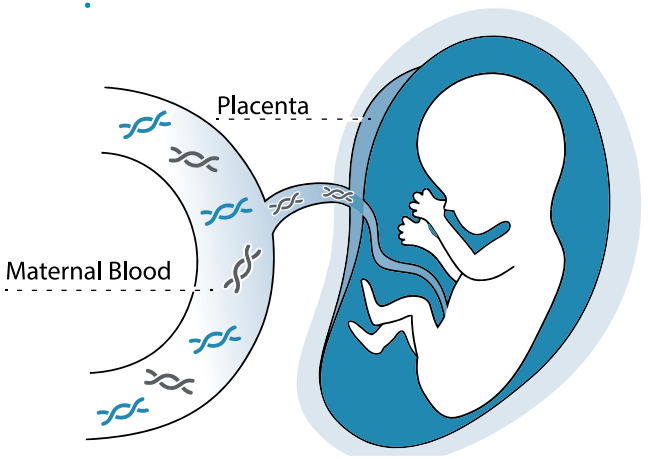
GENOMA®
Molecular Genetics Laboratories Group

GeneSafe™

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

GeneSafe™ the evolution of NIPT

A non-invasive prenatal test that screens multiple genes for mutations causing severe genetic disorders in the fetus



Maternal DNA

Fetal DNA

GeneSafe™ analyzes circulating cell-free fetal DNA **(cfDNA)** from a maternal blood sample.

The test is performed after **10 weeks** of pregnancy.

GeneSafe™ works as a **complementary screen** to traditional and genome-wide NIPT PrenatalSafe® KARYO It screens for several life-altering genetic disorders that are not screened 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 of single-gene disorders.

It involves 3 different levels of screening:

GeneSafe™ INHERITED

This test 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.**

Genes screened: **CFTR, CX26 (GJB2), CX30 (GJB6), HBB**

GeneSafe™ DE NOVO

This test screens for **44 severe genetic disorders** due to ***de novo*** mutations (a gene mutation that is not inherited) in **25 genes**

Genes screened: **ASXL1, BRAF, CBL, CHD7, COL1A1, COL1A2 , COL2A1, FGFR2, FGFR3, HDAC8, JAG1, KRAS, MAP2K1, MAP2K2, MECP2, NIPBL, NRAS, NSD1, PTPN11, RAF1, RIT1, SETBP1, SHOC2, SIX3, SOS1**

GeneSafe™ COMPLETE

This test 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™ INHERITED allows detection of common inherited genetic disorders in the fetus

GENE	GENETIC DISORDER
CFTR	Cystic Fibrosis
CX26 (GJB2)	Deafness autosomal recessive type 1A
CX30 (GJB6)	Deafness autosomal recessive type 1B
HBB	Thalassemia-Beta
HBB	Sickle cell anemia

The inherited recessive disorders screened by GeneSafe™ INHERITED are the most common in the European population

GeneSafe™ DE NOVO

identifies fetal conditions that could be **missed by traditional prenatal screening.**

