Genome Sequencing

Last Literature Review: August 2025 Last Update: November 2025

Genome sequencing is used as a comprehensive first-line test when a genetic condition is suspected but the proband's clinical features are not suggestive of a single disorder.

The American College of Medical Genetics and Genomics (ACMG) strongly recommends exome or genome sequencing as a first- or second-tier test for patients with congenital anomalies or developmental delay/intellectual disability.[1,2]

The American Academy of Pediatrics supports genome sequencing as a first-tier test for children with congenital anomalies or global developmental delay/intellectual disability.[3]

- **Rapid whole genome sequencing (RWGS)** should be ordered in cases of **acute clinical presentation (ARUP test code 3019947)**. Parental comparator specimens are **required** for optimal interpretation of the proband's genomic data.
- **Standard whole genome sequencing (WGS)** should be ordered in cases of **nonacute clinical presentation (ARUP test code 3019943)**. Parental comparator specimens are **highly recommended**, but not required, to aid in interpretation of the proband's genomic data.

For both rapid and standard WGS, the analyzed nuclear genome includes all coding regions and internally curated noncoding regions with known or possible disease associations. Genome sequencing identifies both sequence and copy number variants (CNVs). Sequence variants in the mitochondrial genome are also interrogated.

Genome reanalysis is available for undiagnosed individuals 12-18 months after completion of initial testing or upon encounter of new significant clinical findings.

The results of genome sequencing may or may not:

- Identify the etiology of the proband's clinical presentation
- Determine prognosis
- Predict the severity of the proband's condition
- Guide medical management, including disease surveillance
- Provide information about recurrence risk

Test Summary

Test	Turnaround Time for Final Report	Use to Submit Samples for	Primary Findings	Secondary Findings
Rapid Genome Sequencing (3019947)	3-7 days	Patient (proband) for RWGS	Reported	Reported if opted in

Featured ARUP Testing

Rapid Genome Sequencing 3019947

Method: Qualitative Massively Parallel Sequencing

- Preferred test to establish a diagnosis when a genetic condition is suspected but the proband's clinical features are not suggestive of a single disorder in **acute clinical scenarios**
- **Parental comparator specimens are required** for this test and must be submitted within 7 days of the proband's specimen; specimens from additional informative family members may also be submitted as comparators
  - Order Rapid Genome Sequencing, Familial Comparator (ARUP test code 3019953)
- **Completed Genome Sequencing Intake Form is required**

Rapid Genome Sequencing, Familial Comparator 3019953

Method: Qualitative Massively Parallel Sequencing

- Order for parental comparator samples, or samples from other family members submitted as comparators, in parallel with a proband specimen for Rapid Genome Sequencing (ARUP test code 3019947)
  - Comparator specimens must be submitted within 7 days of the proband's specimen
- Please list the name and date of birth of all familial comparators on the Genome Sequencing Intake Form
- If reporting of secondary findings is desired for familial comparator individual(s), check appropriate opt-in box on the Genome Sequencing Intake Form (additional charges apply)

Genome Sequencing 3019943

Method: Qualitative Massively Parallel Sequencing

- Preferred test to establish a diagnosis when a genetic condition is suspected but the proband's clinical features are not suggestive of a single disorder in **nonacute clinical scenarios**
- Parental comparator specimens are recommended for this test and must be submitted within 7 days of the proband's specimen; specimens from additional informative family members may also be submitted as comparators
  - Order Genome Sequencing, Familial Comparator (ARUP test code 3019951)

Test	Turnaround Time for Final Report	Use to Submit Samples for	Primary Findings	Secondary Findings
Rapid Genome Sequencing, Familial Comparator (3019953)	3-7 days	Parental/familial comparators for RWGS	Not applicable	Reported if opted in (charges will apply)
Genome Sequencing (3019943)	14-21 days	Patient (proband) for WGS	Reported	Reported if opted in
Genome Sequencing, Familial Comparator (3019951)	14-21 days	Parental/familial comparator for WGS	Not applicable	Reported if opted in (charges will apply)
Whole Genome Reanalysis (3005939)	≤21 days	No specimens required; reanalysis of proband and comparator genome sequencing data (only available for probands with previous testing performed at ARUP) for both RWGS and WGS	Reported	Reanalyzed for proband only (using the current ACMG SF genes list)

SF, secondary findings

- Completed Genome Sequencing Intake Form is required

Genome Sequencing, Familial Comparator 3019951

Method: Qualitative Massively Parallel Sequencing

- Order for parental comparator samples, or samples from other family members submitted as comparators, in parallel with a proband specimen for Genome Sequencing (ARUP test code 3019943)
  - Comparator specimens must be submitted within 7 days of the proband's specimen
- Please list the name and date of birth of all familial comparators on the Genome Sequencing Intake Form
- If reporting of secondary findings is desired for familial comparator individual(s), check appropriate opt-in box on the Genome Sequencing Intake Form (additional charges apply)

