Genomic sequencing tests generate less uncertainty and higher diagnostic yield compared to multi-gene panel-based tests: Results of over 1.5 million tests

Heidi L Rehm, PhD[1,2,3], Joseph T Alaimo, PhD[4,5,6], Swaroop Aradhya, PhD[7,8], Pinar Bayrak-Toydemir, PhD[9,10], Hunter Best, PhD[9,10], Rhonda Brandon, MS[11], Jillian G Buchan, PhD[12], Elizabeth C Chao, MD[13], Elaine Chen, PhD[7], Jacob Clifford, PhD[14], Ana S Cohen, PhD[4,5,6], Laura K Conlin, PhD[15], Soma Das, PhD[16], Kyle W Davis, MA[17], Daniela del Gaudio, PhD[16], Florencia Del Viso, PhD[4], Christina DiVincenzo, BS[18], Marcia Eisenberg, PhD[19], Lucia Guidugli, PhD[20], Monia B Hammer, PhD[20], Steven M Harrison, PhD[21], Kathryn E Hatchell, PhD[7], Lindsay Havens Dyer, MS[22], Lily U Hoang, BA[14], James M Holt, PhD[23], Vaidehi Jobanputra, PhD[24], Izabela D Karbassi, PhD[18], Hutton M Kearney, PhD[25], Melissa A Kelly, PhD[23], Jacob M Kelly, BS[23], Michelle L Kluge, MS[25], Timothy Komala, BS[13], Paul Kruszka, MD[26], Lynette Lau, MSC[27], Matthew S Lebo, PhD[28,29,3], Christian R Marshall, PhD[27,30], Dianalee McKnight, PhD[7], Kirsty McWalter, MS[26], Yan Meng, PhD[31], Narasimhan Nagan, PhD[32], Christian S Neckelmann, BA[31], Nir Neerman, BS[33], Zhiyv Niu, PhD[25], Vitoria K Paolillo, PhD[4], Sarah A Paolucci, MS[12], Denise Perry, MS[34], Tina Pesaran, MA, MS[13], Kelly Radtke, PhD[21], Kristen J Rasmussen, MS[25], Kyle Retterer, MS[22], Carol J Saunders, PhD[4,35,6], Elizabeth Spiteri, PhD[36], Christine Stanley, PhD[37], Anna Szuto, MSC[38], Ryan J Taft, PhD[39], Isabelle Thiffault, PhD[4,5,6], Brittany C Thomas, MS[39], Amanda Thomas-Wilson, PhD[24], Erin Thorpe, MS[39], Timothy J Tidwell, PhD[9], Meghan C Towne, MS[13], Hana Zouk, PhD[28,40], on behalf of the Medical Genome Initiative[41]

