PATIENT CONSENT FORM

GeneSafe™: a non-invasive prenatal test that screens for single-gene disorders

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 **GeneSafe™** 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 GeneSafe™ prenatal test

The **GeneSafe™** Non-Invasive Prenatal Test (NIPT) looks at the DNA (genetic material) in your blood. Specifically, it screens multiple genes in cell-free fetal DNA (cfDNA) to assess severe genetic disorders in the fetus.

GeneSafe™ is a complement to Genoma's market-leading **PrenatalSafe®** non-invasive prenatal test, which screens for common aneuploidies, such as trisomy 21 (Down syndrome), trisomy 18, and trisomy 13, or **PrenatalSafe®** Karyo, that also screens for rare aneuploidies segmental chromosome imbalances (gains and losses) in every chromosome in the fetal genome.

GeneSafe™ screens for several clinically significant and life-altering genetic disorders that are not screened for with current NIPT technology, allowing a more complete picture of the risk of a pregnancy being affected by a genetic disorder.

GeneSafe™ involves 3 different levels of screening:

GeneSafe™ ***De Novo*** screens for **44 severe genetic disorders** due to *de novo* mutations (a gene mutation that is not inherited) in **25 genes** that cause skeletal dysplasia, congenital heart defects[1-3], multiple congenital malformation syndromes[4,5], neurodevelopmental disorders, such as autism[6,7], epilepsy[8], intellectual disability[9,10], and sporadic cases of various rare dominant Mendelian disorders, such as Kabuki syndrome[11], Schinzel-Giedion syndrome[12], and Bohring-Opitz syndrome[13]. The rate of de novo variants has been shown to increase as paternal age advances[14,15]. The 44 different disorders screened by this innovative test often occur in the absence of a family history of the condition.

The conditions screened meet at least one of the following criteria:

- Cause cognitive disability
- Require surgical or medical intervention
- Affect quality of life

The genetic disorders screened by **GeneSafe™** ***De Novo*** are listed in Table 1.

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Table 1: Genetic disorders Screened with GeneSafe™ De Novo

Syndromic Disorders	Gene	Noonan Spectrum Disorders	Gene
Alagille syndrome	**JAG1**	Juvenile myelomonocytic leukemia (JMML)	**PTPN11**
CHARGE syndrome	**CHD7**	Noonan syndrome 5/LEOPARD syndrome 2	**RAF1**
Cornelia de Lange syndrome 5	**HDAC8**	Noonan syndrome 8	**RIT1**
Cornelia de Lange syndrome 1	**NIPBL**	Noonan syndrome-like disorder with loose anagen hair	**SHOC2**
Rett syndrome	**MECP2**	Noonan syndrome 4	**SOS1**
Sotos syndrome 1	**NSD1**	**Skeletal Disorders**	
Bohring-Opitz syndrome	**ASXL1**	Achondrogenesis, type II or hypochondrogenesis	**COL2A1**
Schinzel-Giedion syndrome	**SETBP1**	Achondroplasia	**FGFR3**
Holoprosencephaly	**SIX3**	CATSHL syndrome	
Craniosynostosis Syndromes		Crouzon syndrome with acanthosis nigricans	
Antley-Bixler syndrome without genital anomalies or disordered steroidogenesis	**FGFR2**	Hypochondroplasia	
Apert syndrome		Muenke syndrome	
Crouzon syndrome		Thanatophoric dysplasia, type I	
Jackson-Weiss syndrome		Thanatophoric dysplasia, type II	
Pfeiffer syndrome type 1		Ehlers-Danlos syndrome, classic	**COL1A1**
Pfeiffer syndrome type 2		Ehlers-Danlos syndrome, type VIIA	
Pfeiffer syndrome type 3		Osteogenesis imperfecta, type I	
Noonan Spectrum Disorders		Osteogenesis imperfecta, type II	
Cardiofaciocutaneous syndrome 1	**BRAF**	Osteogenesis imperfecta, type III	
Noonan syndrome-like disorder with or without juvenile myelomonocytic leukemia (NSLL)	**CBL**	Osteogenesis imperfecta, type IV	
Noonan syndrome/cancers	**KRAS**	Ehlers-Danlos syndrome, cardiac valvular form	**COL1A2**
Cardiofaciocutaneous syndrome 3	**MAP2K1**	Ehlers-Danlos syndrome, type VIIB	
Cardiofaciocutaneous syndrome 4	**MAP2K 2**	Osteogenesis imperfecta, type II	
Noonan syndrome 6/cancers	**NRAS**	Osteogenesis imperfecta, type III	
Noonan syndrome 1/ LEOPARD syndrome/cancers	**PTPN11**	Osteogenesis imperfecta, type IV	

