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ACMG NEWS

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ACMG Issues New Joint Guidelines for Determining Disease-Causing Potential of DNA Sequence Variations

Bethesda, MD – March 5, 2015 – In an effort to standardize interpretation and reporting of genomic test results, the American College of Medical Genetics and Genomics (ACMG), together with colleagues from the Association for Molecular Pathology and the College of American Pathologists, has developed an evidence-based gene variant classification system and accompanying standard terminology.

The new system, published online ahead of print in ACMG's flagship journal, *Genetics in Medicine*, is designed to assist genetic testing laboratories and clinical geneticists in the critical task of assigning the disease-causing potential to the many different genetic variants that individuals have in their DNA.

"These updated guidelines provide a systematic and sound way to classify genomic variants so that when Lab A on the east coast and Lab B on the west coast are reporting results, they are using the same method to classify that variant," said Sue Richards, Ph.D., a medical director of the Knight Diagnostic Laboratories, and Professor of Molecular and Medical Genetics at Oregon Health & Science University, Portland, OR. and chair of the workgroup that issued the guidelines. To develop the guidelines the multi-disciplinary workgroup sought input from the clinical genetics community through surveys and workshops at professional society meetings. The result is a consensus document that reflects that input. "

"In the past, standard terms such as 'pathogenic' and a consistent strategy for classifying variants have been lacking," Richards said, "leading to wide variation in how laboratories classify individual differences in DNA sequence. Each person carries many thousands of these DNA variants, but determining which of these are causative for disease is a difficult task that requires an abundance of scientific evidence."

"Navigating the complexity of genetic evidence and how to weigh the strength of that evidence is challenging for laboratories and this guidance will help provide a consistent framework for that process," said Heidi Rehm, Ph.D., Chief Laboratory Director at Partners Laboratory for Molecular Medicine and Associate Professor of Pathology, Brigham & Women's Hospital and Harvard Medical School, Boston, Mass., and workgroup co-chair. "Although these guidelines were targeted to clinical laboratories, it is our hope that the same consistent approaches will be

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applied in the research setting and help improve the quality of published literature and the genetic claims being made."

“Recently, clinical laboratories have more broadly begun sharing their variant interpretations in the public domain through ClinVar, a database that aggregates information about genetic sequence variation and its relationship to human health and human disease, allowing differences of interpretation to be identified. Through this process, laboratories are employing the ACMG guidelines as a best standard in resolving any differences in variant interpretation,” said Rehm.

Because genomics is a developing field of research, standards of evidence are also evolving over time and will continue to evolve. Many genetic changes are what’s termed “variants of uncertain significance,” (VUS), which simply means that not enough is known about them to be able to state whether they cause health problems or not. Under the new guidelines, a variant of uncertain significance (VUS) should not be used in clinical decision-making.

The guidelines provide five standard classifications: “pathogenic,” “likely pathogenic,” “uncertain significance,” “likely benign,” and “benign,” along with standard definitions for each term. These new standards may place more variants in the VUS category, Richards said, because there is not enough scientific evidence to state with confidence that they do or do not cause disease.

The workgroup stresses that physicians should combine genomic results with other evidence of disease whenever possible. “Likely pathogenic” results provide enough evidence that a physician can act on it when combined with, for example, prenatal ultrasound, enzyme assays, physical findings or imaging studies.

It is important to note that these new guidelines cover only genetic variants that are inherited, not those genetic changes that arise in a specific cell within a tumor. Neither do the guidelines cover genetic changes that may contribute to complex diseases such as diabetes or heart disease. Guidelines for the interpretation of complex disease traits remain under study.

The ACMG also strongly recommends that clinical molecular genetic testing be performed in a CLIA-approved laboratory with results interpreted by a board-certified clinical molecular geneticist or molecular genetic pathologist or equivalent.

Detailed information about the new guidelines, "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", along with a comprehensive list of resources for clinical practitioners, is available at the *Genetics in Medicine* website:
http://www.nature.com/gim/journal/vaop/ncurrent/index.html

About the ACMG and ACMG Foundation

Founded in 1991, the American College of Medical Genetics and Genomics (www.acmg.net) advances the practice of medical genetics and genomics by providing education, resources and a voice for more than 1750 biochemical, clinical, cytogenetic, medical and molecular geneticists, genetic counselors and other healthcare professionals, nearly 80% of whom are board certified in the medical genetics specialties. ACMG is the only nationally recognized medical organization dedicated to improving health through the practice of medical genetics and genomics. The College's mission includes the following goals: 1) to define and promote excellence in the practice of medical genetics and genomics and to facilitate the integration of new research discoveries into medical practice; 2) to provide medical genetics and genomics education to fellow professionals, other healthcare providers, and the public; 3) to improve access to medical genetics and genomics services and to promote their integration into all of medicine; and 4) to serve as advocates for providers of medical genetics and genomics services and their patients. *Genetics in Medicine*, published monthly, is the official ACMG peer-reviewed journal. ACMG's website (www.acmg.net) offers a variety of resources including Policy Statements, Practice Guidelines, Educational Resources, and a Find a Geneticist tool. The educational and public health programs of the American College of Medical Genetics are dependent upon charitable gifts from corporations, foundations, and individuals through the ACMG Foundation for Genetic and Genomic Medicine (www.acmgfoundation.org.)

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