

**APPLICATION FORM AND INFORMED CONSENT  
INFORMATION ON THE POTENTIAL AND LIMITATIONS OF THE TEST**

PLEASE COMPLETE ALL RELEVANT DATA IN CAPITAL LETTERS

**PATIENT**

Surname \_\_\_\_\_

Name \_\_\_\_\_

Date of birth DD / MM / YYYY   /   /

Place of birth \_\_\_\_\_

Address - Post Code - City \_\_\_\_\_

Country \_\_\_\_\_

C.F. \_\_\_\_\_

Phone Number \_\_\_\_\_

Email \_\_\_\_\_

Date DD / MM / YYYY   /   /

**REQUIRED TEST**

BASIC

BASIC PLUS  DIGEORGE SYNDROME

BASIC PLUS + 90 MICRODELETIONS/MICRODUPLICATIONS

KARYOTYPE

KARYOTYPE PLUS

KARYOTYPE PLUS + MONOGENIC DISEASES

TOTAL SCREEN

MONOGENIC DISEASES

MINI CGS 1  
BASIC PLUS + 90 MICRODELETIONS/MICRODUPLICATIONS + MATERNAL CARRIER SCREENING

MINI CGS 2  
KARYOTYPE + MATERNAL CARRIER SCREENING

MINI CGS 3  
KARYOTYPE PLUS + MONOGENIC DISEASES + MATERNAL CARRIER SCREENING

FRAA  
FOLATE RECEPTOR ALPHA AUTOANTIBODIES

**PREGNANCY (ALL FIELDS REQUIRED)**

I want to be informed of fetal sex? YES  NO

**PARITY**

**PREGNANCY**

Single  Monochorional twin  Bicornial twin

**GRAVIDANZA**

Spontaneous  Homologous IVF  Heterologous IVF (Donor Age)

Date Last Period DD / MM / YYYY   /   /

Actual gestational age at the date of blood collection

WEEKS   DAYS

**ETHNIC GROUP (required)**

Caucasian  African  North African   
Asian  Other

Weight (required) \_\_\_\_\_ Height (required) \_\_\_\_\_

Smoker YES  NO

**CLINICAL HISTORY**

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

**DOCTOR / LABORATORY**

Surname of the doctor (required) \_\_\_\_\_

Name of the doctor (required) \_\_\_\_\_

Doctor's phone number \_\_\_\_\_

Laboratory / Clinical Diagnostic Center of Belonging (required) \_\_\_\_\_

Address \_\_\_\_\_

Post Code \_\_\_\_\_ City \_\_\_\_\_

Email \_\_\_\_\_

Date DD / MM / YYYY   /   /

Doctor's signature that has collected the informed consent

## INFORMATION ON THE POTENTIAL OF THE TEST AND ACCEPTANCE OF ITS LIMITATIONS

### TEST SELECTION

THE ANALYSES AVAILABLE WITHIN THIS TEST MUST BE SELECTED BY THE PREGNANT WOMAN UNDER THE GUIDANCE OF A SPECIALIST, WHO WILL ENSURE THAT THIS INFORMED CONSENT IS FULLY UNDERSTOOD IN ACCORDANCE WITH THE NEEDS AND REQUESTS OF THE PARENTAL COUPLE.

**I hereby declare that I have received detailed information regarding the NIPT screening test that I have selected and requested.**

I fully understand that, although the test I am undergoing demonstrates extremely high diagnostic accuracy, as stated by the current guidelines in use in our country, definitive diagnostic certainty is provided exclusively by invasive tests (Amniocentesis and Chorionic Villus Sampling). I also understand that all fetal DNA tests (NIPT) do not provide definitive diagnostic certainty. While rare, cases of both false positives and false negatives have been reported, and I accept this rare eventuality. Additionally, I understand that the likelihood of incorrect interpretation of fetal sex, as estimated in global literature, is 3%.

