Exome Sequencing

Last Literature Review: July 2021 Last Update: October 2024

Exome sequencing may be used to determine the diagnosis when a Mendelian genetic condition is suspected. The entire exome, including all known nuclear genes (approximately 1-2% of the human genome) is analyzed to identify the causative variant(s). Submission of control samples from the patient's parents, and, when relevant, other similarly affected family members, is recommended to aid in result interpretation.

Test Overview

- Approximately 85% of pathogenic variants can be detected by exome sequencing.
  - The function of approximately 4,500 genes is currently known.
- Results of exome sequencing may or may not:
  - Identify the etiology of the patient's medical condition
  - Determine prognosis
  - Predict the severity of the patient's condition
  - Guide medical management

Test Submission Requirements

A completed Exome Sequencing Intake Form is **required** for the patient.

Parental/familial control samples: Submission of parental specimens is recommended to identify de novo variants and the chromosomal phase of variants, and to optimally interpret patient results. Samples from additional informative relatives (eg, family members suspected to have the same condition as the patient) may also be submitted as controls to aid interpretation. Submit comparator samples within 7 days of the proband's sample.

Medical records: Medical records detailing the patient's clinical findings, relevant previous testing/imaging results, and family history are **required** for optimal interpretation of the patient's results. The ability to identify causative variant(s) for the patient's presentation is influenced by the quality of the clinical information provided.

Informed consent: Healthcare provider attestation of informed consent is **required**. Reporting of secondary findings is available for the proband and familial comparators if desired.

Test Description

Methodology

- Targeted capture of all (or selected) coding exons and exon-intron junctions of the targeted genes is performed, followed by massively parallel sequencing (MPS).
- Sanger sequencing is performed as necessary to confirm reported variants.
- Human genome build 19 (Hg 19) is used for data analysis.

Clinical Sensitivity

Varies based on clinical testing indication, family history, previous clinical evaluations, and availability of parental control samples

Featured ARUP Testing

Exome Sequencing 3016583

Method: Massively Parallel Sequencing

- Preferred test to diagnose an individual with a suspected Mendelian genetic condition
- Parental control specimens are recommended for this test; order Exome Sequencing, Familial Control (3016589).
  - Control samples should be submitted within 7 days of submission of the proband's sample.
- Additional samples from similarly affected family members may be submitted when relevant; order Exome Sequencing, Familial Control (3016589).
- Submission of a completed Exome Sequencing Intake Form is required for the proband.

Exome Sequencing, Familial Control 3016589

Method: Massively Parallel Sequencing

- Use to submit parental and/or familial control samples for Exome Sequencing (3016583).
  - Submit within 7 days of submission of the proband's sample.
- Secondary findings, including pathogenic variants in the American College of Medical Genetics and Genomics (ACMG) recommended genes, will be reported for the control individual if opted in (charges apply).

Exome Reanalysis (Originally Tested at ARUP - No Specimen Required) 3001457

Method: Bioinformatic Processing and Variant Analysis

- Consider ordering 12–18 months after exome sequencing was performed if a causative variant that explains the proband's condition was not identified.
- First reanalysis performed at no charge; additional charges apply for subsequent reanalysis requests.
- New clinical report will be issued using current variant calling pipeline, variant classification, genotype/phenotype knowledge, and updated clinical phenotype.

- A diagnosis is determined in approximately 20-40% of individuals; higher diagnostic rates are reported when parental samples are submitted as exome sequencing controls.[1,2,3]
- Mode of inheritance, reduced penetrance, and genetic heterogeneity can reduce clinical sensitivity.

- Exome reanalysis can only be performed if the original exome testing was ordered from ARUP Laboratories after April 1, 2015.

Reporting

Primary Findings

- Variants that are causative or suspected to be causative for the patient's phenotype are reported.
- Candidate variants that are not known to be causative for the patient's phenotype may be reported (eg, de novo variants in a gene of uncertain significance, trans-heterozygous variants of uncertain significance in an autosomal recessive gene, heterozygous variants in an autosomal recessive gene which has clinical overlap with the patient's phenotype).

