

TruGenome™ Predisposition Screen

Test Description

Test Indication

The TruGenome Predisposition Screen is intended to be used as a screen for genetic predisposition and genetic carrier status for a pre-defined set of monogenic conditions. The analysis and interpretation are designed to detect and report on single nucleotide variants (SNVs) and small insertions and deletions found within approximately 1,700 genes that have well-established associations with more than 1200 conditions (as found in the NIH Genetic Testing Registry and Online Mendelian Inheritance in Man®). This set of genes/conditions includes genes recommended by the American College of Medical Genetics and Genomics (ACMG) for secondary findings. The test is intended for adults 18 years of age in the United States or the age of majority established in the country from which the test is ordered.

Reasons for referral

- Identification of genetic predisposition
- Identification of genetic carrier status

Test method

Whole-genome sequencing is performed for this test utilizing Illumina's Sequencing-By-Synthesis (SBS) chemistry and paired-end read technology. Alignment and variant identification is performed with NCBI Human Genome Reference build 37.1. All variant calls are annotated to facilitate review of evidence for clinical importance. Utilizing publically available resources, the annotation includes: allele frequency in population studies (1000 Genomes, Exome Aggregation Consortium, etc.), category of variant (nonsense/missense, etc), amino acid change, and literature searches to identify any clinical associations that have been reported.

Test specifications

We sequence to an average of ≥ 30 fold coverage. Over 99% of the genome is covered at 10 fold coverage or more and 96.5% of the genome is callable (passes all quality filters). Based on the quality filters and through the analysis of an extended, multigeneration family set (Platinum Genomes, <http://www.illumina.com/platinumgenomes/>), for SNVs, sensitivity is 97.7% and the analytical Positive Predictive Value (PPV), i.e. $TP/[TP+FP]$ is 99.9%. Small insertion and deletion events are detected and reported for this test. Insertions up to 28 bases and deletions up to 12 bases have a sensitivity and analytical PPV of approximately 80-85%, determined through Platinum Genomes.

Clinical interpretation is provided for variants within the genes and the gene-disease relationships as specified in the Gene-Disease List. The assay covers the clinically interpreted genes with >95% callability for most exons. We limit interpretation to VCF variant positions that lie in an exon as well as 15 base pairs upstream and downstream of the exon.

Criteria for variant classification

We follow modified ACMG guidelines for variant classification and reporting (Richards et al., 2015). Additionally, a sub-category termed, variant of unknown significance-suspicious (VUS-S), was developed for variants of unknown significance with evidence suggestive of pathogenicity that make them noteworthy.

- Pathogenic: Reported in multiple unrelated cases with control data. Functional or expression evidence suggests deleterious effect on gene function.
- Likely Pathogenic: Reported in limited cases, or in a single-family cohort, with or without control data. Limited or no functional evidence available, but overall biological consistent with a deleterious effect.
- VUS-Suspicious: Some evidence that the variant could be causative of disease. The information available, however, is insufficient to categorize the variant as likely pathogenic. This category was added to bring attention to variants that are on the border between unknown significance and likely pathogenic.
- Unknown Significance: Little or nothing has been reported on this specific variant or its effects, or, evidence is weak or contradictory to assess whether the variant is pathogenic or benign at the time of interpretation.
- Likely Benign: This variant has been seen in cases, but also in controls. Variant may be present in a high percentage of the population, and may be present in a non-conserved region.
- Benign: Established in the literature as a variant that is not associated with Mendelian (single-gene inherited) disease, or known to have an allele frequency that is far too high to be compatible with the prevalence of disease, mode of inheritance and penetrance patterns known for that condition.

Deliverables

- A Clinical Report, which includes variants classified as pathogenic, likely pathogenic and variant of unknown significance-suspicious. Literature references used to support the classifications will be provided.
- A Clinical Appendix outlining all variants identified within the genes analyzed and their variant classifications
- A Pharmacogenomics Report including 11 medically actionable genes associated with response to 16 different drugs (as specified by the FDA or the Clinical Pharmacogenomics Implementation Consortia (CPIC))
- A gVCF file with all calls through the genome

Technical data in BAM file format (sequence information provided in a standard open source binary format (Li et al., 2009, <http://samtools.sourceforge.net/>) is available for return with a fee only to clinical researchers operating under an approved IRB protocol or through a CLIA-certified laboratory for clinical use.

Limitations

It is not technically possible to capture and sequence the entire human genome at present. Only known bases of the human reference genome will be assessed. Only single nucleotide substitutions and small insertion and deletion events are reported for this test. Other types of genetic variants that may also lead to genetic disease, but are not reported, include copy number variants, triplet repeat expansions, and other structural chromosomal rearrangements. If clinically indicated, additional testing and analyses, such as karyotyping, microarray or MLPA may be appropriate. The clinical sensitivity for the test varies depending on the gene and condition of interest, and therefore, clinical sensitivity is unknown.

The clinical variant interpretation report represents our current best understanding of the clinical implications of the variants identified. As information within the field increases, this understanding may change and the interpretation reported may change.

It is important to note that the test results may have implications for the patient's biological family members. Genetic counseling is recommended.

Lab Statement

The TruGenome Predisposition Screen is a Laboratory Developed Test. It was developed and its performance characteristics determined by the Illumina Clinical Services Laboratory (CLIA #05D1092911). It has not been cleared or approved by the U.S. Food and Drug Administration. Pursuant to the requirements of CLIA '88, this laboratory test has established and verified the test's accuracy and precision. The laboratory is regulated under CLIA as qualified to perform high-complexity testing. This test is used for clinical purposes. It should not be regarded as investigational or for research. We cannot accept orders from the state of New York at this time.

References

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL; ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-24