**BASIC** exclusively investigates the most common forms of chromosomal anomalies, **Down syndrome** (trisomy of chromosome **21**), **Edwards syndrome** (trisomy of chromosome **18**), and **Patau syndrome** (trisomy of chromosome **13**), with a **sensitivity of 99,8%**, as outlined in the current guidelines. **If requested, fetal sex determination can also be provided; however, as previously stated, it does not include the detection of sex chromosome anomalies.**

**BASIC PLUS** investigates the three main fetal chromosomal **aneuploidies** associated with **chromosomes 21, 18, and 13** (as previously described), as well as the X and Y sex chromosomes, with a **sensitivity of 99,8%**. It also determines fetal sex, which, upon our request, can remain undisclosed.

If requested, the test can be extended to include screening for **DiGeorge Syndrome**, a sporadic genetic condition caused by the deletion of a portion of chromosome 22, with an incidence of approximately 1 in 3,500 live births.

I confirm my request for the screening of **DiGeorge Syndrome**? YES  NO

**BASIC PLUS + 90 MICRODELETIONS/MICRODUPLICATIONS** investigates the three main fetal chromosomal **aneuploidies** associated with **chromosomes 21, 18, and 13**, as well as the **X and Y sex chromosomes (with a sensitivity of 99,8%)**. The test also includes the screening of a large number of small chromosomal alterations caused by structural rearrangements (referred to as **microdeletions/microduplications**) at an average resolution of 5Mb, which is nonetheless correlated to the fetal fraction (**sensitivity increases with a higher fetal fraction, up to 90%**). Higher sensitivity values cannot be achieved by any NIPT test. The term microdeletions/microduplications refers to anomalies characterized by the absence of a small chromosomal segment, resulting in the loss of genetic information (microdeletions), or the addition of extra genomic material (microduplications). Other molecular variants than microdeletions and microduplications associated with the same conditions cannot be detected by this test.

<i>1p31, microduplication</i>	<i>5q12, microdeletion</i>	<i>11p13, WAGR</i>	<i>17q11.2, microduplication</i>
<i>1p36, microdeletion</i>	<i>5q35.3, Sotos</i>	<i>11p15-p14, microdeletion</i>	<i>17p11.2, Potocki-Lupski</i>
<i>1q21q32, monosomy</i>	<i>6p21, Cleidocranial Dysplasia</i>	<i>11q, Jacobsen</i>	<i>17p11.2, Smith-Magenis</i>
<i>1q21.1, microdeletion</i>	<i>6q24-q25, microdeletion</i>	<i>11q23.3-q25, microdeletion</i>	<i>17p13.3, Miller-Dieker</i>
<i>1q21.1, microduplication</i>	<i>7q11.23, microduplication</i>	<i>12q14, microdeletion</i>	<i>17q21, Koolen-de Vries</i>
<i>1q23-qter, trisomy</i>	<i>7q11.23, Williams-Beuren</i>	<i>13q14, microdeletion</i>	<i>17q21.31, microduplication</i>
<i>1q41-q42, microdeletion</i>	<i>7q21.q31, trisomy</i>	<i>13q21-qter, monosomy</i>	<i>18p, microdeletion</i>
<i>1q42-qter, monosomy</i>	<i>7q32-qter, monosomy</i>	<i>13q21-qter, trisomy trisomy</i>	<i>18pter-q12, trisomy</i>
<i>2p15-p16.1, microdeletion</i>	<i>7q32-qter, partial trisomy</i>	<i>14q11-q22, microdeletion</i>	<i>18q, microdeletion</i>
<i>2q22.3, Mowat-Wilson</i>	<i>8p23.1, microdeletion</i>	<i>14q24-qter, trisomy</i>	<i>18q12-qter, trisomy</i>
<i>2q33.1, microdeletion</i>	<i>8p23.1, microduplication</i>	<i>14q32.13, Wilms tipo 1</i>	<i>19p13, microduplication</i>
<i>2q33.1, microduplication</i>	<i>8q12.1-q21.2, microdeletion</i>	<i>15q11, Angelman</i>	<i>19q13.11, microdeletion</i>
<i>2q35, microduplication</i>	<i>8q13.3, Branchio-Oto-Renal Syndrome</i>	<i>15q11-q13, Prader-Willi</i>	<i>20p, trisomy</i>
<i>2q37, microdeletion</i>		<i>15q14, microdeletion</i>	<i>20p12, Alagille</i>
<i>3p11-p21, monosomy</i>	<i>8q21-qter, monosomy</i>	<i>15q22-qter, trisomy</i>	<i>20q13.1-q13.3, microduplication</i>
<i>3q22, Dandy-Walker</i>	<i>8q21.11, microdeletion</i>	<i>15q26-qter, microdeletion</i>	<i>22q11.2, DiGeorge</i>
<i>3p25-pter, monosomy</i>	<i>8q24.11, Langer-Giedion</i>	<i>15q26-qter, microduplication</i>	<i>22q11.2, microduplication</i>
<i>3q29, microdeletion</i>	<i>9p, microdeletion</i>	<i>15q26.1, Congenital Diaphragmatic Hernia Type 1</i>	<i>22q13, Phelan-mcdermid</i>
<i>3q29, microduplication</i>	<i>9q22.3-q33, microdeletion</i>		<i>Xp11.3, microdeletion</i>
<i>4p16.3, Wolf-Hirschhorn</i>	<i>9q33.2-q34.3, microduplication</i>	<i>16p11.2-p12.2, microdeletion</i>	<i>Xp11.23-p11.22, microduplication</i>
<i>4q21q31, monosomy</i>	<i>9q34, Kleefstra</i>	<i>16p11.2-p12.2, microduplication</i>	<i>Xp21.3, Lissencefalia X-linked</i>
<i>4q31-qter, monosomy</i>	<i>10q26, microdeletion</i>	<i>16p13.3, Rubinstein-Taybi</i>	<i>Xq27.3-q28, microduplication</i>
<i>5p, Cri-du-chat</i>	<i>11p, Potocki-Shaffer</i>	<i>17q11.2, microdeletion</i>	<i>Xq28, microdeletion</i>

