Clinical Blended Genome Exome (cBGE) for Translational Genomics

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Introduction

Comprehensive genetic screening plays a vital role in advancing precision medicine, but traditional screening methods can pose challenges. The ideal approach should:

- Detect both rare and common variants
- Enable monogenic and polygenic risk estimation from a single data type
- Support implementation and clinical utility studies
- Be scalable, cost-effective, and unbiased

Clinical Blended Genome Exome (cBGE) sequencing meets these standards by combining the strengths of whole-genome and exome sequencing into a single, efficient test.

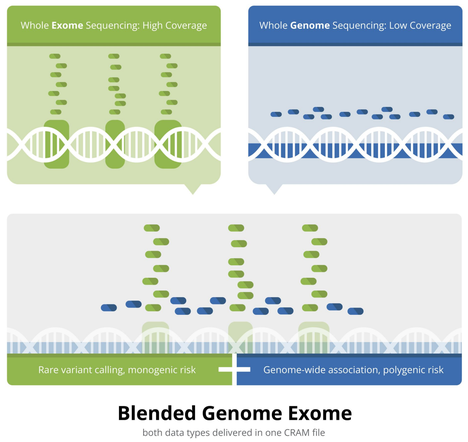


Figure 1. cBGE data types and uses

cBGE delivers low-pass genome coverage for imputation based SNV analysis and deep exome coverage for accurate identification of clinically actionable mutations.[1]

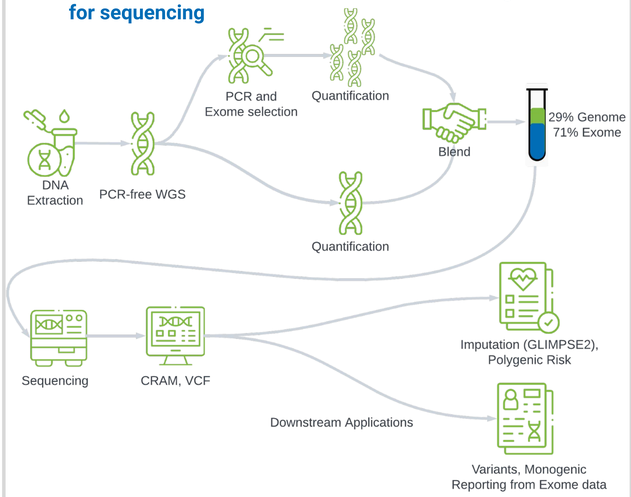
- A 2-3x Genome is paired with >85x Exome (which has an observed coverage of 90-100x) (*Table 1*)
- A single data output (CRAM, hard-filtered VCF) is generated
- cBGE is validated for SNPs, Indels, and CNVs
- It is suitable for clinical use due to coverage and quality targets (*Table 1*)

Category	Metric	Minimum Threshold
Library Quality/ Identity	Percent Contamination	≤2.5%
	Percent Mapped	≥75%
Exome Data Quality/ Quantity	Percent Bases >20X	≥90%
	Mean Target Coverage	≥60x
Genome Data Quality/ Quantity	Genome Mean Coverage	≥1x
Variant Calling Quality	Percent Callability	≥95%

Table 1. Minimum product thresholds

Approach

Exome (Twist Alliance Clinical Research Exome) and Whole Genome libraries are combined into a single tube for sequencing



- Starting with a blood or saliva sample, a PCR-free whole genome library is constructed.
- An aliquot is amplified via PCR and undergoes exome selection
- The libraries are recombined and sequenced on the Illumina NovaSeqX Plus (NVX)
- A single CRAM file is generated, containing both low-coverage whole genome data and high-coverage exome data

Validation Results

Performance was assessed using reference samples with gold standard (NIST) variant truth data. Sequencing was performed on the NVX with alignment and variant calling on DRAGEN v4.2.7.

Small Variants and Indels

- Intra-run precision:
  - HG001 replicates showed high precision and recall across variant types. (*Figure 3*)
  - HG002 replicates demonstrated SNP genotype precision of 99.87-99.89% and indel precision of 97.35-98.12%.

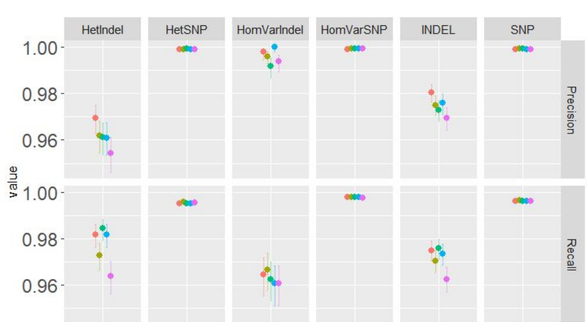


Figure 3. Precision and recall of 5 HG001 replicates

CNVs

- **Sensitivity and PPV (*Figure 4*):**
  - Deletions with at least 3 exons achieved a PPV of 76% and recall of 83%.
  - Duplications achieved a PPV of 87% and recall of 63%.

