# PATIENT INFORMATION LEAFLET
## PRENATALSEQ (NON-INVASIVE PRENATAL SCREENING)

1 **INTRODUCTION**

1.1 Genseq Diagnostics Limited (Genseq) is an accredited laboratory that provides clinical genetic testing services to health practitioners who order one or more specific genetic tests on behalf of their patients. Non-Invasive Prenatal Screening (NIPS) genetic testing is available for persons who are 16 years of age and over and have capacity to consent to undergo genetic testing.

1.2 A health practitioner is required to order the test, and responsible for test selection. The health practitioner collects a patient's biological sample and refers it to Genseq, together with a completed Test Request Form specifying the test(s) to be performed and a signed Informed Consent Form confirming patient consent to the test(s). The Test Request Form also provides Genseq with relevant patient information including pregnancy information. Genseq relies on the adequacy and accuracy of the information provided by the health practitioner in the Test Request Form. Genseq performs the specific test(s) listed in the Test Request Form and issues a report on the test result(s) to the patient's health practitioner(s) whose contact details are provided in the Test Request Form including those registered under the patient's health practitioner's account.

2 **WHAT IS NIPS TESTING**

2.1 NIPS is a non- invasive **screening** test in pregnancy. **NIPS is not a diagnostic test**. NIPS is performed on a sample of peripheral blood collected from a pregnant woman of at least 10 weeks gestation (based on the results of an early pregnancy dating ultrasound scan) to screen the foetus for specific chromosomal abnormalities. Genseq offers NIPS screening using illumina® VeriSeq NIPT Solution v2 for Trisomy 13 (Patau Syndrome), 18 (Edwards Syndrome) and 21 (Down Syndrome) which are reported by Genseq as "high probability" and "low probability" results. For twin pregnancies, "low probability" results apply to both foetuses, and "high probability "results apply to at least one foetus. Please see paragraphs 4 and 5 for further information.

2.2 Analysis of sex chromosomes for aneuploidies (X, XXX, XXY, XYY) is an option only available for singleton pregnancies. If analysis of sex chromosomes aneuploidies is performed, and an aneuploidy is detected, the sex of the foetus will also be determined, even if it was not requested.

2.3 Patients may opt to have the sex of the foetus(es) included in the report. Sex of the foetus will be reported as "male "when a Y chromosome is detected or "female "when no Y chromosome is detected in the sample of DNA tested. For twin pregnancies, "male "means that a Y chromosome was detected **in at least one** of the Foetuses, and "female "means that a Y Chromosome was **not** detected in either foetus. Please see paragraphs 4 and 5 for further information.

3 **INFORMED CONSENT, DATA PROTECTION AND CONFIDENTIALITY**

**Informed consent**

3.1 Under Irish law, the informed consent of a person undergoing genetic testing must be obtained prior to the testing and the processing of associated genetic data. There is a legal presumption that persons who have reached the age of 16 have capacity to give consent. If a patient is under 16 years of age or lacks capacity to give informed consent to genetic testing, the patient's health practitioner who is organising the genetic test can contact Genseq to discuss the individual patient's circumstances.

3.2 Genetic testing is entirely voluntary. Before making a decision to proceed with genetic testing, the patient is entitled to receive all appropriate information concerning NIPS testing and processing of genetic data, including indication(s), purpose and scope, risks, potential outcomes and implications, and alternatives. Obtaining informed consent to NIPS testing including the processing of the associated genetic data by Genseq is the responsibility of the patient's health practitioner under whose responsibility the genetic testing has been ordered from Genseq.

3.3 By signing the Informed Consent Form, the patient acknowledges that she has received and understands all the relevant information and agrees to the NIPS testing specified in the Test Request Form and processing of associated genetic data by Genseq. By signing the Informed Consent Form the patient consents to the disclosure by Genseq of the genetic test results to the health practitioners whose details have been provided in the Test Request Form including those registered under the patient's health practitioner's account.

3.4 By signing the confirmation of health practitioner, the patient's health practitioner confirms that all appropriate information concerning the NIPS test has been provided to the patient, that all the patient's questions/ queries have been answered and that the patient has voluntarily given informed consent to NIPS testing and processing of associated genetic data. The patient's health practitioner also confirms that patient consent has been obtained for Genseq to issue the NIPS test results to the ordering health practitioner(s) whose details are provided in the Test Request Form including those registered under the patient's health practitioner's account via its online portal.

3.5 The patient has the right to withdraw consent at any time. To do this the patient should inform her health practitioner of her decision. The health practitioner is responsible for notifying Genseq of the patient's decision. On receipt of notification of the patient's decision to withdraw consent Genseq shall take reasonable operational steps to cease further testing and processing of personal data as soon as is reasonably practicable. Genseq will destroy the patient's samples and all of the patient's genetic data generated prior to the cessation of services. Genseq reserves the right to charge for the services it has provided prior to notification to Genseq of the patient's withdrawal of consent to testing.

