FETALDNA
IL TEST PRENATALE DI ULTIMA GENERAZIONE

APPLICATION FORM AND INFORMED CONSENT

PLEASE COMPLETE ALL RELEVANT DATA IN CAPITAL LETTERS

AFFIX LABEL

☐ BASIC ☐ BASIC PLUS ☐ BASIC PLUS+21 MICRODELETIONS ☐ KARYOTYPE ☐ KARYOTYPE PLUS ☐ KARYOTYPE PLUS +MONOGENIC FETAL DISEASES ☐ TOTAL SCREEN ☐ MONOGENIC FETAL DISEASES

PATIENT

Surname

Name

Date of birth
DD / MM / YYYY ☐☐ / ☐☐ / ☐☐☐☐

Luogo di Nascita

Address - Post Code - City

Country

C.F.

Phone Number

Email

Date
DD / MM / YYYY ☐☐ / ☐☐ / ☐☐☐☐

By signing below, I hereby acknowledge that I have completely read and fully understand the present informed consent. I declare that I have had the opportunity to ask my doctor about the objectives and possible risks of the test, and I get satisfactory answers. I am aware that it would be advisable to request professional genetic counseling before and after the test. I am also aware of the possibility of visiting the website www.fetaldna.it to obtain further information regarding the latest regulatory updates and the technical or medical information concerning FetalDNA. I am aware that the information contained on the website www.fetaldna.it does not replace medical advice, diagnosis or treatment. Artemisia S.p.A., established in Viale Liegi n. 41, Rome, as the controller, in accordance with articles 4 and 24 of EU REG. No 2016/679, informs you that the data collected will be managed in compliance with the provisions of current legislation, directive no 2016/680 and EU Regulation No 2016/679 (articles 12, 13, 14). We inform you that, dealing with sensitive data referred to in art. 9 GDPR, on the protection of personal data (suitable i.e. to reveal genetic, ethnic, health and sexual origin) we are required to preserve the absolute anonymity on your person if the data were to be used for research purposes and were the subject of publications in scientific literature (the anonymous scientific publication of the results is permitted).

I authorize, under my full responsibility, to send my medical report to my email address from both the laboratory and my doctors

Patient's signature

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

INFORMAZIONI PRELIEVO

I want to be informed of **fetal sex?** Yes ☐ NO ☐

PREGNANCY (ALL FIELDS ARE REQUIRED)

Parity

Pregnancy

Single ☐ Monochorional twin ☐ Bicorial twin ☐

Spontaneous pregnancy ☐ Homologous IVF ☐ Heterologous IVF (Age) ☐☐

Date Last Period
DD / MM / YYYY
☐☐ / ☐☐ / ☐☐☐☐

Actual gestational age at the date of collection

WEEKS ☐☐ DAYS ☐

Ethnic Group
(required)

Caucasian ☐ African ☐ North African ☐

Asian ☐ Other ☐

Weight (required) Height (required)

Smoker Yes ☐ No ☐

Clinical History

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INFORMED CONSENT
CHOICE TEST TO EXECUTE

The searches that can be performed in this test must be optioned by the pregnant woman under the indication of the specialist who will make this informed consent perfectly understandable according to the needs and requests of the parental couple.

I hereby declare that I have received exhaustive information regarding the level of Non Invasive Prenatal screening Test (NIPT screening) that I have chosen and requested.

☐ **BASIC FETALDNA** investigates exclusively on the most common forms of chromosomal anomaly, that is **Down syndrome** (trisomy of chromosome 21), 18 or **Edwards syndrome** and 13 or **Patau syndrome**, as foreseen by the current guidelines.
On request it can be supplied also the fetal sex but as said, not the chromosomal anomalies of sex.

I fully understand that, although the test I am going to do has a very high diagnostic performance, we have been fully informed that, as stated by genetic's guidelines of our country, diagnostic results are provided exclusively by invasive tests (Amniocentesis and Chorionic villus sampling). In fact, I have well understood that all Prenatal Screening tests (NIPT) do not provide a diagnosis results. Although rare, both cases of false positives and false negatives are reported. I accept this rare eventuality. **Furthermore, the possibility of misinterpretations on fetal sex, as estimated in scientific literature, in about 3%.**

Signature / Signatures
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☐ **BASIC PLUS FETALDNA** investigates the 3 main fetal **chromosomal aneuploidies** related to **chromosomes 21, 18, 13** and the **X, Y sexual chromosomes**, also determining fetal sex which, at our request, may be kept silent.

