XomeDxInsights
Clinical Exome Sequencing for Generally Healthy Adults

Overview:
XomeDxInsights is a clinical exome sequencing service for individuals who seek to know more about medically relevant changes in their genes. XomeDxInsights can be used in individuals who are interested in knowing their risk to have or develop certain genetic disorders but who have a medical history and physical exam that are not suggestive of a specific genetic disorder. Clinically affected individuals desiring diagnostic exome sequencing should pursue XomeDx or XomeDxPlus.

XomeDxInsights provides information in three primary areas: personal health, reproductive risk, and pharmacogenomic (drug metabolism), each of which are described in more detail below. XomeDxInsights targets the protein-coding regions of the human genome, which represent ~20,000 genes and accounts for approximately ~2% of all human genetic material (Bamshad et al., 2011). These targeted regions of an individual's genes, called exons, are captured and sequenced using massively parallel sequencing. XomeDxInsights also analyzes genetic information about how a person metabolizes, or processes, certain medications, known as pharmacogenomics. All results should be discussed with a healthcare provider.

Individuals pursuing XomeDxInsights may also choose to participate in the Personal Genome Sequencing Outcomes Study (PeopleSeq) study. PeopleSeq is one of the first large-scale studies to examine the experiences, attitudes, and outcomes of healthy adults who have pursued exome sequencing. Participation is completely voluntary and will not impact test results of XomeDxInsights.

<u>Personal Health</u>
Studies of exome sequencing in generally healthy individuals to date have reported the identification of variants potentially relevant to personal health in 103/951 (10.8%) of participants (Linderman et al., 2016).

What personal health information will be reported?

- Pathogenic and likely pathogenic variants in genes known to cause disease. This includes variants that significantly increase risk for hereditary cancer, heart disease, and neurological conditions.
  Individuals may opt out of personal health information from disorders associated with progressive, central nervous system (CNS) diseases for which there may not be currently available treatments, such as Parkinson's disease or dementia, by noting opt-out on the consent form. An example list of the disorders excluded is available upon request, though GeneDx continually analyzes the literature and refines reported information accordingly.

Reproductive Risk

Assessment of carrier status has traditionally relied on targeted panels based on family history and ethnicity information; however, this approach can be limited by inaccurate or incomplete knowledge (Committee Opinion No. 690, 2017; Edwards et al., 2015). Screening for many conditions simultaneously by using exome sequencing can address these limitations and may help explain adverse reproductive outcomes. Previous studies utilizing exome sequencing to detect carrier status have identified an average of 5-10 deleterious variants per individual screened (Salleelt et al., 2016; Gambin et al., 2015). Prenatal diagnostic testing is available at GeneDx if a couple is determined to have a shared genetic risk. Exome sequencing has also been used to identify changes in genes leading to infertility, recurrent pregnancy loss, and fetal demise (Patiño et al., 2017; Qin et al., 2015; Amiri-Yekta et al., 2016; Ray et al., 2017; Tsuraskaki et al., 2014; Qiao et al., 2016; Yates et al., 2017).

What reproductive risk information will be reported?

- Carrier status for pathogenic and likely pathogenic variants in known autosomal recessive and X-linked disease genes
- Carrier status for variants of uncertain significance **only** if the partner is known to carry a pathogenic or likely pathogenic variant in the same gene
- Variants contributing to infertility or other adverse reproductive outcomes

Pharmacogenomic (Drug Metabolism) Information

Pharmacogenetic testing analyzes specific genetic variants to better understand how a person may respond to certain medications (Weinshilboum et al., 2017). The choice and dose of medications are largely determined based on population data; however significant variation in drug response exists. Some of this variation can be attributed to genetic variants in genes associated with drug metabolism and response (Van Driest et al., 2014). On average, 50-75% of individuals prescribed a particular medication will have the intended response (Spear et al., 2001). Pharmacogenetic testing may be useful to avoid adverse drug reactions (ADRs) as well as the chance that a medication or dose won't work well, which may be cost-effectively beneficial for patient care (Verbelen et al., 2017).

Over 90% of people who undergo panel-based pharmacogenetic testing are expected to have a clinically actionable result (Van Driest et al., 2014; Dunnenberger et al., 2015). Evidence suggests that the chance of clinical actionability may vary in people of different ancestries (Van Driest et al., 2014; Dunnenberger et al., 2015).

