PrenatalSafe Full Risk information

ANALYSIS INCLUDE INTHE PRENATALSAFE FULL RISK PANEL	
WOMAN	**MAN**
PRENATALSAFE KARYO PLUS GENESAFE COMPLETE GENESCREEN FOCUS (ITALIAN PANEL)	GENESCREEN FOCUS (ITALIAN PANEL)

PrenatalSAFE® Karyo Plus

PrenatalSAFE® is a non-invasive prenatal test which, by analyzing free circulating fetal DNA isolated from a maternal blood sample, assesses the presence of common fetal aneuploidies in pregnancy, such as those relating to chromosome 21 (Down's syndrome), chromosome 18 (Edwards syndrome), chromosome 13 (Patau syndrome) and sex chromosomes (X and Y), such as for example Turner syndrome or X chromosome monosomy. fetal structural chromosomal alterations affecting each chromosome, with results very similar to the analysis of the fetal karyotype using invasive prenatal diagnostic techniques.
The PrenatalSAFE® Karyo Plus test represents an evolution of the PrenatalSAFE® Karyo test, and adds to the potential of PrenatalSAFE® Karyo the possibility of identifying the presence in the fetus of submicroscopic structural chromosomal alterations, such as some common microdeletion syndromes. The exam includes the determination of fetal sex (optional).
The PrenatalSAFE® Complete Plus test, consisting of the combination of the PrenatalSAFE® Karyo Plus test with the GeneSAFE ™ Complete test, provides the most in-depth level of information obtainable during pregnancy through a non-invasive prenatal screening test.

Genetic Disorders investigated by the GeneSAFE™ Complete

The GeneSAFE ™ Complete test screen in the fetus for both inherited and de novo onset genetic diseases.
In particular, the GeneSAFE ™ Complete test allows to identify mutations on 4 genes responsible for the genetic diseases with hereditary transmission most frequently found in the Italian population, such as Cystic Fibrosis, Sickle Cell Anemia, Beta Thalassemia and Hereditary Deafness. The genes investigated by the GeneSAFE ™ Complete test, and the related genetic pathologies, are shown in the table below.

Table: List of hereditary genetic diseases investigated by the GeneSAFE™ Complete test

Genetic Disorders investigated by GeneSAFE™	Gene
Cystic Fibrosis	**CFTR**
Thalassemia-Beta	**HBB**
Sickle cell Anemia	**HBB**
Deafness autosomal recessive type 1A	**CX26(GJB2)**
Deafness autosomal recessive type 1A	**CX30(GJB6)**

The GeneSAFE ™ Complete test also allows the detection of mutations on 25 genes in relation to 44 monogenic diseases not inherited from the parents, but which appeared de novo in the fetus. The identified mutations can occur randomly for the first time in the fetus and in these cases are referred to as de novo.

These mutations are not detectable with pre-conception screening tests performed on parents as they are non-hereditary. The aforementioned de novo mutations can lead to skeletal dysplasias, heart defects, multiple congenital anomalies, and / or intellectual deficits in the child. The genes investigated by the test, and the related genetic pathologies, are shown in the table below.

Table: List of de novo onset genetic diseases investigated by the GeneSAFE™ *Complete* test

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
CraniosynostosisSyndromes	
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 anagenhair	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	

The pathologies investigated by the GeneSAFE ™ test are often not detectable by ultrasound examinations in the first trimester (some are only detectable by ultrasound in the second or third trimester) and are independent of maternal age.
Unlike traditional NIPTs, which identify fetal abnormalities associated with advanced maternal age (eg. Down syndrome), the GeneSAFE ™ test identifies genetic diseases associated with advanced paternal age (eg Achondroplasia, Pfeiffer's, Apert's, Crouzon's, Osteogenesis Imperfecta, etc.), caused by genetic errors that arise during the spermatogenesis process, providing older couples with the opportunity to use a more comprehensive screening test.
Biological samples are identified with a barcode and numeric ID, so no identifying data is associated with the tube. It is therefore impossible for anyone to trace personal data.

How the PrenatalSAFE® test is performed?

During pregnancy, some fragments of the fetus's DNA circulate in the maternal blood. Fetal DNA is detectable starting from the 5th week of gestation. Its concentration increases in the following weeks and disappears immediately after delivery. The amount of fetal DNA circulating from the 9th -10th week of gestation is sufficient to ensure the high specificity and sensitivity of the test.
The test is carried out by drawing a blood sample of the expectant mother with a gestational age of at least 10 weeks. The test is performed by analyzing circulating free DNA (cfDNA) in maternal blood using the innovative massively parallel sequencing (MPS) technology of the entire fetal genome, using ILLUMINA Next Generation Sequencing (NGS) sequencers. The chromosomal sequences are then quantified through an advanced bioinformatics analysis, to determine the presence of any fetal chromosomal aneuploidies, identified by a supernumerary of sequences that can be aligned to a specific chromosome. Similarly, the analysis is carried out to detect the pathological variants due to inherited or de novo genetic diseases in the fetus.

