THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

Exome Sequencing

The UCGS Exome Sequencing Test evaluates the protein-coding regions of the human genome, which represents approximately 20,000 genes. These regions of DNA are referred to as 'exome'. The exome accounts for approximately 2% of the genome and comprises the majority of DNA variations that cause human disease (1). Exome sequencing is a useful and powerful tool for diagnostic applications and has been utilized to identify mutations in disorders that are both genetically and phenotypically heterogeneous and to identify mutations in genes associated with Mendelian disorders. Exome sequencing has been observed to identify the underlying genetic defect in approximately 25 – 35% of patients referred for evaluation of a possible genetic condition (2).

Test methods:

Exome sequencing is performed using the Agilent SureSelect Clinical Research Exome kit that is designed to target the exome with greater coverage of known disease-associated genes. Sequencing is performed using the Illumina technology and reads are aligned to the reference sequence. Approximately 97-98% of all exons are targeted at a minimum depth of 10X in the diagnostic Exome Sequencing test. Variants are identified and evaluated using a custom collection of bioinformatic tools and comprehensively interpreted by our team of directors and genetic counselors. All pathogenic and likely pathogenic variants are confirmed by Sanger sequencing. In some cases, exome sequencing data may be used to detect larger copy number variations (CNVs) such as whole or partial gene deletions/duplications. The sensitivity of exome sequencing to detect intragenic deletions/duplications >20bp in size is not currently known.

Testing Analysis

Of the thousands of variants identified by exome sequencing, a list of variants in genes that could potentially be related to the phenotype in the patient is generated. Most variants identified as part of exome sequencing will NOT undergo interpretation by a laboratory staff member. Only those variants identified that are considered to be potentially relevant to the patient's condition are reviewed by a team of Board-Certified PhD geneticists, MD geneticists, and genetic counselors who will determine the likelihood of the variant being related to the patient's disorder.

Parental Analysis

We strongly recommend sending samples from both biological parents, in addition to the proband's sample, in order to facilitate the interpretation of results. Exome sequencing will be performed on parental samples, and is included in the cost of the Exome Sequencing Trio test. A separate parental report will not be issued.

Limitations

Not all the exons in the genome are targeted and captured due to certain inherent characteristics of the genome. In addition, there is limited or no coverage in regions outside of the exome. Certain types of mutations are not detectable by this test. This methodology will not detect low level mosaicism, copy number variations (i.e such as the deletion or duplication of an exon) and trinucleotide repeat expansions.

Reporting Results

UCGS will report on genetic variants that have been reported to be pathogenic, predicted to be pathogenic, possibly pathogenic as well as unclassified variants in established genes for the clinical features/suspected condition indicated for the patient. In addition, truncating pathogenic variants and variants that have been previously reported to be pathogenic or possibly pathogenic in genes hypothesized to be related to the cause of the patient's phenotype will also be reported.

Secondary/Incidental Findings Reporting Results

Mutations in genes unrelated to the individual's reported phenotype are considered secondary or incidental findings.

The American College of Medical Genetics and Genomics (ACMG) recommends a minimal list of secondary findings to report from clinical sequencing. All of the included disorders are rare and were selected because

preventative measures and/or treatments are available. Many individuals with pathogenic variants in these conditions might be asymptomatic for long periods of time. UCGS will report pathogenic variants in 59 genes as recommended by the ACMG. For further information please refer to the ACMG Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016. Patients have the choice to opt-out of receiving incidental findings in the 59 genes recommended by ACMG.

Carrier status for autosomal recessive conditons that are recommended by ACMG or ACOG can also be reported. UCGS will report pathogenic variants in the following conditions: Bloom syndrome, Canavan disease, Cystic Fibrosis, Familial Dysautonomia, Fanconi Anemia type C, Gaucher disease type 1, Hb Beta Chain Related Hemoglobinopathy (Beta Thalassemia & Sickle Cell Disease), Tay Sachs disease, Mucolipidosis IV, Niemann Pick Type A. Patients have the choice to receive results related to carrier status of the above autosomal recessive conditions. The UCGS Exome is not meant to be utilized as a comprehensive carrier test as an individual may be a carrier of a type of mutation not screened for by this test or may be a carrier of a mutation in a region of a gene that is not well covered.

Required Forms:

- Exome Sequencing Test Requisition Form
- Completed Clinical Checklist – in addition, please send detailed clinic notes, pedigree, results of previous genetic testing, and brain imaging reports if available.
- Completed Exome Sequencing Consent Form

Exome Sequencing (Proband only)

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$4000
CPT codes:	81415
Turn-around time:	6 weeks

Note: We cannot bill insurance for the above test.

Exome Sequencing (Trio)

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$5800
CPT codes:	81415, 81416
Turn-around time:	6 weeks

Note: We cannot bill insurance for the above test.

STAT Exome Sequencing (Proband only)

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$8000
CPT codes:	81415
Turn-around time:	Preliminary results provided within 2 weeks of test initiation

Note: We cannot bill insurance for the above test.
****Please contact UCGSL staff prior to ordering STAT testing.***

STAT Exome Sequencing (Trio)

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$11,600
CPT codes:	81415, 81416
Turn-around time:	Preliminary results provided within 2 weeks of test initiation

Note: We cannot bill insurance for the above test.
****Please contact UCGSL staff prior to ordering STAT testing.***

* We currently only offer institutional billing and self-pay for our exome sequencing tests. Insurance prior authorization is not mandatory before sending a sample to our laboratory. Insurance prior authorization services are offered as a courtesy and can be requested PRIOR to sending a sample to our laboratory (please see website for prior authorization request form). Samples received with appropriate billing information (institutional billing or self-pay) will be processed accordingly.

For more information about our testing options, please visit our website at dnatesting.uchicago.edu or contact us at 773-834-0555.

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