Illumina, Inc.
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TruGenome™ Predisposition Screen

Test Description

Test Indication

The TruGenome Predisposition Screen is intended to be used as a genetic predisposition evaluation, and in assessing genetic carrier status, for a pre-defined set of highly penetrant, monogenic conditions. Additionally, information on well-established relationships between genetic variants and drug response is provided in a separate report (see Pharmacogenomics Screen Intended Use document). This information may help physicians make informed management decisions about an individual's health. The analysis and interpretation are designed to detect and report on single nucleotide variants (SNVs) and small insertions and deletions found within 1691 genes that have well-established associations to a set of 1232 conditions (as found in the NIH Genetic Testing Registry and Online Mendelian Inheritance in Man®), and 11 genes linked to response to 16 different drugs (as specified in FDA and CPIC guidelines). This set of genes/conditions includes those recommended by the American College of Medical Genetics and Genomics (ACMG). The test is intended for adults only.

Reasons for Referral

- Identification of genetic predisposition
- Identification of genetic carrier status
- Identification of genetic drug implications

Test Method

Whole-genome sequencing is performed for this test utilizing Illumina 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 (dbSNP, 1000 Genomes, etc.), category of variant (nonsense/missense, etc), amino acid change, and literature searches to identify any clinical associations that have been reported.

Test Specifications

The TruGenome Predisposition Screen provides sequence for >90% of the reportable genome. However, clinical interpretation is only provided for variants within the 1691 genes encompassing 1232 well-characterized gene-disease relationships as specified in the Gene-Disease List, and 34 genomic positions, encompassing 11 genes and 16 drugs as specified in the Pharmacogenomics Screen document. The test meets the specifications of the TruGenome Technical Sequence service. The assay covers the clinically interpreted 1691 genes with >95% coverage for all coding regions. We sequence to an average of ≥30 fold coverage. Our validations demonstrate that 30 fold coverage with quality scores of ≥Q30 results in the average call having greater than 99.99% accuracy in detecting SNVs in a diploid genome. Less than 3% of our total reported data are at 10 fold coverage, and these calls achieve 98% accuracy. Insertion and deletions events are detected and reported on in the range of 1-7 base pairs (+ /- 7 base pairs). The sensitivity and specificity of insertion and deletion detection at this size range is approximately 80%, determined through analysis of an extended, multigeneration family set that has been externally validated.

Deliverables

- A clinical report that includes variant interpretation of genomic findings deemed clinically significant in accordance with ACMG guidelines, and references used to establish the classifications.
- A separate report which includes detailed information and references regarding the drugs, genes and genomic positions interpreted for the test.
- A clinical appendix outlining all variants identified within the genes analyzed and their variant classifications.
- A technical report describing the analytical performance of the sample.
- A gVCF file with all variant calls through the genome.

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Criteria for variant classification

We adhere to the ACMG guidelines for variant classification and reporting (Richards et al., 2008; Richards et al., 2005). Additionally, a sub-category termed, VUS-suspicious, was developed internally for variants of unknown significance, but has suggestive or weak evidence of pathogenicity that make them noteworthy for reporting.

- 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 expectations suggestive of deleterious effect.
- VUS-Suspicious: There is some evidence that the variant could be causative of disease. However, the information available 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 variant or its effects.
- 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.

Drug response implications

Clinical Interpretation is provided for well-characterized, high impact pharmacogenomics results in accordance with the Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Food And Drug Administration (FDA) guidelines. Interpretation is provided for 11 genes associated with 16 different drugs.

Limitations

It is not technically possible to capture and sequence the entire human genome at present. It is anticipated that approximately 90-95% 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. 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 due to the nature of whole-genome sequencing, the test results will have implications for the patient's 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.

Required Information and Forms

- Completed Test Requisition Form with Ordering Physician signature, Clinical History, and Billing Information.
- 100% pre-payment, unless other institutional arrangements have been made.

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Specimen Requirements

We require that all samples be collected and returned using our Sample Collection Kits. To request a collection kit, please fill out and return the kit request form.

Blood: 4-8ml whole blood in a provided PAXgene DNA tube. Ship overnight at ambient temperature in the provided, pre-paid envelope. Specimens may be refrigerated (4˚C) for >5 days if needed to avoid weekend delivery.

Price and Turn-Around Time

TruGenome Predisposition Screen: $9,500

Timeframe: 90 days

Contact

Please contact the lab with any questions you may have regarding test selection, ordering, sample submission and results interpretation and implications.

Phone: 858.736.8080

Fax: 858.255.5285

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