

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.
- 1.2 A patient's health practitioner is responsible for test selection. A patient's biological sample (3 mls of a patient's peripheral blood or patient extracted genomic DNA) is referred 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 or in the case of a child the patient's legal guardian(s) consent to the test(s).
- 1.3 The health practitioner identifies, from the available options offered by Genseq, the relevant target disease or condition based on his or her clinical analysis of the patient. Genseq offers gene panel(s) sequencing to test a patient's DNA to detect the presence of gene abnormalities (e.g., single nucleotide variants (SNV), small insertions or deletions (indels) and copy number variation (CNV)) which, based on current scientific knowledge, are considered to be associated with the specific target disease or condition. Some panels also include mitochondrial genome variant analysis.
- 1.4 The Test Request Form completed by the patient's health practitioner also provides Genseq with relevant patient information including the suspected genetic disease or condition, the relevant medical diagnosis, the patient's clinical symptoms, the patient's characteristics, family history, and relevant prior test results of the patient and family (where relevant). Genseq relies on the adequacy and accuracy of the information provided by the health practitioner in the Test Request Form.
- 1.5 Genseq performs Whole Exome Sequencing (WES) and mitochondrial genome sequencing on patient DNA which has been extracted from a blood sample. This extraction may have been performed by Genseq or another laboratory. Although all genes will be sequenced (approximately 22,000 protein-coding genes) using WES a target analysis of a subset of genes specified on the relevant gene panel will be conducted. The data generated will be analysed and reported on by Genseq.
- 1.6 Genseq analyses and reports on the genes on the specific gene panel(s) listed in the Test Request Form and issues a report 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.
- 1.7 A patient's health practitioner is responsible for the clinical interpretation of the test results and the future management of the patient.

2 WHAT IS GENE PANEL SEQUENCING TESTING

- 2.1 Genseq offers gene panel sequencing testing for multiple conditions including cardiac, lipid, nephrology, ophthalmology, and neurology disorders, and inherited cancer which are known to have a significant level of gene-disease association based on scientific and clinical literature.
- 2.2 The specific gene panels have been developed based on the data from large international databases, and the gene content of each panel is documented at appendix 2 of the Genseq Laboratory User Guide. The patient's health practitioner determines the suitability of a patient for gene panel sequencing testing. Genseq performs WES and mitochondrial sequencing, applies the computerised filter relevant to the selected panel(s), and analyses and reports on the genetic data generated in respect of the test panel(s).

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. Legal guardian(s) can give consent on behalf of persons who are under the age of 16, or on behalf of persons who are 16 years but not yet 18 years of age and lack capacity to consent.
- 3.2 If a patient is 18 years of age or older and their decision making capacity is in question or they have been assessed by their health practitioner as lacking capacity to give informed consent to genetic testing, the patient's health practitioner, who is organising the genetic testing, can contact Genseq to discuss the individual patient's circumstances and the appropriate assisted decision making arrangements that are or will be put in place consistent with the requirements of the Assisted Decision Making (Capacity) Act 2015, (as amended) (the 2015 Act).
- 3.3 Genetic testing is entirely voluntary. Before making a decision, the patient or the patient's legal guardian(s) where the patient is a child is /are entitled to receive all appropriate information concerning the genetic testing and processing of genetic data, including indication(s) such as the relevant target disease or condition, purpose and scope, risks, potential outcomes, implications, and alternatives. Obtaining informed consent for genetic testing and the processing of the associated genetic data is the responsibility of the patient's health practitioner under whose responsibility the genetic testing has been ordered from Genseq.
- 3.4 By signing the Informed Consent Form, the patient, or the patient's guardian(s) (as applicable), acknowledge that he / she / they have received and understand all the relevant information and agrees to the genetic testing specified in the Test Request Form and processing of associated genetic data by Genseq. By signing the Informed Consent Form the patient or the patient's legal guardian(s) where the patient is a child, 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.
- 3.5 By signing the confirmation of health practitioner, the patient's health practitioner confirms that all appropriate information concerning the gene panel(s) testing has been provided to the patient / the patient's guardians (as applicable), that all the patient's / legal guardian(s) questions / queries have been answered and that the patient or where the patient is a child his / her legal guardian(s) has / have voluntarily given informed consent to gene panel(s) 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 gene panel(s) 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.
- 3.6 The patient or where the patient is a child his or her legal guardian(s) has / have the right to withdraw consent at any time. To do this the patient / legal guardian(s) (as applicable), should inform the patient's health practitioner, who organised the test, of the patient's / patient's legal guardian(s) decision. The health practitioner is responsible for notifying Genseq of the patient's / the patient's legal guardian(s) decision, as applicable. On receipt of notification of the patient's / the patient's legal guardian(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 / patient's legal guardian(s) withdrawal of consent to testing.

Data Protection

- 3.7 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 or where the patient is a child his / her guardian(s) should direct any queries about the processing of the patient's 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.
- 3.8 The processing of personal data relating to the patient is undertaken on the basis of consent (specifically given in the Informed Consent Form) by the patient or where the patient is a child by the patient's legal guardian(s) on behalf of the patient. Associated consent is also sought to the necessary processing of the names of the legal guardian(s) in connection with the processing of the personal data of the patient.
- 3.9 Further information may be sought on the processing of such personal data from the health practitioner.

