Informed consent for the NEO5 non-invasive pre-natal test

I. PRIOR INFORMATION FOR PATIENTS

This consent describes the benefits, risks, and limitations of the Neo5 test. It is recommended to have a pre-test counselling with a genetic counsellor or an experienced healthcare provider prior to undergoing this kind of screening test. Read this document carefully and ask your doctor any questions you may have before making your decision about the test.

Healthy people normally have 23 pairs of chromosomes, microscopic rod-shaped structures that exist inside virtually every cell in the body. Chromosomes are made of DNA and are the sites where genes, chemical instructions for building and operating the body, are located. Occasionally a pregnancy can occur with an embryo that has the wrong number of chromosomes, either too many or too few. This condition is called "aneuploidy". Aneuploidy normally occurs in about 1 in 300 pregnancies, but becomes significantly more common with advancing maternal age and is present at much higher levels in miscarriages and stillbirths. Although most aneuploid pregnancies end in miscarriage, it is also possible to give birth to a child with intellectual or physical disabilities of varying severity. The types of aneuploidy most frequently seen during pregnancy are trisomy 21 (Down syndrome), trisomy 18 (Edwards' syndrome), and trisomy 13 (Patau's syndrome), although other types are also known.

II. WHAT IS THE NEO5 NON-INVASIVE PRE-NATAL TEST?

Prenatal testing methods aim to reveal whether a foetus has 23 pairs of chromosomes or has an aneuploidy. Traditionally, a sample of cells belonging to the foetus is obtained by amniocentesis or chorionic villus sampling (CVS) and analysed. However, these methods are invasive and carry a small risk of inducing a miscarriage.

Neo5 test is an advanced prenatal test that aims to assess the risk of a pregnancy being affected by a chromosomal abnormality in a non-invasive way. The test provides information on whether there may be extra (trisomy) or missing (monosomy) copies of 5 chromosomes (chromosomes 13, 18, 21 and the two sex chromosomes, X and Y).

Side effects to blood collection are uncommon but can include dizziness, fainting, pain, bleeding, bruising and, rarely, infection.

This test screens for specific chromosomal abnormalities by analysing fetal DNA (genetic material) in maternal blood. The blood sample contains millions of DNA fragments, some from the mother's cells and some from the foetus. Neo5 test uses a technology known as Next Generation Sequencing (NGS) to "sequence" the DNA fragments (read the letters of the genetic code), which allows the determination of the chromosome from which each fragment originally came. The number of DNA fragments derived from each chromosome can be counted. In this way, the test attempts to measure the amount of DNA from each chromosome. The laboratory then uses a method of analysis to estimate whether or not there is a correct number of chromosomes. In a healthy pregnancy, two copies of chromosomes 13, 18 and 21 are expected, along with two copies of the X chromosome in girls and one X and one Y chromosome in boys.

III. WHEN IS NEO5 TEST INDICATED?

Any pregnant woman can take this non-invasive test as early as at a gestational age of 10 weeks. However, it is particularly indicated in the following cases:

- When screening tests performed in the first trimester of pregnancy show an elevated risk.
- If there is a history of previous pregnancies with abnormalities.
- When the karyotype of either parent is altered.

IV. PROCEDURE

A blood sample will be taken and sent to Juno Genetics Spain. DNA will be isolated from the blood and subsequently sequenced using NGS, as described above. After sequencing, specialised software is used to calculate the number of copies of each chromosome in the foetus.

Collecting information on the pregnancy after testing is part of a laboratory's standard practice in order to control the quality of its testing . As such, Juno Genetics or its designee may contact your health care provider to obtain this information. By signing this informed consent, you agree to allow your health care provider to give this information to Juno Genetics or its designee.

V. RESULTS

Your test results will be sent to your doctor or other healthcare provider of your choice.

The turnaround time for results will be 5 working days from the time the sample blood and documentation arrive at the laboratory.

VI. LIMITATIONS OF NEO5 AND SECONDARY FINDINGS

The Neo5 test is a screening test that only examines for specific chromosomal abnormalities affecting chromosomes 13, 18, 21, X and Y. This means that other abnormalities that could affect pregnancy may not be detected. It should be noted that the Neo5 test is not able to detect balanced chromosomal rearrangements and is not intended for the detection of ploidy (e.g. triploidy). It will not be able to detect all possible

microdeletion syndromes (conditions caused by the loss of a small part of a chromosome), as the chromosome pieces involved are sometimes too small to be accurately measured during the test.

Results reported as NO ALTERATION DETECTED do not eliminate the possibility of chromosomal abnormalities in the chromosomes tested. A negative result does not eliminate the possibility that the pregnancy has other chromosomal abnormalities, genetic conditions, or birth defects (e.g. open neural tube or autism).

