Overview

Useful For

Identifying a molecular diagnosis in patients with a known or suspected genetic disorder, which can allow for:

- Better understanding of the natural history/prognosis
- Targeted management (anticipatory guidance, management changes, specific therapies)
- Predictive testing of at-risk family members
- Testing and exclusion of disease in siblings or other relatives
- Recurrence risk assessment
- Reproductive decision-making

Serving as a second-tier test for patients in whom previous genetic testing for specific syndromes was negative

Providing a potentially cost-effective alternative to establishing a molecular diagnosis compared to multiple independent molecular assays

Genetics Test Information

This test evaluates patients with suspected genetic disorders for germline mutations within the coding regions of approximately 23,000 genes using next-generation sequencing. This test requires that samples are submitted from the patient, the patient's biological mother, and the patient's biological father (trio analysis).

Highlights

This test uses whole exome sequencing to evaluate patients with a suspected genetic disorder, including diagnostic odyssey patients who have had previous genetic testing that has been uninformative.

Next-generation sequencing is utilized to test for germline mutations in the exome (ie, coding regions of the genome).

This test cannot be performed unless whole blood samples are submitted from the patient and both biological parents.

Medically-actionable secondary findings in the list of genes recommended by the American College of Medical Genetics and Genomics (ACMG)(1) will be reported, unless the patient opts-out of receiving these.

Testing Algorithm

Whole blood samples must be collected from the patient's biological parents and are required for the analysis of the patient's results. Analysis of these samples is included in the list price for the patient's test and additional charges will not be applied to the parental samples.

In addition to analysis of variants associated with the patient's reported phenotype, analysis for reportable secondary findings in genes included in the American College of Medical Genetics and Genomics' (ACMG) recommendations will be included.(1) Patients may opt-out of receiving these test results.

Complete the Patient Information and Informed Consent forms and send to the laboratory along with the specimen.
The forms are located within the Whole Exome Sequencing: Ordering Checklist, Patient Information, and Informed Consent forms in Special Instructions. The completed forms may also be faxed directly to the whole exome sequencing genetic counselors at 507-284-0670.

See Whole Exome Sequencing (WES): Questions and Answers for Providers in Special Instructions for additional information.

Sanger sequencing may be performed for verification of results.

The following algorithms are available in Special Instructions:

- Inherited Motor Neuron Disease Testing Algorithm
- Epilepsy: Unexplained Refractory and/or Familial Testing Algorithm
- Neuromuscular Myopathy Testing Algorithm
- Hereditary Peripheral Neuropathy Diagnostic Algorithm

Special Instructions

- GenomeConnect Patient Portal
- Whole Exome Sequencing: Ordering Checklist, Patient Information, and Informed Consent
- Hereditary Peripheral Neuropathy Diagnostic Algorithm
- Whole Exome Sequencing (WES): Questions and Answers for Providers
- Inherited Motor Neuron Disease Testing Algorithm
- Epilepsy: Unexplained Refractory and/or Familial Testing Algorithm
- Neuromuscular Myopathy Testing Algorithm

Method Name

Next-Generation Sequencing followed by Polymerase Chain Reaction (PCR) and Sanger Sequencing

NY State Available

Yes

Specimen

Specimen Type

Varies

Advisory Information

This test is only available for trios (proband, biological mother, and biological father).

Clients must provide all 3 samples for this test to be performed; each specimen must be on a separate order for WES / Whole Exome Sequencing.

Shipping Instructions

Specimen preferred to arrive within 96 hours of collection.

Necessary Information

1. Complete the Patient Information and Informed Consent forms within the Whole Exome Sequencing: Ordering Checklist, Patient Information, and Informed Consent forms, available in Special Instructions.
2. In addition, submit relevant clinic notes and a pedigree. Send all paperwork with the specimens to the laboratory. The paperwork may also be faxed directly to the whole exome sequencing genetic counselors at 507-284-0670.

**Specimen Required**

Samples from both biological parents and the patient are required. Each specimen must have a separate order for WES / Whole Exome Sequencing.

