Overview

Useful For

Serving as a first-tier test to identify a molecular diagnosis in patients with suspected genetic disorders, 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

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

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

Reflex Tests

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Genetics Test Information

This test utilizes next-generation sequencing to detect single nucleotide and copy number variants within the protein-coding regions of approximately 20,000 genes. See Method Description for additional details.

Identification of a disease-causing variant may assist with diagnosis, prognosis, clinical management, recurrence risk assessment, familial screening, and genetic counseling.
It is highly recommended that specimens are submitted from the patient (proband), the patient’s biological mother, and the patient’s biological father (trio analysis). However, testing for singletons (patient only), duos (patient and one relative to be used as a comparator), and nontraditional trios (patient and two relatives to be used as comparators) will also be accepted if the patient’s biological mother and biological father are not available for testing.

Additional first-tier testing may be considered/recommended. For more information see the Ordering Guidance section.

Prior Authorization is available for this assay.

Testing Algorithm
If a cord blood specimen is received, maternal cell contamination testing will be added and performed at an additional charge.

If skin biopsy is received, fibroblast culture and cryopreservation for biochemical studies will be added and performed at an additional charge.

Special Instructions
- Whole Exome Sequencing: Ordering Checklist
- Whole Exome Sequencing (WES): Questions and Answers for Providers
- Blood Spot Collection Card-Spanish Instructions
- Blood Spot Collection Card-Chinese Instructions
- Blood Spot Collection Instructions
- Whole Exome Sequencing (WESDX) Prior Authorization Ordering Instructions

Method Name
Sequence Capture and Targeted Next-Generation Sequencing followed by Sanger Sequencing or Quantitative Polymerase Chain Reaction (qPCR), as needed.

NY State Available
Yes

Specimen

Specimen Type
Varies

Ordering Guidance
The American College of Medical Genetics and Genomics (ACMG) recommends that whole exome sequencing be considered as a first-tier or second-tier test for patients with one or more congenital anomalies, or developmental delay or intellectual disability with onset prior to age 18 years.(1)
If a specific diagnosis is suspected, single gene or panel testing may be a more appropriate first-tier testing option.

**This test is for affected patients (probands) only.** For family member specimens being sent as comparators, order CMPRE / Family Member Comparator Specimen for Exome Sequencing, Varies. If this test is ordered on a family member comparator, this test will be canceled and CMPRE performed as the appropriate test.

This test cannot support detection of deep intronic variants, trinucleotide repeat variants, or variants in the mitochondrial genome.

- For whole exome sequencing plus analysis of the mitochondrial genome, order WESMT / Whole Exome and Mitochondrial Genome Sequencing, Varies.

- If separate mitochondrial genome testing is needed, order MITOP / Mitochondrial Full Genome Analysis, Next-Generation Sequencing (NGS), Varies

This test is not appropriate for identification of somatic variants in solid tumors. If this testing is needed, order MCSTP / MayoComplete Solid Tumor Panel, Next-Generation Sequencing, Tumor.

This testing does not provide genotyping of patients for pharmacogenomic purposes. For an assessment for genes with strong drug-gene associations, order PGXQP / Focused Pharmacogenomics Panel, Varies.

Targeted testing for familial variants (also called site-specific or known variant testing) is available for variants identified by this test. See FMTT / Familial Mutation, Targeted Testing, Varies.

Prenatal specimens (amniocentesis or chorionic villi) are not currently accepted for this test.

**Additional Testing Requirements**

To order whole exome testing for the patient and the family member comparator specimens, see the following steps:

1. Order this test on the patient (proband).

2. Order CMPRE / Family Member Comparator Specimen for Exome Sequencing, Varies on all family members’ specimens being submitted as comparators.

   a. When available, the patient’s biological mother and biological father are the preferred family member comparators.

   b. If one or both of the patient’s biological parents are not available for testing, specimens from other first-degree relatives (siblings or children) can be used as comparators. Contact the laboratory at 800-533-1710 for approval to send specimens from other relatives.

   c. The cost of analysis for family member comparator specimens is applied to the patient’s (proband’s) test. Family members will not be charged separately.

3. Collect patient (proband) and family member specimens. Label specimens with full name and birthdate. Do not label family members’ specimens with the proband’s name.


