# Introducing GeneSafe™:

## The first non-invasive prenatal test that screens for single-gene disorders.

**GeneSafe™: Summary**

Building on its long history of genetic innovation, Genoma Group introduces **GeneSafe™**, the first non-invasive prenatal test that screens for both **de novo** and **inherited single-gene disorders**.

Current non-invasive prenatal tests screen for aneuploidies and microdeletions. **PrenatalSafe® Karyo** also screens for rare aneuploidies and segmental chromosome imbalances (gains and losses) in every chromosome in the fetal genome, providing karyotype-level insight.

**GeneSafe™** goes further by screening fetal DNA for pathogenic (disease-causing) and likely pathogenic mutations associated with selected single gene conditions.

**GeneSafe™ works as a complementary screen to traditional NIPT, allowing a more complete picture of the risk of a pregnancy being affected by a genetic disorder.**

**GeneSafe™** detects mutations in **4 genes** causing **5 common inherited genetic disorders** and *de novo* mutations in **25 genes** causing **44 different *de novo* genetic disease**.

**GeneSafe™** allows for the detection of mutations that cause clinically significant and life-altering genetic disorders, such as **Cystic Fibrosis**, **Thalassemia-Beta**, **Sickle cell anemia**, **Deafness**, **Noonan spectrum disorders**, **Cornelia de Lange syndrome**, and **Osteogenesis imperfecta**.

The risk of having a child with single-gene disorders such as **Achondroplasia** and **Crouzon syndrome** increases with advanced paternal age. **GeneSafe™** is now the first non-invasive prenatal screen to detect disorders with an increased prevalence linked to advanced paternal age.

### GeneSafe™: the evolution of NIPT

GeneSafe™ is the first non-invasive prenatal test (NIPT) that screens multiple genes in cell-free fetal DNA (cfDNA) to assess severe genetic disorders in the fetus, simply using a maternal blood sample.

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™ facilitates early diagnosis for single-gene disorders

GeneSafe™ involves 3 different levels of screening:



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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 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]. 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.

**Table 1: Genetic disorders Screened with GeneSafe DE NOVO**

| Syndromic Disorders | Gene |
|---|---|
| Alagille syndrome | **JAG1** |
| CHARGE syndrome | **CHD7** |
| Cornelia de Lange syndrome 5 | **HDAC8** |
| Cornelia de Lange syndrome 1 | **NIPBL** |
| Rett syndrome | **MECP2** |
| Sotos syndrome 1 | **NSD1** |
| Bohring-Opitz syndrome | **ASXL1** |
| Schinzel-Giedion syndrome | **SETBP1** |
| Holoprosencephaly | **SIX3** |
| **Craniosynostosis Syndromes** | |
| Antley-Bixler syndrome without genital anomalies or disordered steroidogenesis | **FGFR2** |
| Apert syndrome | |
| Crouzon syndrome | |
| Jackson-Weiss syndrome | |
| Pfeiffer syndrome type 1 | |
| Pfeiffer syndrome type 2 | |
| Pfeiffer syndrome type 3 | |
| **Noonan Spectrum Disorders** | |
| Cardiofaciocutaneous syndrome 1 | **BRAF** |
| Noonan syndrome-like disorder with or without juvenile myelomonocytic leukemia (NSLL) | **CBL** |
| Noonan syndrome/cancers | **KRAS** |
| Cardiofaciocutaneous syndrome 3 | **MAP2K1** |
| Cardiofaciocutaneous syndrome 4 | **MAP2K2** |
| Noonan syndrome 6/cancers | **NRAS** |
| Noonan syndrome 1/ LEOPARD syndrome/cancers | **PTPN11** |

