

Overview

Useful For

Submitting a biological family member's specimen to be used as a comparator for affected patients (proband) undergoing whole exome sequencing

Reflex Tests

| Test Id | Reporting Name | Available Separately | Always Performed |
|---------|----------------------------------|----------------------|------------------|
| FIBR | Fibroblast Culture | Yes | No |
| CRYOB | Cryopreserve for Biochem Studies | No | No |

Genetics Test Information

This test is for the biological family members whose specimens are being submitted as comparators for patients undergoing WESDX / Whole Exome Sequencing for Hereditary Disorders, Varies.

Testing Algorithm

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](#)
- [Blood Spot Collection Card-Spanish Instructions](#)
- [Blood Spot Collection Card-Chinese Instructions](#)
- [Blood Spot Collection 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

This test is **not appropriate** for affected patients (probands) undergoing whole exome sequencing (WES). This test is intended to be ordered for biological family member comparator specimens only. For WES testing for the proband, order WESDX / Whole Exome Sequencing for Hereditary Disorders, Varies.

Each specimen must be on a separate order.

Additional Testing Requirements

[To order whole exome testing for the patient and the family member comparator specimens, see the following steps:](#)

1. Order WESDX / Whole Exome Sequencing for Hereditary Disorders, Varies on the patient (proband).
2. Order this test 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.
4. Complete the signature sections of the Informed Consent (required for New York State clients) portion of [Whole Exome Sequencing: Ordering Checklist](#).
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.

Shipping Instructions

Specimen preferred to arrive within 96 hours of collection.

Necessary Information

[Whole Exome Sequencing: Ordering Checklist](#) is required. Fill out one form for the family and send with the specimens. A separate form is not needed for each family member.

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

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 fibroblasts

Container/Tube: T-25 flask

Specimen Volume: 2 Flasks

Collection Instructions: Submit confluent cultured fibroblast cells from a skin biopsy. 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 (Filter 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 1 year of age or older is a 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](#) in Special 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.

Reject Due To

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

Specimen Stability Information

| Specimen Type | Temperature | Time | Special Container |
|---------------|---------------------|---------|-------------------|
| Varies | Ambient (preferred) | 0 hours | |
| | Frozen | 0 hours | |
| | Refrigerated | 0 hours | |

Clinical & Interpretive

Clinical Information

This test uses next-generation sequencing technology to assess for single nucleotide and copy number variants within the protein-coding regions (exons and splice junctions) of approximately 20,000 genes simultaneously. This information is used to assist in the interpretation of the patient's (proband's) whole exome sequencing results (WESDX / Whole Exome Sequencing for Hereditary Disorders, Varies). Ordering this test on biological family members of the affected proband can help determine the inheritance of genetic variants that are identified and if the variants segregate with a phenotype in the family. Submitting comparator samples from biological family members increases the chance of identifying a diagnosis in the proband. Whole exome sequencing has been shown to be most informative when samples from both biological parents are used as comparators.(1-3) Therefore, it is highly recommended that samples are also submitted from the patient's biological mother and biological father.

If more than two biological family member comparator specimens are submitted, the additional comparator specimens may not be fully sequenced but rather used for confirmatory presence or absence of identified variants of interest after initial variant calling and review.

Reference Values

An interpretive report will be provided.

Interpretation

Interpretive information will only be provided on the proband's whole exome sequencing report (WESDX / Whole Exome Sequencing for Hereditary Disorders, Varies).

Secondary Findings

Patients are evaluated for medically actionable secondary findings and these findings are reported in accordance with the American College of Medical Genetics and Genomics recommendations.⁽⁴⁾ The presence of a variant in family member comparator samples is stated on the proband's report. Variants that are present in family member comparator samples but absent from the proband sample are not evaluated. Variants in these genes will not be evaluated or reported if the proband opts out of this evaluation.

Cautions

This testing is intended to be used for biological family members whose specimens are being submitted as comparators for affected patients (proband) undergoing whole exome sequencing. Although test results will only be provided in the context of the proband, it is possible for family members serving as comparators to learn unexpected genetic information about themselves, for example, if biological relationships are not as described. It is also possible for individuals to learn that they carry certain genetic variants that are being reported in the proband.

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.

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

Clinical Reference

1. Yang Y, Muzny DM, Xia F, et al: Molecular findings among patients referred for clinical whole-exome sequencing. *JAMA*. 2014;312(18):1870-1879
2. Lee H, Deignan JL, Dorrani N, et al: Clinical exome sequencing for genetic identification of rare Mendelian disorders. *JAMA*. 2014;312(18):1880-1887
3. 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;17:578-586
4. Miller DT, Lee K, Gordon AS, et al: Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2021 update: a policy statement of the American College of Medical Genetics and Genomics (ACMG). *Genet Med*. 2021 Aug;23(8):1391-1398

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 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.

LOINC® Information

| Test ID | Test Order Name | Order LOINC® Value |
|---------|------------------------------------|--------------------|
| CMPRE | Family Member Comparator for Exome | In Process |

| Result ID | Test Result Name | Result LOINC® Value |
|-----------|------------------|---------------------|
| 616414 | Interpretation | 69047-9 |
| 616415 | Specimen | 31208-2 |
| 616416 | Source | 31208-2 |
| 616417 | Released By | 18771-6 |