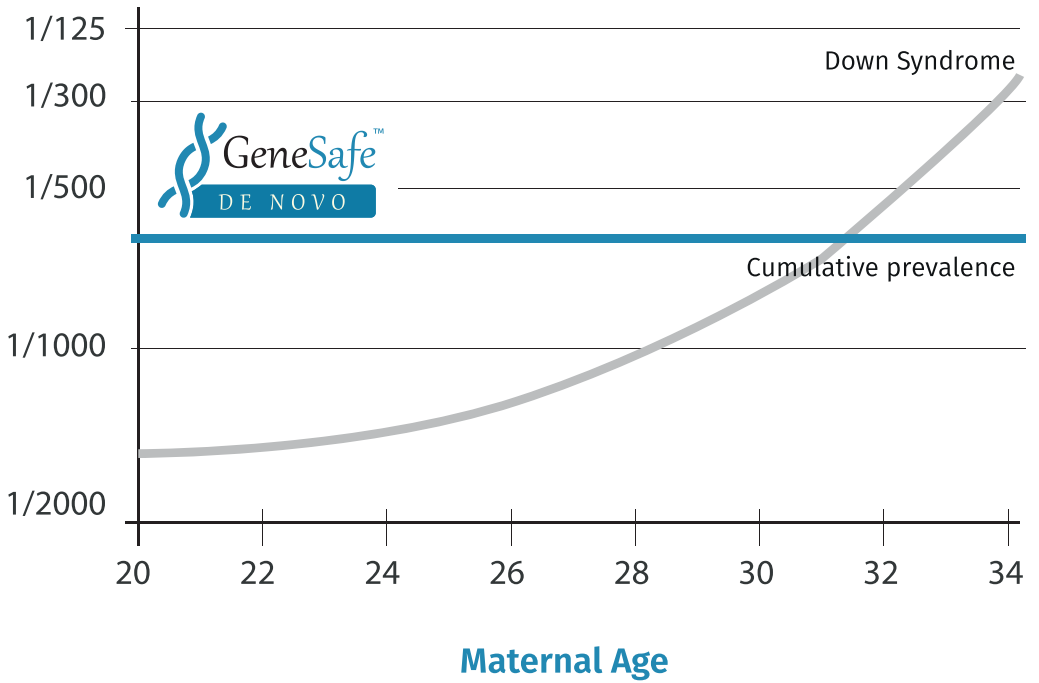
GENE	SYNDROMIC DISORDERS
JAG1	Alagille syndrome
CHD7	CHARGE syndrome
HDAC8	Cornelia de Lange syndrome 5
NIPBL	Cornelia de Lange syndrome 1
MECP2	Rett syndrome
NSD1	Sotos syndrome 1
ASXL1	Bohring-Opitz syndrome
SETBP1	Schinzel-Giedion syndrome
SIX3	Holoprosencephaly
	NOONAN SYNDROMES
BRAF	Cardiofaciocutaneous syndrome 1
CBL	Noonan syndrome-like disorder with or without juvenile myelomonocytic leukemia (NSLL)
KRAS	Noonan syndrome/cancers
MAP2K1	Cardiofaciocutaneous syndrome 3
MAP2K2	Cardiofaciocutaneous syndrome 4
NRAS	Noonan syndrome 6/cancers
PTPN11	Noonan syndrome 1/ LEOPARD syndrome/cancers
PTPN11	Juvenile myelomonocytic leukemia (JMML)
RAF1	Noonan syndrome 5/LEOPARD syndrome 2
RIT1	Noonan syndrome 8
SHOC2	Noonan syndrome-like disorder with loose anagen hair
SOS1	Noonan syndrome 4

GENE	SKELETAL DISORDERS
COL2A1	Achondrogenesis, type II or hypochondrogenesis
FGFR3	Achondroplasia
	CATSHL syndrome
	Crouzon syndrome with acanthosis nigricans
	Hypochondroplasia
	Muenke syndrome
	Thanatophoric dysplasia, type I
	Thanatophoric dysplasia, type II
COL1A1	Ehlers-Danlos syndrome, classic
	Ehlers-Danlos syndrome, type VIIA
	Osteogenesis imperfecta, type I
	Osteogenesis imperfecta, type II
	Osteogenesis imperfecta, type III
	Osteogenesis imperfecta, type IV
COL1A2	Ehlers-Danlos syndrome, cardiac valvular form
	Ehlers-Danlos syndrome, type VIIB
	Osteogenesis imperfecta, type II
	Osteogenesis imperfecta, type III
	Osteogenesis imperfecta, type IV
	CRANIOSYNOSTOSIS SYNDROMES
FGFR2	Antley-Bixler syndrome without genital anomalies or disordered steroidogenesis
	Apert syndrome
	Crouzon syndrome
	Jackson-Weiss syndrome
	Pfeiffer syndrome type 1
	Pfeiffer syndrome type 2
	Pfeiffer syndrome type 3