**KARYOTYPE** extends the investigation of numerical alterations to all chromosomes. This NIPT, in other words, detects the presence of an **altered number in all 23 pairs of chromosomes related to the fetal karyotype**, including the sex chromosomes X and Y (with a **sensitivity of 99,8%**).

**KARYOTYPE PLUS** is a highly elaborate, complete, non-invasive test of circulating free fetal DNA (NIPT). It includes all the investigations mentioned so far: **numerical alterations**, known as aneuploidies (alterations in chromosome number only), for **all chromosomes**, including **13, 18, 21**, and the **sex chromosomes (X and Y, along with their numerical alterations)** with a **sensitivity of 99,8%**. Additionally, it includes the analysis of **90 syndromes caused by microdeletions/microduplications**, at an average resolution of 5Mb, which depends on the fetal fraction (**sensitivity increases with a higher fetal fraction, up to 90%**). Higher sensitivity values cannot be achieved by any test. The list of the 90 main syndromes investigated in this screening will be included in the results and is clearly outlined on the FetalDNA.it website and on the previous page under the section 'Base Plus+90 Microdeletions/Microduplications'. **The FetalDNA Karyotype Plus also includes, at no additional cost, the screening for the most common maternal Cystic Fibrosis mutations.** I confirm that I request the screening for **the most common maternal Cystic Fibrosis mutations**? YES  NO

**MONOGENIC FETAL DISEASES** (can be requested individually or in combination with the levels described above)

Monogenic disorders represent a broad and clinically significant group of rare diseases caused by point mutations in single genes. Their overall incidence, **when considering the combined frequencies of the various conditions, exceeds that of all other conditions commonly included in prenatal screening.**

**Note:** Results must always be interpreted within the clinical context of the pregnant patient and her family history. The test does not replace invasive prenatal diagnosis (chorionic villus sampling or amniocentesis), but it represents an advanced screening tool for the majority of genetic mutations responsible for fetal monogenic disorders, both inherited and «de novo»

The panel analyzes a total of 102 genes associated with hereditary conditions, corresponding to approximately 90–100 monogenic diseases:

- **52 genes are associated with autosomal recessive disorders** (from two healthy carrier parents; approximately 0.27% of genetic diseases).
- **50 genes are associated with autosomal dominant or X-linked disorders occurring «de novo»** (approximately 0.24% of genetic diseases).