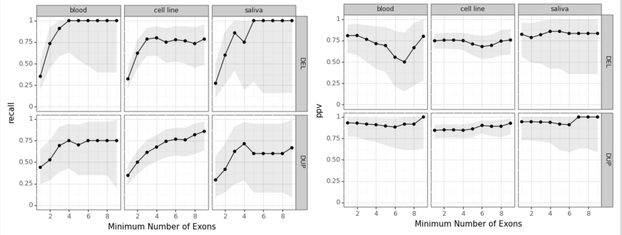


Figure 4. Recall and PPV for different Input Material types and CNV types, as a function of Minimum Exon Size. Shaded areas represent 95% confidence intervals.

Sample Callability

cBGE demonstrated slightly better callability in the exome territory than clinical WGS in matched samples, with 2.19% and 2.65% of bases undercovered in cBGE and WGS respectively (Figure 5a). CDC Tier 1 genes are well-covered in the assay (Figure 5b).

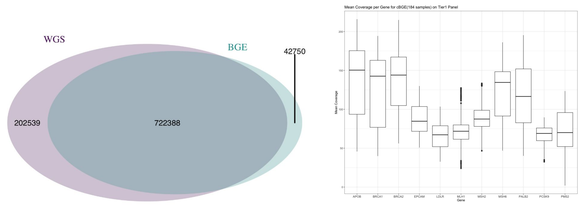


Figure 5a. Undercovered bases in cBGE vs WGS. Each base in each gene interval from the exome (as defined by MANE) was checked. A base is considered undercovered when in 80% of samples the base does not achieve ≥20 for depth, base quality, and mapping quality. Analysis over the exome region in 320 matched samples.

Figure 5b. Coverage in CDC Tier 1 genes.

General Performance

- **Minimum Input Amount:** Libraries constructed with ≥100ng input DNA successfully met product deliverables and performance characteristics.
- **Material Type:** Saliva samples showed a higher failure rate (2%) compared to blood samples due to chimeric reads exceeding the 5% specification, but still performed well on the assay.

Applications

PRS and Monogenic Reporting for New England VA

ProGRESS: The Prostate Cancer, Genetic Risk, and Equitable Screening Study

Jason Vassy, MD,

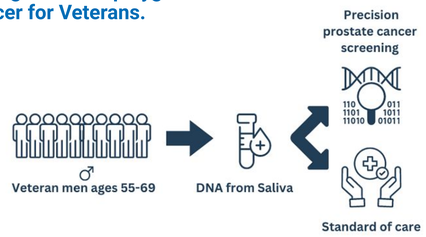
VA | U.S. Department of Veterans Affairs, Veterans Health Administration, Boston Healthcare System

ProGRESS

ProGRESS is a clinical trial that takes a precision medicine approach to prostate cancer screening, giving physicians the ability to tailor care to each individual's genetic risk.

It could transform prostate cancer screening practices within the Veterans Health Administration and beyond, leading to more targeted and efficient care.

ProGRESS is utilizing cBGE to generate both monogenic and polygenic risk estimation in Prostate Cancer for Veterans.



Another project leveraging the high quality and low price point of cBGE is Southern Research. Supported by Myome, They recently launched Catalyst, an initiative that **will provide patients across Alabama with access to free genetic testing and clinical insights about medications and risks for certain chronic diseases, with a focus on underserved communities.**

catalyst BY SOUTHERN RESEARCH

MyOme, Broad Clinical Labs Supporting Genetics-Based Personalized Health Risk Program in Alabama

Free genetic medical tests coming to Alabama; expected to improve care, expand access

Conclusion

cBGE offers a **cost-effective, scalable solution for comprehensive genetic screening**, combining low-pass genome data with high-coverage exome sequencing to support both monogenic and polygenic risk assessment.

By reducing biases related to genomic ancestry and improving access to clinically relevant genetic information, **cBGE broadens the potential for providing personalized care to diverse populations**.

References

1. DeFelice, Matthew, et al. "Blended Genome Exome (BGE) as a Cost Efficient Alternative to Deep Whole Genomes or Arrays." *bioRxiv : The Preprint Server for Biology*, Apr. 2024, https://doi.org/10.1101/2024.04.03.587209.
2. Boltz, Toni A., et al. "A Blended Genome and Exome Sequencing Method Captures Genetic Variation in an Unbiased, High-Quality, and Cost-Effective Manner." *bioRxiv*, 9 Sept. 2024, p. 2024.09.06.611689, https://doi.org/10.1101/2024.09.06.611689.
3. https://www.research.va.gov/for_veterans/progress.cfm

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