**Specimen Type:** Whole blood

**Container/Tube:**

- **Preferred:** Lavender top (EDTA) or yellow top (ACD)
- **Acceptable:** Any anticoagulant

**Specimen Volume:** 3 mL

**Collection Instructions:**

1. Invert several times to mix blood.
2. Send specimen in original tube.
3. Label the parental samples with full name and date of birth. **Do not** label the parental samples with the child's name.

**Additional Information:** To ensure minimum volume and concentration of DNA is met, the preferred volume of blood must be submitted. Testing may be canceled if DNA requirements are inadequate.

**Forms**

Whole Exome Sequencing: Ordering Checklist, Patient Information, and Informed Consent in Special Instructions

**Specimen Minimum Volume**

1 mL

**Reject Due To**

No specimen should be rejected.

**Specimen Stability Information**

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**Clinical and Interpretive**
Clinical Information

Many patients with suspected genetic disorders remain without a diagnosis despite having a phenotype that is suggestive of an underlying genetic etiology, such as developmental delay and dysmorphic features. These diagnostic odyssey patients have often had numerous negative or inconclusive genetic tests previously, including karyotype, chromosomal microarray, and various single or multigene assays. Identification of a specific diagnosis can assist in understanding the natural history of a condition, targeting medical management, and providing information to family members about the inheritance pattern and recurrence risks of the condition.

This test uses next-generation sequencing technology to assess for variants within the coding regions (exons) of approximately 23,000 genes simultaneously. The patient's biological parents must be available and able to provide a blood sample, which is used for comparison purposes. Based upon published reports, a diagnosis is identified in trio-based whole exome sequencing in approximately 25% to 37% of cases.(2-4)

Indications for whole exome sequencing include but are not limited to(5):

- Patient with a phenotype and/or family history that strongly suggests an underlying genetic cause, yet genetic tests for that phenotype have failed to arrive at a diagnosis (diagnostic odyssey patient)
- Patient with a phenotype and/or family history that strongly suggests an underlying genetic cause, but the phenotype does not fit with one specific disorder (numerous individual genetic tests would be required for evaluation)
- Patient with a suspected genetic disorder that has numerous underlying genetic causes, making analysis of numerous genes simultaneously a more practical approach than single-gene testing (condition is genetically heterogeneous)
- Patient with a suspected genetic disorder for which specific molecular genetic testing is not yet available

See Whole Exome Sequencing (WES): Questions and Answers for Providers in Special Instructions for additional information.

Reference Values

An interpretive report will be provided that includes variants likely causative of the patient’s reported clinical features, variants possibly relevant to the patient’s reported clinical features, variants in genes of uncertain significance (GUS), and medically actionable secondary findings (unless the patient opts out).

Interpretation

All detected variants are evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations.(6) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments and/or additional data detailing their potential or known significance.

Patients who consent to receive medically actionable secondary findings are evaluated for pathogenic and likely pathogenic variants as recommended by ACMG.(1) Variants of uncertain significance (VUS) in these genes are not reported. Parental origin of reportable variants is stated. Variants that are present in a parent but absent from the proband are not evaluated.

The absence of a reportable secondary finding does not guarantee that there are no pathogenic or likely pathogenic variants in these genes, as portions of the genes may not be adequately covered by this testing methodology. If a patient opts-out of receiving these results, these variants will not be reported unless they occur in a gene that is clinically related to the patient's presenting phenotype.

Cautions
Test results should be interpreted in the context of clinical findings, family history, and other laboratory data. Errors in the interpretation of results may occur if information given is inaccurate or incomplete.

It is possible that a variant may not be recognized as the underlying cause of disease due to incomplete scientific knowledge about the function of all genes in the human genome and/or the impact of variants in those genes. Deidentified variant information may be shared in public genetic databases, such as GeneMatcher or ClinVar.

