The Ripple Effect of Gene Discovery: Real-World Impact of GeneMatcher-Facilitated Collaborations

Erin Torti, Olivia L Redlich, Bobbi McGivern, Michelle M Morrow, Dana V Mitchell, Sarah R Poll, Emma C Bedoukian, Amber Begtrup, Deanna Alexis Carere, Amy Crunk, Julie Frank, Jane Juusola, Kirsten Kelly, Patricia C Lopes, Alison M Muir, Melanie P Napier, Amanda G Noyes, Rasim Ozgur Rosti, Ingrid M Wentzensen, Maria J Guillen Sacoto, Flavia M Facio

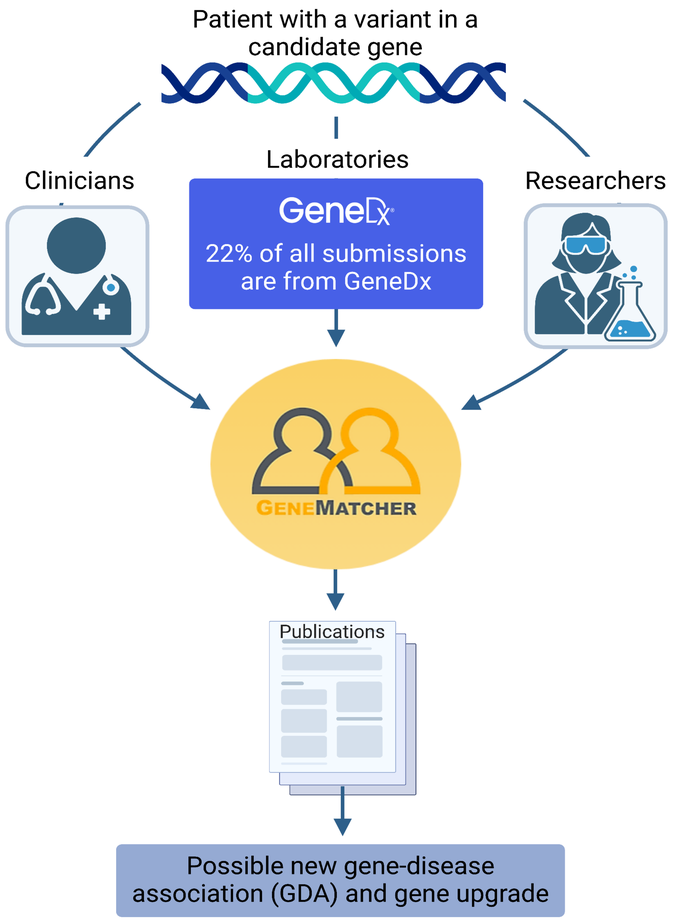
Affiliation: GeneDx LLC., Gaithersburg, MD, USA; Contact: etorti@genedx.com

BACKGROUND

- Establishing gene-disease associations (GDA) is the foundation of getting answers to patients. Variants in genes at the candidate GDA stage can only be classified as variants of uncertain significance. However, once a GDA is validated, variants can be interpreted in the context of the confirmed gene-disease relationship and can receive diagnostic pathogenic or likely pathogenic classification.[1]
- GeneMatcher is a platform that facilitates cohort-gathering for candidate gene studies, leading to sizeable cohorts supporting validation of new GDAs[2] (Fig. 1).
- Reporting of candidate genes is inconsistent among clinical laboratories.[3] GeneDx submits all candidate genes from exome/genome sequencing (ES/GS) to GeneMatcher. Between 2014 and 2021, these efforts led to the discovery of over 200 new GDAs or expanded genetic conditions.[4]

Our goal was to assess the recent impact of GeneMatcher-facilitated collaborative gene discovery efforts in a real-world cohort undergoing testing at a clinical diagnostic laboratory.

