myome® | Rare Disease

WHITE PAPER

Transforming Rare Disease Diagnosis with High-Quality Genetic Testing Powered by Whole-Genome Sequencing

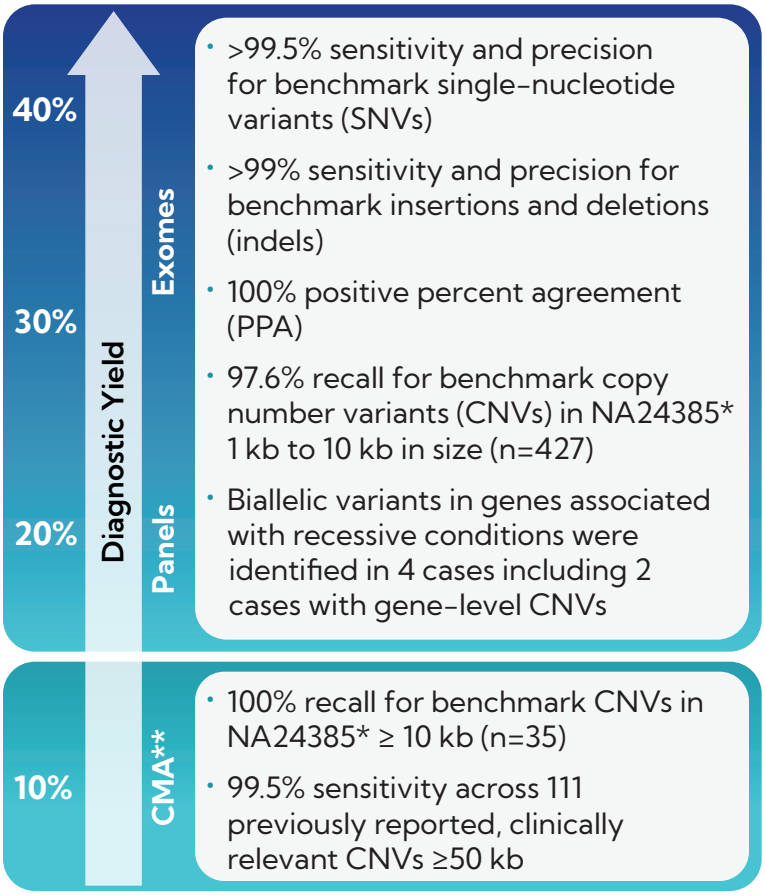
Executive Summary

In aggregate, 1 in 10 people have a rare disease. A genetic diagnosis can aid in the assessment of prognosis, determination of recurrence risk, or selection of treatment plans.[1]

Whole-genome sequencing (WGS) is estimated to result in a ~40% diagnostic yield among pediatric patients with suspected genetic disorders.[2]

In a comprehensive validation study using extracted DNA derived from clinical and control samples, MyOme demonstrated its ability to consistently and precisely detect a wide range of genetic variants across the human genome using WGS. In particular, across 111 samples, previously reported copy number variants (CNVs) were observed with 99.5% sensitivity.

WGS Validation Results



*Benchmark variant set obtained from Genome in a Bottle consortium
**Chromosomal Microarray

Introduction

The Impact of Rare Disease

Rare diseases are a diverse group of disorders. While each rare disease is individually uncommon, more than 10,000 distinct rare conditions collectively affect about 1 in 10 people–totalling over 350 million people worldwide.[1,3] Neurodevelopmental Delay Disorders (NDDs)–a clinically and etiologically heterogeneous group of conditions that includes autism spectrum disorder (ASD), developmental delay/intellectual disability (DD/ID), epilepsy, and cerebral palsy–impact greater than 3% of children in the US.[4-6] These rare diseases often lead to severe, chronic, and life-threatening conditions.[7,8]

Figure 1. The Rare Disease Landscape

Collectively, Rare Diseases Are:		
Common	**Heterogeneous**	**Debilitating**
350M people are diagnosed with a rare disease worldwide[1]	**10K** distinct rare diseases have been identified[3]	**~65%** of rare diseases are associated with a shortened lifespan[8]
>3% of children are diagnosed with an NDD[3-6]	**23%** of patients diagnosed with a rare disease have an NDD[7]	**80%** of surveyed patients and caregivers had difficulties completing daily tasks[9]

