Test Requisition Form NACE® NACE®24

The fields marked with * are required to perform the test

Patient details	Prescribing clinician details
*Name	*Prescribing clinician
*Surnames	*Prescribing clinician email
*Date of birth	*Name of centre Telephone

Test indications

- ☐ Advanced maternal age
- ☐ Abnormal ultrasound
- ☐ Family or personal history of aneuploidy
- ☐ High-risk combined screening

Risk value _____

- ☐ Patient request

Would you like to know the sex?

☐ YES ☐ NO

Clinical information

***Gestational age:** _____/_____ **Unique Patient ID** _____

Previous children ☐ YES ☐ NO

***Pregnancy:** ☐ Singleton ☐ Twin ☐ Vanishing Twin

Previous miscarriages ☐ YES ☐ NO

Type of pregnancy:
- ☐ Natural
- ☐ IVF — Transferred embryos: ☐ 1 ☐ 2
- ☐ Egg donation — Transferred embryos: ☐ 1 ☐ 2
- ☐ Surrogacy — ☐ Full/Gestational ☐ Partial/Traditional — Transferred embryos: ☐ 1 ☐ 2

***Date of blood sampling:** _____/_____/____

Weight: _____ kg **Height:** _____ cm

*Sample collection performed by (full name): _____

Other relevant clinical information for testing:

☐ Organ transplant ☐ Blood transfusion (<60 days) ☐ Cancer history

*Mark the appropriate option for your patient with a ✓

Singleton and twin pregnancy

☐ **NACE®**

- Detection of foetal aneuploidy in chromosomes 13, 18, 21 and determination of foetal sex
- Singleton pregnancies: includes aneuploidies for sex chromosomes
- Twin pregnancies: does not include aneuploidies for sex chromosomes.

Singleton pregnancy only

☐ **NACE® 24**

- Detection of foetal aneuploidies in all chromosomes and determination of foetal sex
- Detection of partial/segmental alterations, greater than 7MB, in all chromosomes
- Includes aneuploidies for sex chromosomes

Clinician authorisation

I certify that the patient and prescribing clinician details given in this request form are accurate to the best of my knowledge and that I have requested the test indicated above based on my professional judgement. I have explained the limitations of this test and have answered any questions based on medical judgement. I understand that Igenomix may require further information and I agree to provide this information if necessary.

*Clinician's signature_____ Date: _____/_____/_____

Patient consent

By signing this application form, I voluntarily ask Igenomix to perform the test indicated above. I have read and received a copy of the informed consent included in these pages. I have also been adequately informed of the risks, benefits and limitations of this test.

*Patient's signature _____ Date: _____/_____/_____

INFORMED CONSENT FOR NACE® AND NACE® 24

DESCRIPTION, PURPOSE AND ADVANTAGES OF ANALYSES

NACE® is a non-invasive prenatal genetic screening test designed to detect the most frequent chromosomal alterations without posing a risk to the ongoing pregnancy. It is recommended for pregnancies from 10 weeks of gestation.

Every cell in the body has chromosomes; these are organised structures containing genetic material (DNA) and proteins. There are 24 different types of chromosomes in humans, numbered from 1 to 22, plus the sex chromosomes X and Y. Most cells contain a total number of 46 chromosomes, comprising 22 pairs of autosomes and one pair of sex chromosomes (XX for a female and XY for a male). Under normal conditions, both the sperm and the egg must have 23 chromosomes, thus following fertilisation the resulting embryo has 46 chromosomes in total.

Embryo aneuploidy (extra or missing chromosomes) may develop as a result of an abnormal egg (risk groups include women over the age of 35), an abnormal sperm (severe male factor), couples with balanced structural rearrangements (translocations and inversions), or due to a subsequent error during cell division. Chromosomal abnormalities can give rise to reproductive failure or prevent assisted reproductive treatment from resulting in pregnancy. They can also be responsible for miscarriages in the first trimester, foetal death, or newborns with chromosomal abnormalities. A common example of a chromosomal abnormality is Down's syndrome, which is caused by the presence of three copies of chromosome 21 instead of two. Other trisomies compatible with life are associated with chromosomes 18 and 13. In the event of monosomy, one chromosome from a specific pair is present, instead of two, making up a total of 45. The most common monosomy is associated with chromosome X, also known as Turner Syndrome.