[1]Center for Genomic Medicine, Massachusetts General Hospital, Boston, MA, USA, [2]Medical and Population Genetics, Broad Institute of MIT and Harvard, Cambridge, MA, USA, [3]Pathology, Harvard Medical School, Boston, MA, USA, [4]Department of Pathology and Laboratory Medicine, Children's Mercy Hospital, Kansas City, MO, USA, [5]Department of Pediatrics, School of Medicine, University of Missouri, Kansas City, MO, USA, [6]Center for Pediatric Genomic Medicine, Children's Mercy Hospital, Kansas City, MO, USA, [7]Global Medical Affairs, Invitae, San Francisco, CA, USA, [8]Department of Pathology, Stanford University School of Medicine, Palo Alto, CA, USA, [9]ARUP Laboratories, Salt Lake City, UT, USA, [10]Department of Pathology, University of Utah School of Medicine, Salt Lake City, UT, USA, [11]Informatics, GeneDx, LLC, Gaithersburg, MD, USA, [12]Genetics Division, Laboratory Medicine and Pathology, University of Washington, Seattle, WA, USA, [13]Medical Sciences, Ambry Genetics, Aliso Viejo, CA, USA, [14]Advanced Analytics, Ambry Genetics, Aliso Viejo, CA, USA, [15]Genomic Diagnostics, Pathology and Laboratory Medicine, Children's Hospital of Philadelphia, Philadelphia, PA, USA, [16]Human Genetics, University of Chicago, Chicago, IL, USA, [17]Marketing, Variantyx, Framingham, MA, USA, [18]Quest Diagnostics, Marlborough, MA, USA, [19]Womens Health and Genetics/Labcorp, Research Triangle Park, NC, USA, [20]Rady Children's Institute for Genomic Medicine, San Diego, CA, USA, [21]Clinical Operations, Ambry Genetics, Aliso Viejo, CA, USA, [22]GeneDx, LLC, Gaithersburg, MD, USA, [23]HudsonAlpha Clinical Services Lab, LLC, Huntsville, AL, USA, [24]Molecular Diagnostics, New York Genome Center, New York, NY, USA, [25]Division of Laboratory Genetics and Genomics, Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA, [26]Medical Affairs, GeneDx, LLC, Gaithersburg, MD, USA, [27]Division of Genome Diagnostics, Department of Paediatric Laboratory Medicine, The Hosptial for Sick Children, Toronto, ON, Canada, [28]Laboratory for Molecular Medicine, Mass General Brigham, Cambridge, MA, USA, [29]Pathology, Brigham and Women's Hospital, Boston, MA, USA, [30]Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, ON, Canada, [31]Curation, Fulgent Genetics, Temple City, CA, USA, [32]Molecular Genetics and Genomics, Women's Health and Genetics/Labcorp, Westborough, MA, USA, [33]Bioinformatics, Variantyx, Framingham, MA, USA, [34]Medical Genomics Research Dept, Illumina, Inc, San Diego, CA, USA, [35]Department of Pediatrics and Pathology, School of Medicine, University of Missouri, Kansas City, MO, USA, [36]Clinical Genomics, Department of Pathology, Stanford Medicine, Palo Alto, CA, USA, [37]Clinical Genomics, Variantyx, Framingham, MA, USA, [38]Clinical and Metabolic Genetics, The Hospital for Sick Children, Toronto, ON, Canada, [39]Medical Genomics Research , Illumina, Inc, San Diego, CA, USA, [40]Pathology, Harvard Medical School, Massachusetts General Hospital, Boston, MA, USA, [41]https://medgenomeinitiative.org

Manuscript under review; Preprint posted on medRxiv

Background

- Genetic testing frequently identifies variants of uncertain significance (VUSs).
- Providers are often ill-prepared or too time-constrained to manage these findings, and insurers are concerned about impacts on clinical care and cost.
- We sought to explore which test type (panels versus genomic testing) leads to more uncertainty in results due to VUSs, while also examining the diagnostic yield.

Methods

We collected panel, exome and genome data from 19 laboratories in North America spanning January 2020 – December 2021

Ambry	GeneDx	Mayo Clinic	SickKids
ARUP	HudsonAlpha	NYGC	Chicago
Children's Mercy	Illumina	Quest	Univ. Wash.
CHOP	Invitae	Rady	Variantyx
Fulgent	MassGenBrigham	Stanford	

Race/ancestry/ethnicity was available for approximately half of the data:
59% White, 10% Hispanic, 8% Black, 4% Asian, 12% Mixed/Other and 8% Not Specified

Results

- **Dataset:** Panels: 1,463,812 multi-gene panel tests (96.8%)
  - Genomic tests: 42,165 exome tests (2.8%) and 6329 genome tests (0.4%)

- **Overall results:** The rate of inconclusive test results (due to the presence of at least one VUS in the absence of a causal etiology) was lower for genomic tests than the rate from panel tests (Fig. 1A).
- For panel tests, the rate of inconclusive results correlated with panel size (Fig. 1B).
- Diagnostic yield from genomic testing was higher than that from panel testing (Fig. 2).
- The use of trios led to higher yield and lower inconclusive rates (Table 1).
- The use of genome sequencing compared to exome led to higher yield but did not increase the rate of inconclusive results (Table 1).

