Whole exome & whole mitochondrial genome sequencing

ORDER NAME

Cerner: UPMC Whole Exome Sequence Proband
WESMOM, WESDAD, WESSIB, WESOTH-Sunquest codes for label generation only (no charge)

EPIC: Whole Exome Proband Test (LAB13685)
WHOLE EXOME SEQUENCE, FATHER(LAB15549); WHOLE EXOME SEQUENCE, MOTHER(LAB15583); WHOLE EXOME SEQUENCE, SIBLING(LAB15584);WHOLE EXOME SEQUENCE, OTHER(15585)

The healthcare provider is also required to complete a Whole Exome & Genome Sequencing Proband requisition form and a signed Whole Exome & Genome Sequencing Family requisition form for each participant as well as submit the pedigree and relevant clinical notes to GenomicsLab@upmc.edu

- These forms can be found on the INFONET. Search for “whole exome proband” and “whole exome family.”

BACKGROUND

Whole exome sequencing (WES) targets the protein-coding regions (exons) of the human genome, representing about 20,000 genes and accounting for approximately 2% of all genetic material. Most genetic variants that cause disease are in the exons This test includes mitochondrial DNA (mtDNA) which encodes 37 genes. It is intended to be used as a diagnostic test in individuals with clinical features suggestive of an underlying genetic disorder. You can also choose to receive secondary findings which may be unrelated to the reason for referral but may impact medical decision-making if identified.The American College of Medical Genetics and Genomics (ACMG) identified 81 genes and disorders, as secondary findings, for which treatment is available that may reduce morbidity and/or mortality. Trio testing to include the biological parents is encouraged to compare the patient’s genetic variants to those of the parents.

INDICATIONS FOR TESTING

- Provides a diagnostic rate ranging from 25% to 40%, which is two to three times higher than traditional genetic testing methods.
- First-tier test substantially reduces the time to diagnosis at only 25%-50% of the cost of traditional testing.
- An early and accurate molecular diagnosis can lead to optimal care and dramatic prognostic improvements for patients and their families.
- Identifying a disease-causing variant in a patient provides preconception and prenatal options for at-risk family members of reproductive age.

RESULTS

Pathogenic, likely pathogenic, and variants of uncertain significance related or possibly related to the patient’s symptoms are reported. Only pathogenic and likely pathogenic variants are reported for ACMG secondary findings.

1. Positive: A pathogenic or likely pathogenic variant(s) were found which would either explain the patient’s symptoms or increases the risk to develop a disease. The healthcare provider can use the result to guide the patient’s medical management. Family members can be tested for the variant to determine their risk for disease and/or reproductive risk.

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2. Negative: No clinically significant variants were found in the test. This does not rule out the possibility of variants in other genes or variants that are not detectable in this assay. Risk may still be increased based on the family history. The healthcare provider will discuss these risks and develop a screening plan based on the patient's personal risk factors. The healthcare provider may also discuss more testing either now or in the future.

3. Variant of Uncertain Significance (VUS): A variant was detected, however, it is uncertain whether this variant is the cause of a patient's symptoms since current information about the variant is limited. The result is not clinically actionable. Medical management should be based on personal and family history.

METHOD

Custom oligonucleotide-based capture method followed by next generation sequencing with 2x150bp reads. Reads are mapped to GRCh38 for variant calling and annotation. This test is designed to detect nucleotide substitutions, small deletions (≤ 20bp), small insertions (≤ 10bp), small indels, and deletions/duplications of at least 2-3 exons in size.

LIMITATIONS

This assay is not intended to detect gross rearrangements, deep intronic variants, insertions of repetitive elements, variants in homopolymer regions > 10bp, and other unknown abnormalities. Some complex areas of the genome result in suboptimal data that could increase the chance of a variant not being detected. The assay is not designed to detect mosaicism and its accuracy detecting mosaicism has not been established. The detected limit for mitochondrial heteroplasmy is approximately 5%. The detection of CNVs in mitochondrial DNA has not been validated.

SPECIMEN REQUIREMENTS

- Whole blood – EDTA tube required, 3-5 ml
- Previously extracted DNA (concentration >25 ng/ul, volume >20 ul, minimum of 1 ug total DNA, 260/280>1.7)
- Saliva provided in Oragene (OGD-500) collection kits accepted for relatives only

TURNAROUND TIME

Eight weeks from the receipt of all family members who choose to participate, which is no later than 30 days from receipt of the patient's sample.

CPT CODE

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