Information on the NACE® test: Trisomy 13, trisomy 18 and trisomy 21 are three common chromosomal abnormalities that are normally due to the presence of an additional complete copy of chromosome 13, 18 and 21, respectively. Individuals with these disorders are characterised by having an intellectual disability and characteristic facial features, usually accompanied by other defects. There is currently no curative treatment for these disorders. The purpose of this genetic screening test is to detect foetal trisomy in chromosomes 13, 18 and 21 in singleton and twin pregnancies. Furthermore, in singleton pregnancies the test also reports the foetal sex and analyses possible numerical alterations of the sex chromosomes. In twin pregnancies, information is not available regarding foetal sex or numerical alterations of the sex chromosomes, only an indication of the presence or absence of the Y chromosome is possible. The NACE® test is based on a non-invasive method that assesses the risk of foetal chromosomal aneuploidy by analysing foetal DNA circulating in the maternal plasma, using the latest generation sequencing technology and advanced bioinformatics analysis. Detection rates are very high which makes it possible to significantly reduce the number of invasive procedures (amniocentesis or chorionic villus sampling), thus avoiding unnecessary foetal loss or risk of miscarriage and/or intra-uterine infection.

Information on the NACE® 24 test: NACE® 24 is only valid for singleton pregnancies. In addition to the scope covered by the NACE® test (trisomy 13, 18, 21 and sex chromosomes), the aim of the NACE® 24 version is to additionally detect trisomies in all 23 pairs of chromosomes, including large partial/segmental clinically relevant aneuploidies (with a size >7Mb). Abnormalities of certain chromosomes are associated with a high risk of miscarriage. The ability to identify these abnormalities offers valuable information that, in certain clinical situations, will help manage the pregnancy and/or prepare for newborn care. It can also help assess future risks and help monitor and manage future pregnancies.

The specificity and sensitivity of the technique used for the NACE® / NACE®24 tests are very high. For trisomies 13, 18 and 21, the specificity and sensitivity is greater than 99.9%. In the case of trisomies for the rest of chromosomes, the specificity is 99.8% and the sensitivity is 96.4%. For partial alterations with a size >7Mb, the specificity is 99.8% and the sensitivity is 74.1%. The accuracy regarding the determination of the fetal sex (female or male) is greater than 99% in single gestations. The rate of accuracy in determining the sex of the foetus (male or female) is 99% in singleton pregnancies. In single gestation cases that began as twins with an early loss of one of the foetuses, reliability in determining the foetal sex may be lower.

The foetal sex must coincide with findings in ultrasounds.

PROCEDURES, RISKS AND LIMITATIONS

The process for conducting the test is as follows:

1. Extraction of a blood sample.
2. Extraction of DNA from the biological sample.
3. Massive sequencing (NGS)
4. Bioinformatic analysis of the sequencing results (NGS).
5. Final review of result and issue diagnosis

To process the sample, the test request form will need to be correctly completed. If this is not the case, the analysis may be delayed until the information required has been given to the laboratory. The patient shall be given a period of 24 hours after the sample is received to provide the additional information required. Once this period has elapsed, the sample can be discarded.

Given the complexity of the genetic tests and the significant implications of the test results, the report obtained must be interpreted in conjunction with other clinical data, within the general context of a medical practice run by health professionals. The result reports are strictly confidential.

The biological sample –in this case, blood– to be used in the genetic test, will be obtained using standard techniques with little or no risk to the patient's health, such as side effects of blood extraction including mild pain, haematoma or, in rare cases, infection at the injection site or fainting.

The report of the NACE® and NACE®24 tests will be available within 10 working days following receipt of the sample at the laboratory. In all cases, report release periods may be delayed if the sample needs to be retested or a new blood sample is required due to problems in sending the sample that are unrelated to Igenomix.

If the field 'Would you like to know the sex?', is not completed, the foetal sex will be communicated by default.

Incidental findings. In extremely rare cases, the results of the NACE® and NACE®24 tests may reveal what is known as incidental findings, i.e., clinically relevant genetic information that is beyond the aims of these tests. Examples of these cases include an XXX chromosomal abnormality, or the presence of genetic abnormalities related to benign or malignant neoplasms in the mother/surrogate. In these cases, Igenomix is authorised to contact your doctor to ensure the situation is suitably handled.