Whole Genome Reanalysis 3005939

Method: Bioinformatic Processing and Variant Analysis

- Reanalysis of genome data may be considered for undiagnosed individuals 12-18 months after completion of initial testing or upon encounter of new significant clinical findings; rapid genome sequencing reanalysis (for ARUP test codes 3005935 or 3019947) or genome sequencing reanalysis (for ARUP test codes 3016493 or 3019943) may be performed
- A new clinical report will be issued for the proband using current variant calling pipeline, current variant classification, current genotype/phenotype knowledge, and updated clinical phenotype
- Only available for genome sequencing initially performed at ARUP Laboratories

Test Requirements

- **Parental comparator specimens**:
  - Rapid whole genome sequencing (RWGS) **requires** parental comparator specimens to identify de novo variants, determine chromosomal phasing for multiple variants, and aid in the interpretation of the proband's genomic data.
  - Standard whole genome sequencing (WGS) does not require parental comparator specimens, although they are **highly recommended** to identify de novo variants, determine chromosomal phasing of multiple variants, and aid in the interpretation of the proband's genomic data.
  - Parental comparator specimens or other informative familial comparator specimens must be submitted within 7 days of receipt of the proband's specimen.
- **Medical records**: Medical records detailing the proband's clinical findings, relevant previous testing/imaging results, and family history are **required** for optimal interpretation of the proband's genomic data for both RWGS and WGS. The ability to identify causative variant(s) for the proband's presentation is influenced by the quality of the clinical information provided.
- **Informed consent**: Healthcare provider attestation of informed consent is **required** for both RWGS and WGS. Reporting of secondary findings is available for the proband and each familial comparator, if desired.

Test Description

Methodology

Polymerase chain reaction (PCR)-free genome sequencing is performed using the following sequence of steps:

- Genomic DNA is extracted from whole blood or saliva, prepared into libraries, then sequenced by massively parallel sequencing (MPS; also known as next generation sequencing [NGS]).
- Variant calling is performed using the Illumina DRAGEN Bio-IT Platform incorporated into a custom bioinformatics pipeline.
- Variants are reported according to genome assembly GRCh37, and mitochondrial genome version NC_012920.1 is used for analysis.

- Phenotype-driven analysis is performed. Annotation and prioritization includes:
  - All Human Gene Mutation Database (HGMD) variant positions
  - All coding transcripts from Ensembl and RefSeq
  - Additional noncoding transcripts from Ensembl and RefSeq (These are included if they intersect with HGMD variants.)
  - Intronic variants suspected to influence splicing
  - Internally curated disease-associated gene and genomic region annotation files
- Acceptable results will have overall sample mean genomic coverage >30X, with >90% of bases in the genome >20X. Variant calls for specimens that do not pass quality control metrics will not be reported by the assay.
- The assay is designed to detect known or suspected disease-causing:
  - Homozygous, heterozygous, and hemizygous single nucleotide variants (SNVs) and small insertions/deletions (indels) in the nuclear genome ranging from 1-50 bp
  - CNVs in the nuclear genome ranging from 1 kb to whole chromosome gains/losses (aneuploidy)
  - Mitochondrial SNVs with heteroplasmy levels >10%
  - *SMN1* copy number

Clinical Sensitivity

Clinical sensitivity varies based on clinical testing indication, family history, previous clinical evaluations, and availability of parental comparator specimens.

Reporting

Primary Findings for Rapid Genome Sequencing

- Variants that are known or suspected to be causative for the proband's provided clinical presentation are reported.
  - Inheritance of primary findings is reported when this information is available using familial comparator specimen data.
  - Familial comparator individuals are not issued clinical reports for inherited primary findings identified in the proband.
- Mitochondrial SNVs with heteroplasmy ≥10% are reported with percent heteroplasmy identified in the specimen type tested.
- Variants identified in genes of unknown significance (GUS) and other variants not known or suspected to be causative for the proband's phenotype are typically not reported.

Primary Findings for Standard Genome Sequencing

- Variants that are known or suspected to be causative for the proband's provided clinical presentation are reported.
  - Inheritance of primary findings is reported when this information is available using familial comparator specimen data.
  - Familial comparator individuals are not issued clinical reports for inherited primary findings identified in the proband.
- Mitochondrial SNVs with heteroplasmy ≥10% are reported with percent heteroplasmy identified in the specimen type tested.
- Possibly related candidate variants that are not known to be causative for the patient's phenotype may be reported (e.g., de novo variants involving an emerging disease-associated gene or genomic region, multiple variants of uncertain significance [VUSs] in an autosomal recessive gene, heterozygous variants in an autosomal recessive gene that has clinical overlap with the patient's phenotype).

Secondary Findings

Secondary findings (SF) refer to medically actionable disease-associated variants that are not associated with clinical findings or phenotypes provided upon submission for phenotype-driven analysis from genomic testing. The American College of Medical Genetics and Genomics (ACMG) recommends reporting of certain variants involving genes from a specified, curated gene list for consented individuals undergoing genome sequencing.[4] The current list utilized in analysis can be found in the Supplemental Resources.

Medically actionable variants involving genes outside of the ACMG SF list, which do not overlap with submitted clinical findings and phenotypes (non-ACMG SF), may also be reported as SF for individuals who elect to receive this information.