5. If the patient wishes to opt-out of receiving secondary findings or change the DNA storage selection, select the appropriate boxes in the Informed Consent section.

6. Attach clinic notes from specialists relevant to patient’s clinical features, if available.

7. Attach pedigree, if available.
8. Send paperwork to the laboratory along with the specimens. If not sent with the specimen, fax a copy of the paperwork to 507-284-1759, Attn: WES Genetic Counselors.

For more information see [Whole Exome Sequencing (WES): Questions and Answers for Providers](#).

**Shipping Instructions**

Specimen preferred to arrive within 96 hours of collection.

**Necessary Information**

1. [Whole Exome Sequencing: Ordering Checklist](#) is required. Fill out one form for the family and send with the specimens.
2. Prior Authorization is available for this test. Submit the required form with the specimen.

**Specimen Required**

**Patient Preparation:** A previous bone marrow transplant from an allogenic donor will interfere with testing. Call 800-533-1710 for instructions for testing patients who have received a bone marrow transplant.

Submit only 1 of the following specimens:

**Specimen Type:** Whole blood

**Container/Tube:** 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 whole blood specimen in original tube. **Do not aliquot.**

**Specimen Stability Information:** Ambient (preferred)/Refrigerated

**Additional Information:** If a cord blood specimen is received, MATCC / Maternal Cell Contamination, Molecular Analysis, Varies will be performed at an additional charge.

**Specimen Type:** Skin biopsy

**Supplies:** Fibroblast Biopsy Transport Media (T115)

**Container/Tube:** Sterile container with any standard cell culture media (eg, minimal essential media, RPMI 1640). The solution should be supplemented with 1% penicillin and streptomycin.

**Specimen Volume:** 4-mm punch

**Specimen Stability Information:** Refrigerated (preferred)/Ambient

**Additional Information:** A separate culture charge will be assessed under FIBR / Fibroblast Culture for Biochemical and Molecular Testing, Tissue. An additional 4 weeks is required to culture fibroblasts before genetic testing can occur.

**Specimen Type:** Cultured fibroblast

**Container/Tube:** T-25 flask

**Specimen Volume:** 2 Flasks

**Collection Instructions:** Submit confluent cultured fibroblast cells from a skin biopsy from another laboratory. Cultured cells from a prenatal specimen will not be accepted.
Specimen Stability Information: Ambient (preferred)/Refrigerated (<24 hours)

Additional Information: A separate culture charge will be assessed under FIBR / Fibroblast Culture for Biochemical and Molecular Testing, Tissue. An additional 4 weeks is required to culture fibroblasts before genetic testing can occur.

Specimen Type: Blood spot

Supplies: Card-Blood Spot Collection (Filtration Paper) (T493)

Container/Tube:
Preferred: Collection card (Whatman Protein Saver 903 Paper)
Acceptable: PerkinElmer 226 (formerly Ahlstrom 226) filter paper, or blood spot collection card

Specimen Volume: 5 Blood spots

Collection Instructions:
1. An alternative blood collection option for a patient older than 1 year of age is fingerstick. For infants younger than 1 year, a heel stick should be used. See Dried Blood Spot Collection Tutorial for how to collect blood spots via fingerstick.
2. Let blood dry on the filter paper at ambient temperature in a horizontal position for a minimum of 3 hours.
3. Do not expose specimen to heat or direct sunlight.
4. Do not stack wet specimens.
5. Keep specimen dry.

Specimen Stability Information: Ambient (preferred)/Refrigerated

Additional Information:
1. For collection instructions, see Blood Spot Collection Instructions
2. For collection instructions in Spanish, see Blood Spot Collection Card-Spanish Instructions (T777)
3. For collection instructions in Chinese, see Blood Spot Collection Card-Chinese Instructions (T800)
4. Due to lower concentration of DNA yielded from blood spot, it is possible that additional specimen may be required to complete testing.

Specimen Type: Saliva

Patient Preparation: Patient should not eat, drink, smoke, or chew gum 30 minutes prior to collection.

Supplies: Saliva Swab Collection Kit (T786)

Specimen Volume: 1 Swab

Collection Instructions: Collect and send specimen per kit instructions.

