MAYO CLINIC LABORATORIES

NEW TEST

Notification Date: March 30, 2022
Effective Date: March 31, 2022

Whole Exome Sequencing for Hereditary Disorders, Varies

Test ID: WESDX

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:

Test ID	Reporting Name	Available Separately	Always Performed
FIBR	Fibroblast Culture	Yes	No
CRYOB	Cryopreserve for Biochem Studies	No	No
G226	Null	No (Bill Only)	No
MATCC	Maternal Cell Contamination, B	Yes	No

Methods:

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

Reference Values:

An interpretive report will be provided.

Specimen Requirements:

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.
Minimum Volume:	1 mL

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)
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 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.

Note:

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.

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.
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.

Specimen Stability Information:

Specimen Type	Temperature	Time	Special Container
Varies	Ambient (preferred)		
	Frozen		
	Refrigerated		

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 targets single and multi-exon deletions/duplications; however, in some instances, single exon resolution cannot be achieved 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 reported.

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

CPT Code:

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)

Day(s) Performed: Varies **Report Available:** 12 weeks

Note:

The following referral test code will become obsolete.

Test Name	Test ID	Referral Lab Code	Referral Lab
Trio Whole Exome Sequencing	ZW221	1600	Baylor Medical Genetics Laboratories (Miraca)

Questions

Contact Michelle Raths, Laboratory Technologist Resource Coordinator at 800-533-1710.