What pharmacogenomic information will be reported?

- Anticipated response to specific medications
- Prescribing guidance based on anticipated response
- A detailed summary of the available evidence behind prescribing guidance
- Interpretation for metabolic status for genes involved in drug metabolism
- Patient genotype for each sequenced variant

Requirements for XomeDxInsights:

- Individuals must be at least 18 years of age
- XomeDxInsights must be ordered by a physician
- Relevant clinical information should be submitted with the patient sample to allow for timely and accurate interpretation of genetic data
- XomeDxInsights Test Requisition, Informed Consent and Authorization form

Test Methods:

If provided, an individual's clinical records, family history, 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 captured using a proprietary system developed by GeneDx and sequenced by massively parallel (NextGen) sequencing on an Illumina sequencing system with 100bp or greater paired-end reads. Reads are analyzed for sequence variants using a custom-developed analysis tool (Xome Analyzer). Capillary sequencing or another appropriate method is used to confirm all potentially pathogenic variants identified in the individual. Sequence alterations are reported according to the Human Genome Variation Society (HGVS) nomenclature guidelines. When applicable, phenotype-driven gene lists may be generated using Human Phenotype Ontology and HGMD gene-phenotype associations. Additional resources such as 1000 Genomes database, NHLBI Exome Sequencing Project, ExAC, OMIM, PubMed, and ClinVar are used to evaluate genes and detect sequence changes of interest, which are then interpreted according to the American College of Medical Genetics and Genomics guidelines (Retterer et al., 2016; Richards et al., 2015).

For the pharmacogenomic testing, genomic DNA from the submitted specimen is amplified with primers specific for ABCB1, ABCG2, ADRA2A, ADRB1, AGT, CACNA1C, CES1, COMT, CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4, CYP3A5, DPYD, DRD1, DRD2, DRD3, EDN1, GNB3, GRIK4, HTR1A, HTR2A, HTR2C, IFNL3, KCNIP1, LDLR, MTHFR, NR1H3, OPRM1, RYR1, SLC6A2, SLCO1B1, TPMT & VKORC1 using Nested Patch PCR (Varley, et. al.). Targeted regions are sequenced simultaneously by massively parallel (NextGen) sequencing using an Illumina instrument. Sequences are analyzed using alignment and base call algorithms with Kailos Blue Software for the presence or absence of single nucleotide base changes, insertions and deletions. CYP2D6 duplications and deletions are also detected and used for haplotype calling and interpretation.

Limitations:

The XomeDxInsights test attempts to evaluate the most important regions of the majority of the ~20,000 genes in the human genome. However, it is not technically possible to capture and sequence the entire exome at present. It is anticipated that approximately 95% of the targeted region of an individual's exome will be assessed with the XomeDxInsights test at 10x coverage, while >98% of the target region will be covered at a minimum of 1x. There are genes or portions of genes that are not amenable to capture, sequencing, and alignment.

The XomeDxInsights test cannot detect genetic changes related to some types of genetic disorders, such as those due to nucleotide repeat expansion/contraction, abnormal DNA

methylation and other epigenetic changes, intronic variants, or genomic deletions, duplications, insertions or rearrangements. For example, XomeDxInsights will not detect the genetic changes associated with fragile X syndrome, Huntington disease, and spinal muscular atrophy. XomeDxInsights should not be used as a replacement for standard population-based carrier screening to assess reproductive risk.

The available scientific knowledge about the function of all genes in the human genome is incomplete at this time. It is likely that the XomeDxInsights test will identify the presence of a genetic variant in the exome sequence of an individual that will not be recognized as causative for a genetic disorder. Reanalysis of the personal health and reproductive risk data to incorporate updated clinical information and/or newly emerging gene and variant information is available for a fee. If the XomeDxInsights test identifies a genetic disorder or predisposition in an individual, it is possible that this result will not permit an accurate prediction of the prognosis or severity of the disease. While there is a possibility that knowledge of a disorder may help direct management and treatment of a disease, it is also possible that this knowledge will not change management or treatment.

Due to the complexity of interpreting genetic test results, patients and providers should consider the benefits of consulting with a trained genetic counseling professional, physician, or pharmacogenomics specialist.

References:

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