**Data Protection**

3.6 For data protection purposes, the requesting health practitioner listed in the Test Request Form is the controller of the patient's personal data (i.e., data processed in order to perform and report on the testing sought by the health practitioner). The patient should direct any queries about the processing of her personal data to the requesting health practitioner. Genseq, as the appointed genetic testing services provider, acts as a processor on behalf of the requesting health practitioner. Genseq processes patients' personal data, health data and genetic data on the instructions of the health practitioner as controller of the personal data and retains personal data and samples for such period(s) of time as may be specified by the patient's health practitioner as data controller or for the period required by law, prior to destruction.

3.7 The processing of personal data relating to the patient is undertaken on the basis of consent (specifically given in the Informed Consent Form).

3.8 Further information may be sought on the processing of such personal data from the health practitioner.

**Confidentiality**

3.9 All genetic test results are confidential and will be disclosed by Genseq only to the health practitioner(s) named in the Test Request Form, and those registered under the patient's health practitioner's account, unless otherwise authorised by the patient or required by law.

3.10 By signing the Consent Form the patient consents to the disclosure by Genseq of the genetic test results to the health practitioners whose details have been provided in the Test Request Form including those registered under the patient's health practitioner's account. The patient should discuss and agree approved recipients with her health practitioner. Genseq relies on the information in the Test Request Form and the signed Informed Consent Form to determine the appropriate recipients.

## 4 REPORTING RESULTS OF NIPS

4.1 Results from NIPS testing are reported as High Probability, Low Probability or No Result. Genseq does not report findings which are incidental / unrelated to the specific NIPS test set out in the Test Request Form.

4.2 A **High Probability** result means that the sample screens positive for one or more aneuploidies involving the specific chromosomes tested. A High Probability test result indicates an increased chance that the patient's foetus has one of the chromosome aneuploidies screened for but does not confirm that the foetus has that aneuploidy.

4.3 A **Low Probability** result means that the sample screens negative for any of the aneuploidies involving the specific chromosomes tested. Low Probability indicates a reduced chance that the patient's foetus has the chromosome aneuploidies screened for, but it does not guarantee a healthy foetus or a foetus without genetic abnormalities. Genetic conditions may have many causes, some of which may not be completely known or testable. Therefore, a negative test result does not exclude the possibility of the foetus being affected with the chromosomal aneuploidies screened for or the foetus being affected by or a carrier of other genetic disorders, birth defects or other complications in the patient's foetus.

4.4 A **No Result** may occur due to several factors including but not limited to limitations of laboratory methods, poor sample quality or limitations of the testing. In some cases, a repeat test based on a new maternal blood sample may be the appropriate option. This decision will be made by the patient's health practitioner in consultation with the patient.

4.5 Genseq reports test results as High Probability or Low Probability using language that more closely reflects the explanation provided by the patient's health practitioner when interpreting test results for their patients. The illumina® VeriSeq NIPT Solution v2 analyser used by Genseq reports test results using different terminology and for completeness we have set out the Genseq wording and the Illumina equivalent in the

| Genseq Report | illumina® VeriSeq NIPT Solution v2 Report |
|---|---|
| High Probability | Anomaly Detected |
| Low Probability | No Anomaly Detected |
| No Result | No Result |
| Male | Y chromosome presence |
| Female | Y chromosome absence |

## 5 LIMITATIONS AND RISKS OF NIPS TEST

5.1 It is important to note that NIPS is a screening test and **is not a diagnostic test**. The NIPS test results should not be considered in isolation from other clinical findings and test results. **Therefore, it is advisable that decisions about the patient's pregnancy should not be made based on these screening results alone as they neither confirm nor rule out the presence of a chromosome abnormality in the foetus.**

5.2 Genseq uses illumina® VeriSeq NIPT Solution v2 for NIPS. illumina® VeriSeq NIPT Solution v2 uses whole genome sequencing to detect trisomies of chromosomes 13, 18, 21, and optionally sex chromosomes aneuploidies and foetal sex. illumina® reports very high levels of sensitivity and specificity but not 100% accuracy in screening for the specific chromosomal abnormalities. Therefore, although this screening test will detect the majority of pregnancies where the foetus has one of the chromosomal abnormalities tested for, it cannot detect 100% of cases with these conditions. **The current information provided by illumina® for general performance of specific screening tests using illumina® VeriSeq NIPT Solution v2 is summarised in the tables in the Appendix to this information leaflet (See Page 4).** Please refer to your health practitioner for an explanation of the performance test results.