- The Genome Sequencing Intake Form provides the option to opt in to receive SF for each individual sequenced (proband and familial comparators).
  - SF will be reported for any individual(s) marked as "opt-in" on the genome intake form.
  - SF reported in a proband elected to receive this information will generally include inheritance information unless one or both parents do not elect to receive SF.
  - ACMG SF will be reported for familial comparators who elect to receive this information regardless of whether the SF was also identified in the proband.
- Heterozygous, single variants involving autosomal recessive ACMG SF genes are generally not reported.

Interpretation and Reanalysis

- Disclosure of biological relationships among tested family members is imperative for accurate analysis and interpretation. Misattributed parentage may impact results interpretation.
- Variant classification and results interpretation for whole genome phenotype-driven analysis is based on clinical information provided at the time of testing. As phenotype information may change over time, reanalysis is available.
- Data reanalysis is available for probands whose testing was originally performed at ARUP Laboratories. An additional fee is required for reanalysis.
  - Order Whole Genome Reanalysis (test code 3005939); no specimen is required.
  - Recommended for undiagnosed individuals 12-18 months after completion of initial testing or upon encounter of new significant clinical findings.

Storage and Data Sharing

- Raw genome sequencing data will be stored for a minimum of 5 years in compliance with ARUP's data retention policy.
- Raw genome sequencing data may be requested by the ordering healthcare provider and/or institution that submitted testing to ARUP.
- Original or derivative samples from patient testing may be used for internal test validation, research, and/or training purposes. All samples are deidentified before use outside of clinical testing. Individuals may request that their sample be discarded after testing by contacting ARUP Laboratories at 800-242-2787 ext. 3301.
- ARUP participates in responsible genetic data sharing through submission of deidentified variant-level information to publicly accessible databases such as ClinVar.
  - Individuals may request to opt out of data sharing by calling ARUP Laboratories at 800-242-2787 ext. 3301.
  - Depending on timing of requests, variant records will be either omitted or removed from external databases.
  - Please note that separate opt-out requests are generally required for each genetic test performed at ARUP.

Analytic Sensitivity and Specificity

The analytic sensitivity and specificity are described in the table below.

Variant Class	Analytic Sensitivity (PPA) Estimate (%) and 95% Credibility Region	Analytic Specificity (NPA) Estimate (%) and 95% Credibility Region	PPV Estimate (%) and 95% Credibility Region
SNVs	99.20 (99.19-99.20)	>99.99 (100.00-100.00)	>99.99 (100.00-100.00)
Deletions 1-5 bp	99.32 (99.30-99.35)	>99.99 (100.00-100.00)	99.92 (99.92-99.93)
Deletions 6-15 bp	98.63 (98.51-98.74)	>99.99 (100.00-100.00)	99.82 (99.77-99.85)
Deletions 16-50 bp	97.15 (96.79-97.45)	>99.99 (100.00-100.00)	99.77 (99.65-99.85)
Insertions 1-5 bp	99.27 (99.24-99.30)	>99.99 (100.00-100.00)	99.92 (99.91-99.93)
Insertions 6-15 bp	98.55 (98.43-98.67)	>99.99 (100.00-100.00)	99.83 (99.78-99.86)
Insertions 16-50 bp	96.69 (96.29-97.06)	>99.99 (100.00-100.00)	99.78 (99.65-99.86)
CNVs 1-10 kb	84.60 (59.10-96.67)	n/a	n/a
CNVs ≥10 kb	>99.9 (97.7-100.0)	n/a	n/a
Mitochondrial SNVs	>98.44 (96.34-99.47)	n/a	n/a
SMA state	>99.9 (95.1-100.0)	n/a	n/a

bp, base pairs; kb, kilobases; n/a, not applicable; NPA, negative percent agreement; PPA, positive percent agreement; PPV, positive predictive value; SMA, spinal muscular atrophy

Limitations

- A negative result does not exclude a genetic cause for the proband's condition.

- This assay cannot detect variants within genomic regions unable to be interrogated using short read sequencing due to technical limitations.
- The current iteration of this assay is **not intended** to detect the following:
  - CNVs between 50 bp and 1 kb in size
  - Copy number state for high copy number CNVs
  - Mosaic constitutional or acquired somatic variants
  - Balanced structural variants including translocations, inversions, and insertions
  - SMA carrier status
  - Mitochondrial indels and CNVs
  - Variants in the mitochondrial D-loop
  - Triplet repeat expansions
  - Gene conversion events
  - Variants in high homology regions
  - Variants in low coverage regions
- Pathogenic variants may occur outside the regions analyzed by this assay.
- Results interpretation may be impacted if tested individuals have undergone allogeneic stem cell transplant.
- Results interpretation may be impacted by the absence of parental data, whether through nonsubmission of parental comparator samples, technical failure, or misattributed parentage.

References

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

2. 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.

3. Rodan LH, Stoler J, Chen E, et al. Genetic evaluation of the child with intellectual disability or global developmental delay: clinical report. *Pediatrics*. 2025;156(1):e2025072219.

4. Lee K, Abul-Husn NS, Amendola LM, et al. ACMG SF v3.3 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*. 2025;27(8):101454.

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