) or genetic counselor (where allowed). You must contact your provider to obtain the results of the test. Additionally, the test results could be released to those who, by law, may have access to such data.

Financial Responsibility:

You are responsible for fees incurred with Genoma for services performed. Genoma will submit claims to your medical insurance if requested, but you are ultimately responsible to pay Genoma, any fees reimbursed directly to you or not paid by your insurance provider.

Genetic Counseling:

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

Research and Retention of samples:

Genoma is committed to the continual monitoring and improvement in our testing platforms, thus we may retain and use your leftover de-identified sample and your health information for this purpose, as well as for research purpose. Although future research using the de-identified samples may lead to development of new products, it will be impossible to know if your sample or any other sample was used because they will be stripped of all identifiers and you and your heirs will not receive any payments or benefits from or rights to new products or discoveries. All such uses will be in compliance with applicable law. If you **DO NOT** want any remaining sample to be retained and used for these purposes, you may send a signed request in writing to Genoma within 60 days after fetal results have been issued, whereupon your sample will be destroyed.

Use of Information and Leftover Specimens. Pursuant to best practices and clinical laboratory standards 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 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.

PATIENT CONSENT STATEMENT:

By signing this form, I, the patient having the testing performed, acknowledge that:

- (i) 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;
- (ii) 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;
- (iii) I have discussed with the healthcare provider 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;
- (iv) 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;
- (v) I consent to the use of the leftover specimen and health information as described in the Patient Informed Consent;
- (vi) I consent to having this test performed and I will discuss the results and appropriate medical management with my healthcare provider.

Date: _____

Signature of Patient

Printed Name