PrenatalSAFE® Results

"POSITIVE" - Aneuploidy or structural chromosomal alteration detected: indicates that the test produced a result compatible with fetal aneuploidy or structural chromosomal alteration, at the level of one (or more) of the investigated chromosomes. The reliability of the result is reported in the "Results" section of the report and in the "Test Accuracy" section of the technical report. This result indicates that the fetus has one of the chromosomal conditions indicated but does not ensure that the fetus has this condition. The recommended follow-up is an invasive prenatal diagnostic test, such as chorionic villus sampling (CVS) or Amniocentesis. Our geneticist (or in general a specialist in genetics), in the context of genetic counseling, will explain the test result in detail and will advise you to confirm the result by invasive prenatal diagnosis. In no way is it possible to use Law 194/78 on voluntary termination of pregnancy without first confirming the result of the test by means of Amniocentesis or Villocentesis**.**
"NEGATIVE" - Aneuploidy or structural chromosomal alteration not detected: indicates that the test did not detect aneuploidy or structural chromosomal alterations at the level of the chromosomes examined. The reliability of the result is reported in the "Results" section of the report and in the "Test Accuracy" section of the technical report. This finding, however, does not ensure that the fetus is healthy for such abnormalities. In fact, due to placental physiology, the result obtained may not reflect a real state of normality of the fetus.
In some cases (about 1%) the test may produce a non-optimal or inconclusive result. In such cases, the pregnant woman will be asked to take a new blood sample in order to repeat the test. Even after repetition, the test may not produce a conclusive result. In these cases, it is recommended to resort to alternative prenatal diagnostic methods, such as for example Amniocentesis or Villocentesis, as an increase in the incidence of fetal aneuploidies in samples with inconclusive results has been reported in the scientific literature, for example due to low fetal fraction.
In other cases, the examination could provide a result that indicates a suspicion of fetal chromosomal aneuploidy (borderline result). In this case it will be advised to confirm the result by invasive prenatal diagnosis, as well as for the positive result.
In the event that the analysis of the sex of the fetus is also required, this result can also be provided.
In twin pregnancies, a single result will be reported for both fetuses. Fetal sex in these pregnancies is referred to as male or female, based on the presence or absence of the Y chromosome.

GeneSAFE™ Complete Results

"**POSITIVE**": indicates that the test has detected one or more mutations at the level of one (or more) investigated genes. This finding is consistent with a high risk for a specific genetic disease. The reliability of the result is reported in the "Results" section of the report and in the "Test Accuracy" section of the technical report. This result indicates that the fetus is at high risk for the specific disease indicated but does not ensure that the fetus has this condition. The recommended follow-up is an invasive prenatal diagnostic test, such as chorionic villus sampling (CVS) or Amniocentesis. The Genoma Group geneticist (or in general a specialist in genetics), during the genetic consultation, will explain in detail the result of the test and will advise to confirm the result by invasive prenatal diagnosis. In no way is it possible to make use of Law 194/78 on voluntary termination of pregnancy without first confirming the result of the test by means of Amniocentesis or Villocentesis.
The GeneSAFE ™ test only identifies mutations with known pathological significance. The test does not look for variants with benign meaning, that is, those found in normal individuals and without pathological significance, and variants with uncertain clinical significance, that is, those not yet known or characterized by the medical-scientific community.
"**NEGATIVE**": indicates that the test did not detect any de novo mutation in the fetus with a known pathological significance in the genes examined, nor mutations in compound heterozygosity or homozygosity, in the case of hereditary genetic diseases. This result is compatible with a low risk for a specific genetic disease. The reliability of the result is reported in the "Results" section of the report and in the "Test Accuracy" section of the technical report. This result greatly reduces the chances of the fetus having the genetic diseases tested but cannot guarantee that the fetus is healthy.
In some cases (about 1%) the test may produce a non-optimal or inconclusive result. In such cases, the pregnant woman will be asked to take a new blood sample in order to repeat the test. In other cases, it may be necessary to additionally examine a paternal blood sample for optimal interpretation of the results. A specific report is not required for this last exam.

GeneScreen® FOCUS Information

GeneScreen® FOCUS is a diagnostic test, developed by GENOMA Group, which allows you to perform a multiple analysis of 31 inherited genetic diseases, including those most frequent in the Italian population, such as Cystic Fibrosis, Sickle Cell Anemia, Thalassemia and Hereditary deafness.
GeneScreen® FOCUS allows the couple to know, through the analysis of their DNA, if they are carriers of serious genetic diseases. The test, therefore, allows to identify couples at risk of transmitting a specific genetic disease to their children.

