Custom, Phenotype-Driven, Targeted Exome Sequencing Tests: Single Gene Slice, XomeDx®Slice, Homozygous Slice, & Slice Xpanded®

Description:
The GeneDx Slice tests capture and sequence the entire exome, but analysis is limited to a custom-built, phenotype-driven gene list. Slice 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. ACMG secondary findings reported in comprehensive exome analysis (XomeDx® and XomeDx®*Plus*) are not reported as part of Slice tests unless these genes are on the custom gene list; the analytic pipeline used in Slice tests will only present data on the requested gene list and will not identify secondary findings.

Single Gene Slice (test TG70) for 1 gene; XomeDx® Slice (test 706) for 2-150 genes:
These tests include generation of exome sequence (ES) data for the proband only and does not use family members' samples for analysis. When submitted concurrently, parental samples may be included for targeted variant testing via capillary sequencing or other appropriate method.

Homozygous Slice (test 706H):
This test includes generation of exome sequence (ES) data for the proband only to evaluate all homozygous variants in an individual; submission of a custom gene list is not needed. This is most appropriate for individuals with previously identified regions of homozygosity by array and/or known consanguinity. When submitted concurrently, parental samples may be included for targeted variant testing via capillary sequencing or other appropriate method. Analysis and reporting is phenotype-driven and may not include all variants detected. Relevant clinical records are required to aid in the analysis and reporting of variants.

Slice Xpanded® (test J757) for greater than 150 genes:
This test utilizes a proband-only or a trio approach that includes concurrent generation of ES data and analysis of the affected proband with both biological parents, if available. Depending on the family structure, family history, and the availability of both parents, other family members of the affected proband may be included or substituted for the parents; contact GeneDx for approval of submission for alternate family members.

Analysis and reporting is phenotype-driven and may not include all variants detected. Relevant clinical records are required to aid in the analysis and reporting of variants.

For patients whose medical management may be altered by having a rapid molecular diagnosis, GeneDx offers custom Slice Xpanded®*Xpress* (test TG71) and Slice Xpanded®*Priority* (test TG75) tests with expedited turnaround time of approximately 2 weeks and 4 weeks, respectively. These tests require approval by GeneDx; please email **Xpress@GeneDx.com** prior to sending in samples.

Gene List Instructions:
Prior to submitting the patient's specimen for testing, the gene list must be submitted by the ordering provider using the online Slice Tool (https://www.genedx.com/xomedx-slice-tool). The submitted gene list will be emailed to the ordering provider with the average percent covered at a minimum read depth of 10X. This email will contain a unique tracking number that must be submitted with the patient's sample, and for non-portal orders, it will also include a link to a reusable Custom Slice requisition form. The ordering provider may request assistance from GeneDx in selecting an appropriate list of genes; however, the provider remains solely responsible for the selection of the appropriate genes and the ordering of the genetic testing.

Result Reporting:
The Slice and Slice 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.

Single Gene Slice and XomeDxSlice (2-150 genes):
The report issued for the affected proband will include all variants in the selected gene list that are classified as pathogenic, likely pathogenic, or variant of uncertain significance (VUS). Single heterozygous variants of uncertain significance in genes associated with autosomal recessive disease may be reported as unconfirmed findings in a separate table. Variants that are considered to be benign or likely benign will not be reported.

Homozygous Slice and Slice Xpanded:
The report issued for the affected proband will include reportable variants in genes that are associated with the provided phenotype. The report will include clinically relevant pathogenic or likely pathogenic variants in the selected gene list. In some instances, the report may include 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 received 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 with CNV calling (NGS-CNV) 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 sequence data, and deletions and duplications involving three or more coding exons, only for the genes selected by the ordering clinician prior to starting the test. Potentially pathogenic variants identified in the genes selected for the Slice 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 Slice. 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 any Slice tests.

The coverage data in the online Slice Tool provides an average estimate of gene coverage, but the actual coverage of genes on a requested gene list may vary and will be provided in the test report for each patient. For SliceXpanded and Homozygous Slice, the average coverage for the entire exome may be reported instead. Complete sequencing coverage or NGS-CNV calling 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. The available scientific knowledge about the function of all genes in the human genome is incomplete at this time. It is possible that the Slice 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.