Assessing Medical Actionability of Exome and Genome Sequencing Results in Over 300,000 Individuals from a Large Real-World Diagnostic Laboratory Cohort

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BACKGROUND

- Exome and genome sequencing (ES/GS) are widely used in clinical care, yet their impact on disease management remains incompletely characterized and is often assessed qualitatively.[1,2]
- Medical actionability refers to the potential for a definitive genetic or genomic finding to inform medical management or disease prevention.[3]
- Existing frameworks assess select genes, but medical actionability has not been systematically quantified across large, real-world testing populations.[1,3]

Purpose

This study aims to address this gap by assessing medical actionability of genetic testing results across a diverse cohort of patients tested at a clinical diagnostic laboratory.

METHODS

Harmonized Gene List

- Expert-curated resources were harmonized and deduplicated to identify gene-disease associations where a molecular diagnosis informs medical management or disease prevention (Figure 1).[1,3]

Patient & Gene-Level Analysis

- A total of 363,677 individuals undergoing clinical ES/GS at GeneDx from January 2013 to June 2026 were retrospectively evaluated, of whom 163,781 had reportable findings*.
- P/LP variants in curated actionable genes were classified as medically actionable, while VUS were evaluated separately as potentially actionable (Figure 2).

Medical Actionability Framework

- Gene-disease associations were classified into non-mutually exclusive bins based on the type of medical management informed by a diagnosis (Figure 3).

Over 60% of patients with a P/LP finding had ≥1 finding in a medically actionable gene.

RESULTS

Figure 1. Harmonized gene list development

Published literature and curated resources were harmonized and deduplicated to identify 1,579 unique genes.

- ClinGen (adult + pediatric)
- ACMG secondary findings v3.3
- ASQM
- Minten et al., 2024[4]
- Baby Seq
- BRIDGES-NBS
- Genomics England
- Guardian (Group 1+ 2)
- Rx Gene
- Treatable ID
- Inborn Errors of Metabolism (IEM)

1,579 Unique genes

Table 1. Demographics of the study cohort

Demographic and testing characteristics of 163,781 individuals with reportable ES/GS findings.

Characteristic		N	%
Age at testing	<2 years	25,259	15.4
	2-5 years	46,182	28.2
	6-17 years	64,026	39.1
	≥18 years	28,287	17.3
	Unknown	27	0.02
Sex	Male	93,543	57.1
	Female	69,717	42.6
	Unknown	521	0.3
Genetic Ancestry†	Admixed American	38,032	23.2
	African	22,410	13.7
	East Asian	3,595	2.2
	European	76,753	46.9
	Middle Eastern	8,918	5.4
	South Asian	5,085	3.1
	Unknown	8,988	5.5
Turnaround Time	Rapid	12,128	7.4
	Standard	151,653	92.6

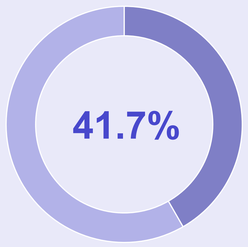
†Inferred based on principal component analysis with 1000 Genomes Reference Populations and one internally developed reference population (Middle Eastern)

Figure 2. Medically actionable findings

A. Gene-level distribution of medically actionable findings

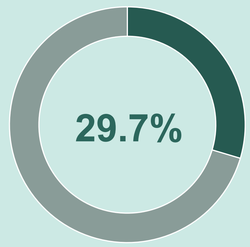
Total unique genes *Across all reportable ES/GS findings** **5,069**

P/LP findings in curated medically actionable genes



1,385 Unique genes of 3,321 genes with P/LP findings

VUS findings in curated medically actionable genes

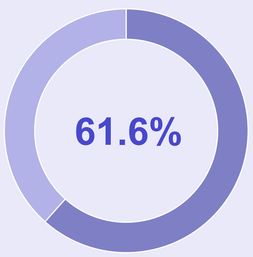


1,444 Unique genes of 4,869 genes with VUS findings

B. Patient-level prevalence of medically actionable findings

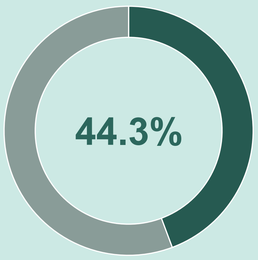
Total unique patients *Across all reportable ES/GS findings** **163,781**

P/LP findings Patients with P/LP findings in curated actionable genes



62,459 Unique patients of 101,390 patients with P/LP findings

VUS findings Patients with VUS findings in curated actionable genes



37,661 Unique patients of 85,105 patients with VUS findings

Figure 3. Medical Actionability Framework

Medical actionability is defined at the gene-disease level and categorized into one or more bins based on the actionability enabled by a genetic diagnosis.

Bin 1
Therapeutic Intervention
Dx enables a direct treatment that modifies disease biology.
Example: GAA – Pompe disease

Bin 2
Acute Management Impact
Dx alters immediate or episodic clinical decision-making.
Example: RYR1- malignant hyperthermia

Bin 3
Surveillance or Risk Mitigation
Dx enables structured monitoring or preventive interventions.
Example: BRCA1 – hereditary cancer risk

Bin 4
Chronic Management & Care Optimization
Dx leads to changes in long-term management & quality of life.
Example: NF1 – neurofibromatosis type 1

CONCLUSIONS

- A harmonized gene-disease list and standardized framework provide a foundation for characterizing medical actionability across clinical genomic testing.
- Medically actionable findings were identified in **61.6% of patients** with P/LP findings in this large real-world ES/GS cohort.
- These findings show how genetic testing can inform medical management or disease prevention, supporting clinical relevance.

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Definitions
*Reportable findings included definitive or possible molecular diagnoses, additional reportable findings, ACMG secondary findings, and previously reported variants

Abbreviations
Dx: Diagnosis; ES/GS: Exome and genome sequencing; P/LP: Pathogenic/likely pathogenic variants; VUS: Variants of uncertain significance

References
1. Goddard KAB, et al. *Annu Rev Genomics Hum Genet*. 2022;23:173–192.
2. Shickh S, et al. *Hum Genet.* 2021;140(10):1403–1416.
3. Hunter JE, et al. *Genet Med*. 2016;18(12):1258–1268.
4. Minten T, et al. *Genet Med.* 2025;27(7):101443.