- **Disease-specific results:** One of twelve disease areas representing broad indications for testing were specified for 50.2% of panel tests and 13.4% of genomic tests. Of six disease areas with >25 cases, cardiovascular, neurologic/muscular, and neurodevelopmental/intellectual disability/autism showed higher diagnostic yield and reduced VUS inconclusive rates for genomic tests as compared to panels (Fig. 3). Metabolic disease showed no difference in yield though a reduction in VUS inconclusive rate for genomic testing. Hematologic/rheumatologic/immunologic showed a marginal increase in diagnostic yield and VUS inconclusive rate with genomic testing. The diagnostic yield for and dysmorphic/skeletal was higher for panels and showed no difference in VUS rate.

- **VUS sub-tier usage:** Two laboratories (Mass General Brigham LMM and Quest) reported VUSs in sub-tiers demonstrating a reduction in VUS-low variant reporting for genomic testing.

Table 1. Comparison of Genomic Testing Dx Yield and Inconclusive Rates by Method

	Volume	Inconclusives due to VUS (n)	Inconclusives due to VUS (%)	p value	Positives (n)	Positives (%)	p value
<Trio	20170	5568	27.6%		3070	15.2%	
Trio	28324	5365	18.9%	<0.001	5518	19.5%	<0.001
Exome	42165	9528	22.6%		6999	16.6%	
Genome	6329	1405	22.2%	ns	1589	25.1%	<0.001
Total	**48494**	**10933**	**22.5%**		**8588**	**17.7%**	