There is a small possibility that the test results may not reflect the chromosomes of the foetus but rather the chromosomal status of the placenta (a situation known as "confined placenta mosaicism") or chromosomal abnormalities that the mother might have within her own cells. Although the test is not designed to assess the mother's health, in some cases, it may reveal information about her health directly or indirectly (when combined with other information). Examples are an incorrect sex chromosome endowment (e.g. XXX) or the presence of a tumour (as tumours often have an incorrect number of chromosomes in their cells).

While Neo5 test can be performed in twin pregnancies, the status of each individual foetus cannot be determined. In addition, Neo5 test can report the presence or absence of Y chromosome material (which is only found in males) but it will not be clear whether both twins are male or only one of them. Also, the occurrence of aneuploidy affecting the sex chromosomes cannot be assessed in twin pregnancies. In the case of an evanescent twin (a pregnancy that starts as a twin but only one of the foetuses continues to develop), the test result may reflect the DNA of the "evanescent twin", leading to a higher probability of false positive or false negative results.

Like any test, Neo5 test can have false negative and false positive results. This means that the chromosomal abnormality being tested for may be present even if you receive a negative result (this is called a "false negative"), or that you may receive a positive result for the chromosomal abnormality being tested for, even though the abnormality is not actually present (this is called a "false positive"). Generally, results are expected to have hit rates of 99% or higher. Situations such as a twin pregnancy or mosaicism (a pregnancy that has a mixture of normal and aneuploid cells) can significantly reduce the rates.

The test results can be invalidated by certain factors. If are aware that any of the following situations to be true, please discuss it with your doctor or contact Juno Genetics to determine if the Neo5 test would be applicable in your case.

- You have recently undergone a blood transfusion.
- You have recently undergone an organ transplant.
- You have recently undergone a surgical procedure.
- You have received immunotherapy or stem cell treatment.
- You have (or have previously had) cancer.
- You are known to have some cells in your body that are chromosomally abnormal (e.g. mosaicism).
- Your pregnancy started as twins but now there is only one foetus.

It is important to remember that the Neo5 test is a screening test. The results should not be treated as diagnostic. Due to the limitations described above, irreversible clinical decisions should not be made based on these results alone. If a definitive diagnosis is desired, prenatal diagnosis by chorionic villus sampling or amniocentesis would be necessary. In some cases, other tests may also be necessary. Some rare chromosomal abnormalities may occur only in mosaic form (where the abnormality is not present in all cells of the foetus). The clinical consequences of such "mosaicism" depend on the chromosomes involved and cannot be predicted prenatally. Mosaic abnormalities may not be detected with the Neo5 test.

During the Neo5 test, unexpected chromosomal alterations may be detected in rare cases. These alterations are known as secondary findings. In some cases, it is unclear whether these findings have clinical relevance. Juno Genetics' policy is NOT TO REPORT secondary findings that are of no or uncertain relevance to health. In the event of such findings, Juno Genetics is empowered to contact your physician for appropriate management of the situation.

VII. ALTERNATIVES TO THE NEO TECHNIQUE

- Amniocentesis
- Chorionic villus sampling ales (CVS)

However, these methods are invasive and carry a small risk of inducing an abortion.

VIII. ECONOMIC INFORMATION

The prices and conditions governing the performance of these tests, if applicable, will be detailed to you at the centre where you are being attended.

IX. GENERAL LEGAL ASPECTS

The biological sample submitted, along with the necessary personal data for the provision of the service, will be sent to the facilities of Juno Genetics Spain, S.L., at Parque Tecnológico de Paterna (46980), Valencia, Spain, Ronda de Guglielmo Marconi, 11, Building A, second floor, premises A-1-2 and A-2-2. The genetic analysis of the sample will be carried out in accordance with the applicable Spanish regulations, primarily the Law 14/2007, on Biomedical Research.

If the performance of this test has been indicated from a country other than Spain, the professional or clinic requesting the test will be responsible for ensuring that both the test itself and its application in the specific case is in accordance with the stipulations of its national or regional regulations, as well as for informing the subject of the test of any particularly relevant issue that such legislation contemplates.

X. DATA PRIVACY, STORAGE, AND USE FOR SAMPLE STUDY

Patient privacy is a top priority at Juno Genetics. All personal information and genetic results are strictly confidential. The only individuals who can access this information are the personnel at 1) the reproductive clinic, 2) the reference laboratories and 3) the relevant authorities if required by the laws of the applicable jurisdiction.