| Noonan Spectrum Disorders | Gene |
|---|---|
| Juvenile myelomonocytic leukemia (JMML) | **PTPN11** |
| Noonan syndrome 5/LEOPARD syndrome 2 | **RAF1** |
| Noonan syndrome 8 | **RIT1** |
| Noonan syndrome-like disorder with loose anagen hair | **SHOC2** |
| Noonan syndrome 4 | **SOS1** |
| **Skeletal Disorders** | |
| Achondrogenesis, type II or hypochondrogenesis | **COL2A1** |
| Achondroplasia | **FGFR3** |
| CATSHL syndrome | |
| Crouzon syndrome with acanthosis nigricans | |
| Hypochondroplasia | |
| Muenke syndrome | |
| Thanatophoric dysplasia, type I | |
| Thanatophoric dysplasia, type II | |
| Ehlers-Danlos syndrome, classic | **COL1A1** |
| Ehlers-Danlos syndrome, type VIIA | |
| Osteogenesis imperfecta, type I | |
| Osteogenesis imperfecta, type II | |
| Osteogenesis imperfecta, type III | |
| Osteogenesis imperfecta, type IV | |
| Ehlers-Danlos syndrome, cardiac valvular form | **COL1A2** |
| Ehlers-Danlos syndrome, type VIIB | |
| Osteogenesis imperfecta, type II | |
| Osteogenesis imperfecta, type III | |
| Osteogenesis imperfecta, type IV | |



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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 genetic disorders 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** |

GeneSafe™ COMPLETE screens for both **inherited** and ***de novo*** single-gene disorders and represents a combination of the tests GeneSafe™ INHERITED and GeneSafe™ DE NOVO, providing a more complete picture of the pregnancy risk.

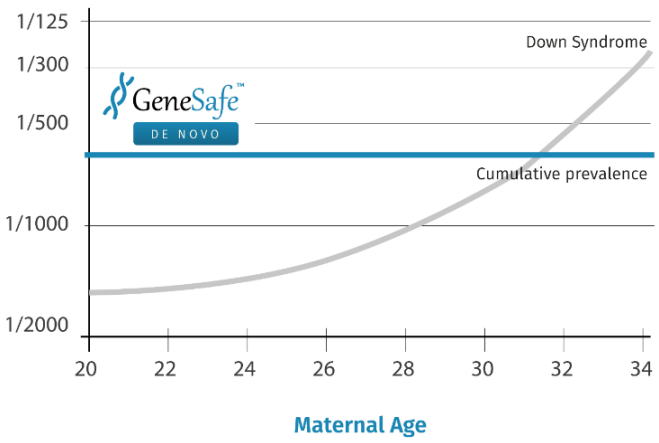
## GeneSafe™ DE NOVO can identify conditions that may have otherwise gone undetected until after birth

Many disorders screened with GeneSafe™ DE NOVO are not typically associated with abnormal prenatal ultrasound findings (especially in the first trimester), or may not be evident until late second/ third trimester, when confirmatory invasive testing can pose a risk of preterm birth, or after delivery. Furthermore, family history is not a good indicator of risk for these conditions, which are commonly caused by *de novo* (not inherited) mutations.

This is a paradigm shift in prenatal screening. This technology screens for new mutations that are common and cannot be detected by standard carrier screening, as these mutations are not present on the parents. In addition, genetic disorders screened by GeneSafe™ DE NOVO are not detectable with current NIPT technology.

## GeneSafe™ screens for *de novo* conditions with a combined incidence of 1 in 600

Although the occurrence of each disorder is relatively rare, the cumulative rate of occurrence of these conditions (**~1 in 600** or **~1 in 300**, for mutations causing development disorders[15]) is similar to that of Down Syndrome. Knowing whether or not a fetus has one of these significant, and often devastating, genetic disorders can allow for healthcare providers and families to form a plan of care including, but not limited to, genetic counseling, specialist referrals, confirmatory studies, and delivery care. The difference in detecting a



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significant genetic disorder in the first/second trimester versus late in pregnancy, or in the neonatal period, can be of immeasurable benefit to healthcare providers and families.

Screening for single-gene disorders early in pregnancy can be extremely helpful and is an important next step in the ability to screen for fetuses with major anatomic abnormalities and chromosome imbalances. As just one example, prenatal screening with confirmatory diagnostic testing for osteogenesis imperfecta (OI) can result in reduced bone fractures through adjusted delivery and post-natal management.

