PRODUCT DATASHEET

Clinical Whole Genome Sequencing

CLIA Certified and College of American Pathologists (CAP) accredited

Built around our tried and tested PCR-Free whole genome sequencing process

OVERVIEW

Clinical Human Whole Genome Sequencing provides validated, high quality sequence data generated through the same processes that have produced >100,000 research genomes - including genomes that have been included in large resource datasets such as TOPMed and GnoMAD. Our in-house developed, PCR-Free library construction process produces extremely even coverage of the entire genome, including exonic, intronic, GC-rich, and regulatory regions.

Whole genome sequencing offers several advantages over traditional approaches of genomic characterization. Targeted panel and exome approaches require amplification of genomic DNA which induces sequence-context specific bias. Analyses of panels and exomes is limited to targeted regions and content must be updated if new regions are identified for study. Several classes of human variation including copy number profiling and structural variation calling are more easily and accurately determined from whole genome sequencing.

Technical performance specifications for our clinical whole genome were determined through pre-validation analysis of >20,000 research genomes as well as through input received from our medical and population genetics community. During validation we sequenced and analyzed over 5000 gigabases of data, including National Institute of Standards and Technology (NIST) reference samples and 30 previously tested clinical patient samples with known orthogonally validated variants. In previously tested patient samples we observed ≥99.98% accuracy in calling pathogenic variants that were targeted by the assay. We also determined callability of ACMG59 gene variants using a metric proposed by Goldfeder and Ashley[1], in which a site is determined to be callable if it: is covered to at least 20X depth; had a base quality of at least Q20 (99.9% probability of being correct); and, had a mapping quality of at least Q20. Using this metric we found that 99.86% of the known 16,781 Pathogenic or Likely Pathogenic[2] variants in the ACMG genes would be considered callable.

The clinical whole genome service is ideal for applications spanning many areas of clinical research including: clinical utility studies, rare and common disease research, translational research, identifying novel biomarkers, and clinical trials.

[1]Goldfeder, R. L. & Ashley, E. A. A precision metric for clinical genome sequencing. (2016). doi:10.1101/051490

[2]Shah, N. et al. Identification of Misclassified ClinVar Variants via Disease Population Prevalence. Am. J. Hum. Genet. 102, 609–619 (2018).

WHAT'S INCLUDED

- Sample receipt and nucleic acid extraction from blood
- QC & plating, sample preparation
- Sample fidelity QC (96 SNP fingerprinting)
- 2x150bp paired sequencing reads
- Coverage of ≥95% of bases ≥20x
- Data delivery through a secure online portal
- Turnaround time ≤28 days from sample receipt

PERFORMANCE METRICS

% Bases at 20X Target:	**≥95%**
Mean Coverage Target for Genome:	≥30X WGS Coverage
% Contamination:	≤2.5% (typically less than 0.2%)
PF HQ Aligned Bases:	≥$8x10^{10}$ bases
Estimated Library Size:	≥$7x10^{9}$ molecules
SNV Sensitivity:	98.8%
Indel Sensitivity:	94.5%
SNV and Indel Specificity:	99.99%

INPUT REQUIREMENTS

- Clinical requisition
- 750ng genomic DNA (@ 7ng/uL minimum concentration)
- 1ml whole blood (EDTA Tube)

DATA DELIVERABLE

- De-multiplexed, aggregated CRAM file aligned to hg38
- Contamination-check, QC and Technical Report

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For information about Validation Limitations see related documentation at www.genomics.broadinstitute.org/resource-page

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