Clinical Blended Genome Exome (cBGE) for Translational Genomics

Katie Larkin[1], Matthew DeFelice[1], Matthew Coole[1], Candace Patterson[1], Michael Gatzen[1], Marissa Gildea[1], Jonna Grimsby[1], Chris Kachulis[1], Sean Hofherr[1], Niall Lennon[1]

For precision medicine to be widely accessible, there is a need for robust and cost-effective next-generation sequencing methods that can support screening applications at scale with the delivery of actionable findings. Population-based studies typically have two requirements, one is to get genome-level single nucleotide variant information and the other is to identify mutations in a specific list of genes that can be returned to study participants. Historically, this would have been accomplished by performing two assays, a screening microarray, and a targeted gene sequencing panel. Clinical whole genome sequencing (WGS) can satisfy both requirements, but while WGS has become less expensive in recent years it can be cost-prohibitive for very large-scale population-based studies. To reduce the cost and complexity of running two independent tests, we developed the Blended Genome Exome (BGE), a novel test that marries the benefits of WGS for single nucleotide variant detection, utilizing imputation, with deep whole exome sequencing (WES) to identify mutations for actionable return of results.

This approach combines an exome library and a whole genome library into a single tube for sequencing (DeFelice et al.). Initially launched in a research setting, BGE yields a 35-45x exome with a 2-3x genome, allowing for low-cost population-scale sequencing. However, this research-oriented approach lacks the exome depth required for clinical applications. We have developed a clinical Blended Genome Exome (cBGE) to address this gap. In the cBGE process, the amount of exome library present in the blend is increased. This brings the exome to >80x mean coverage, in line with the standard for commercially available clinical exome products, while still incorporating whole genome data at 2-3x coverage. This sequencing approach balances cost considerations with clinical utility and can be used for multiple clinical applications (e.g. CDC Tier 1 screening, polygenic risk scores).

We will describe our workflow in detail, including the results of our analytical validation study, which was performed to assess the performance of this clinical-grade assay. A combination of reference samples, and previously tested clinical samples were used to verify that the assay is suitable for its intended use as part of clinical applications. We will also demonstrate the utility of this approach, despite limitations in diagnostic applications, for genetic risk.

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.

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.

(Boltz et al.)