INFORMED LEGAL CONSENT FOR THE NEO24 TEST (NON-INVASIVE PRENATALTEST)

Introduction

This form describes the benefits, risks, and limitations of the Neo24 test. You should seek pre-test counselling by a genetic counsellor or other experienced health care provider prior to undergoing this kind of screening test. Read this form carefully – and ask your doctor any questions you may have — before making your decision about testing.

Purpose

Healthy people usually have 23 pairs of chromosomes, microscopic rod-shaped structures that exist inside virtually every cell of the body. The chromosomes are made of DNA and are the site where genes, chemical instructions for building and operating the body, are located. Sometimes a pregnancy may begin with an embryo that has the wrong number of chromosomes, either too many or too few – this condition is called 'aneuploidy'. In general, aneuploidy occurs in about 1 in 300 pregnancies, but it becomes significantly more common as mothers age and is present at much higher levels amongst miscarriages and stillbirths. Although most aneuploid pregnancies end in miscarriage, the birth of children with intellectual or physical disabilities of varying severity is also possible. The types of aneuploidy most often seen during pregnancy are trisomy 21 (Down syndrome), trisomy 18 (Edwards syndrome), and trisomy 13 (Patau syndrome), but other types are also known.

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

Neo24 test is an advanced prenatal test, which aims to assess the risk that a pregnancy is affected by a chromosome abnormality in a non-invasive manner. The test gives information about whether there may be extra (trisomy) or missing (monosomy) copies of any of the 24 chromosomes (chromosomes 1 to 22 and the two sex chromosomes, X and Y).

Neo24 test will also detect instances where a large piece of a chromosome (>7 Mb) has been lost or duplicated. The test can be used for twin pregnancies as well as singletons.
Neo24 test can be performed as early as at a gestational age of 10 weeks.

How does the test work?

This test screens for specific chromosomal abnormalities by looking at the foetal DNA (genetic material) in the maternal blood. The sample of blood contains millions of fragments of DNA, some from the mother's cells and some from the foetus. Neo24 test uses a technology called massively parallel sequencing (MPS) to "sequence" the DNA fragments (reading the letters of the genetic code), which allows determination of the chromosome that each fragment originally came from. The number of DNA fragments derived from each chromosome can then be counted. In this way, the test aims to measure the amount of DNA from each chromosome. The laboratory then uses an analysis method to estimate whether or not there are two copies of each whole chromosome, as should be seen in a healthy pregnancy with a normal number of chromosomes.

Limitations of the test

Neo24 test is a screening test that looks only for specific chromosomal abnormalities. This means that other chromosomal abnormalities that could affect the pregnancy may not be detected. Of note, Neo24 test is not able to detect balanced chromosome rearrangements and is not intended for the detection of polyploidy (e.g. triploidy). It will not be able to detect all possible microdeletion syndromes (conditions caused by loss of a small part of a chromosome), as the pieces of chromosome involved are sometimes too small to be accurately measured using this test.

Results reported as NO ANOMALY DETECTED do not eliminate the possibility of chromosomal abnormalities of the tested chromosomes. 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 defect or autism).

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

While Neo24 test can be performed in twin pregnancies, the status of each individual foetus cannot be determined. Moreover, Neo24 test can report the presence or absence of Y chromosome material (found only in males) but it will not be clear whether both twins are male or just one of them. Furthermore, the occurrence aneuploidies affecting the sex chromosomes cannot be evaluated in twin pregnancies. In the case of a vanishing twin (a pregnancy that begins as twins, but where only one foetus continues to grow), the test result may reflect the DNA of the 'vanishing' twin, leading to a higher probability of false positive or false negative results.

The sensitivity and specificity for detection of chromosomal aneuploidies for Neo24 test (using VeriSeq NIPT v2) are detailed in the table below:

Sensitivity and Specificity of the VeriSeq NIPT Solution v2 for detecting **Trisomy** 21, 18, & 13.

CLINICAL PERFORMANCE DATA	Trisomy 21	Trisomy 18	Trisomy 13
Sensitivity	> 99.9% (130/130)	> 99.9% (41/41)	> 99.9% (26/26)
2-sided 95% CI	97.1%, 100%	91.4%, 100%	87.1%, 100%
Specificity	99.90% (1982/1984)	99.90% (1995/1997)	99.90% (2000/2002)
2-sided 95% CI	99.63%, 99.97%	99.64%, 99.97%	99.64%, 99.97%

Sensitivity and Specificity of the VeriSeq NIPT Solution v2 (Genomewide Screen) for detecting various chromosomal anomalies (including trisomies, monosomies, and partial deletions or duplications of 7 Mb or greater) for any chromosome are provided in the table below.

CLINICAL PERFORMANCE DATA	Rare Autosomal Aneuploidy (RAA)*	Partial deletions and duplications (>7Mb)	OVERALL PERFORMANCE FOR ANY ANEUPLOIDY
Sensitivity	96.4% (27/28)	74.1% (20/27)	95.5% (318/333)
2-sided 95% CI	82.3%, 99.4%	55.3%, 86.8%	92.7%, 97.3%
Specificity	99.80% (2001/2005)	99.80% (2000/2004)	99.34% (1954/1967)
2-sided 95% CI	99.49%, 99.92%	99.49%, 99.92%	98.87%, 99.61%

**These are trisomies and monosomies of chromosomes 1 – 12, 14 – 17, 19, 20 and 22 as well as monosomies of chromosomes 13, 18 and 21.*

Like any test, Neo24 test has 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 accuracy rates of 99% or higher. Complicating factors such as twin pregnancy or mosaicism (a pregnancy having a mixture of normal and aneuploid cells) can reduce accuracy rates significantly.