This test is designed to detect single nucleotide variants and small insertions and deletions within the exome. Due to limitations of next-generation sequencing, some variants will not be detected by this test (e.g., some deletions and insertions, structural chromosome rearrangements, polyploidy, intronic variants outside of the consensus splice site, variants in repetitive regions, variants occurring in regions with pseudogenes, mitochondrial variants, and other unknown abnormalities). De novo mosaic variants present at 25% mosaicism will be detected approximately 93% of the time. Approximately 95% of the exome is captured by this methodology. Thus, a negative result does not rule out the possibility of a diagnosis of a genetic disorder.

Genomic copy number variants are not assessed or reliably detected. Chromosomal microarray should be ordered for the formal evaluation of clinical relevant copy number variants.

DNA variants of uncertain significance may be identified.

Patients who received a heterologous blood transfusion within the preceding 6 weeks, or who have received an allogeneic blood or marrow transplant, can have inaccurate genetic test results due to presence of donor DNA.

A genetic consultation is recommended for patients undergoing this test, both prior to testing and after results are available.

In-silico evaluation tools may be used to assist in the interpretation of results. Because these tools are updated regularly, changes to algorithms may result in different predictions for a given variant over time. These tools have not been clinically validated for the determination of pathogenicity and therefore should not be relied upon solely for variant classification.

Classification of Variants:

Variant nomenclature is based on genomic build GRCh37 (hg19). Variants are evaluated and classified according to ACMG recommendations.(6) Variants classified as benign or likely benign are not reported. Variant classification may change over time if additional information becomes available. At this time, it is not standard practice for the laboratory to systematically re-review the classification of variants that have been detected and reported. Health care providers are encouraged to contact the laboratory at any time to learn how the classification of a particular variant may have changed over time.

Reanalysis of Exome:

Mayo Clinic Laboratories' policy is to continue reanalyzing patient results to account for any changes in broader genetic knowledge. If new information becomes available that warrants a change to a patient’s test report, the laboratory will issue an amended report. In addition, healthcare providers may contact the laboratory at 800-533-1710 any time to discuss the classification of a variant or new phenotypic information.

Clinical Reference


5. ACMG Board of Directors: Points to consider in the clinical application of genomic sequencing. Genet Med 2012;14(8):759-761


Performance

Method Description

Whole exome sequencing is performed on genomic DNA extracted from all samples submitted. The exome is captured utilizing a custom reagent developed by Mayo Clinic and Agilent Technologies. Sequencing is performed on an Illumina HiSeq 2500 Next-Generation Sequencing instrument, using HapMap Sample NA12878 as an internal control. Paired-end 101 base-pair reads are aligned to a modified human reference genome (GRCh37/hg19) using Novoalign (Novocraft Technologies, Malaysia). Sequencing quality is evaluated using FastQC (available at www.bioinformatics.babraham.ac.uk/projects/fastqc/). All germline variants are jointly called through GATK Haplotype Caller and GenotypeGVCF. Each variant is annotated using the BioR Toolkit and subsequently evaluated for clinical relevance by a team of scientists, genetic counselors, and laboratory directors. Variants of interest in the patient are confirmed by automated fluorescence dideoxy sequencing (aka Sanger sequencing) if technically necessary.(McKenna A, Hanna M, Banks E, et al: The Genome Analysis Toolkit: a MapReduce framework for analyzing next-generation DNA sequencing data. Genome Res 2010;20[9]:1297-1303; Kocher JP, Quest DJ, Duffy P, et al: The Biological Reference Repository [BioR]: a rapid and flexible system for genomics annotation. Bioinformatics 2014 Jul 1;30[13]:1920-1922)

PDF Report

Supplemental

Day(s) and Time(s) Test Performed

Performed weekly, Varies

Analytic Time

12 weeks

Maximum Laboratory Time

16 weeks
Specimen Retention Time
Whole Blood: 2 weeks (if available) Extracted DNA: Indefinitely

Performing Laboratory Location
Rochester

Fees and Codes

Fees
- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their Regional Manager. For assistance, contact Customer Service.

Test Classification
This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the U.S. Food and Drug Administration.

CPT Code Information
Codes Applied to Proband Sample:

81415
81416 x 2

LOINC® Information

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