It is important to emphasize that the number of genes and the number of disorders do not necessarily coincide, for two reasons:

- a single gene may be associated with multiple clinical conditions;
- the same disease may result from mutations in different genes.

**The list of analyzed conditions is available at: [www.fetalDNA.it/dettaglioindagini](http://www.fetalDNA.it/dettaglioindagini)**

I have been informed that the test does not provide diagnostic certainty regarding the possible presence of fetal abnormalities; however, it has demonstrated high reliability, with an **average sensitivity of 99.5% and an average specificity of 98%**. This means that it correctly identifies the disease in 99.5% of affected fetuses and excludes the condition in 98% of unaffected fetuses. False negatives, approximately 0.5 per 100 fetuses actually affected, and false positives (results suggesting a disease in a healthy fetus) are approximately 2 per 100 unaffected fetuses.

**If the analysis returns a positive result**, the laboratory may perform parental transmission testing by analyzing the maternal fraction of the sample and, if necessary, paternal DNA (buccal swab). **This additional analysis, not included in the cost of the test, is applied exclusively to cover processing costs due to ethical considerations. Reporting times may therefore be extended depending on the additional investigation.**

**TOTAL SCREEN** represents a highly advanced and comprehensive non-invasive prenatal test (NIPT) performed on circulating free fetal DNA.

It analyzes all **23 pairs of chromosomes** related to the fetal karyotype, including the investigation of **sex chromosome aneuploidies (X, Y)** as well as the three main fetal chromosomal aneuploidies associated with **chromosomes 21, 18, and 13: Down syndrome** (Trisomy 21), **Edwards syndrome** (Trisomy 18), and **Patau syndrome** (Trisomy 13), with a **sensitivity of 99.8%**.

It also includes the screening of 90 small chromosomal alterations caused by structural rearrangements (referred to as **microdeletions/microduplications**) at an average resolution of 5Mb, which depends on the fetal fraction (**sensitivity increases with a higher fetal fraction, reaching up to 90%**). Additionally, it investigates genetic mutations responsible for **fetal monogenic diseases** as listed in the previous section, with a **sensitivity of up to 90%**.

The FetalDNA Total Screen also includes investigations related to the pregnant woman, specifically:

- Screening for mutations responsible for **maternal Cystic Fibrosis**.
- Screening for exon 7 and 8 deletions of the SMN1 and SMN2 genes associated with **Spinal Muscular Atrophy** (this test excludes the vast majority of molecular alterations linked to SMA; however, extremely rare mutations cannot be detected with this test).
- Screening for **infectious agents** present in the maternal blood, allowing early detection prior to the positivity of antibody tests routinely used during pregnancy (while reliable and thorough, it does not rule out fetal damage caused by infections occurring before or after the test).
- Screening for mutations associated with **predisposition to preterm birth** (this test does not exclude preterm birth caused by other clinical factors).
- Biochemical risk assessment for **preclampsia** (provides a risk value that, although highly useful for the treating physician, does not offer diagnostic certainty).
- Screening for the most common mutations responsible for **hereditary thrombophilia** (these investigations, considered by much of the international literature to be useful for preventing maternal-fetal complications such as miscarriage, growth restriction, placental abruption, and thrombosis, must be evaluated in the clinical context and do not exclude the existence of other factors causing the same conditions).

**MINI CGS 1** includes the investigations indicated in the Base Plus + 90 Microdeletions/Microduplications combined with Maternal Carrier Screening, which analyzes:

- Cystic Fibrosis, Congenital Deafness, and Spinal Muscular Atrophy (SMA) inherited from both parents (recessive transmission).
- Muscular Dystrophy and Fragile X Syndrome inherited from healthy carrier mothers (X-linked transmission).

**If any positive results are found in the Maternal Carrier Screening, I will be contacted for genetic counseling.**

**MINI CGS 2** includes the investigations indicated in the Karyotype Plus combined with Maternal Carrier Screening, which analyzes:

- Cystic Fibrosis, Congenital Deafness, and Spinal Muscular Atrophy (SMA) inherited from both parents (recessive transmission).
- Muscular Dystrophy and Fragile X Syndrome inherited from healthy carrier mothers (X-linked transmission).