## GeneSafe DE NOVO screens for genetic disorders associated with advanced paternal age

While traditional NIPT screens for conditions typically associated with advanced maternal age (e.g. Down Syndrome), GeneSafe DE NOVO screens also for genetic disorders that are associated with advanced paternal age (men that are >40 years old)[14], ensuring a more comprehensive screen for couple of advanced age.
Disorders associated with advanced paternal age typically are caused by errors (mutations) in DNA arising during spermatogenesis. As a man ages, the chance for these errors to occur substantially increases.
Several genetic diseases show a stronger association advanced paternal age. For example, the risk for some genetic disorders, such as Achondroplasia, is up to 8 times higher in fathers with advanced paternal age. Other genetic diseases associated with advanced paternal age are Pfeiffer syndrome, Crouzen syndrome, Apert syndrome, thanatophoric dysplasia and Osteogenesis Imperfecta.

GeneSafe is the next step in the evolution of screening for genetic disorders during pregnancy, providing information that can affect medical decisions, preparation, and peace of mind for families and physicians. Simply put, GeneSafe is the most comprehensive single gene cell-free fetal DNA screen available.

## 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
- patients at risk for genetic conditions screened

**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

GeneSafe test screens for pathogenic and likely pathogenic mutations associated with selected single gene conditions, by analyzing circulating cell-free fetal DNA from a maternal blood sample.
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



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**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, and will not report variants of uncertain significance or benign variants.

## Results of the GeneSafe™ test

**"POSITIVE" – Pathogenic/Likely Pathogenic mutation(s) detected:** this result shows that the test detected one or more **Pathogenic / Likely Pathogenic mutation** in one or more genes. A positive screening result mean that there is a **high risk** that the fetus has one of the disorders screened with GeneSafe™. 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 mutation(s) 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.

## Parameters used to report the genetic variations

The test analyses only the genes listed in Table 1. Only mutations classified as "**Known pathogenic**" and "**Likely pathogenic**", in accordance with the relevant scientific literature and the current classification in the ClinVar – NCBI, dbSNP – NCBI, and other NCBI resources, Human Gene Mutation Database (HGMD), updated on the date of the sample collection, will be reported.

## Target Coverage

Target Coverage is the average number of sequencing reads for each nucleotide base of the gene. Variations with a read depth (i.e. number of reads) **higher than 500X** are obtained with the sequencing protocol used for this test.

## Accuracy of the GeneSafe™ test

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 singleton pregnancies after nine weeks gestation. Even though this test is very



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accurate, the limitations of this analysis are to be always taken into consideration. Please read below.

## Limitation of the GeneSafe™ test

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 – Pregnancy at Low Risk for a genetic disorder"** 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. The ability to report results may be impacted by maternal body mass index (BMI), maternal weight, and/or maternal systemic lupus erythematosus (SLE).
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 low DNA from the fetus in the maternal blood sample, placental, maternal or fetal mosaicism, vanishing twin, prior maternal organ transplant, fetal demise, cancer, 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.
This test analyses only genetic diseases and genes listed in Tables 1 and 2. The test does not detect other genetic disorders or genes or gene regions that were not specifically targeted. The test only detects mutations in exons and adjacent intronic regions (± 5 nucleotides). It cannot detect deletion or duplications >20 base pair and mosaicism occurrences.
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.



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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.

