# Improving Expectations: Retrospective Review of Clinical Cases to Understand Outcomes and Diagnostic Yields in the Era of Whole Genome Sequencing

Katherine A Lafferty[1], Areesha Salman[1], Andrea Oza[1], Marcie Steeves[1], Caitlyn Ark[1], Kelley Paris[1], Cynthia Fowler[1], Heidi Rehm[1,2], Sean Hofherr[1], Marina DiStefano[1], Diana M Toledo[1]

[1] *Broad Clinical Labs, The Broad Institute of MIT and Harvard, Burlington, MA*; [2] *Massachusetts General Hospital, Boston, MA*

## Introduction

Whole genome sequencing (WGS) is becoming more prevalent in clinical practice. In a diagnostic setting for symptomatic individuals, these tests take an indication-based approach to analyzing genomic data, reporting findings centric to the provided clinical features. However, diagnostic yield for this testing may vary widely between indications and testing approaches. Clinical laboratories have the opportunity to periodically review and share their diagnostic rates with the community, ultimately improving understanding and expectations of genetic testing for both providers and patients. Here we explore a retrospective review of outcomes from WGS performed at our clinical laboratory. Results are stratified by indication, testing approach, and secondary findings.

Broad Clinical Labs (BCL), a CLIA-certified and CAP-accredited wholly owned subsidiary of Broad Institute, offers services to power customers' multi-omic data generation and analysis needs, across a range of research, translational, and clinical applications. BCL launched indication-based clinical whole genome sequencing testing in 2023.

Broad Clinical Labs (BCL) is a CLIA-licensed, CAP-accredited laboratory and a subsidiary of the Broad Institute. To date, it has sequenced over **900k** whole genomes.

In April 2023, BCL used this expertise to launch an expanded service including **patient-specific clinical interpretation.**

In the fall of 2023, the first clinical WGS report with interpretation was signed out.

Now, **611 clinical WGS tests** have been reported. Additionally **over 500 research indication-based WGS tests** have been completed.

Genetic counselors are often involved in pre-testing discussions and consenting for whole genome sequencing where expectations of the genetic testing experience are established from sample collection, turnaround times, to likelihood of various outcomes. Therefore, a clear understanding of these outcomes is imperative when exploring these conversations. We describe the outcomes of the tests completed so far, as a tool to help providers and patients establish testing outcome expectations.

## Materials & Methods

- Results from indication-based WGS performed at our clinical laboratory were assessed. Cases were categorized by indication, approach (proband-only versus family-based), and secondary findings.
- Diagnostic yield was determined as the proportion of cases with a "Positive" result that explains the indication for testing. In addition, the proportion of inconclusive results and reportable secondary findings were also calculated.
- Indications were categorized by a laboratory genetic counselor into the groups listed in Figure 1. For individuals with indications spanning multiple indication categories, the more severe and/or most specific feature was assigned. Clinical history assessment was limited to clinical information provided by the ordering provider at the time of the order which may or may not include additional clinical records for review.
- All individuals undergoing indication-based WGS had the option to opt-in to return of result for secondary findings (PMID: 40568962). ACMG secondary findings recommendation versions may vary based on the available version at the time of testing with current clinical testing receiving the v3.3 gene list.

*Note: BCL testing orders are often from project-based relationships with clients and so indications in this investigation are skewed to a specific client's area of interest or patient cohort. Reanalysis orders and pilot study cases were not included in the outcomes analysis.*

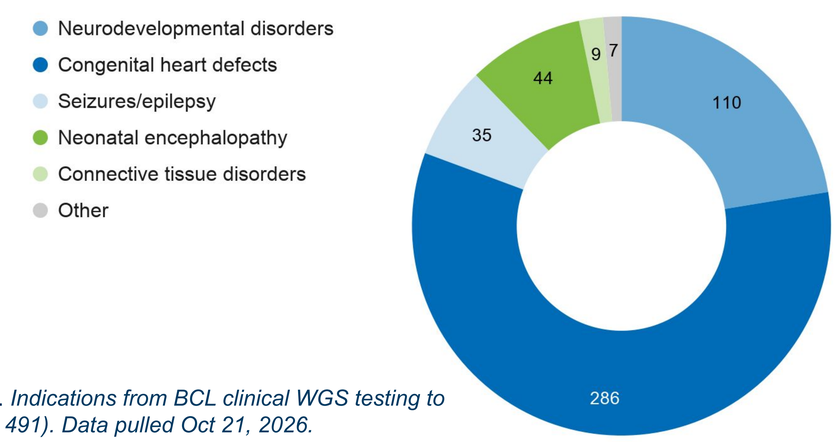



Figure 1. *Indications from BCL clinical WGS testing to date (n= 491). Data pulled Oct 21, 2026.*