The main limitations of the NACE®/NACE®24 tests are:

a) These tests have a detection rate of nearly 100% but are not diagnostic tests. For a definitive diagnosis, invasive prenatal testing involving karyotyping (analysis of all the chromosomes), prenatal arrays, or rapid screening for the chromosomes analysed in the NACE®/NACE®24 tests (QFPCR or FISH techniques) is required.

b) In some cases, the results may not be informative in the first sequencing analysis and therefore a second sequencing may be necessary, which would delay delivery of the results. On very rare occasions, due to a circulating foetal DNA percentage that is below the detection level for this technique (2%), it is necessary to request a new sample of maternal blood.

c) These tests are more accurate for the trisomy disorders analysed than the current first trimester screening. However, erroneous results may be obtained:
   i. A positive result (abnormality detected) must be confirmed by an invasive procedure in order to be certain.
   ii. A negative result (no normality detected) must be consistent with other clinical findings (ultrasounds, etc.) and does not completely rule out the presence of all types of genetic abnormalities in the foetus, birth defects or other diseases, tested or not.

d) This test neither detect triploid syndrome, nor open neural tube defects.

e) The accuracy of these tests may be compromised if there is:

   i. maternal chromosomal aneuploidy;
   ii. mosaicism (foetal or confined to the placenta).
   iii. allogenic blood transfusion, transplant or stem cell therapy;
   iv. vanishing twin syndrome;
   v. multiple gestation (3 or more foetuses).
   vi. Maternal cancer
   vii. Chronic treatment with low-molecular-weight heparin. If this is your case, contact Igenomix before performing the test.

f) The ability to accurately screen for segmental imbalances (>7Mb) is determined by the amount of fetal cell-free DNA in the sample (fetal fraction), the depth of sequencing, the segment size, and the genomic region involved. For these reasons, NACE®24 test is not a replacement for CVS or amniocentesis, but it can provide additional reassurance compared with standard methods of NIPT.

g) The massive sequencing technique (NGS) used in this test does not detect other genetic disorders different to those outlined in the DESCRIPTION section of this consent (e.g. segmental imbalances less than 7Mb size, Monogenic diseases are not detected).

DATA PRIVACY, STORAGE AND RESEARCH USE OF SAMPLES

Your privacy is a priority for the Igenomix Group ("Igenomix"). Your identity and all data referring to your personal information will be confidential and only Igenomix personnel will be permitted access to this information, along with the relevant authorities when required by the laws of the applicable jurisdiction. You will find further information on the Igenomix Privacy Policy, along with all your rights at www.igenomix.com, or this information may be provided to you upon request by sending an email to privacy@igenomix.com.

We would like to inform you that your personal data will only be processed to: (1) Fulfil the obligations arising from the provision of the services contracted by you; (2) Check and guarantee the quality of the services provided (internal audits, quality controls, laboratory validation studies); (3) For educational purposes, provided that it remains anonymous throughout and you cannot be identified during the analysis of the data, which will be removed from any publication; (4) For research purposes, scientific publications and presentations, provided that it remains anonymous throughout and you cannot be identified during the analysis of the data, which will be removed from any publication; and (5) Personally address any doubts or suggestions made by the patient during the process and monitor the proper performance and resolution of the test, including the indefinite retention of your data, except where local laws of the applicable jurisdiction state otherwise.

You also declare that you understand and accept that you will not obtain, either now or in the future, any economic benefit for any research carried out, and that there is no intention to compensate you for the products developed from any research.

The sample will be analysed by Igenomix or an associated group selected by Igenomix on an international level. Igenomix reserves the right to carry out part or all of the analyses included in the test through Third Party Laboratories certified with recognised international quality standards, or failing this, they will be periodically assessed by Igenomix. Any results obtained in this way will be inspected by Igenomix and this circumstance will be indicated in the final report issued.

Pursuant to the laws on the Protection of Personal Data[1], the requesting party must have the patient's consent to perform the diagnostic tests requested and to process their data. You may, at any time, exercise your rights regarding access, rectification, opposition, erasure, automated decisions, limitation, portability, by sending an email to privacy@igenomix.com, providing proof of the requesting party's identity.

HAVING READ AND UNDERSTOOD THE FOREGOING, I AM AWARE OF:

The indications, procedure, success rate, risks and complications of the proposed treatment, as well as the financial cost of said test(s).

The fact that medical staff are at my disposal to expand on any aspect of the information that is not sufficiently clear to me.

I have understood the explanations given to me in clear and simple language, and the doctor who saw me allowed me to make comments, clarifying any issues I raised and informing me that I may freely withdraw my consent at any time.

I am satisfied with the information received and I freely consent to my blood sample being sent to the Igenomix facilities for the purpose of carrying out the test.

[1] **For non-US patients:** customers residing outside the United States under certain jurisdictions may at any time request to have their personal information deleted from our active databases, subject to the applicable laws and regulations in each jurisdiction. Although we can delete your personal information from our active databases, part or all of your personal information shall remain stored in back-up files for the purpose of complying with legal, regulatory or other requirements. Information that has already been coded and/or anonymised may not be recoverable or traceable for destruction, deletion or modification. If you wish to have your personal information removed from our active databases, please contact us at privacy@igenomix.com.