## 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.

## References

1. Homsy J, Zaidi S, Shen Y, Ware JS, Samocha KE, Karczewski KJ, et al. De novo mutations in congenital heart disease with neurodevelopmental and other congenital anomalies. Science. 2015;350:1262–6.
2. Zaidi S, Choi M, Wakimoto H, Ma L, Jiang J, Overton JD, et al. De novo mutations in histone-modifying genes in congenital heart disease. Nature. 2013;498:220–3.
3. Sifrim A, Hitz M-P, Wilsdon A, Breckpot J, Turki SH A, Thienpont B, et al. Distinct genetic architectures for syndromic and nonsyndromic congenital heart defects identified by exome sequencing. Nat Genet. 2016;48:1060–5.
4. Ng SB, Bigham AW, Buckingham KJ, Hannibal MC, McMillin MJ, Gildersleeve HI, et al. Exome sequencing identifies MLL2 mutations as a cause of Kabuki syndrome. Nat Genet. 2010;42:790–3.
5. Hoischen A, van Bon BWM, Rodríguez-Santiago B, Gilissen C, Vissers LELM, de Vries P, et al. De novo nonsense mutations in ASXL1 cause Bohring-Opitz syndrome. Nat Genet. 2011;43:729–31.
6. Iossifov I, O'Roak BJ, Sanders SJ, Ronemus M, Krumm N, Levy D, et al. The contribution of de novo coding mutations to autism spectrum disorder. Nature. 2014;515:216–21.
7. O'Roak BJ, Deriziotis P, Lee C, Vives L, Schwartz JJ, Girirajan S, et al. Exome sequencing in sporadic autism spectrum disorders identifies severe de novo mutations. Nat Genet. 2011;43:585–9.
8. Allen AS, Berkovic SF, Cossette P, Delanty N, Dlugos D, Eichler EE, et al. De novo mutations in epileptic encephalopathies. Nature. 2013;501:217–21.
9. de Ligt J, Willemsen MH, van Bon BWM, Kleefstra T, Yntema HG, Kroes T, et al. Diagnostic exome sequencing in persons with severe intellectual disability. N Engl J Med. 2012;367:1921–9.
10. Rauch A, Wieczorek D, Graf E, Wieland T, Endele S, Schwarzmayr T, et al. Range of genetic mutations associated with severe non-syndromic sporadic intellectual disability: an exome sequencing study. Lancet. 2012;380:1674–82.
11. Ng SB, Bigham AW, Buckingham KJ, Hannibal MC, McMillin MJ, Gildersleeve HI, Beck AE, Tabor HK, Cooper GM, Mefford HC, Lee C, Turner EH, Smith JD, Rieder MJ, Yoshiura K, Matsumoto N, Ohta T, Niikawa N, Nickerson DA, Bamshad MJ, Shendure J: Exome sequencing identifies MLL2 mutations as a cause of Kabuki syndrome. Nat Genet 2010, 42:790–793.
12. Hoischen A, van Bon BW, Gilissen C, Arts P, van Lier B, Steehouwer M, de Vries P, de Reuver R, Wieskamp N, Mortier G, Devriendt K, Amorim MZ, Revencu N, Kidd A, Barbosa M, Turner A, Smith J, Oley C, Henderson A, Hayes IM, Thompson EM, Brunner HG, de Vries BB, Veltman JA: De novo mutations of SETBP1 cause Schinzel-Giedion syndrome. Nat Genet 2010, 42:483–485.
13. Hoischen A, van Bon BW, Rodriguez-Santiago B, Gilissen C, Vissers LE, de Vries P, Janssen I, van Lier B, Hastings R, Smithson SF, Newbury-Ecob R, Kjaergaard S, Goodship J, McGowan R, Bartholdi D, Rauch A, Peippo M, Cobben JM, Wieczorek D, Gillessen-Kaesbach G, Veltman JA, Brunner HG, de Vries BB: De novo nonsense mutations in ASXL1 cause Bohring-Opitz syndrome. Nat Genet 2011, 43:729–731.
14. Kong A, Frigge ML, Masson G, Besenbacher S, Sulem P, Magnusson G, Gudjonsson SA, Sigurdsson A, Jonasdottir AA, Wong WSW et al.: Rate of de novo mutations and the importance of father's age to disease risk. Nature 2012, 488:471-475.
15. McRae J, et al.: Prevalence and architecture of de novo mutations in development disorders Nature 2017: 542:433-438.



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