Test Definition: CMPRE

Family Member Comparator Specimen for
Exome Sequencing, Varies

Overview

Useful For

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

Reflex Tests

Test Id	Reporting Name	Available Separately	Always Performed
CULAF	Amniotic Fluid Culture/Genetic Test	Yes	No
_STR1	Comp Analysis using STR (Bill only)	No, (Bill only)	No
_STR2	Add'l comp analysis w/STR (Bill Only)	No, (Bill only)	No
CULFB	Fibroblast Culture for Genetic Test	Yes	No
MATCC	Maternal Cell Contamination, B	Yes	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

For skin biopsy or cultured fibroblast specimens, a fibroblast culture will be performed at an additional charge. If viable cells are not obtained, the client will be notified.

Maternal cell contamination testing may be performed at an additional charge for postnatal umbilical cord blood specimens.

Special Instructions

- Whole Exome Sequencing: Ordering Checklist
- Blood Spot Collection Card-Spanish Instructions
- Blood Spot Collection Card-Chinese Instructions
- Blood Spot Collection Instructions
- Whole Exome and Genome Sequencing Information and Test Ordering Guide

Highlights

Additional information is available; see Whole Exome and Genome Sequencing Information and Test Ordering Guide.

Method Name

Sequence Capture and Targeted Next-Generation Sequencing (NGS) 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. If this test is ordered on a proband, the test will be canceled and WESDX will be performed as the appropriate test.

If this test is ordered on a family member comparator of a proband having WGSDX / Whole Genome Sequencing for Hereditary Disorders, Varies, this test will be canceled and CMPRG / Family Member Comparator Specimen for Genome Sequencing, Varies performed as the appropriate test.

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.

For more information see Whole Exome and Genome Sequencing Information and Test Ordering Guide.

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 hematopoietic stem cell transplant from an allogenic donor will interfere with testing. For information about testing patients who have received a hematopoietic stem cell transplant, call 800-533-1710.

Submit only 1 of the following specimens:

Specimen Type: Whole blood
Container/Tube:
Preferred: Lavender top (EDTA) or yellow top (ACD)
Acceptable: Green top (sodium heparin)
Specimen Volume: 3 mL
Collection Instructions:
1. Invert several times to mix blood.
2. Send whole blood specimen in original tube. **Do not aliquot**.
3. Whole blood collected postnatal from an umbilical cord is also acceptable. See Additional Information

Specimen Stability Information: Ambient (preferred) 4 days/Refrigerated 4 days/Frozen 4 days
Additional Information:
1. Specimens are preferred to be received within 4 days of collection. Extraction will be attempted for specimens received after 4 days, and DNA yield will be evaluated to determine if testing may proceed.
2. To ensure minimum volume and concentration of DNA are met, the requested volume must be submitted. Testing may be canceled if DNA requirements are inadequate.
3. For postnatal umbilical cord whole blood specimens, maternal cell contamination studies are recommended to ensure test results reflect that of the patient tested. A maternal blood specimen is required to complete maternal cell contamination studies. Order MATCC / Maternal Cell Contamination, Molecular Analysis, Varies on both the cord blood and maternal blood specimens under separate order numbers.

Specimen Type: Saliva
Patient Preparation: Patient should not eat, drink, smoke, or chew gum 30 minutes prior to collection.
Supplies:
DNA Saliva Kit High Yield (T1007)
Saliva Swab Collection Kit (T786)
Container/Tube:
Preferred: High-yield DNA saliva kit
Acceptable: Saliva swab
Specimen Volume: 1 Tube if using T1007 or 2 swabs if using T786
Collection Instructions: Collect and send specimen per kit instructions.

Specimen Stability Information: Ambient (preferred) 30 days/Refrigerated 30 days
Additional Information: Saliva specimens are acceptable but not recommended. Due to lower quantity/quality of DNA yielded from saliva, some aspects of the test may not perform as well as DNA extracted from a whole blood sample. When applicable, specific gene regions that were unable to be interrogated will be noted in the report. Alternatively, additional specimen may be required to complete testing.