I fully understand that, although the test I am going to do has a very high diagnostic performance, we have been fully informed that, as stated by genetic's guidelines of our country, diagnostic results are provided exclusively by invasive tests (Amniocentesis and Chorionic villus sampling). In fact, I have well understood that all Prenatal Screening tests (NIPT) do not provide a diagnosis results. Although rare, both cases of false positives and false negatives are reported. I accept this rare eventuality. **Furthermore, the possibility of misinterpretations on fetal sex, as estimated in scientific literature, in about 3%.**

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☐ **BASIC PLUS + 21 MICRODELETIONS** investigates the 3 main fetal **chromosomal aneuploidies** related to **chromosomes 21, 18, 13** and the **X, Y sexual chromosomes**, **(with an average accuracy of 99.8%)**. This test also includes the screening of a large number of small chromosomal alterations caused by **structural rearrangements** (which are defined **microduplications / microdeletions**) at an average resolution of 5Mb however correlated to the fetal fraction (**the sensitivity increases with the increase of the fetal fraction but the average accuracy does not exceed 85%**).

Higher values are not obtainable with any other NIPT test). The term microdeletions / microduplications refers to abnormalities characterized by the absence of a small chromosomal tract with consequent loss of gene information (microdeletions) or by the addition of supernumerary genomic material (microduplications). For the list of the 21 investigated syndromes (not indicated here for reasons of space), the site and the report delivered are valid.

I fully understand that, although the test I am going to do has a very high diagnostic performance, we have been fully informed that, as stated by genetic's guidelines of our country, diagnostic results are provided exclusively by invasive tests (Amniocentesis and Chorionic villus sampling). In fact, I have well understood that all Prenatal Screening tests (NIPT) do not provide a diagnosis results. Although rare, both cases of false positives and false negatives are reported. I accept this rare eventuality. **Furthermore, the possibility of misinterpretations on fetal sex, as estimated in scientific literature, in about 3%.**

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☐ **KARYOTYPE** represents a NIPT that extends the investigation of numerical alterations to all chromosomes. **In particular it investigates the existence of an abnormal number of all 23 pairs of chromosomes related to fetal karyotype**, including X, Y sexual chromosome (**with an average accuracy of 99.8%**).

I fully understand that, although the test I am going to do has a very high diagnostic performance, we have been fully informed that, as stated by genetic's guidelines of our country, diagnostic results are provided exclusively by invasive tests (Amniocentesis and Chorionic villus sampling). In fact, I have well understood that all Prenatal Screening tests (NIPT) do not provide a diagnosis results. Although rare, both cases of false positives and false negatives are reported. I accept this rare eventuality. **Furthermore, the possibility of misinterpretations on fetal sex, as estimated in scientific literature, in about 3%.**

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☐ **KARYOTYPE PLUS** is a highly elaborate, complete, non-invasive test of circulating free fetal DNA (NIPT). This text includes all the surveys that you perform on the **FetalDNA Karyotype test**: numerical alterations, called **aneuploidies**, (alterations of the number only) of all the other chromosomes, included**13**, **18**, **21** and **sexual chromosomes** (X and Y) with **an accuracy of 99.8%**. It includes the analysis of the most important **microdeletion / microduplication syndromes** at a resolution of about 5Mb related to fetal fraction (the sensitivity increases with the increasing of the fetal fraction) but **the average accuracy never exceeds 85%**. Higher values are not obtainable from any other NIPT test. The list of the 21 main microdeletion syndromes investigated in the screening will be reported in the response and is clearly listed on the site: FetalDNA.it.

I fully understand that, although the test I am going to do has a very high diagnostic performance, we have been fully informed that, as stated by genetic's guidelines of our country, diagnostic results are provided exclusively by invasive tests (Amniocentesis and Chorionic villus sampling). In fact, I have well understood that all Prenatal Screening tests (NIPT) do not provide a diagnosis results. Although rare, both cases of false positives and false negatives are reported. I accept this rare eventuality. **Furthermore, the possibility of misinterpretations on fetal sex, as estimated in scientific literature, in about 3%.**

The FetalDNA Karyotype Plus also includes, free of charge, the investigation of the most frequent mutations in maternal cystic fibrosis.