**If any positive results are found in the Maternal Carrier Screening, I will be contacted for genetic counseling.**

**MINI CGS 3** includes the investigations indicated in the Karyotype Plus and monogenic diseases combined with Maternal Carrier Screening, which tests for:

- Cystic Fibrosis, Congenital Deafness, and Spinal Muscular Atrophy (SMA) inherited from both parents (recessive transmission).
- Muscular Dystrophy and Fragile X Syndrome inherited from healthy carrier mothers (X-linked transmission).

**If any positive results are found in the Maternal Carrier Screening, I will be contacted for genetic counseling.**

**FOLATE RECEPTOR ALPHA AUTOANTIBODIES (FRAA)** In addition to the test I have selected, I request that an immunological assay be performed for the detection of autoantibodies against the folate receptor alpha. According to the scientific literature, these autoantibodies are considered among the potential causes of cerebral folate deficiency and are therefore associated with an increased risk of neurodevelopmental disorders, including autism spectrum disorders, in the fetus.

## INFORMATION ON THE POTENTIAL OF THE TEST AND ACCEPTANCE OF ITS LIMITATIONS

- Regarding the detection of fetal anomalies in maternal blood (NIPT), I fully understand that the test I am undergoing, as stated by the current Guidelines in use in our country, does not provide diagnostic certainty, which is exclusively offered by invasive tests (Amniocentesis and Chorionic Villus Sampling). I also understand that all fetal DNA tests (NIPT) do not provide definitive diagnostic results. Although rare, cases of false positives and false negatives have been reported. I accept this rare eventuality. Furthermore, the possibility of incorrect fetal sex determination is 3%. While this occurrence has no clinical relevance, it must be acknowledged due to its emotional impact.
- Additionally, NIPT does not detect balanced chromosomal rearrangements. It may fail to detect fetal and/or placental chromosomal mosaicisms (two cell lines with different chromosomal configurations). It does not analyze all point mutations associated with the investigated genes, and its sensitivity does not exceed 90%. It does not detect methylation defects, triploidy, polyploidy, or any chromosomal and molecular rearrangements that cannot be identified using NIPT techniques.
- If the analysis returns a positive result**, current guidelines require confirmation through invasive prenatal diagnosis (**Chorionic Villus Sampling or Amniocentesis**). These procedures will be scheduled at our Rome center **free of charge**, covering both the sampling technique and genetic testing.
- Result reporting times vary depending on the test requested and may be delayed due to technical issues or additional analytical checks.
- I understand that this NIPT, although performed using the most advanced molecular technologies, may not provide a result and might need to be repeated (approximately 1% of cases in the literature). This can also occur when a low percentage of fetal DNA is detected (generally below 4%). In such cases, an invasive diagnostic procedure is recommended, as a low level of fetal DNA in maternal blood may indicate an increased risk of chromosomal abnormalities. FetalDNA (like all NIPT tests) is performed by quantitatively comparing the DNA of selected chromosomes in maternal blood with that of fetal origin. Most of this DNA is of maternal origin, with only a small proportion being fetal. The test determines if the amount of DNA from a specific chromosome deviates from the expected amount. For example, an excess of DNA from chromosome 21 could indicate that the fetus has three copies of this chromosome (causing Down syndrome) instead of the usual two. The minimum threshold of **4%** required to obtain a sufficiently reliable diagnosis has been defined through statistical models based on the minimum number of readings of aneuploid chromosome fragments sufficient to detect fetal aneuploidy at various levels of fetal fraction (FF). According to this model, at low FF levels, differences in circulating cfDNA between pregnancies with fetal trisomies and those with euploid fetuses may not be detectable, leading to false negatives. A factor associated with low fetal cfDNA percentages and the potential failure of the test is increased maternal body weight. The increased amount of maternal cfDNA in obese women may mask the fetal fraction, complicating the screening for aneuploidies and increasing the risk of test failure due to a high body mass index (**BMI >30 in obesity and between 25 and 30 in overweight cases**). **It is emphasized and reiterated that any mutations other than those specifically targeted and reported in the test results will not be investigated, and the test has no capability to verify their presence.**
- When the test needs to be repeated, a new blood sample is collected at **no additional cost**.
- In dizygotic twin pregnancies, it is not possible to distinguish the condition of each fetus or accurately assess sex chromosome aneuploidies.** However, the presence or absence of the Y chromosome can be detected. If the Y chromosome is identified, it cannot be determined whether one or both fetuses are male. In pregnancies that began as twin or multiple gestations followed by spontaneous miscarriage of one or more fetuses with reabsorption of the gestational sac (vanishing twin), the maternal blood may contain free fetal DNA from the miscarried fetus. This could interfere with the quality of results, leading to false positives if the miscarriage was caused by chromosomal aneuploidies in the lost fetus. Similarly, there may be discrepancies in sex determination (e.g., male sex identified due to the presence of the Y chromosome originating from the miscarried fetus).
- In cases of **chromosomal mosaicism** (with a frequency of approximately 1-2%), result discrepancies (false positives or false negatives) may occur. Specifically, the test may produce a positive result (aneuploidy detected), but the chromosomal anomaly is confined to the placenta due to chromosomal mosaicism. In such cases, the fetus may present a normal karyotype during invasive prenatal diagnosis (false positive). Conversely, the test may produce a negative result (aneuploidy not detected), but the fetal DNA without aneuploidy may be confined to the placenta due to chromosomal mosaicism, resulting in a fetus with an aneuploid karyotype during invasive prenatal diagnosis (false negative).

