Whole Exome Plus

**Test code: WE0301**

Whole Exome Plus includes high-quality Whole Exome sequence analysis of single patient cases, coupled with Whole Genome Deletion/Duplication analysis by low-coverage Whole Genome sequencing. Deletion/Duplication analysis enables detection of large copy-number variants.

Whole-exome sequencing (WES) is a robust and one of the most comprehensive genetic tests to identify the disease-causing changes in a large variety of genetic disorders. In WES, protein-coding regions of all genes (~20,000) of the human genome, i.e., exome, are sequenced using next-generation sequencing technologies. While the exome constitutes only ~1% of the whole genome, 85% of all disease-causing mutations are located there.

**WES is most suitable for individuals with:**

- a complex, unspecific genetic disorder with multiple differential diagnoses.
- a genetically heterogeneous disorder.
- a suspected genetic disorder where a specific genetic test is not available.
- unsuccessful previous genetic testing.

Blueprint Genetics Whole Exome tests have been developed to maximize diagnostic yields, first of all, by generating high-quality and uniform sequencing data. The sequencing data are analyzed using in-house, state-of-the-art bioinformatics pipeline. Furthermore, the genetic information of patients is carefully interpreted by our team of geneticists and clinicians, utilizing information from latest publications and up-to-date databases.

**Availability**

Whole Exome Plus test is available with TAT of 6-9 weeks. Exome testing is not currently available in the US. Please contact customer support (support.us@blueprintgenetics.com) for more detailed information on the availability.

**Test performance**

We utilize high-quality exome capture technology (Agilent SureSelect V6) and next-generation sequencing methods to obtain clinical-grade WES data, maximizing coverage of clinically relevant genes.

- Highly uniform sequencing depth across all protein-coding genes of the genome
  - Mean sequencing coverage on average 148x, we guarantee at least 100x
  - On average, 98.9% of base pairs in RefSeq genes’ coding regions covered at least 15x
  - Highly sensitive and specific detection of single-nucleotide variants and indels
    - 99.5% sensitivity and >99.99% specificity for single-nucleotide variant detection within coding regions of RefSeq genes.
    - 97.2% sensitivity and >99.99% specificity for indel detection within coding regions of RefSeq genes.
    - 97.2% sensitivity and >99.99% specificity for indel detection within coding regions of RefSeq genes.
    - Deletions up to 35bp detected, insertions up to 27bp
    - Assay performs with high precision
      - Within-run precision (repeatability) 99.4%

**Bioinformatics**

Analysis of WES data is a complex process, imposing challenging requirements both in terms of computing resources and software. The proprietary automated bioinformatics pipeline developed and employed at Blueprint Genetics enables fast, reliable and highly accurate results.

We utilize state-of-the-art algorithms for quality control and processing of sequence reads as well as for detection of single-nucleotide and small indel variants from WES data (large copy-number variants are analyzed by low-coverage whole-genome sequencing in Whole Exome Plus or Whole Exome Family Plus tests). Furthermore, the pipeline employs accurate methods to determine consequence of variants as well as filtering steps to remove common variants based on allele frequencies in
population cohorts.

WES data are primarily analyzed for changes in genes that are known to be associated with conditions showing overlap with the one observed in the patient. We monitor recent literature and up-to-date databases to link genes observed in patients with up-to-date information regarding the genes’ association with relevant diseases. To further aid the process of variant interpretation, observed variants are matched against a comprehensive set of databases of disease-related mutations, collected and curated in-house, and accessed from the public domain or licensed from commercial sources.

WES data analysis needs to be tailored on individual basis. In the analysis process, we consider the clinical and family history of the patient, including symptoms, age of onset and prevalence and inheritance pattern of the disease. The applied filters for variant analysis are then selected based on this information to achieve an accurate diagnosis. Therefore, it is important that the clinical and family history information is delivered to us in as much as detail as possible when ordering the test.

A final component of the analysis is the Sanger confirmation of the variants classified as likely pathogenic or pathogenic. Other variants are confirmed upon judgment. Customers are distinctly informed about the variants that were confirmed using Sanger sequencing.

Clinical interpretation

We provide the customers with the best-informed clinical report on the market. Clinical interpretation requires fundamental clinical and genetic understanding. At Blueprint Genetics our geneticists and clinicians, who together evaluate the results from the sequence analysis pipeline in the context of phenotype information provided in the requisition form, prepare the clinical statement. Our goal is to provide clinically meaningful statements that are understandable for all medical professionals, even without training in genetics.

In our statements, we provide a comprehensive description of our rationale for the classification of the variant. Variants reported in the statement are always classified using the Blueprint Genetics Variant Classification Scheme modified from the ACMG guidelines (Richards et al. 2015), which has been developed by evaluating existing literature, databases and with thousands of clinical cases analyzed in our laboratory. Please review our variant classification scheme here.

We constantly follow genetic literature adapting new relevant information and findings to our diagnostics. Relevant novel discoveries can be rapidly translated and adopted into our diagnostics without delay. These processes ensure that our diagnostic tests and clinical statements remain the most up-to-date on the market.

Secondary Findings

As WES covers all protein-coding genes of the genome, it enables detection of variants that are not associated with the indication for ordering the sequencing but are of medical value for patient care. These kind of findings are called secondary or incidental findings. We follow the ACMG Recommendations for Reporting Incidental Findings in Clinical Exome and Genome Sequencing to seek and report clinically actionable mutations of specified types in 56 genes determined by ACMG, if the patient or the caregiver has opted-in for analysis and reporting of secondary findings. If parents or other family members are also subjected to WES, they also have the possibility to opt-in for analysis and reporting of secondary findings. Secondary findings are reported in a separate statement document and reported variants are confirmed using Sanger sequencing.

Accepted sample types

For Whole Exome tests, sample requirements are:

- EDTA blood, min. 2 ml
- Purified DNA, min. 10μg
- Saliva (Oragene DNA OG-500 kit)

When Whole Exome Family or Whole Exome Family Plus product is ordered, we require to send samples from first-degree relatives of the index patient at the start of testing.