Invitae Boosted Exome

The Invitae Boosted Exome provides a clear evidence-based analysis of an individual's exome through systematic evaluation of genetic variants informed by the patient's clinical presentation and history.

Invitae's medical team consists of PhD scientists, certified genetic counselors, and ABMGG board-certified molecular geneticists with extensive experience performing clinical exome sequencing.

The Invitae Boosted Exome includes:

- Robust sequencing coverage of the whole exome to ensure high sensitivity and specificity—150x average sequencing depth and >99.4% of reportable bases covered at ≥20x depth
- Customized capture baits that boost coverage of hard-to-sequence areas of the exome and allow detection of intragenic copy number variants
- An average turnaround time of 6-8 weeks
- Annotated supplemental reports with all rare variants (<1% frequency) upon request

Rigorous gene curation for every exome

- Every exome undergoes comprehensive gene curation prior to analysis, ensuring recently published gene-disease relationships are included.
- Gene-disease curation categories:
  - Strong: conclusively causes a specific disease
  - Suggested: evidence supports a possible disease association (e.g., "candidate genes")
  - Unconvincing: current evidence is inconclusive

Beyond sequencing—accurate and reproducible variant classification

- Invitae's 5-tier variant classification framework,[1] called Sherloc, begins with the most recent ACMG guidelines[2] and builds on them to generate rigorous variant interpretations. Invitae's stringent procedures provide reproducibility and reduce subjectivity through critical evaluation of all applicable evidence of pathogenicity.
- As part of Sherloc, Invitae has developed and applies computational methods—known as functional modeling—to resolve variants of uncertain significance (VUS) and improve test results across all clinical areas in accordance with ACMG guidelines.

1. Nykamp K, *et al.* Sherloc: a comprehensive refinement of the ACMG-AMP variant classification criteria. *Genet Med.* 2017;19(10):1105-7.
2. Richards S, *et al.* 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;17(5):405-24.

Invitae Boosted Exome analysis

What do we cover?	What do we evaluate?	What do we report?
Proband	**Proband**	**Proband**
• Average 150x coverage (per base) across all included exons • >99.4% of reportable bases covered at ≥20x • Invitae's high-quality variant calling detects: ▪ single nucleotide variants ▪ insertions/deletions (indels) ▪ intragenic copy number variants*	• Genes identified by a phenotype-to-gene matching tool based on the Human Phenotype Ontology system plus OMIM and other relevant databases • Genes specifically requested by the ordering clinician • Disease-associated genes with variants that are: ▪ independent of the proband's phenotype ▪ likely to be disruptive (e.g. premature truncation events, canonical splice site variants, or whole-exon deletions) ▪ homozygous or hemizygous ▪ reported to cause disease in publications but are absent in population databases ▪ reported pathogenic or likely pathogenic in clinical databases (e.g., ClinVar)	• A clinical summary describing relevant findings • Detailed information including: ▪ a list of analyzed genes with coverage statistics ▪ pathogenic and likely pathogenic variants related to the indication for testing, and some variants of uncertain significance that follow an appropriate inheritance mode, and closely match the patient's phenotype ▪ a description of evidence for variant classification with relevant citations ▪ medically important incidental findings • An optional secondary findings report (based on the latest ACMG recommendations) for all sequenced individuals • A supplemental genes and variants for discovery and investigation (GVDI) file (upon request). This file contains all variants within the reportable range of the assay that are <1% frequency or filtered in the ExAC database. Each variant is annotated with population frequency, proband zygosity, parental zygosity (duo/trio only), sequence ontology term, Human Genome Mutation Database identifier, and ClinVar accession ID (if available).
Trio	**Trio**	**Trio**
• Exome sequencing of all three samples with joint calling	• All genes analyzed above • Disease-associated genes with variants that are: ▪ de novo ▪ segregating as X-linked or autosomal recessive	• Parental inheritance associated with all reported variants

**In contrast to Invitae's gene panel sequencing where single-exon del/dups are detected, the greater variability in depth of coverage across an exome permits reliable detection of del/dups spanning 4 exons or more with high confidence; smaller events are also often detected and will be reported when sufficient resolution exists.*

Turnaround time: 6–8 weeks on average

Specimen types: Blood, saliva, or gDNA

Price: Proband $1,250; Duo/Trio $2,500, with insurance billing, institutional billing, and patient-pay options available. Full billing options available at www.invitae.com/billing.

Questions? Our team is ready to assist you!

Reach us at www.invitae.com/contact.