I confirm that I request the research **for the most frequent mutations in maternal cystic fibrosis**? ☐ YES ☐ NO

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

This test is a screening and nondiagnostic test. Although very accurate, the results have no diagnostic value and must be evaluated in the clinical context of pregnancy together with the gentic family history. It is not a substitute test for invasive prenatal diagnosis (CVS or Amniocentesis). This test investigates the genetic mutations for the following fetal monogenic diseases:
Cystic fibrosis (gene **CFTR**), Congenital deafness (gene **GJB2**), Beta thalassemia (gene **HBB**), Congenital adrenal hyperplasia (gene **CYP21A2**), Emochromatosis (gene **HFE**), Achondroplasia, (gene **FGFR3**), Hypochondroplasia (gene **FGFR3**), Thanatophoric dysplasia (gene **FGFR3**), Apert syndrome (gene **FGFR2**), Crouzon syndrome (gene **FGFR2**), Pfeiffer syndrome (gene **FGFR2**), Leopard syndrome (gene **PTPN11**), Noonan syndrome (gene **PTPN11**), Noonan syndrome (gene **SOS1**), Noonan syndrome (gene **RAF1**), Phenylketonuria (gene **PAH**), Rett syndrome (gene **MECP2**), Autosomal recessive polycystic kidney (gene **PKHD1**).

We have been fully informed that, from maternal blood, it is not possible to obtain a definitive result about the presence of such abnormalities in the fetus. The test I am going to do has **an accuracy of up to 90%**. Higher values are NOT real or certified and cannot be obtained with any other NIPT on fetal DNA. Defitive results as confirmed by the genetics guidelines of our country) can be obtain only using invasive examinations (Amniocentesis or CVS).

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☐ **TOTAL SCREEN** is the most elaborate and complete non-invasive test of circulating free fetal DNA (NIPT) available today.
Analyzes **all 23 pairs of chromosomes** relating to the fetal karyotype and therefore includes the detection of aneuploidies of **sex chromosomes X, Y** including the 3 main fetal chromosomal aneuploidies related to chromosomes **21**, **18**, **13**, in particular the **Down syndrome** (Trisomy of chromosome 21), **Edwards syndrome** (Trisomy of chromosome 18) and **Patau syndrome** (Trisomy of chromosome 13) with **an accuracy of 99.8%**. It includes the screening of a large number of small chromosomal alterations caused by structural rearrangements (which are defined as **microduplications / microdeletions**) at an average resolution of 5Mb however related to the fetal fraction (the accuracy increases with the increase of the fetal fraction but **never exceeds 85%**). It also includes the search for genetic mutations that give rise to fetal monogenic diseases as per the list indicated in the previous point **with accuracy up to 90%**. The **FetalDNA Total Screen** also includes investigations relating to the pregnant woman, in particular:

- The search for some mutations responsible for Maternal Cystic Fibrosis as already reported in the description of the FetalDNA Karyotype Plus
- It also includes the search for deletions of exons 7 and 8 of the SMN1 gene and the SMN2 gene related to Atrofia Muscolare Spinale (SMA). This research excludes almost all of the molecular alterations associated with SMA, but there are extremely rare mutations that cannot be investigated with this test.
- The search for infectious agents present in the blood of the pregnant woman, so it is possible to detect a possible positivity at an early stage, before the antibody tests, routinely used during pregnancy, are positivized. This investigation, however certain and thorough, does not preclude the existence of fetal damages resulting from such infections when they have occurred before or after the test
- The search for mutations currently associated with **predisposition to preterm birth** (this examination does not preclude that the preterm birth can take place for different reasons on a clinical basis)
- The risk assessment of **preeclampsia** on a biochemical basis. (This research expresses a risk value and therefore, although very useful for the treating physician, cannot provide certainties.)
- The search for the most frequent mutations responsible for **hereditary thrombophilia.** Such investigations considered by a large part of international literature useful to prevent the development of maternal fetal complications (from abortion to growth retardation, placenta abruption, and thrombosis) must be assessed in the clinical context and they do not exclude the existence of other factors caused by the same problems.

I fully understand that, although the test I am going to do has a very high diagnostic performance, we have been fully informed that, as stated by genetics guidelines of our country, diagnostic results are provided exclusively by invasive tests (Amniocentesis and Chorionic villus sampling). In fact, I have well understood that all Prenatal screening Test (NIPT) do not provide a diagnosis results. Although rare, both cases of false positives and false negatives are reported. I accept this rare eventuality. Furthermore, the possibility of misinterpretations on fetal sex, is estimated in scientific literature in about 3%.