In accordance with the current data protection regulations, such as the EU General Data Protection Regulation (EU2016/679) and national data protection laws including the Spanish Organic Law 3/2018 on the Protection of Personal Data and Guarantee of Digital Rights, you have the right to exercise your rights, if desired, including the right to access, rectify, erase, and revoke your consent, as well as the right to restrict processing, data portability, and to not be subject to automated decision-making based solely on your data. These rights can be exercised by contacting the following postal address:

- Juno Genetics España, S. L., Parque tecnológico de Paterna (46980), Valencia, Spain, Ronda de Guglielmo Marconi, 11, edificio A, segunda planta, locales A-1-2 y A-2-2 (if your analysis is carried out at this laboratory).
- Juno Genetics DPO (Data Protection Officer) at: Juno.DPO@junogenetics.com

Personal data will only be processed for the following purposes: (1) fulfilling obligations arising from the requested services (legitimate basis under Art. 6(1)(b) and 9(2)(h) of the GDPR); (2) reviewing and ensuring the quality of the provided services (internal audits, quality controls, laboratory validation studies based on Art. 6(1)(f) of the GDPR); (3) educational/training purposes, always subject to anonymization prior to use to prevent identification of the patient in question; (4) research purposes, scientific publications, and presentations, always subject to prior anonymization to ensure non-identifiability of individuals. Research will be conducted in compliance with the General Data Protection Regulation and national data protection laws. (5) providing personalized responses to inquiries or suggestions from patients requesting the test and ensuring that the test has been carried out correctly and addressing any concerns (legitimate basis under Art. 6(1)(b) of the GDPR); and (6) monitoring patients in the future to obtain feedback on the service received (legitimate basis under Art. 6(1)(f) of the GDPR). Data will be stored for a minimum of five years unless local laws in the applicable jurisdiction state otherwise. Finally, if you believe that your data protection rights have been violated, you have the right to lodge a complaint with the competent Data Protection Authority.

In addition to the above, Juno Genetics will only distribute test results to your physician unless otherwise specified in writing by you (or a person legally authorized to act on your behalf) or required by a court of law.

Recipients of the data

In order to improve research and development in assisted reproduction techniques, other centres or entities within the group may have access to personal and genetic data in cases where information derived from the tests performed may be used in clinical studies by any of these entities, in accordance with the General Data Protection Regulation and national data protection laws. It is important to note that any data that may reveal your personal identity and/or that of your family will be anonymized, treated with absolute confidentiality, and used only for research and development purposes related to the services provided by the group. Necessary security measures will be implemented to ensure the security and confidentiality of your data.

Regarding the communication of data for research and development purposes:

☐ YES, I wish for Juno Genetics to share my information for research and development purposes

☐ NO, I do not wish for Juno Genetics to share my information for research and development purposes

XI. ONCE READ AND UNDERSTOOD THE ABOVE, WE ARE INFORMED OF:

- I have been informed that I am not obligated to undergo this genetic analysis, and I freely and voluntarily consent to its performance.
- The indication, procedure, success probabilities, limitations, risks and complications of the proposed test.
- My test results may have implications for other members of my family. I acknowledge that my results may sometimes be used to provide appropriate medical care for others. This could be done by discussing it with me or in such a way that I am not personally identified in this process.

- Procedures may be cancelled at any time during their implementation, either for medical reasons or at the request of the interested party, provided that it does not cause harm to patients or viable pre-embryos produced.
- Both my test results and the test report will be part of my patient record.
- I am informed of the availability of the healthcare staff at this facility to further clarify any aspect of the information that has not been sufficiently clarified.

We have understood the explanations provided to us in clear and simple language. In the event that the test has been conducted in the context of assisted reproductive treatment, the healthcare professional who has attended to us at the clinic where we are patients has allowed us to make all observations, clarified all doubts we have raised, and explained the implications of potential test results.

We also understand that at any time and without the need to provide any explanation, we can revoke the consent we are now giving. However, please note that, depending on when the test is revoked, you may have to pay for any costs associated with the test that have already been incurred prior to the revocation. Mainly the materials and reagents associated with the test, as well as the costs of transporting the samples.

Therefore, we declare that we are satisfied with the information received and that we understand the scope and risks of the treatment.

Information on the sex of the pregnancy:

☐ YES, I want to know the sex of the pregnancy

☐ NO, I do not want to know the sex of the pregnancy if it can be avoided. However, I understand that if an abnormality affecting the sex chromosomes (X and Y) is detected, the sex of the pregnancy will be revealed.

In case no answer is ticked, Juno Genetics will not report the sex of the pregnancy.

XII. PATIENT AND AUTHORISED HEALTHCARE PROFESSIONAL INFORMATION

Name of PATIENT	PATIENT Identification Number	Date of birth of PATIENT
Address PATIENT		

Authorisation:

After reading the COMPLETE document, I authorize the healthcare staff to carry out the test indicated in this consent form.

Signature and date

Name of the AUTHORISED HEALTH CARE PERSONNEL	Professional Registration Number	Date and Signature
I declare that:		
I have explained the content of these tests and their risks, and clarified any doubts and questions raised by the individual. Furthermore, commit to providing the necessary genetic counselling based on the test results.		