Specimen Stability Information: Ambient 30 days

Additional Information: Due to lower concentration of DNA yielded from saliva, it is possible that additional specimen may be required to complete testing.

Forms
1. Whole Exome Sequencing: Ordering Checklist is required.
2. New York Clients-Informed consent is required, included in the above form. Document on the request form or electronic order that a copy is on file.
3. Whole Exome Sequencing (WESDX) Prior Authorization Ordering Instructions

Reject Due To
All specimens will be evaluated at Mayo Clinic Laboratories for test suitability.

Specimen Stability Information
Test Definition: WESDX
Whole Exome Sequencing for Hereditary Disorders, Varies

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Clinical Information
This test uses next-generation sequencing technology to assess patients with suspected underlying genetic disorders for single nucleotide and copy number variants within the protein-coding regions (exons and splice junctions) of approximately 20,000 genes simultaneously. Indications for whole exome sequencing include but are not limited to:(1,2)
- Patients with one or more congenital anomalies
- Patients with developmental delay or intellectual disability with onset prior to age 18 years
- Patients 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)
- Patients 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)
- Patients 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)
- Patients with a suspected genetic disorder for which specific molecular genetic testing is not yet available
- Patients with an atypical presentation of a genetic disorder

It is highly recommended that specimens are also submitted from the patient's biological mother and biological father, which are used for comparison purposes (trio analysis). Based upon published reports, a diagnosis is identified in trio-based whole exome sequencing (WES) in approximately 25% to 37% of cases, with slightly lower diagnostic yield in non-trio WES.(3-5) However, testing for singletons (patient only), duos (patient and one family member to be used as a comparator), and non-traditional trios (patient and two family members to be used as comparators) will also be accepted if both biological parents are unavailable.

Reference Values
An interpretive report will be provided.

Interpretation
Variants of interest 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 detailing their potential or known significance.

Variants are reported in one of the following categories:
- Likely Causative: variants with a high degree of suspicion for causing the patient’s reported clinical features
- Possibly Relevant: variants that may be related to the patient’s clinical features or variants in genes of uncertain significance (GUS)
- Secondary Findings: medically actionable variants unrelated to the indication for testing (see below for additional
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.

Secondary Findings:
Patients are evaluated for medically actionable secondary findings and these findings are reported in accordance with the ACMG recommendations. Variants in these genes will not be evaluated or reported if the patient opts out of this evaluation unless they overlap with the patient’s reported clinical features.

The presence of a variant in family member comparator samples is stated on the patient’s (proband’s) report unless family members opt-out of secondary findings. If the patient (proband) opts out, secondary findings will not be reported for any family member. Variants that are present in family member comparators but absent from the patient (proband) are not evaluated.

The absence of a reportable secondary finding does not guarantee that there are no disease-causing or likely disease-causing variants in these genes, as portions of the genes may not be adequately covered by this testing methodology.

Exome Reanalysis:
Healthcare providers may contact the laboratory at 800-533-1710 to request reanalysis of the patient’s exome due to new patient clinical features, advances in genetic knowledge, or changes in testing methodology. A charge may apply for reanalysis.

Raw Data Requests:
Requests for the raw data obtained from whole exome sequencing should be directed to the laboratory. A separate fee may apply. Raw data will be released for individuals who complete a Mayo Clinic release of information form. If raw data for family member comparators is requested, it will only be released with an accompanying request for the proband’s raw data. Contact the laboratory for instructions on completing the release of information form. The laboratory is not responsible for providing software or other tools needed to visualize, filter, or interpret this data.

Cautions
Clinical Correlations:
Test results should be interpreted in the context of clinical findings, family history, and other laboratory data. Misinterpretation of results may occur if the information provided is inaccurate or incomplete.

To discuss the availability of additional testing options or for assistance in the interpretation of these results, contact Mayo Clinic Laboratories genetic counselors at 800-533-1710.

Technical Limitations:
Whole exome sequencing may not detect all types of genomic variants. In rare cases, false-negative or false-positive results may occur. The depth of coverage may be variable for some target regions. Given these limitations, negative results do not rule out the diagnosis of a genetic disorder. If a specific clinical disorder is suspected, evaluation by alternative methods can be considered.
There may be regions of genes that cannot be effectively evaluated by sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine (GC) content, and repetitive sequences. Confirmation of select reportable variants will be performed by alternate methodologies based on internal laboratory criteria.