5.3 NIPS using illumina® VeriSeq NIPT Solution v2 is not suitable for pregnant women with multiple gestation pregnancies who are pregnant with three or more foetuses. You are also referred to paragraphs 2.1 and 2.3 above for potential limitations in reporting of trisomy "High Probability" test results and "Male" sex based on Y chromosome presence in the case of foetal sex test results in twin pregnancies. There is a risk in twin pregnancies when one foetus is male (chromosomes XY) and the other foetus is female (chromosomes XX) that the report on the DNA sample will accurately identify the sex of the male twin only and will not identify the presence of a female twin due to the limitation of the illumina® VeriSeq NIPT Solution v2 which tests the DNA sample for the presence or absence of a Y chromosome. Additionally, since the sex of the foetus is not

determined solely by the presence of the Y chromosome, a foetus with Y chromosome presence may still be female.

5.4 **The patient's health practitioner is responsible for explaining the patient's NIPS results and for making any appropriate recommendations regarding follow up steps including invasive diagnostic testing, which may include cytogenetic analysis of either amniotic fluid or chorionic villus sampling, genetic counselling and / or specialist referral for treatment, or advice on the future management of the patient's pregnancy.**

5.5 Although genetic test results are usually accurate, illumina® reports based on the literature evidence, the accuracy of screening results can be adversely affected by certain maternal and foetal factors, including but not limited to: recent maternal blood transfusion; maternal prior bone marrow / organ transplant / stem cell transplant; radiation/ immune/ stem cell therapy; maternal autoimmune disease or cancer unless in remission; maternal neoplasms (benign and malignant); maternal mosaicism; maternal copy number variations, balanced translocations or whole chromosomal abnormalities; foetoplacental mosaicism / confined placental mosaicism and foetal demise / vanishing twin.

## APPENDIX

### General Performance Test Results For Specific NIPS Tests Using illumina® VeriSeq NIPT Solution v2 Package

The performance of VeriSeq NIPT Solution v2 was estimated on a study reported by Illumina® on the Illumina® VeriSeq NIPT Solution v2 Package Insert.

Evidence supporting sensitivity and specificity for the test covers singleton and twin pregnancies. A total of 2,236 singleton pregnancies were included in the analysis. Due to the low prevalence of trisomy 13, 18, and 21 in twin pregnancies, the performance of the test was calculated using 4,500 twin pregnancies *in silico* models:

| Condition | Singleton pregnancies | | Twin pregnancies only | |
|---|---|---|---|---|
| | Sensitivity[1] | Specificity[2] | Sensitivity[1] | Specificity[2] |
| **Trisomy 13** | > 99.9% (26/26) | 99.90% (2000/2002) | 93.6% | > 99.9% |
| **Trisomy 18** | > 99.9% (41/41) | 99.90% (1995/1997) | 95.7% | > 99.9% |
| **Trisomy 21** | > 99.9% (130/130) | 99.90% (1982/1984) | 96.4% | > 99.9% |
| **Presence of Y** | - | - | > 99.9% | > 99.9% |

[1] Sensitivity is the ability to correctly identify a foetus with one of the tested conditions as “anomaly detected” result. For instance, in a group of singleton pregnancies with Trisomy 21, this test will correctly identify more than 99.9% of those cases.

[2] Specificity is the ability to correctly identify a foetus without the tested conditions as “no anomaly detected” result.

Positive predictive value (PPV) and negative predictive value (NPV) of the test provide information regarding the ability of the test to inform clinical decisions based on test sensitivity, specificity, and pretest probability that a foetus is trisomy affected (prevalence).

Because PPV and NPV depend on prevalence and the prevalence for these aneuploidies can vary across different subject populations, PPV and NPV were calculated for a range of plausible prevalence values based on the sensitivity and specificity values observed in the screen (without known mosaics) of the clinical accuracy study:

| Trisomy 13 | | |
|---|---|---|
| Prevalence (%) | PPV (%) | NPV (%) |
| 0.01 | 9.10 | > 99.99 |
| 0.02 | 16.68 | > 99.99 |
| 0.05 | 33.37 | > 99.99 |
| 0.10 | 50.05 | > 99.99 |
| 0.20 | 66.73 | > 99.99 |

| Trisomy 18 | | |
|---|---|---|
| Prevalence (%) | PPV (%) | NPV (%) |
| 0.03 | 23.06 | > 99.99 |
| 0.05 | 33.31 | > 99.99 |
| 0.10 | 49.99 | > 99.99 |
| 0.20 | 66.68 | > 99.99 |
| 0.30 | 75.03 | > 99.99 |
| 0.40 | 80.04 | > 99.99 |
| 0.50 | 83.38 | > 99.99 |

| Trisomy 21 | | |
|---|---|---|
| Prevalence (%) | PPV (%) | NPV (%) |
| 0.05 | 33.17 | > 99.99 |
| 0.10 | 49.82 | > 99.99 |
| 0.20 | 66.53 | > 99.99 |
| 0.50 | 83.29 | > 99.99 |
| 1.00 | 90.93 | > 99.99 |
| 1.50 | 93.79 | > 99.99 |
| 2.00 | 95.29 | > 99.99 |

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