GeneSafe™ detects de novo mutations in 25 genes causing 44 different genetic disorders. The genetic conditions screened by this innovative test often occur in the absence of a family history of the condition. This is a paradigm shift in prenatal screening. GeneSafe™ screens for de novo mutations that cannot be detected by standard carrier screening, as these mutations are not present on the parents. The genetic disorders screened by GeneSafe™ can cause **skeletal dysplasias, cardiac defects,** [1-2-3] **multiple congenital anomalies,** [4-5] **autism,** [6] **epilepsy** [7] **and/or intellectual disability.** [8-9]

1. Homsy J, et al. *Science. 2015;350:1262–6.* **2.** Zaidi S, et al. *Nature. 2013;498:220–3.* **3.** Sifrim A, et al. *Nat Genet. 2016;48:1060–5.* **4.** Ng SB, et al. *Nat Genet. 2010;42:790–3.* **5.** Hoischen A, et al. *Nat Genet. 2011;43:729–31.* **6.** O'Roak BJ, et al. *Nat Genet. 2011;43:585–9.* **7.** Allen AS, et al. *Nature. 2013;501:217–21.* **8.** de Ligt J, et al. *N Engl J Med. 2012;367:1921–9.* **9.** Rauch A, et al. *Lancet. 2012;380:1674–82.*

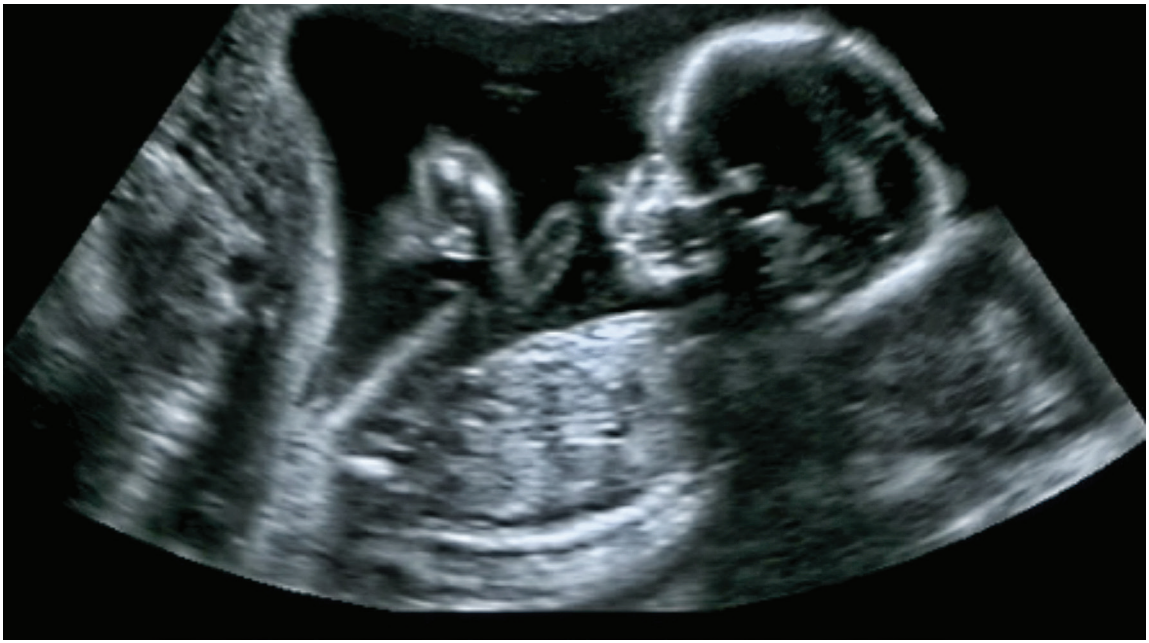
GeneSafe™ DE NOVO screens for conditions common across all maternal ages



All pregnant women – **regardless of age** – are at equal risk for the genetic conditions screened by GeneSafe™. Although the occurrence of each disorder is relatively rare, the cumulative rate of occurrence of these conditions **(~1 in 600)** is similar to that of Down Syndrome, in younger women. [10]

10. McRae J, et al. Prevalence and architecture of de novo mutations in developmental disorders. *Nature 542, 433–438*

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



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.