GeneScreen® FOCUS Indications

GeneScreen® FOCUS is indicated:
• For couples who plan to become parents, both through natural conception and through access to medically assisted procreation (MAP) techniques;
• For couples who are expecting a child, and who wish to reduce the risk of transmitting a hereditary genetic disease to the latter;
• For couples who use heterologous fertilization techniques, in order to identify a gamete donor who is not a carrier of mutations in the same genes found in one of the couple's partners.
The examination can be performed on a single individual or, preferably, on both partners of the couple.

How the GeneScreen® FOCUS is performed?

The test is done using a buccal swab or taking a blood sample. Through a complex laboratory analysis, the DNA is isolated from the nucleated cells and **amplified by PCR**. Subsequently, through an advanced technological process of **parallel massive sequencing (MPS)**, which uses **Next Generation Sequencing (NGS) techniques**, completely 30 genes (exons and adjacent intronic regions, ± 5 nucleotides) at a high reading depth. The gene sequences obtained are **analyzed through an advanced bioinformatics analysis**, to determine the presence of any mutations in the genes under examination. The genes analyzed are the following: ACADM, AGXT, ARSA, ATP7B, BTD, CBS, CFTR, DHCR7, EMD, FMR1, GAA, GALC, GALT, GBA, GJB1, GJB2, GJB6, GLA, HADHA, HBA1, HBA2, HBB , HEXA, MEFV, MMACHC, PAH, PMM2, SERPINA1, SLC26A2, SMN1.

The analysis to identify the deletion of exons 7 and 8 of the SMN1 gene is performed by MLPA technique and subsequent capillary electrophoresis in an automatic sequencer with fluorescent technology.
The evaluation of the expansion of the nucleotide triplets repeated in the FRAXA fragile site is performed by fluorescent PCR and subsequent capillary electrophoresis in an automatic sequencer.
The genes investigated were selected on the basis of the incidence in the population of diseases caused by mutations in these genes, the severity of the clinical phenotype at birth and the importance of the associated pathogenetic picture, following the indications of the American College of Medical Genetics (ACMG) (Grody et al., Genet Med 2013: 15: 482–483).

GeneScreen® FOCUS Results

"**POSITIVE"** - Presence of one or more mutations: indicates that the test has detected one or more mutations at the level of one or more genes. During the genetic counseling, our geneticist will explain in detail the meaning of the test result and will suggest, if necessary, the need to extend the examination to the other partner of the couple, in order to verify that the latter is not a carrier. of the same genetic disease, in which case there would be a risk of transmitting the disease to children.
Mutations detectable by the **GeneScreen® FOCUS** test can fall into the following prognostic categories:
or with known pathological significance;
If both partners of the couple test positive for the test, carrying a mutation with known pathological significance in the same gene, our geneticist will be able to provide an overview of the diagnostic options currently available to verify the health of the fetus, in case of future pregnancy.
"**NEGATIVE**" - Absence of mutations: indicates that the test did not detect the presence of mutations in the genes examined.

RhSafe®

On specific request, it is also possible to associate the **RhSafe®** test with the **PrenatalSAFE®** test, only in pregnancies with a Rh (D) negative pregnant woman and a Rh (D) positive male partner.
The **RhSafe®** test, a non-invasive prenatal examination which, by analyzing the fetal DNA isolated from a blood sample of the pregnant woman, allows to determine the fetal Rh (D) factor. The test is applied in pregnancies with Rh (D) negative pregnant women and Rh (D) positive partners.

The advantages of the RhSafe® test

The test for the early non-invasive determination of fetal Rh (D) factor, through the analysis of free fetal DNA in maternal blood, is a reliable and useful test, which has now become a routine in the management of pregnancies characterized by maternal-fetal incompatibility.
The test allows to identify pregnancies at risk for haemolytic disease of the fetus and newborn, and therefore to reduce the use of anti-D prophylaxis in cases where the fetus is Rh (D) negative like the mother. In these cases, in fact, there is no risk of sensitization, therefore the administration of anti-D immunoglobulins can be avoided.

Who can undergo the RhSafe® test?

All Rh (D) negative pregnant women with a gestational age of at least 10 weeks. The **RhSafe®** test is performed (on request) only in pregnancies with Rh (D) negative pregnant and Rh (D) positive male partner. To carry out the test it is necessary to produce reports certifying the Rh factor of the couple. In the event that the reports in question are not produced within 30 days from the date of acceptance of the sample, the examination will not be performed.