

CGS-infinity (Complete Genetic Scan - Infinity)

APPLICATION FORM AND INFORMED CONSENT

INFORMATION ON THE POTENTIAL AND LIMITATIONS OF THE TEST PLEASE COMPLETE ALL RELEVANT DATA IN CAPITAL LETTERS

FEMALE PARTNER

Surname _____

Name _____

Date of birth DD / MM / YYYY / /

Place of birth _____

Address - Post Code - City _____

Country _____

C.F. _____

Phone Number _____

Email _____

ETHNIC GROUP (required)

Caucasian	African	North African	Asian	Other
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Smoker Yes No

PREGNANCY (ALL FIELDS ARE REQUIRED)

PARITY _____

PREGNANCY

Single Monochorionic twin Bicornal twin

Spontaneous Homologous IVF Heterologous IVF (Donor Age)

Date Last Period DD / MM / YYYY / /

Actual gestational age at the date of blood collection

WEEKS DAYS

Weight (required) _____ Height (required) _____

Clinical History _____

ADDITIONAL INFORMATION

I want to be informed of fetal sex? Yes NO

FOLATE RECEPTOR ALPHA AUTOANTIBODIES (FRAA) 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.

DOCTOR / LABORATORY

Surname of the doctor (required) _____

Name of the doctor (required) _____

Doctor's phone _____

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 _____

Female Partner's signature _____

Male Partner's signature _____

MALE PARTNER

Surname _____

Name _____

Date of birth DD / MM / YYYY / /

Place of birth _____

Address - Post Code - City _____

Country _____

C.F. _____

Phone Number _____

Etnia

Caucasian	African	North African	Asian	AltOthe
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Clinical History _____

INFORMATION ON THE POTENTIAL AND LIMITATIONS OF THE TEST

By signing this informed consent, I/we declare to have clearly understood the following general information, applicable to all commercially available NON-INVASIVE PRENATAL TESTS (NIPT) and to the new FetalDNA – Complete Genetic Scan Infinity (CGS-Infinity) to which I am submitting.

FetalDNA Complete Genetic Scan (CGS) Infinity is the only NIPT worldwide capable of analyzing the **fetal genome in TRIO mode**, simultaneously including the genetic profiles of both parents (patent filed). The examination combines two specific protocols for exome analysis, performed respectively on circulating fetal DNA and on the parents' genomic DNA. In international literature, the TRIO approach is usually performed only through invasive or postnatal procedures.

Thanks to the expertise of the **Altamedica Genetics Institute**, the same methodology has been applied— for the first time— to **fragments of circulating fetal DNA in maternal blood**, thus avoiding invasive procedures.

Both protocols rely on **Next Generation Sequencing (NGS)** to ensure in-depth, high-accuracy analysis. The only intrinsic limitation of the test is related to the quantity and completeness of fetal DNA present in the maternal blood sample: in some cases the fetal fraction may be reduced (detectable during analysis) or partially incomplete (not always predictable).

CGS-Infinity in TRIO is an advanced genetic test designed to detect thousands of **monogenic diseases** (conditions caused by a pathogenic variant in a single gene). The test is based on clinical **exome analysis** (the protein-coding portion of DNA) performed simultaneously in the parents and the fetus. This comparison allows:

- variants shared with an unaffected parent to be considered unlikely to be disease-causing;
- a significant reduction of VUS (Variants of Uncertain Significance), since transmission by a healthy parent suggests probable non-pathogenicity.

Through the TRIO approach, CGS-Infinity improves diagnostic accuracy, facilitating clinical interpretation of variants and enabling more reliable, targeted prenatal diagnosis.

In the event of a positive non-invasive result, confirmation with invasive procedures (chorionic villus sampling or amniocentesis) may be required.

FetalDNA includes:

1. FETALDNA CARYOTYPE + 90 MICRODELETION SYNDROMES (Fetus Analysis)

2. TRIO FETAL EXOME

a. **SCREENING OF THE COMPLETE FETAL KARYOTYPE.** Average accuracy: 99%.

b. **SCREENING OF 90 MICRODELETION SYNDROMES.** Average accuracy ~85%, depending on fetal fraction and specific condition.

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

c. **FETAL CLINICAL EXOME IN TRIO – Fetal genetic screening.** Infinity explores the fetal clinical exome and compares it with that of the parents for correct variant interpretation, including classification of **VUS**. It is the only non-invasive test worldwide able to analyze **over 5,000 genes**, enabling early detection of numerous autosomal recessive, autosomal dominant and X-linked monogenic disorders, including severe, frequent, de novo variants with prenatal onset. According to international literature (OMIM, ClinVar, *Deciphering Developmental Disorders Study, Nature, 2017*), clinical exome sequencing allows the study of >5,000 genes associated with ~**5,200 monogenic disorders of prenatal relevance**. Infinity is the only non-invasive exam reaching this level of coverage, with an **average accuracy of 90%**, which varies according to the fetal DNA fraction in the maternal sample. **Note:** variants associated with genetic predisposition to **cardiovascular, oncological, and neurodegenerative diseases are excluded** from analysis.

d. The test also includes screening in the mother for **Spinal Muscular Atrophy (SMA), Duchenne Muscular Dystrophy, and Fragile X**.

e. Upon request, immunological testing for **folate receptor alpha autoantibodies (FRAA)** can be performed, reported in the literature among causes of cerebral folate deficiency and therefore potentially related to autistic spectrum disorders in the fetus.

INFORMATION ON THE POTENTIAL AND LIMITATIONS OF THE TEST

- 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.
- The study of **~5,200 diseases is performed by TRIO clinical exome sequencing**. Test performance depends on the amount and quality of fetal DNA in maternal blood. In pilot studies preceding patent filing, the test showed **high diagnostic performance** with mean **sensitivity 99.5%** and mean **specificity 95%**. Thus, it correctly detects disease presence in **99.5% of truly affected cases** and excludes it in **95% of truly unaffected cases**. False negatives are **~0.5 per 100 affected fetuses**; false positives are **~5 per 100 unaffected fetuses**. Because each genetic disease analyzed is individually rare, the chance of an incorrect result, especially a false negative, is extremely low. Any positive result must be confirmed by invasive testing according to national Guidelines.
- The list of **>5,000 genes** analyzed is available at www.fetaldna.it/dettaglioindagini (this list is the reference). Exome analysis is targeted to known, clinically relevant genes to search for pathogenic variants. Only these will be investigated and reported.
- **NIPT does not detect balanced chromosomal rearrangements (which are asymptomatic)**, may fail to detect fetal and/or placental chromosomal mosaicisms, rare methylation defects, triploidies, polyploidies, and other rearrangements not detectable by NIPT technologies..
- **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).
- **The analysis is performed in TRIO on parental and fetal DNA via clinical exome sequencing (~5,000 genes associated with ~5,200 monogenic disorders of prenatal relevance)**. For performance details see sections above.

INFORMATION ON THE POTENTIAL AND LIMITATIONS OF THE TEST

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 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 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.

Female Partner's signature

Male Partner's signature

Doctor's signature
that has collected the informed consent

Date
DD / MM / YYYY

 / /

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. Alternatively, you may contact the company's designated Data Protection Officer (DPO) at dpo@artemisia.it.

We Authorize

We Do Not Authorize

storage of residual biological material, anonymized or pseudonymized, to be used exclusively for scientific research and study purposes.

Female Partner's signature

Male Partner's signature