GeneSafe™ *Inherited* screens for **5 common inherited recessive genetic disorders**, such as **Cystic Fibrosis**, **Thalassemia-Beta**, **Sickle cell anemia**, **Deafness autosomal recessive type 1A, Deafness autosomal recessive type 1B**. The genes screened by **GeneSafe™ *Inherited*** are listed in Table 2.

Table 2: Genetic disorders Screened with GeneSafe™ Inherited

Genetic Disorder	Gene
❖ **Cystic Fibrosis**	**CFTR**
❖ **Deafness autosomal recessive type 1A**	**CX26 (GJB2)**
❖ **Deafness autosomal recessive type 1B**	**CX30 (GJB6)**
❖ **Thalassemia-Beta**	**HBB**
❖ **Sickle cell anemia**	**HBB**

Your healthcare provider or genetic counselor can also give you more information about these conditions.

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GeneSafe™: Indication for testing

GeneSafe™ is intended for patients who meet any of the following criteria:

- Advanced paternal age (men that are >40 years old)
- Abnormal ultrasound finding(s) suggestive of monogenic disorder
- patients wishing to avoid an invasive diagnostic procedure.

The test is suitable for:

- both single and twin pregnancies.
- patients whose pregnancies have been achieved by IVF techniques, including pregnancies with egg donation or surrogacy.

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.
Circulating cell-free fetal DNA is first purified from the plasma component of anti-coagulated maternal whole blood.
Through a state-of-the-art technological process, named ***Next Generation Sequencing*** (**NGS**) technique, **29 genes** are completely sequenced (exons and adjacent intronic regions, ± 5 nucleotides) (Table 1 and 2) at high read depth (**>500X**). The resulting genetic sequences are analysed via an **advanced bioinformatics analysis**, to check for the presence of potential mutations in the genes under investigation.
The screen, developed by the experts at **GENOMA Group**, assesses fetal DNA for pathogenic and likely pathogenic mutations associated with selected single gene disorders, and will not report variants of uncertain significance or benign variants.

Some important points about the testing and reporting process:

- Your test results are confidential to the extent required by law. The GENOMA Group Notices of Privacy Practices set forth the companies' privacy policies and are available on the company websites at http://www.laboratoriogenoma.eu.
- Only GENOMA Group 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 Group genetic counselors 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 Group laboratory, the test results will be returned to your healthcare provider, who will discuss them with you.

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Obtaining and Interpreting Test Results

Your test results will be returned to your healthcare provider after analysis by GENOMA Group. The results will be reported by GENOMA Group only to the qualified health care provider(s) indicated on the front of this form.
Your results will tell your healthcare provider whether pathogenic and likely pathogenic mutations associated with selected single gene disorders have been identified. 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:

"POSITIVE" – Pathogenic / Likely Pathogenic mutation detected: this result shows that the test detected one or more mutations in one or more genes. Our geneticist will explain you in detail during a genetic counselling session the meaning of this test result.
A patient with a **positive GeneSafe™** test result should be referred for genetic counseling and should always be followed-up with an invasive diagnostic test for confirmation of test results, before any medical decisions are made.
Mutations detectable through the **GeneSafe™** test may be classified under the following prognosis categories:

- **Known pathogenic**: clinical relevant mutations causing well-established syndromes;
- **Likely pathogenic**: variants that are likely clinical relevant and may cause well-established syndromes.

The following variants are not reported with **GeneSafe™** test:

- **Benign:** variants that are common or observed in the normal population without known phenotypic signs or inherited from a healthy parent;
- **Variants of uncertain clinical significance (VOUS):** findings with insufficient evidence available for unequivocal determination of clinical significance.

"NEGATIVE" - No Pathogenic / Likely Pathogenic mutations detected: this result shows the test has not detected any disease causing mutation in the targeted genes screened. Negative screening results mean that there is a **very low risk** that the fetus has one of the disorders screened with **GeneSafe™**, although no guarantee may be given that the fetus is actually healthy.