Secondary Findings

Secondary findings refer to medically actionable disease-associated variants that are not associated with the patient's clinical phenotype. The American College of Medical Genetics and Genomics (ACMG) recommends analysis of certain genes for secondary findings in all individuals undergoing exome sequencing.[4]

Please refer to the ACMG Secondary Findings Gene List for an up-to-date list of genes analyzed. ACMG genes are only analyzed to the extent that routine exome sequencing allows.

- Providers may opt in to receive secondary findings for each individual (proband and parental/familial controls) whose exome is sequenced using the Exome Sequencing Intake Form.
  - Secondary findings will **not** be reported for individuals who do not opt in.
  - Secondary findings will be reported for individuals who opt in; charges will apply.
  - Secondary findings will be reported for familial controls who elect to receive this information regardless of whether the finding was also identified in the patient.
- Single disease-causing variants in autosomal-recessive ACMG genes are not reported.
- Additional medically actionable variants in non-ACMG genes may be reported at ARUP's discretion.

Interpretation, Storage, Reanalysis, Data Sharing

- Accurate representation of biological relationships among family members is imperative for correct test interpretation.
- Test interpretation is based on information available at the time of testing and may change in the future.
- Exome sequencing data will be stored for a minimum of 5 years in compliance with ARUP's data retention policy.
- Many samples are discarded after testing is complete; however, samples may be stored indefinitely for test validation or education purposes after personal identifiers are removed.
  - Individuals may request disposal of their sample by calling ARUP Laboratories at 800-242-2787 ext. 3301.
- Data reanalysis is available; order Exome Reanalysis (Originally Tested at ARUP - No Specimen Required) (3001457).
  - The first request for exome data reanalysis is available at no cost; subsequent reanalysis requests will be associated with charges.
- Deidentified information about genetic variants and clinical findings may be published in international databases.
  - Individuals may request that their test results not be shared with public databases by calling ARUP Laboratories at 800-242-2787 ext. 3301.
- Patients have the opportunity to participate in patient registries and research.
  - For more information, refer to www.aruplab.com/genetics.
- Raw exome sequencing data may be requested by the ordering healthcare provider and hospital that submitted the test to ARUP.

Analytic Sensitivity

The analytic sensitivity of this test is approximately 98% for single nucleotide variants (SNVs) and greater than 93% for insertions/duplications/deletions from 1-10 base pairs in size. Deletions/duplication greater than 10 base pairs may be detected, but the analytic sensitivity may be reduced.

Limitations

- A negative result does not exclude a genetic cause for the patient's disorder.
- The human exome cannot be completely analyzed.
  - Some genes have not been identified.
  - Some genes cannot be sequenced or interpreted due to technical limitations.

- The following will not be evaluated:
  - Variants outside the coding regions and intron-exon boundaries
  - Large deletions/duplications
  - Mitochondrial DNA (mtDNA)
- The following may not be detected:
  - Deletions/duplications/insertions of any size by MPS
  - Some variants due to the presence of pseudogenes, repetitive, or homologous regions
  - Low-level somatic variants
  - Chromosomal phase of identified variants
  - Pathogenic ACMG variants that cannot be detected by routine exome analysis
- Result interpretation may be impacted if the tested individual has had an allogeneic stem cell transplantation.
- Diagnostic errors can occur due to rare sequence variations.

References

1. Farwell KD, Shahmirzadi L, El-Khechen D, et al. Enhanced utility of family-centered diagnostic exome sequencing with inheritance model-based analysis: results from 500 unselected families with undiagnosed genetic conditions. *Genet Med*. 2015;17(7):578-586.

2. Retterer K, Juusola J, Cho MT, et al. Clinical application of whole-exome sequencing across clinical indications. *Genet Med.* 2016;18(7):696-704.

3. Manickam K, McClain MR, Demmer LA, et al. Exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability: an evidence-based clinical guideline of the American College of Medical Genetics and Genomics (ACMG). *Genet Med*. 2021;23(11):2029-2037.

4. Miller DT, Lee K, Abul-Husn NS, et al. ACMG SF v3.2 list for reporting of secondary findings in clinical exome and genome sequencing: A policy statement of the American College of Medical Genetics and Genomics (ACMG). *Genet Med*. 2023;25(8):100866.

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