Custom XomeDxSlice and XomeDxSlice Xpanded: Phenotype-Driven Targeted Exome Tests

Description:
XomeDxSlice tests capture and sequence the exome, but analysis is limited to a custom-built, phenotype-driven gene list. XomeDxSlice tests are 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. Individuals having XomeDxSlice testing are not eligible to receive the recommended ACMG secondary findings reported in comprehensive exome analysis (XomeDx and XomeDxPlus); the analytic pipeline used in XomeDxSlice tests will only present data on the phenotype driven gene list and therefore will not identify secondary findings.

XomeDxSlice – for 1-150 genes. Test includes generation of exome sequence (ES) data for the proband only and does not use family members' samples for exome analysis. Family member samples may be included for targeted variant testing via capillary sequencing or other appropriate method.

XomeDxSlice Xpanded – for greater than 150 genes. Test utilizes proband-only or a trio approach that includes concurrent generation of ES data and analysis of the affected proband and both parents. Depending on the family structure, family history, and the availability of both parents, other family members of the affected individual may be evaluated in conjunction with the proband. Please contact GeneDx for prior approval when both parents are not available to submit samples for the XomeDxSlice Xpanded trio. Analysis and reporting is phenotype-driven and may not include all variants detected; variants of uncertain significance are not routinely reported, only at our discretion.

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 denied by the GeneDx clinical staff within 3 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. Upon request, GeneDx may elect to offer assistance to the ordering provider in selecting an appropriate list of genes for a specific test indication or genetic disorder. However, the provider remains solely responsible for the selection of the appropriate genes and the ordering of the genetic testing.

Result Reporting:
The XomeDxSlice and XomeDxSlice Xpanded tests are performed on an affected proband. When submitted concurrently, parental samples may be included for analysis. A single report will be issued on the affected proband in the family. A separate report will not be issued for parents or other relatives who may have submitted a specimen for the purpose of allowing better interpretation of the results from the affected individual. If reports are requested for other affected family members, additional fees will apply.

XomeDxSlice: The report issued for the affected proband will include all variants in the selected gene list that are classified as variant of uncertain significance (VUS), likely pathogenic or pathogenic. Single heterozygous variants of uncertain significance in genes associated with autosomal recessive disease may be reported as unconfirmed findings in a separate table.

XomeDxSlice Xpanded: The report issued for the affected proband will include reportable variants in genes that have been previously associated with the provided phenotype. The report will include pathogenic or likely pathogenic variants in the selected gene list. In some instances, the report may include specific variants of uncertain significance (VUS) in genes that are possibly associated with the patient's phenotype. Variants that are considered to be benign or likely benign will not be reported.

Reasons for Referral:
1. Confirmation of a clinical diagnosis
2. Genetic counseling and recurrence risk assessment

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), exome sequencing is paired with an analytic pipeline that presents data on only the genes 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. 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 SliceGC@genedx.com. 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. For XomeDxSlice Xpanded, the average coverage for the entire exome may be reported instead. 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.