## Indication Based Outcomes

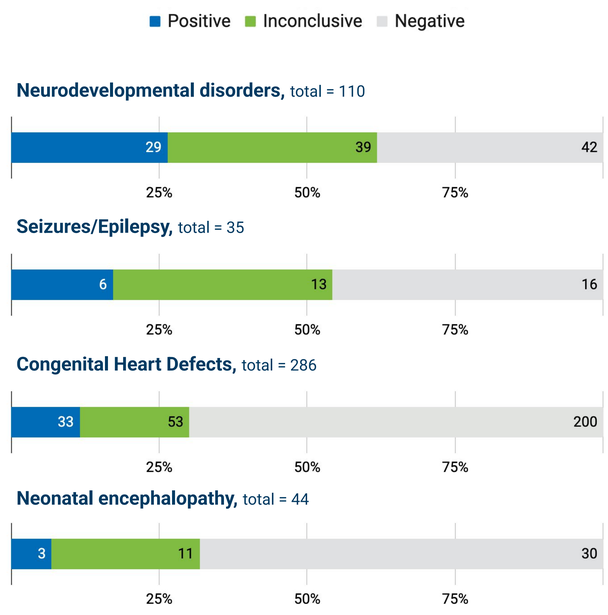



Figure 2. *The diagnostic outcomes of testing based on indiciation.*

Overall, testing with an indication of neurodevelopmental disorders had a reportable finding in 61.8% of cases with a 26.4% positive rate. This was the highest indiciation yield. The lowest yield was for neonatal encephalopathy where a reportable finding was identified in 31.8% of cases, but only 6.8% of those were positive results. Connective tissue disorders was an indication in 9 orders; 7 of those had a reportable finding with 4 Positive results which would be a 44.4% positive yield. However, this is not a reliable representation of yield given the small sample size. Cases with an indication related to autoimmune disease, immunodeficiency, and metabolic disorders totaled less than 5 cases, respectively, so outcomes were not calculated.

## Testing Approach Outcomes

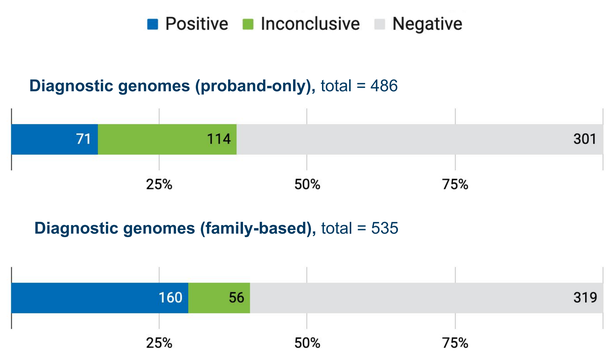



Figure 3. *The diagnostic rates from proband-only and family-based testing approaches*

Overall, the cases with reportable findings was similar for proband-only and family-based approaches in 38.8% and 40.4% of cases, respectively. However, the proportion of reportable findings that were positive was nearly double in the family approach with a positive rate of 29.9% compared with proband-only cases which had a 14.6% positive rate.

*Note: Genomes from a research-based cohort were not stratified for indication comparison but were used in this comparison of family-based versus proband-only outcomes.*

## Secondary Findings Outcomes

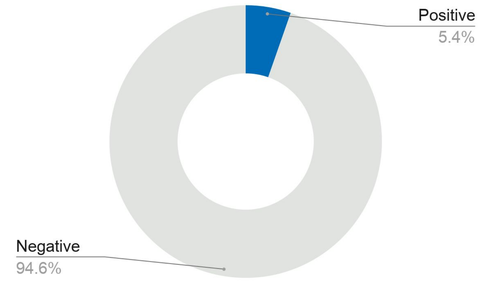



Figure 4. *Outcomes of 410 individuals who opted in to receive secondary findings*

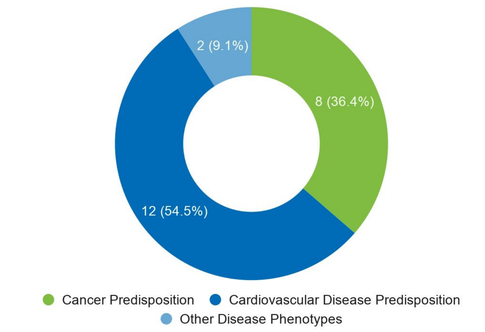



Figure 5. *Disease domains of the positive secondary findings results reported (n = 22)*

In total, 410 individuals opted in to secondary findings. A reportable finding was identified in 22 individuals resulting in a 5.4% positive rate. This is consistent with rates previously reported in the literature (PMID: 34404389). Of the positive findings, 12 were in genes related to cardiovascular disease predisposition, 8 in genes related to cancer predisposition, and 2 were in other disease phenotypes (*TTR* and *ACVRL1*).

## Discussion

A common source of frustration regarding clinical testing is unmet expectations and therefore, establishing realistic expectations is imperative for more satisfying patient experiences. Demonstrating diagnostic outcomes in clinical testing helps inform genetic counselors and ultimately improves patient care. A genetic counselor can adapt conversations and support based on likely outcomes from the current clinical scenario. Furthermore, it is clear that there is significant increase in yield with family-based testing, compared to proband-only approaches. Patients face many barriers to genetic testing, and including family members may introduce additional challenges. However, genetic counselors are well positioned to advocate for families and increase access. Therefore, being informed increases genetic counselors' advocacy impact and exemplifies why this information should be regularly assessed and shared by clinical laboratories.

Here the outcomes of one clinical laboratory are explored. This insight holds value in how genetic counselors can talk with patients about testing expectations; however, further investigation is still needed as the number of individuals tested and indication spectrum grows. Furthermore, as testing technologies continue to evolve, more information can be uncovered from the genome further emphasizing the importance of transparency with current outcomes from testing laboratories and need for genetic counselors continuing education.