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Important New Joint Consensus Recommendation from the ACMG and ClinGen Provides Technical Standards for the Interpretation and Reporting of Constitutional Copy Number Variants

Bethesda, MD – November 6, 2019 | The American College of Medical Genetics and Genomics (ACMG) and the Clinical Genome Resource (ClinGen) have released an important new joint consensus recommendation that will guide the evaluation of constitutional copy number variants (CNVs), encourage consistency and transparency across clinical laboratories, and lead to improved quality of patient care.

The extensive and detailed recommendation, "Technical standards for the interpretation and reporting of constitutional copy number variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics (ACMG) and the Clinical Genome Resource (ClinGen)," is the result of a joint collaborative working group of ACMG and ClinGen, working together since 2015, to update the existing ACMG clinical laboratory practice standards for evaluating CNVs. Copy number analysis is recommended as a first-tier approach for the evaluation of individuals with neurodevelopmental disorders, such as intellectual disability, developmental delay and autism spectrum disorder, as well as for individuals with multiple congenital anomalies and for fetuses with ultrasound abnormalities.

"It is our hope that having standards that are widely available, up to date, and flexible enough to incorporate lessons learned from the ever-evolving clinical genomics knowledge base will help to reduce discordance in clinical classifications and will improve clinical care," said Christa Lese Martin, PhD, FACMG, the paper's senior author.

The recommendation represents a significant update from previous recommendations published in 2011 entitled "American College of Medical Genetics standards and guidelines for interpretation and reporting of postnatal constitutional copy number variants," and is intended to complement the widely cited 2015 paper for sequence variants, "Standards and Guidelines for the Interpretation of Sequence Variants: A Joint Consensus Recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology."

The updated technical standards include several major changes from the previous document. The first major change is using the same five-tier system used in sequence variant classification: pathogenic, likely pathogenic, uncertain significance, likely benign, and benign. The previous standards recommended utilizing "likely pathogenic" and "likely benign" as sub-categories under "uncertain significance" (essentially a 3-tier system). Harmonizing copy number and sequence variant terminology will become increasingly important as the identification and classification of both types of variants within a single platform becomes more commonplace.

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The second major change encourages laboratories to uncouple the classification of the variant from the clinical significance for the patient. While the patient's phenotype may be an important piece of evidence to consider when determining the classification of the variant, it should not override other evidence for or against the pathogenicity of the variant, and it should not be used to justify different classifications of the same variant in different individuals. For example, loss of function variants in a particular gene are known to cause hearing loss; there is enough evidence to warrant calling deletions of this gene pathogenic. A deletion of this gene in an individual not reported to have hearing loss should not be called "uncertain significance" solely because hearing loss was not their reason for referral; this could represent an incidental finding with potential implications for the individual's future health, or a cause for a phenotype that was not reported. The practice of changing the variant classification based on whether it explained the stated reason for referral has the potential to result in both inter- and intra-laboratory variant classification discrepancies; this change is intended to help reduce this issue.

The most substantial change is the incorporation of points-based scoring metrics to systematically guide laboratories through the classification of copy number losses and gains. In this scoring system, the various types of evidence considered when evaluating CNVs are awarded points based on their relative strengths, with positive point values for evidence for pathogenicity and negative point values for evidence against pathogenicity. At the end of the evaluation, the sum of all accumulated points leads to a suggested classification. "The scoring metrics are intended to be a guide to provide more structure and transparency to the CNV evaluation," said Erin Rooney Riggs, MS, CGC, the paper's lead author. "We have developed this type of quantitative metric for other types of curation within ClinGen which are being used successfully to increase consistency in data interpretation. With education and experience, we anticipate that the use of these metrics, as well as the other recommendations in these updated technical standards, will lead to increased consistency in constitutional CNV classification."

The recommendation states, "Although these standards attempt to comprehensively incorporate commonly available resources and processes used in CNV classification and interpretation, it is important to recognize that no singular algorithm will be applicable in all potential scenarios. The semi-quantitative scoring framework is meant to serve as a guide. Professional judgment should always be used when evaluating the evidence surrounding a particular genomic variant and assigning a classification."

The working group and authors on the new joint consensus recommendations include: Erin Rooney Riggs, MS, CGC; Erica F. Andersen, PhD; Athena M. Cherry, PhD; Sibel Kantarci, PhD; Hutton Kearney, PhD; Ankita Patel, PhD; Gordana Raca, MD, PhD; Deborah I. Ritter, PhD; Sarah T. South, PhD; Erik C. Thorland, PhD; Daniel Pineda-Alvarez, MD; Swaroop Aradhya, PhD and Christa Lese Martin, PhD.

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About the American College of Medical Genetics and Genomics (ACMG) and ACMG Foundation for Genetic and Genomic Medicine

Founded in 1991, the American College of Medical Genetics and Genomics (ACMG) is the only nationally recognized medical society dedicated to improving health through the clinical practice of medical genetics and genomics and the only medical specialty society in the US that represents the full spectrum of medical genetics disciplines in a single organization. The ACMG is the largest membership organization specifically for medical geneticists, providing education, resources and a voice for more than 2,300 clinical and laboratory geneticists, genetic counselors and other healthcare professionals, nearly 80% of whom are board certified in the medical genetics specialties. ACMG's mission is to improve health through the clinical and laboratory practice of medical genetics as well as through advocacy, education and clinical research, and to guide the safe and effective integration of genetics and genomics into all of medicine and healthcare, resulting in improved personal and public health. Four overarching strategies guide ACMG's work: 1) to reinforce and expand ACMG's position as the leader and prominent authority in the field of medical genetics and genomics, including clinical research, while educating the medical community on the significant role that genetics and genomics will continue to play in understanding, preventing, treating and curing disease; 2) to secure and expand the professional workforce for medical genetics and genomics; 3) to advocate for the specialty; and 4) to provide best-in-class education to members and nonmembers. *Genetics in Medicine*, published monthly, is the official ACMG peer-reviewed journal. ACMG's website (www.acmg.net) offers resources including policy statements, practice guidelines, educational programs and a 'Find a Genetic Service' tool. The educational and public health programs of the ACMG are dependent upon charitable gifts from corporations, foundations and individuals through the ACMG Foundation for Genetic and Genomic Medicine.

About the Clinical Genome Resource

The Clinical Genome Resource (ClinGen) is a National Institutes of Health (NIH)-funded resource dedicated to building an authoritative central resource that defines the clinical relevance of genes and variants for use in precision medicine and research. Since 2012, ClinGen has worked to facilitate responsible genomic and phenotypic data sharing between clinicians, clinical laboratories, researchers, and patients; to develop and implement standards to support clinical annotation and interpretation of genes and variants; to enhance and accelerate expert review of the clinical relevance of genes and variants; and to disseminate and integrate ClinGen knowledge and resources to the broader community. ClinGen is primarily funded by the National Human Genome Research Institute (NHGRI) through the following three grants: U41HG006834, U41HG009649, and U41HG009650.

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