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. There is also a chance that a paternal blood sample could be required, in order to achieve a conclusive interpretation of the results. For this sample no genetic report will be issued, because it will be used only for the purpose of strengthen the reliability of the results.

Genetic counseling before and after testing is recommended. Results of **"POSITIVE" – Pathogenic / Likely Pathogenic mutation detected** is 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 **GeneSafe™** prenatal test does not test for all health problems. Normal results do not eliminate the possibility that your pregnancy may have chromosomal or other genetic conditions, birth defects, or other complications. A '**"NEGATIVE" - No Pathogenic / Likely Pathogenic mutations detected** result on

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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. **GeneSafe™** has a combined analytical sensitivity of **>99%** and a combined analytical specificity of **>99%** in validation studies. Given the combined high incidence of these disorders, **GeneSafe™** may be used to screen all pregnancies after ten weeks gestation. Even though this test is very accurate, the limitations of this analysis are to be always taken into consideration. Please read below.

Test limitations

While the results of the **GeneSafe™** prenatal test are highly accurate, discordant results may occur. Cell-free DNA (cfDNA) testing does not replace the accuracy and precision of prenatal diagnosis with CVS or amniocentesis.
GeneSafe™ is a screening test. This means that pregnancy decisions should not be based solely on the results of **GeneSafe™**. The purpose of the **GeneSafe™** test is to indicate if the fetus is at increased risk for a genetic disorder allowing for follow-up invasive prenatal studies or newborn studies.
The **GeneSafe™** prenatal test does not test for all health problems. Performing this screening allows for an assessment for known pathogenic and likely pathogenic mutations in selected genes associated with selected disorders. Normal results do not eliminate the possibility that your pregnancy may have other genetic conditions, birth defects, or other complications.
GeneSafe™ does not screen for fetal chromosome, or other copy number, abnormalities commonly detected by traditional (aneuploidy) NIPT.
A **"NEGATIVE" - No Pathogenic / Likely Pathogenic mutations detected** result greatly reduces the chances that your fetus has one of the monogenic disorders screened but it cannot guarantee a healthy baby. The result of this test does not eliminate the possibility of other untested genetic disorders, birth defects, or other complications in your fetus or pregnancy.
A patient with a **positive GeneSafe™** test result should be referred for genetic counseling and should always be followed-up with an invasive diagnostic test for confirmation of test results, before any medical decisions are made.
An **uninformative result** may be reported, the causes of which may include, but are not limited to, insufficient sequencing coverage, noise or artifacts, amplification or sequencing bias, or insufficient fetal fraction.
While results of this screen are highly accurate, incorrect 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, vanishing twin, prior maternal organ transplant, fetal demise, genetic or somatic variants that interfere with analysis, an unrecognized twin pregnancy, other circumstances beyond our control, or unforeseen problems that may arise, or other causes.
Incorrect test results may also occur due to metastatic cancer, caused by cell-free tumor DNA (ctDNA) mutation in several genes screened by **GeneSafe™** test involved in cancer development (e.g. BRAF, KRAS, NRAS, etc.).

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This test analyses only genetic diseases and genes listed in Tables 1 and 2. The test does not detect other genetic disorders or genes that were not specifically targeted.
The interpretation of genetic variations is based upon the most updated knowledge available upon examination. Such interpretation may change in the future, when new scientific and medical information on the structure of the genome are acquired and may affect the evaluation of the genetic variations themselves.
The analytical sensitivity for single nucleotide variants is **>99%** with a test specificity at **>99%**. Complex mutations including small insertions, duplications, and indels might be detected at a lower sensitivity. Exonic, gene or chromosomal copy number changes are not detected by this screen.
GeneSafe™ should be offered in conjunction with genetic counseling, including review of family history, to help determine the most appropriate prenatal studies for any pregnant woman.
The ability to report results may be impacted by maternal body mass index (BMI), maternal weight, and/or maternal systemic lupus erythematosus (SLE).

Alternatives

This non-invasive prenatal screening test is only one option for detecting pregnancies at high risk for fetal monogenic disorders. There are multiple other diagnostic options available during pregnancy. For women who want or need more conclusive information about the fetal genetic disorders, commonly used invasive diagnostic tests such as CVS or amniocentesis are available, and will genetic diseases not evaluated with this screening tests.

Genetic Counseling

If you have remaining questions about non-invasive prenatal testing of single gene disorders 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.

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 genetic disorders 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.

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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 **GeneSafe™** 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

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