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Exome Sequencing

Frequently Asked Questions

What is Exome Sequencing?

Exome sequencing is a new technique that 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. 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.

Common reasons for ordering exome sequencing:

- To confirm a genetic diagnosis in a patient who presents with features that could be applicable to a number of different conditions, or in which the differential diagnosis and sequential genetic testing would be cost prohibitive.
- To confirm a genetic diagnosis in a patient who presents with features of a condition that is highly genetically heterogeneous
- To confirm a genetic diagnosis in a patient who has had previous extensive genetic testing with no molecular diagnosis in which a Mendelian condition is suspected.

What will the Report Contain?

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.

What will the Report not Contain?

- Benign sequence changes not associated with disease and are commonly identified in healthy people.
- Synonymous (silent) sequence changes not associated with a change in the amino acid sequence.
- Variations associated with increased or decreased risk to develop common disorders (like high blood pressure) or involved in drug metabolism.
- Variations that have been associated with an increased risk for diseases that might present at an advanced age (like Alzheimer's Disease) in which there is no treatment or preventative measures.
- Heterozygous unclassified variants associated with a recessive disorder unless a deleterious mutation or a second unclassified variant in the same gene is also detected.
- Pathogenic mutations and variants in genes with no current known association with disease.

Will you report findings that are not associated with the patient's reported phenotype?

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 57 genes as recommended by the ACMG. For further information please refer to the **American College of Medical Genetics and Genomics (ACMG) recommendations for Reporting Incidental Findings in Clinical Exome and Genome Sequencing**. Patients have the choice to opt-out of receiving incidental findings in the 57 genes recommended by ACMG.

Carrier status for autosomal recessive conditions 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 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.

What types of mutations are not detected by this methodology?
Not all the exons in the genome are targeted and captured due to certain inherent characteristics of the genome. Approximately 90-95% of exons at a minimum depth of 30X are targeted in the diagnostic exome test. In addition, there is limited or no coverage in regions outside of the exome.

This methodology will not detect low level mosaicism, copy number variation mutations (i.e such as the deletion or duplication of an exon) and trinucleotide repeat expansions.

Pathogenic variants may be present in a region of a gene not covered by this test. Absence of findings for any particular gene does not mean that there are no pathogenic variants present in that gene.

Are reported variants confirmed by another methodology?
All reported variants are confirmed by Sanger sequencing. Some variants in which the likelihood of pathogenicity is low will not be reported and not Sanger confirmed, but will be available upon request.

Is a list of the genes that were analyzed available?
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. The list of genes analyzed in a patient as well as their extent of coverage is available upon request.

What is the policy regarding parental samples?
Biological parental samples are requested in order to facilitate the interpretation of results. Exome sequencing will be performed on parental samples. A separate parental report will not be issued.

What if parental samples are not available?
If parental samples are not available, exome sequencing can still be ordered on the proband. Please keep in mind that there may be higher likelihood of results that the clinical significance is difficult to interpret.

What type of platform are you utilizing and what are the statistics for coverage and quality.
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. Approximately 90-95% of all exons are targeted at a minimum depth of 30X in the diagnostic Exome Sequencing test.

How are the variants filtered?
Variants are identified and evaluated using a custom collection of bioinformatic tools and comprehensively interpreted by our team of directors and genetic counselors.

What type of samples are accepted?
Please send 3-10cc of blood in an EDTA (lavender top) tube. Please contact the laboratory before obtaining an alternative specimen type than stated.

How much does the testing cost and will my or my child's health insurance cover it?
The cost for the Exome Sequencing in a patient only is $4800. The cost for the Exome Sequencing in a patient and parents is $6500. All insurance companies are different. You can contact your insurance company to learn more about your coverage prior to testing. You will want to ask your insurance company what your coverage is for the following CPT (Current Procedural Terminology) codes: 81407. Insurance companies use these codes to define the method of testing. In most cases, The University of Chicago will bill your hospital or lab, which will then bill your insurance company. You may receive a bill for any amount not covered by your insurance company, i.e. co-payment, deductible, etc. In some cases, The University of Chicago cannot bill your hospital or lab. In this case, we will need payment from you by check or credit card before testing. You will need to get repaid from your insurance company; The University of Chicago is not responsible for this.

We currently only offer institutional billing and self-pay for our exome sequencing tests. Insurance prior authorization is not absolutely 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

If a change or variant is found in your child, cost for testing other family members is $390. Prenatal testing for known change or variant is $540.

When/how will I get the results?
Testing takes approximately 8-10 weeks. Your physician will be informed of the results as soon as it is complete. Results will be faxed to your physician.

Will you perform re-analysis?
As new gene discoveries and associations are reported in the literature, we can review past cases for findings in these genes. Re-analysis of exome sequencing data is available once per patient at no additional charge, if requested within 12 months of receiving the original exome results.

What paperwork is required in order to send a sample?

- 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