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- As regards the research of fetal anomalies in maternal blood (NIPT) I have perfectly understood that the test I undergo, as stated by today's guidelines in use in our country, does not give diagnostic certainty and this is provided exclusively by invasive tests. (Amniocentesis and Villocentesis). In fact, I have well understood that all fetal DNA tests (NIPT) do not provide a diagnosis of certainty. Although rare, cases of false positives and false negatives are reported. I accept this rare eventuality. The possibility of misinterpretations of fetal sex is also 3%. This occurrence has no clinical value but must be known for its emotional impact.
- The Fetaldna does not detect balanced chromosomal rearrangements. It may not detect fetal and/or placental chromosomal mosaicism (two cell lines with different chromosome structure). It does not analyze point mutations not included in the Total Screen, methylation defects, triploidies, polyploidies and all chromosomal and molecular rearrangements which cannot be detected by NIPT techniques.
- When the screening test provides a pathological result, this must be confirmed by prenatal invasive diagnosis (amniocentesis/ chorionic villus test). These procedures will be scheduled at our Centre in Rome for free, both for the sampling technique and for the genetic examination.
- The test result has different timing and may be subject to slippages based on a technical problems or the need for further analytical feedback.
- I am aware that the present NIPT, although it is performed through the use of the most innovative molecular technologies may not provide a result and should be repeated (in approximately 1% of literature reports). This occurs even when there is a low percentage of fetal DNA (generally less than 4%). In this case it is advisable to perform a diagnostic invasive since the low amount of fetal DNA in the maternal blood may indicate an increased risk of chromosomal aberration.
- The FetalDNA is achieved through the quantitative DNA comparison of selected chromosomes in the mother's blood compared to the fetal ones. Most of this DNA is of maternal origin. The test determines whether the amount of DNA on a chromosome is different from the one expected. For example, a larger portion of chromosome 21 provenance DNA could mean that the child has three copies of that chromosome (which causes Down syndrome) rather than the usual two copies. The minimum FF value of 4% was defined using statistical models based on the minimum number of aneuploidy chromosome fragment readings sufficient to highlight fetal aneuploidy according to different levels of FF. According to this model, at low levels of FF, differences in circulating cfDNA between pregnancies with fetal trisomies and pregnancies with euploid fetuses may not be detected, causing false negatives. One factor associated with the low percentage of fetal cfDNA, with the consequent possibility of failure of the test, is an increased maternal body weight. The increased amount of maternal cfDNA in obese women could, in fact, mask the fetal fraction by making difficult the detection of fetal aneuploidies. Thus, high body mass index (> 30) in the case of obesity and (between 25 and 30) in the case of overweight increase the risk of test failure or false positive/negative,
- We inform and reiterate that any other and different mutations from those specifically sought in the test and reported in the report will not be investigated therefore the test has no possibility of verifying their existence.When the need to repeat the test occurs, a new blood sample is performed without any other additional costs.
- In dizygotic twin pregnancies it is not possible to distinguish the condition of the single fetus, nor to accurately assess the aneuploidy of the sex chromosomes. However, it is possible to detect the presence/absence of the Y chromosome. If the presence of the Y chromosome is detected, it is not possible to discern whether only one or both fetuses are male. In pregnancies that began as twins or multiple, followed by the spontaneous abortion of one or more fetuses with resorption of the gestational sac (vanishing twin), the free fetal DNA of the aborted fetus may also be present in the maternal blood. This could interfere with the accuracy of the results, causing false positives if the cause of the abortion was due to the presence in the aforementioned fetus of chromosomal aneuploidies affecting one of the chromosomes analyzed. Similarly, there could be an inconsistency in the sex results (eg diagnosis of male sex, in which the presence of the Y chromosome originates from the aborted fetus DNA).
- In case of chromosomal mosaicism (the frequency is about 1-2%), discrepancies in the results (false positives or false negatives) may occur. In particular, the test may give a positive result (aneuploidy detected), but this chromosomal abnormality is confined to the placenta due to chromosomal mosaicism. In this case the fetus could result with a normal karyotype at the control in invasive prenatal diagnosis (false positive). On the contrary, the test could give a negative result (aneuploidy not detected), but due to the chromosomal mosaicism the fetal DNA without aneuploidy could be confined to the placenta giving rise to a fetus with aneuploid karyotype at the control in invasive prenatal diagnosis (false negative) .

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