The results of the test can be invalidated by certain factors. If you are aware that any of the following are true, please discuss with your doctor or contact Juno Genetics to determine whether Neo24 test would be applicable in your case.

- You have had a recent blood transfusion
- You have had an organ transplant
- You have had a recent surgical procedure
- You have undergone immunotherapy or stem cell therapy
- 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 began as a twin pregnancy but now there is only one foetus

It is important to remember that Neo24 test is a screening test. Results should not be treated as diagnostic. Because of the limitations outlined above, no irreversible clinical decisions should be made based on these results alone. If a definitive diagnosis is desired, a prenatal diagnosis by chorionic villus sampling or amniocentesis would

be necessary. In some cases, other testing may also be needed. Some rare chromosomal aneuploidies may only occur in mosaic form (where the abnormality is not present in all the cells of the foetus). Clinical consequences of such 'mosaicism' depend on the chromosome involved and cannot be predicted prenatally. Mosaic abnormalities may not be detected using Neo24 test.

Test procedure

A blood sample will be drawn and sent to Juno Genetics Laboratory in Oxford, UK. The DNA will be isolated from the blood and then sequenced using MPS, as described above. After sequencing, specialist software is used to calculate the number of copies of each chromosome in the foetus.

Physical risks

Side effects of having blood drawn are uncommon, but may include dizziness, fainting, soreness, bleeding, bruising, and, rarely, infection.

Privacy

Test results are kept confidential. The test results will only be released in connection with the testing service, to your doctor, his or her designee, other health care providers involved in your medical care (for example, your obstetrician), or to another health care provider as directed by you (or a person legally authorized to act on your behalf) in writing, or otherwise as required or authorized by applicable law.

Cross-border data transfer

For patients from outside the United Kingdom, the sample and the associated health information will be sent to the UK in order for the testing to be completed. As part of the testing, Juno Genetics Ltd will create and maintain information concerning your pregnancy.

Test results

Your test results will be sent to your doctor or any other health care provider you designate.

Pregnancy outcome information

Collecting information on the pregnancy after testing is part of a laboratory's standard practice for monitoring the quality of its tests and is required for accreditation of the laboratory. As such, Juno Genetics or its designee may contact your doctor to obtain this information. By signing this informed consent, you agree to allow your doctor to give this information to Juno Genetics Ltd or its designee.

Secondary findings

In the course of performing the Neo24 test, unexpected chromosomal alterations are sometimes (rarely) detected. These are known as "secondary findings". In some cases, it is not clear whether the secondary findings have any clinical importance. The policy of Juno Genetics Ltd is to NOT REPORT any secondary findings that do not affect health or are of uncertain relevance to health. If there are secondary findings of certain significance to health, Juno Genetics Ltd will contact your doctor for the best management of the situation.

Authorisation to use surplus or discarded patient samples for research:

Juno Genetics Ltd would like to use any leftover specimen and health information, including genetic information, in a de-identified form, for research purposes. Such uses may assist in the development of commercial tests and services or the publication of scientific papers. If you consent, you will not receive notice of any specific uses nor any compensation for these uses. All such uses will comply with any applicable law. Juno Genetics Ltd will strictly maintain your confidentiality at all times and will not be able to re-identify the samples for any purpose.

☐ YES, I authorise Juno Genetics Ltd to use leftover specimen and health information in a de-identified form, for research and development purposes

☐ NO, I do not authorise

INFORMED LEGAL CONSENT FOR THE NEO24 TEST (NON-INVASIVE PRENATALTEST)

Confirmation of consent

By signing this form, I, the patient having this screening performed, acknowledge that:

i) I have been offered the opportunity to ask questions and discuss with my doctor the benefits, risks, and limitations of the test to be performed;
ii) I have discussed the test limitations with my doctor (reliability of positive and negative test results; the predictive value of the test results) and understand that the test is not a diagnostic test, but a screening test and is not definitive;
iii) I have been informed about the availability and importance of genetic counselling and have been provided with information identifying an appropriate health care provider from whom I might obtain such counselling.

Pregnancy sex information:

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

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

I have received, read, and understood the Patient Informed Consent in its entirety, and I may retain a copy for my records. I understand that information on this form may be processed and shared for the purposes described.

I understand that I can consult my doctor for more information about my results and what they may mean for my pregnancy, what options I will have for further testing, and whether additional testing is recommended based on my clinical history.

Patient's name (PRINT): _____

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

Doctor's name (PRINT): _____

Doctor's signature: _____ **Date:** _____

Contact details:

Hayakawa Building Edmund Halley Road, Oxford Science Park,
Oxford, England, OX4 4GB
Email: Neo24@junogenetics.com
Telephone: 00442037431944 or 00442037431945