GeneDx Announces Data Demonstrating that Whole Exome and Genome Sequencing Report Fewer Variants of Uncertain Significance (VUS) than Multi-Gene Panel Testing Published in Genetics in Medicine

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STAMFORD, Conn., Aug. 21, 2023 (GLOBE NEWSWIRE) -- GeneDx, a leader in delivering improved health outcomes through genomic and clinical insights, today announced that *Genetics in Medicine*, the official journal of the American College of Medical Genetics and Genomics (ACMG) has published a peer-reviewed research analysis resulting from a multi-lab collaboration involving GeneDx. The study, "The landscape of reported VUS in multi-gene panel and genomic testing: Time for a change," evaluated the rate of inconclusive genetic variants, or variants of uncertain significance (VUS), reported with multi-gene panels versus exome and genome sequencing. Study findings concluded that VUS are reported more frequently on multi-gene panels (32.6%) than exome and genome sequencing (22.5%).

"The high rates of VUS found with multi-gene panel tests create an unnecessary burden on clinicians and our hospital systems, and as the title of the paper suggests, it's time for a change," said Heidi L. Rehm, Ph.D., Professor of Pathology, Massachusetts General Hospital and lead author. "We must examine our current approaches to reduce VUS rates while directing clinician resources towards important VUS follow-up."

The high rate of VUS observed in multi-gene panel testing warrants broader adoption of approaches used in whole exome and genome testing. This is in line with evidenced-based ACMG clinical guidelines, as well as practice guidelines issued by the National Society of Genetic Counselors Society (NSGC) that have also been endorsed by the American Epilepsy Society (AES), which recommend exome or genome testing over chromosomal microarray or multi-gene panels as a first-tier test for individuals with congenital anomalies, developmental delay, intellectual disability, or epilepsy.[1, 2]

"The results of this study help to address a long-held perception that whole exome and genome sequencing introduce more variants of uncertain significance than multi-gene panels, which may be a barrier to broader adoption," said Paul Kruszka, M.D., Chief Medical Officer, GeneDx. "These data help reinforce the benefits and value of exome and genome testing to improve diagnosis and to help end the diagnostic odyssey for more families."

Study Design:
For this study, 19 clinical laboratories in North America provided deidentified summary data from a two-year period (January 1, 2020 - December 31, 2021) for a collective 1.5 million sequencing test results. Aggregate statistics were calculated for tests with inconclusive results that included at least one VUS. Test types such as carrier screening that do not include reporting VUS were excluded. Panel test results were grouped based on size (number of genes analyzed). Exome and genome tests were further categorized based on available family samples (trio, duo, or patient-only). For some laboratories, test results were also categorized across twelve broad disease indications.

Study Results Include:
Exome and genome sequencing tests demonstrated lower rates of reported VUS compared to multi-gene panel tests. Importantly, the study found:

- Variants of uncertain significance were reported less frequently on exome and genome sequencing (22.5%) than multi-gene panels (32.6%).
- The use of trios reduces the rate of VUS for exome and genome sequencing (18.9%) compared to proband-only or duo testing (27.6%).

Data from this study was previously presented at the American Society of Human Genetics (ASHG) 2022 Annual meeting.

About GeneDx
GeneDx (Nasdaq: WGS) delivers personalized and actionable health insights to inform diagnosis, direct treatment and improve drug discovery. The company is uniquely positioned to accelerate the use of genomic and large-scale clinical information to enable precision medicine as the standard of care. GeneDx is at the forefront of transforming healthcare through its industry-leading exome and genome testing and interpretation, fueled by one of the world's largest, rare disease data sets. For more information, please visit www.genedx.com and connect with us on LinkedIn, Facebook, Twitter and Instagram.

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[1] Manickam K, McClain MR, Demmer LA, et al. Exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability: an evidence-based clinical guideline of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2021;23(11):2029-2037. doi: 10.1038/s41436-021-01242

[2] Smith L, Malinowski J, Ceulemans S, et al. Genetic testing and counseling for the unexplained epilepsies: An evidence-based practice guideline of the National Society of Genetic Counselors. J Genet Couns. 2022 Oct 24. Doi.org/10.1002/jgc4.1646