Approximately 80% of rare diseases have a genetic basis, resulting from variants that disrupt normal biological functions.[10] A genetic diagnosis can provide valuable insights into the expected progression of a disease (prognosis), thus helping clinicians and patients anticipate potential complications and long-term outcomes. Understanding the genetic basis of a rare disease also allows for a more accurate determination of the likelihood that the condition may recur in the patient or be passed on to future generations (recurrence risk), which is particularly important for family planning. Additionally, identifying the specific genetic variant responsible for a disorder can guide treatment decisions by enabling the selection of targeted therapies, optimizing medication choices, and informing the use of gene-based or personalized treatment approaches.

of rare diseases have a genetic basis[10]

Methods

MyOme's Rare Disease Exome and Genome tests use a PCR-free WGS backbone with an average depth of coverage of ≥30X and ≥90% of the genome covered at ≥20X. Genomic DNA for reference samples was obtained from Coriell Institute. MyOme's in-house analysis pipeline aligns reads to the human genome reference and uses a suite of tools to call SNVs, small indels (<50 bp in length), and CNVs (i.e., deletions and duplications ≥50 bp). The CNV calling algorithm utilizes depth, paired read, and split read information to identify variants and determine breakpoints, leveraging the advantages of WGS. Variants in segmentally duplicated or tandem repeat regions were excluded from benchmark sample evaluation.

Results

SNVs and small indels

This validation study tested the detection of SNVs and indels using 79 benchmark, reference, and clinical samples. For benchmark samples, part of the Genome in a Bottle (GIAB) consortium, more than 3 million SNVs and 375,000 indels were tested across each sample. Recall and precision of 99.9% and 99.8% for SNVs and 99.1% and 99.2% for indels (averaged across samples), respectively, was achieved. For 151 SNVs and indels across 40 clinically relevant genes in reference and clinical samples, 100% positive percent agreement (PPA) was observed (**Table 1**).

Table 1. PPA of SNVs and indels across reference and clinical samples

Samples	SNVs	Indels	Total
Reference samples	40/40 (100%)	17/17 (100%)	57/57 (100%)
Clinical samples	85/85 (100%)	9/9 (100%)	94/94 (100%)
Total	**125/125 (100%)**	**26/26 (100%)**	**151/151 (100%)**

Additionally, detection of one SNV in each of 3 healthy volunteers was tested across DNA extracted from saliva, buccal, and blood from the same individual. MyOme's analysis pipeline was able to detect 42/42 (100%) SNVs.

Results

CNVs

MyOme's analysis pipeline is also designed to detect deletions and duplications across the genome. This validation study evaluated the detection of 2795 CNVs in the NA24385 benchmark variant set obtained from GIAB, which was generated by integrating variant calls from multiple algorithms and sequencing technologies.[11] The overall recall rate of CNV detection across all size categories was 88.4%. When restricting the analysis to the subset of 2042 CNVs that are ≥100 bp in length, recall increased to 94.6% (**Table 2**).

Table 2. Recall of CNVs in the NA24385 dataset across different sizes

Size	True Positives	False Negatives	Recall
100–1000 bp	1480	100	93.7%
1 kb–10 kb	417	10	97.6%
≥10 kb	35	0	100%
Total	**1932**	**110**	**94.6%**

To further assess sensitivity, we analyzed 54 reference and clinical samples for the detection of 56 small, partial, or full-exon CNVs, as well as full-chromosome aneuploidies. This dataset included 37 deletions and 19 duplications, all of which had been previously identified using orthogonal methods. MyOme extended its validation to include WGS data (150 bp, paired-end Illumina sequencing with an average depth of ≥30X) from 68 individuals available through the Autism Speaks MSSNG research initiative, all of whom had CNVs ≥50 kb previously identified using CMA. For larger CNVs, where exact breakpoints may be influenced by genome build, segmental duplications, or other complex sequence contexts, calls were considered concordant if the clinical interpretation remained unchanged. Across all CNVs, the analysis demonstrated a PPA of 99.6% with a 100% PPA for 25 partial to full gene CNVs and 99.5% PPA for 111 CNVs ≥50 kb in size.