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 filter paper or blood spot collection card
Specimen Volume: 2 to 5 Blood spots
Collection Instructions:
1. An alternative blood collection option for a patient older than 1 year is a fingerstick. For detailed instructions, see How to Collect a Dried Blood Spot Sample.
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. Blood spot specimens are acceptable but not recommended. Multiple extractions will be required to obtain sufficient yield for supplemental analysis, and there is significant risk for test failure due to insufficient DNA.
2. Due to lower concentration of DNA yielded from blood spot, some aspects of the test may not perform as well as DNA extracted from a whole blood sample. When applicable, specific gene regions that were unable to be interrogated will be noted in the report. Alternatively, additional specimen may be required to complete testing.
3. For collection instructions, see Blood Spot Collection Instructions
4. For collection instructions in Spanish, see Blood Spot Collection Card-Spanish Instructions (T777)
5. For collection instructions in Chinese, see Blood Spot Collection Card-Chinese Instructions (T800)

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: Ambient (preferred) <24 hours/Refrigerated <24 hours
Additional Information:
1. Specimens are preferred to be received within 24 hours of collection. Culture and extraction will be attempted for specimens received after 24 hours and will be evaluated to determine if testing may proceed.
2. A separate culture charge will be assessed under CULFB / Fibroblast Culture for Biochemical or Molecular Testing. An additional 3 to 4 weeks are required to culture fibroblasts before genetic testing can occur.

Specimen Type: Cultured fibroblasts
Source: Skin or tissue

Container/Tube: T-25 flask
Specimen Volume: 2 Flasks
Collection Instructions: Submit confluent cultured fibroblast cells from a skin or tissue biopsy. Cultured cells from a prenatal specimen will not be accepted.
Specimen Stability Information: Ambient (preferred) <24 hours/Refrigerated <24 hours
Additional Information:
1. Specimens are preferred to be received within 24 hours of collection. Culture and extraction will be attempted for specimens received after 24 hours and will be evaluated to determine if testing may proceed.
2. A separate culture charge will be assessed under CULFB / Fibroblast Culture for Biochemical or Molecular Testing. An additional 3 to 4 weeks are required to culture fibroblasts before genetic testing can occur.

Specimen Type: Extracted DNA
Container/Tube:
Preferred: Screw Cap Micro Tube, 2 mL with skirted conical base
Acceptable: Matrix tube, 1mL
Collection Instructions:
1. The preferred volume is at least 100 mcL at a concentration of 75 ng/mcL.
2. Include concentration and volume on tube.
Specimen Stability Information: Frozen (preferred) 1 year/Ambient/Refrigerated
Additional Information: DNA must be extracted in a CLIA-certified laboratory or equivalent and must be extracted from a specimen type listed as acceptable for this test (including applicable anticoagulants). Our laboratory has experience with Chemagic, Puregene, Autopure, MagnaPure, and EZ1 extraction platforms and cannot guarantee that all extraction methods are compatible with this test. If testing fails, one repeat will be attempted, and if unsuccessful, the test will be reported as failed and a charge will be applied. If applicable, specific gene regions that were unable to be interrogated due to DNA quality will be noted in the report.

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. If not ordering electronically, complete, print, and send a Neurology Specialty Testing Client Test Request (T732) with the specimen.

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	Varies		

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 2 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 (probands) 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.

Patient data is not guaranteed to be stored indefinitely.

If the patient has had an allogeneic hematopoietic stem cell transplant or a recent non-leukocyte reduced blood transfusion, results may be inaccurate due to the presence of donor DNA. Call Mayo Clinic Laboratories at 800-533-1710 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(7):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;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 3 or more exons. In some instances, copy number variants less than 3 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

56 to 70 days

Specimen Retention Time

Whole blood: 28 days (if available); Extracted DNA: 3 months, Saliva: 30 days (if available; Blood Spots: 1 year (if available)

Performing Laboratory Location

Mayo Clinic Laboratories - Rochester Main Campus

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 account representative. 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. It 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	86205-2

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