Figure 1. Schematic Overview of GeneMatcher



METHODS

- We identified peer-reviewed publications involving GeneDx that:
  - were published between January 2022 and April 2026;
  - resulted from GeneMatcher collaborations; and
  - included ES/GS-tested patient(s) and their ordering clinician(s).
- We determined the impact of these publications by measuring how many of them met internal laboratory criteria for validated GDA[5] and by analyzing the number and characteristics of research-eligible patients who received a molecular diagnosis as a result.

RESULTS

Figure 2. Outcomes of GDA validity assessments

GDA validity assessments conducted by GeneDx based on collaborative GeneMatcher candidate gene publications.

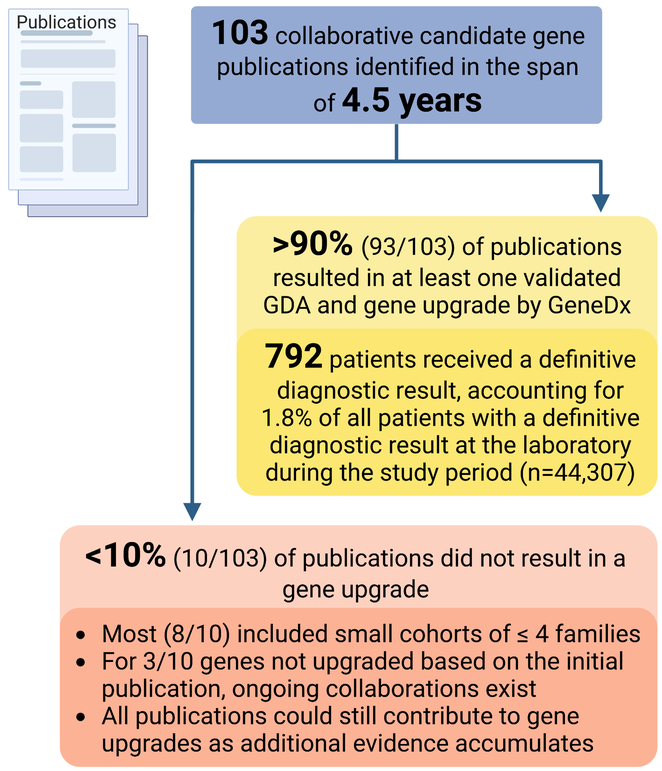


Figure 3. Distribution of diagnostic findings

Number of patients with a diagnostic result per gene. Each orange line represents a gene. Top five genes with the largest number of patients are labeled.

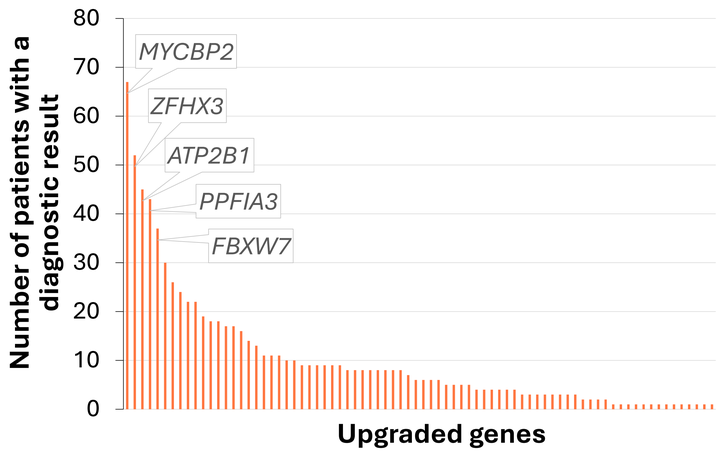


Figure 4. Demographics of individuals who received a definitive diagnostic result

Genetic ancestry inferred based on principal component analysis with 1000 Genomes Reference Populations and 1 internally developed reference population (MDE).[6]