Confidentiality

- 3.10 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.
- 3.11 By signing the Consent Form the patient or the patient's legal guardians, as applicable, 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 or the patient's legal guardian(s), as applicable, should discuss and agree approved recipients with the patient's 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 OF GENE PANEL TESTS RESULTS

- 4.1 Results from gene panel tests are reported as "pathogenic or likely pathogenic variant(s) was/were identified", "No pathogenic or likely pathogenic variants were identified", or "no result".
- 4.2 A "**pathogenic or likely pathogenic variant(s) was/were identified**" result means that the DNA sample tested positive for one or more pathogenic or likely pathogenic variants with possible relevance to the patient's clinical details on genes within the scope of a specific panel test. A positive test result may confirm whether a person is affected with, a carrier of, or at risk of developing a genetic disease or condition. In the case of a positive test result a patient's health practitioner may recommend a second test to confirm the result sometimes using a different test.
- 4.3 A "**No pathogenic or likely pathogenic variants were identified**" result means that the DNA sample tested did not identify pathogenic or likely pathogenic variants with possible relevance to the patient's clinical details on genes within the scope of a specific panel test. A negative result does not exclude the possibility of a person being affected with a genetic disease or condition, including the target diseases or condition associated with the genes on the specific gene panel or being a carrier of pathogenic variants in respect of genetic disorders. Genetic conditions may have many causes, some of which may not be known, completely known or testable. In addition, a person may have a pathogenic variant in a gene that is not included in the subset of genes tested in the relevant gene panel(s).

- 4.4 A “no result “means that no results were returned in response to the relevant gene panel test. This may occur due to several factors including limitations of laboratory methods or poor sample quality. In this case, the health practitioner may request a new test by submitting a new specimen or make other recommendations to the patient.
- 4.5 Genseq issues reports which include a table with variant information: gene, variant description, exon or intron location, dbSNP identifier (if available), zygosity, and variant classification. In addition, the report includes a summary of the result, detailed variant description explaining the rationale for the variant classification, and the associated phenotype.
- 4.6 Genseq does not routinely report Variants of Unknown Significance (VUS) because scientific proof of pathogenicity has not been established. However, Genseq will report, as a supplemental finding in the patient’s report, certain VUS identified in clinically relevant genes, where there is strong suspicion, reflected in scientific evidence, of an association between the VUS and the relevant target disease or condition, although proof of pathogenicity has not been scientifically established at the date of reporting. The Supplementary finding may add value to the information available to the patient’s health practitioner where further family history, familial testing or phenotypic evidence may help re-classify the variant.
- 4.7 Genseq does not report findings which are incidental, secondary or unrelated to the specific target disease or condition set out in the Test Request Form. Genseq does not report VUS except in the circumstance outlined in paragraph 4.6 above. On the request of a patient’s health practitioner to within 6 months of the date of the report Genseq will discuss any questions raised by the health practitioner regarding the gene panel test results which may include a discussion of VUS. Supplementary reports prepared on request of a patient’s health practitioner will incur an additional charge.
- 4.8 Genseq reports based on its analyses of the WES and mitochondrial genome data generated in respect of the specific gene panel(s) set out in the Test Request Form. Genseq does not review or analyse the genetic raw data which is not specific to the relevant gene panel(s) set out in the Test Request Form.
- 4.9 For patient cases reported as pathogenic or likely pathogenic, Genseq will securely store patient DNA for 5 years to facilitate potential future and/or family based testing.

5 LIMITATIONS AND RISKS OF WES PANEL TESTS

- 5.1 The technology used by Genseq for WES, gene sequencing panel testing is Illumina DNA Prep with Exome 2.5 Enrichment and associated automated platforms for sequencing, bioinformatics and validation as well as a number of other platforms and assays developed by other manufacturers. Reported SNVs and Indels are validated by Sanger Sequencing. Reported CNV are not validated by Sanger sequencing due to assay limitations.
- 5.2 In the case of a “no pathogenic or likely pathogenic variants were identified” result or a “no result”, the absence of an identified disease-causing variant does not exclude the possibility of a genetic basis for the disorder in the patient. It is possible that a particular variant may not be recognised as the underlying cause of a patient’s genetic disorder because the clinical implications of this variant may not be known at the time of the testing and report. Genseq relies on information which is currently available in the healthcare literature and scientific databases, and selected bioinformatic platforms. It is also possible that the classification of variants may change in the future due to improvements in scientific understanding and/or new knowledge / information being discovered and published to the scientific community.
- 5.3 The patient’s health practitioner is responsible for the patient’s clinical management including the interpretation of the test results, recommendations regarding healthcare treatment (if available), recommendation of any appropriate further testing and future clinical management. Test results should

always be interpreted in the context of clinical findings, family history, and other relevant laboratory data. Inaccurate, or incomplete information may lead to misinterpretation of the results.

- 5.4 Some genetic abnormalities may not be detectable with the technologies performed, including variants in untargeted regions (e.g., variants in the promoter or intergenic regions), inversions, balanced translocations, repeat expansions, non-coding variants deeper than ± 20 base pairs from exon-intron boundary.
- 5.5 Gene panel testing may not reliably detect some types of variants, including low level mosaicism, low level mitochondrial heteroplasmy, variants in mononucleotide repeat regions, indels larger than 50 base pairs, deletions or duplications with size lower than 10 Kb, variants within regions with suboptimal coverage (e.g., variants within pseudogene regions, repeat elements, segmental duplications, and high GC content regions). Detection sensitivity and specificity for SNVs calculated by Genseq using a reference standard sample is: 97.8% and 99.8%, and for indels: 90.4% and 97.8%, respectively. The sensitivity and specificity for CNV detection is dependent on location and size, therefore the absence of a reported CNV does not exclude the possibility of the presence of a CNV.
- 5.6 Although genetic test results are usually accurate, several sources of error are possible, including clinical misdiagnosis of a condition, inaccurate clinical information concerning the patient and family provided to Genseq sample mislabelling or contamination, recent patient blood transfusion and bone marrow transplantation.

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