This test is validated to detect 95% of deletions up to 75 base pairs (bp) and insertions up to 47 bp. Deletions-insertions (delins) of 40 or more bp, including mobile element insertions, may be less reliably detected than smaller delins.

Deletion/Duplication Analysis:
This analysis detects multi-exon deletions/duplications; however, in some instances, single exon resolution can be achieved. The reliability of detection can be variable due to isolated reduction in sequence coverage or inherent genomic complexity. Balanced structural rearrangements (such as translocations and inversions) may not be detected.

This test is not designed to detect low levels of mosaicism or to differentiate between somatic and germline variants. If there is a possibility that any detected variant is somatic, additional testing may be necessary to clarify the significance of results.

If the patient has had an allogeneic hematopoietic stem cell transplant or a recent heterologous blood transfusion, results may be inaccurate due to the presence of donor DNA. Call Mayo Clinic Laboratories for instructions for testing patients who have received a bone marrow transplant.

Reclassification of Variants:
At this time, it is not standard practice for the laboratory to systematically review previously classified variants on a regular basis. The laboratory encourages health care providers to contact the laboratory at any time to learn how the classification of a particular variant may have changed over time. Due to broadening genetic knowledge, it is possible that the laboratory may discover new information of relevance to the patient. Should that occur, the laboratory may issue an amended report.

Variant Evaluation:
Evaluation and categorization of variants are performed using published American College of Medical Genetics and Genomics and the Association for Molecular Pathology recommendations as a guideline.(6) Other gene-specific guidelines may also be considered. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Variants classified as benign or likely benign are not reported.

Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and periodic updates to these tools may cause predictions to change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgement.

Rarely, incidental findings or secondary findings outside of the genes recommended by the ACMG may implicate another predisposition or presence of active disease. These findings will be carefully reviewed to determine whether they will be
Test Definition: WESDX
Whole Exome Sequencing for Hereditary Disorders, Varies

Data Sharing:
Deidentified variant information may be shared in public genetic databases, such as ClinVar and Matchmaker Exchange.

Clinical Reference

Performance

Method Description
Next-generation sequencing (NGS) is performed on DNA extracted from the patient and all submitted comparator samples to test for the presence of variants in coding regions and intron/exon boundaries. The human genome reference GRCh37/hg19 build is used for sequence read alignment. Variants are called using an optimized bioinformatics package. At least 99% of the bases are covered at a read depth over 30X. Sensitivity is estimated at above 99% for single nucleotide variants, above 94% for deletion-insertions (delins) less than 40 base pairs (bp), above 95% for deletions up to 75 bp, and insertions up to 47 bp. This assay also detects most copy number variants (deletions/duplications) involving three or more exons. In some instances, copy number variants less than three exons may be detected, however, the reliability of this detection is variable due to isolated reduction in sequence coverage or inherent genomic complexity. Resulting variants are filtered and annotated using public and proprietary resources and presented for analysis and interpretation using a vended interpretation tool. Confirmation of select reportable variants in the proband and submitted comparator samples may be performed by alternate methodologies based on internal laboratory criteria.

There may be regions of genes that cannot be effectively evaluated by sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine (GC) content, and
Test Definition: WESDX
Whole Exome Sequencing for Hereditary Disorders, Varies

repetitive sequences. (Unpublished Mayo method)

PDF Report
Supplemental

Day(s) Performed
Varies

Report Available
12 weeks

Specimen Retention Time
Whole blood: 2 weeks (if available); Extracted DNA: 3 months; Blood spots, saliva, cultured fibroblasts, skin biopsy, cord blood: 1 month

Performing Laboratory Location
Rochester

Fees & 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 US Food and Drug Administration.

CPT Code Information
81415-Patient only
81415, 81416-Patient and one family member comparator sample (duo) (as appropriate)
81415, 81416 x 2-Patient and two family member comparator samples (trio or non-traditional trio) (as appropriate)
81415, 81416 x 3-Patient and three family member comparator samples (quad) (as appropriate)

LOINC® Information

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