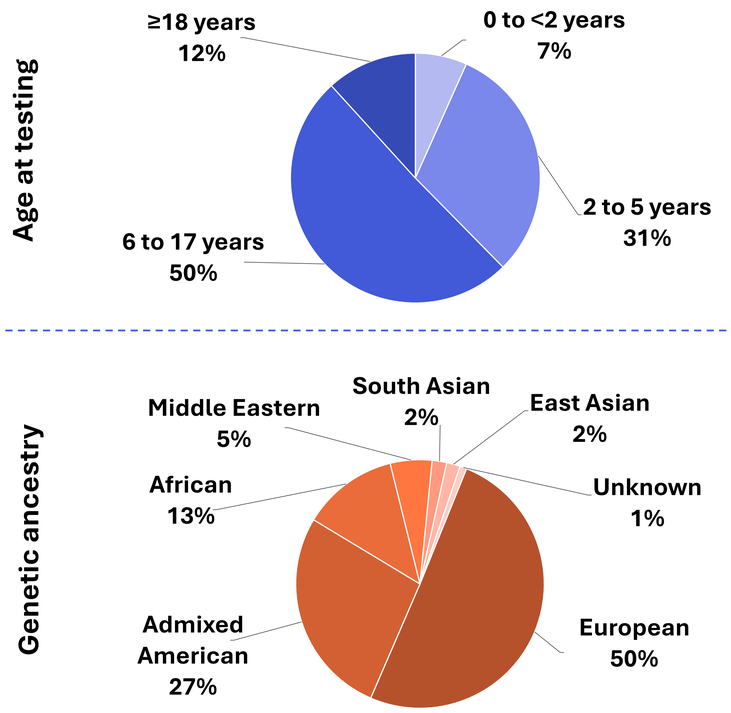
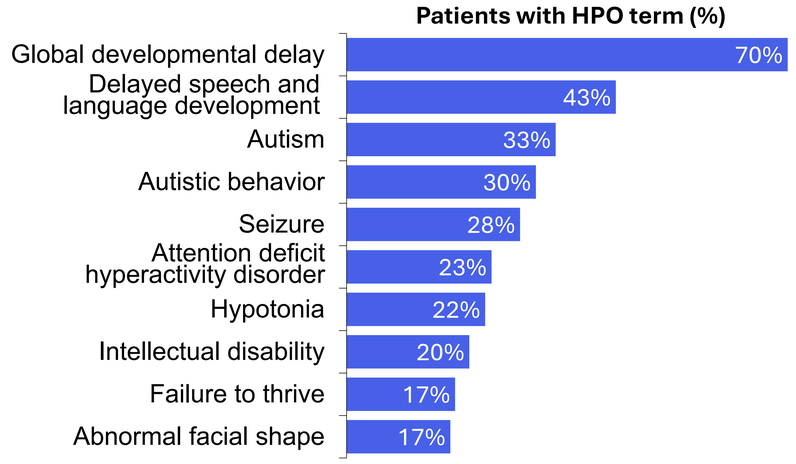


Figure 5. Common HPO terms

Ten most frequent Human Phenotype Ontology (HPO) terms clinically abstracted from individuals who received a definitive diagnostic result (n=792).



CONCLUSIONS

- In this real-world analysis, GeneMatcher-facilitated publications led to the validation of most candidate GDAs studied and enabled definitive molecular diagnoses for hundreds of patients.
- The resulting diagnoses were observed across diverse patient populations and phenotypic presentations, demonstrating the importance of candidate gene reporting by clinical laboratories.
- These findings support the use of comprehensive genomic testing approaches that enable candidate gene reporting and subsequent reinterpretation as gene-disease evidence evolves.

References

1. Richards S, et al. Genet Med. 2015;17(5):405-24.
2. https://genematcher.org
3. Chong JX, et al. Genet Med. 2024;26(10):101199.
4. McWalter K, et al. Hum Mutat. 2022;43(6):760-764.
5. Guillen Sacoto MJ, et al. Poster Board 2057F. Presented at: ASHG 2025 Annual Meeting, Boston, MA.
6. Poll S, et al. Genet Med. 2026. *In press.* doi.org/10.1016/j.gim.2026.102727

Disclosures

Authors were employees of GeneDx at the time the work was completed and may be shareholders of GeneDx.

(C) 2026 GeneDx, LLC. All rights reserved.