# 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 pharmacogenomics (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, using the OneOme RightMed PGx test. 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 genes 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. Refer to the latest version of the CNS Disorder Opt-Out Gene List for the complete list of genes and associated genetic disorders.*

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). 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

On average, only 50-75% of individuals prescribed a particular medication will have the intended response (Spear et al., 2001). Adverse drug reactions account for up to 7% of all hospital admissions, and an estimated 10-20% of adverse drug reactions may be due to genetic factors (Lazarou et al., 1998; Plumpton et al., 2016). The RightMed test targets known sequence variants in over 20 genes to identify information on drug response to over 300 medications that may be prescribed for many different clinical indications (Ji et al., 2016; Van Driest et al., 2014; Relling and Evans et al., 2015).
*Pharmacogenomic information is not available for residents of New York at this time.

**What pharmacogenomic information will be reported?**

- Information on drug response to over 300 medications across many clinical indications.
- Healthcare providers also receive access to the RightMed Advisor, an interactive tool to assist with test result interpretation, explore more information about the medications in the OneOme database, and evaluate drug-drug interactions.

**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
- Email address for ordering physician in order to access RightMed Advisor
- **Two** tubes of 2-5mL blood in EDTA (purple top)

**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 RightMed test, all genotyping and CNV analysis is performed with PCR-based methods utilizing Thermo Fisher TaqMan® and/or LGC Biosearch BHQplus® assays. The absence of a detectable gene variation (designated as *1 for cytochrome P450 genes) does not rule out the presence of other variants not assessed by this assay. For a comprehensive listing of allele coverage for the RightMed test, visit https://oneome.com/rightmed-test.

**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.

In the RightMed test, CYP2D6 copy number status will be assessed, but this test cannot differentiate duplications in the presence of deletions in this gene.

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.

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