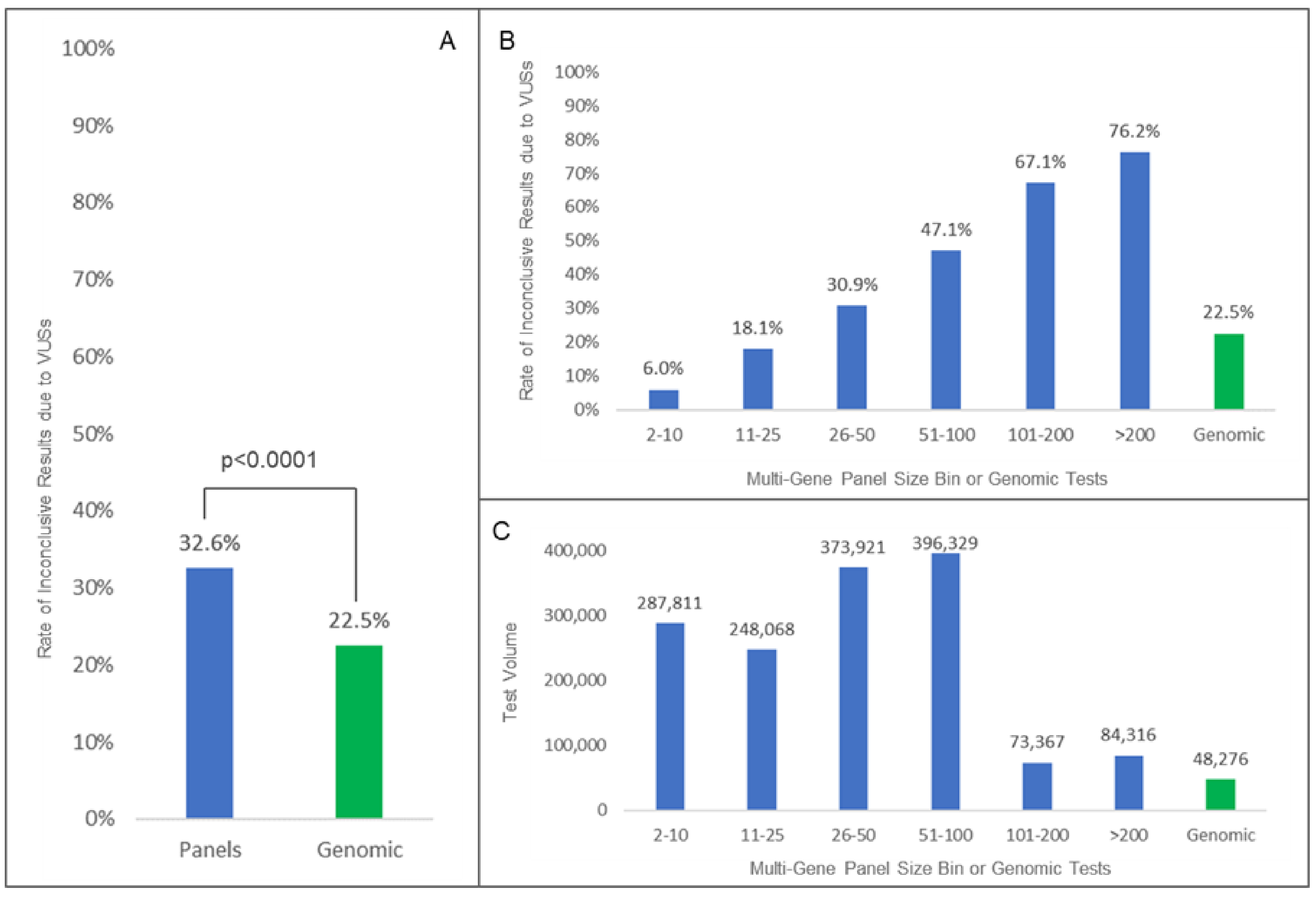

Figure 1. Comparison of Rates of Inconclusive Results due to VUS by Multi-Gene Panel versus Genomic Testing. Panel A shows a statistically significant reduction in inconclusive rates due to VUSs in genomic sequencing compared to panels. Panel B shows a breakdown in rates by panel size. Panel C shows test volume for each bin.

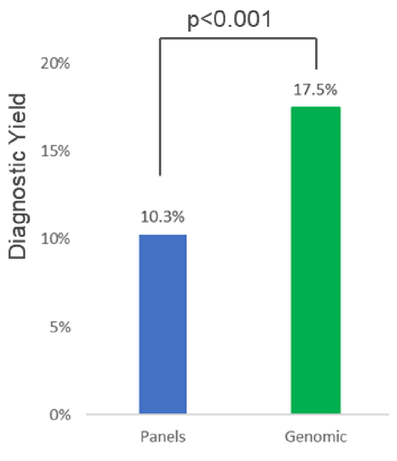

Figure 2. Diagnostic Yield by Test Type. Diagnostic yield was higher for genomic testing compared to panel testing

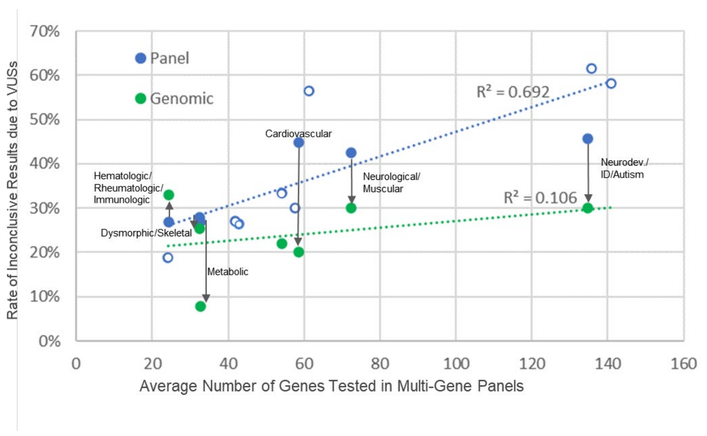

Figure 3. Rate of Inconclusive Results due to VUS by Disease Area. Use of genomic testing reduces VUS rate across most disease areas.

Summary

- This study identified the largest source of inconclusive results from multi-gene panel tests, whereas the use of genomic sequencing tests both reduced the inconclusive rate while improving diagnostic yield.
- This is best explained by the current laboratory practice for the reporting of all VUSs in panel-based testing, based on societal guidelines, compared to genomic testing where correlation with phenotype is used to constrain and limit the reporting of VUS.
- These results set the basis for future reporting practices and guidelines, may guide payor coverage in genetic and genomic testing, and provide a heightened appreciation for the professional skills deployed during genomic test interpretation.