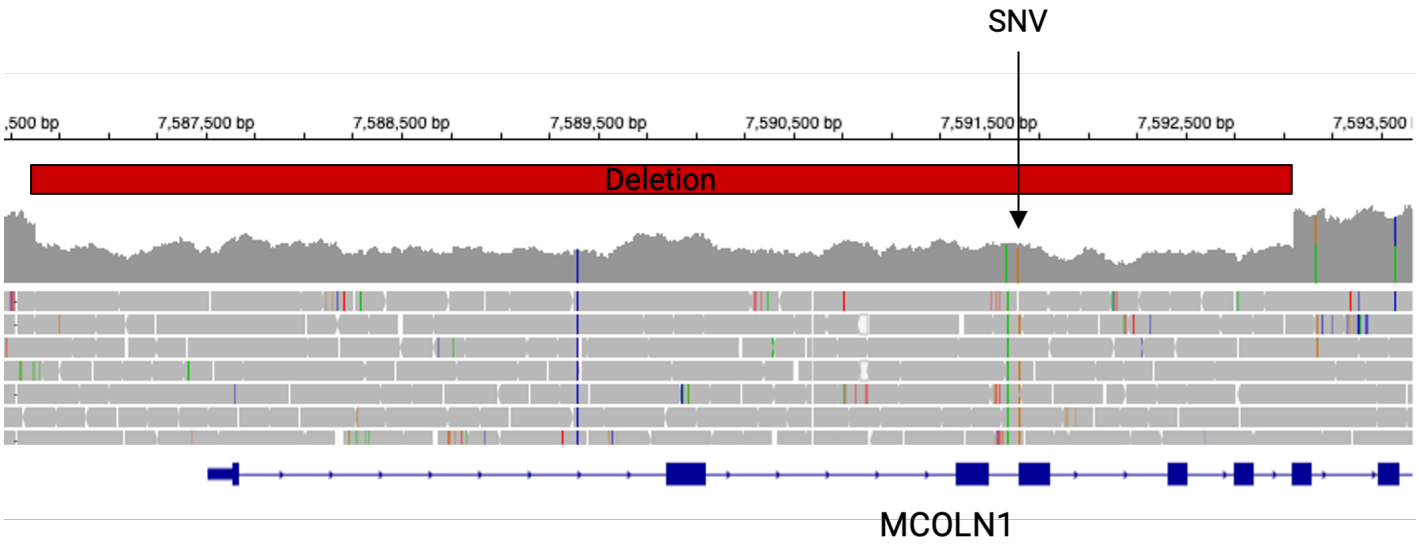
Additionally, detection of one CNV in each of 5 healthy volunteers was tested across DNA extracted from saliva, buccal, and blood from the same individual. MyOme's analysis pipeline was able to detect 65/65 (100%) CNVs.

Results

Compound Heterozygotes

This validation study included samples from seven individuals who are compound heterozygotes, each carrying two distinct variants *in trans* within the same gene—one variant on each chromosome. All variants were successfully identified in these samples, including three cases in which one chromosome harbors an SNV or indel, while the other carries a CNV (**Figure 1**).

Figure 1. Example of biallelic variants of different types detected in the ***MCOLN1*** gene in a sample from an affected individual.



Conclusions

WGS serves as a strong foundation for rare disease testing, enabling the detection of a range of variant types, including SNVs, small indels, and both intragenic and large CNVs. MyOme has developed a robust WGS-based assay that demonstrates high sensitivity across a broad range of variants and the capability to detect biallelic variants—essential for diagnosing autosomal recessive rare genetic disorders.

Get Started With MyOme

MyOme provides a customizable end-to-end solution for providers and patients.

Provider-friendly Workflow

Submit test orders, review test reports, and reflex to broader tests through our accessible online portal.

Reimbursement Support

We navigate billing complexities for our users, including prior authorizations, reimbursement, and affordable patient-pay options.

Assured Data Privacy

Our platform is HIPAA-compliant and features enterprise-scale data encyrption. We never sell or share data without permission.

Future-proofed Platform

Our unique whole-genome sequencing approach enables reanalysis as clinical profiles evolve and technology and knowledge advance.

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Contact support@myome.com to get started.

This test was developed, and its performance characteristics were determined, by MyOme, Inc., a clinical laboratory certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) and College of American Pathologist (CAP) accredited to perform high complexity clinical laboratory testing. This test has not been cleared or approved by the U.S. Food and Drug Administration (FDA). Test results should always be interpreted by a clinician in the context of clinical and familial data with the availability of genetic counseling when appropriate. MyOme is not responsible for the content or accuracy of third-party websites.

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