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 (e.g. **Achondroplasia, Pfeiffer syndrome, Crouzen syndrome, Apert syndrome, Thanatophoric dysplasia, Osteogenesis Imperfecta**, etc.) that are associated with **advanced paternal age** (men that are **>40 years old**)[11], ensuring a more comprehensive screen for couple of advanced age. These disorders typically are caused by **mutations** arising during s**permatogenesis**. As a man ages, the chance for these errors to occur substantially increases.

11. Kong A, et al.: Rate of de novo mutations and the importance of father's age to disease risk. *Nature 2012, 488:471-475.*

GeneSafe™ clear test results reporting

POSITIVE
Pathogenic / Likely Pathogenic mutation(s) detected

This result shows that the test detected one or more mutations in one or more genes.
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.

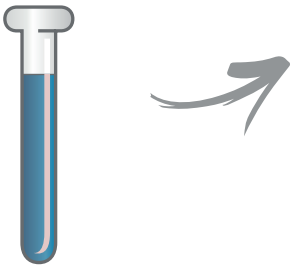
Only **known pathogenic** and **likely pathogenic** mutations are reported.

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.

GeneSafe™ **a groundbreaking technology allowing for a genetic analysis that is revolutionary**

cfDNA isolation
from maternal plasma



Next Generation
Sequencing (NGS)

Fetal Fraction
determination

cfDNA mutation analysis

Advanced bioinformatic analysis to identifiy de novo mutations

GeneSafe™

Superior accuracy

High Resolution: *coverage* **>550X**

Exceptional performance:
Sensitivity and specificity **>99%**

Accurate measurement of Fetal Fraction (FF)

Low limit of detection: highly accurate at **low cfDNA quantity** (FF: **2%**)

Low incidence of inconclusive results (<1%)

GeneSafe™ Test Characteristics

SIMPLE: a simple **blood sample (8-10 ml)** collected at **10^ weeks** of gestation is required

SAFE: it is a **non-invasive** test, **no risk** for the fetus and the mother

RELIABLE:

Sensitivity and **specificity >99%**

FAST:

Turnaround time of **10 days**

GeneSafe™

Indication for testing

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.*

GeneSafe™ 5 easy steps

Order the shipping kit

Fill in all required TRF information and enclose the informed consent signed from the patient

Draw a maternal blood sample (10 ml) at 10+ weeks of pregnancy

Ship the blood sample to Processing Lab

Receive results within 10 days

Complementary pre- and post-test counseling

GeneSafe™ Complimentary services

GeneSafe™ includes

Free **follow-up** of abnormal results

Reimbursement of the test fee
for cases with inconclusive test results

GeneSafe™

Advanced molecular diagnostics solutions using state-of-the art technologies

Test performed in Italy
(Rome or MIlan)

Fast TAT: 10 days

20 years experience in prenatal molecular diagnostics

Personalized genetic counseling with genetic counselors experts in discussing genetic test results and familial risks.

Laboratories with **groundbreaking technologies**

Test available **worldwide**

Over **200.000** genetic tests/year

Dedicated R&D team
Numerous peer-reviewed papers published in renowned international journals

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GENOMA® Molecular Genetics Laboratories Group

ROMA - Laboratori e Studi Medici
Via Castel Giubileo, 11 – 00138 Roma (RM)
Tel.: +39 06 8811270 (6 linee PBX)
Fax: +39 06 64492025
E-mail: info@laboratoriogenoma.eu

MILANO - Laboratori e Studi Medici
Via Enrico Cialdini, 16 (Affori Centre) – 20161 Milano (MI)
Tel.: +39 02 39297626 (12 linee PBX)
Fax: +39 02 392976261
E-mail: info@genomamilano.it

www.laboratoriogenoma.eu | www.genesafe.it | www.prenatalsafe.it