XomeDxSlice: A Phenotype-Driven Targeted Exome Test

Description:
XomeDxSlice captures and sequences the whole exome, but analysis is limited to a phenotype-driven gene list. XomeDxSlice is best suited for individuals with a clearly defined, oligogenic phenotype where a comprehensive gene panel is not available, or the patient has a single gene disorder for which clinical testing is not currently available. WES data is only generated on the proband and does not use family members' samples for whole exome analysis. Individuals having XomeDxSlice testing are not eligible to receive the recommended ACMG secondary findings reported in whole exome sequencing (XomeDx and XomeDxPlus); the analytic pipeline used in XomeDxSlice will only present data on the phenotype driven gene list and therefore will not identify secondary findings.

Gene List Instructions:
Prior to submitting the patient's specimen for testing, the phenotype-driven gene list must be submitted by the ordering provider using the XomeDxSlice online submission tool. The submitted gene list will be reviewed and approved or declined by the GeneDx medical specialists within 3-5 business days. The approved gene list will be emailed to the ordering provider with the average percent coverage at 10X or higher. This email will contain a unique tracking number that must be submitted with the patient's sample and XomeDxSlice requisition form. The final responsibility for the appropriateness and relevance of any XomeDxSlice gene list lies with the ordering clinician.

Reasons for Referral:
1. Confirmation of a clinical diagnosis
2. Genetic counseling and recurrence risk assessment
3. Preparation for prenatal testing in future pregnancies

Test Methods:
An affected individual's clinical records and prior genetic testing results will be reviewed prior to analysis. Using genomic DNA from the submitted specimen(s), the exonic regions and flanking splice junctions of the genome are sequenced by massively parallel (NextGen) sequencing on an Illumina sequencing system with 100bp or greater paired-end reads. Reads are aligned to human genome build GRCh37/UCSC hg19.

Using a custom-developed analysis tool (Xome Analyzer), whole exome sequencing is paired with an analytic pipeline that presents data on only the genes that were pre-selected by the ordering clinician prior to starting the test. Potentially pathogenic variants identified in the genes selected for the XomeDxSlice test will be confirmed by a second, independent method

such as capillary sequencing or other appropriate method. Sequence alterations will be reported according to the Human Genome Variation Society (HGVS) nomenclature guidelines.

Limitations:

Only the genes selected and included in the approved gene list will be analyzed. Changes can only be made to the gene list by contacting GeneDx directly at genedx@genedx.com and asking to speak with an Exome genetic counselor. Genes that have poor coverage by exome sequencing, are significantly affected by homology to other regions of the genome, have other technical issues with sequencing, or are offered by single gene or panel testing at GeneDx or an outside laboratory may not be appropriate for XomeDxSlice. Genes in the mitochondrial genome, non-coding genes, and regulatory or deep intronic regions are not captured by this technology and are therefore not analyzed by XomeDxSlice.

The coverage data in the XomeDxSlice online submission tool provides an average estimate of gene coverage, but the actual coverage of genes on a requested gene list will be provided in the test report for each patient. Complete sequencing coverage for the genes selected may not be available. There may be some genes or portions of genes that are not amenable to capture, sequencing, and alignment. Additionally, certain types of sequence variations are difficult to identify by this technology, including repeat expansions and copy number variants. The available scientific knowledge about the function of all genes in the human genome is incomplete at this time. It is possible that the XomeDxSlice test may identify the presence of a genetic variant in an affected individual, but it will not be recognized as causative for the affected individual's disorder due to insufficient knowledge about the variant or the gene and its function.