### By signing this form, I declare that:

- I have read and understood the information provided in this informed consent document, in accordance with Law No. 219 of 22 December 2017 ("Provisions on informed consent and advance healthcare directives");
- I have had the opportunity to ask the physician questions regarding the objectives, benefits, and potential risks of the test, and I have received clear and comprehensive answers;
- I am aware that, according to national Guidelines (e.g., SIMGeN-SIGU guidelines and indications from the Ministry of Health), professional genetic counseling is recommended both before and after the test;
- I have been informed that it is possible to consult the website [www.fetaldna.it](http://www.fetaldna.it) for additional information and for regulatory, technical, and medical updates related to the FetalDNA test;
- I am aware that the information available on the website [www.fetaldna.it](http://www.fetaldna.it) does not replace medical advice, diagnosis, or treatment provided by a qualified healthcare professional.

### FIELD REQUIRED

I hereby declare that I have **FULLY UNDERSTOOD** the limitations of the selected screening test.

I hereby declare that I have **NOT FULLY UNDERSTOOD** the limitations of the selected screening test.

Signature / Signatures  
pregnant woman

Doctor's signature  
that has collected the informed consent

*Your privacy is a priority for ALTAMEDICA. Artemisia SpA, whose registered office is located in Rome at Viale Liegi, 41 as the data controller, informs you that your data will be handled in compliance with the applicable laws and EU Regulation No. 2016/679. Your identity and all data related to your personal information will remain confidential, and only authorized personnel will have access to this information, along with competent authorities when required by local jurisdiction laws. We wish to inform you that your personal data will be processed solely for the following purposes: (1) To fulfill obligations arising from the provision of services you have subscribed to; (2) For research purposes, scientific publications, and presentations, provided that your data remains anonymous and cannot be identified during data analysis, and any identifiable data will be removed from any publication.*

*In accordance with personal data protection laws, the requesting party must have the patient's consent to perform the requested diagnostic tests and process their data, which will be stored for no longer than permitted by the current legislation.*

*You may exercise your rights at any time, including access, rectification, objection, deletion, withdrawal, automated decision-making, restriction, and portability, by contacting the company at Artemisia spa con sede in Viale Liegi 41 - Roma via registered letter with acknowledgment of receipt, or at the following certified email address: [artemisiasp@pec.it](mailto:artemisiasp@pec.it). Alternatively, you may contact the company's designated Data Protection Officer (DPO) at [dpo@artemisia.it](mailto:dpo@artemisia.it).*

Signature / Signatures  
pregnant woman