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The American College of Medical Genetics and Genomics (ACMG) Releases Highly Anticipated Evidence-Based Clinical Guideline for Phenylalanine Hydroxylase Deficiency

BETHESDA, MD – December 4, 2024 | The American College of Medical Genetics and Genomics has just published its highly anticipated Evidence-Based Clinical Guideline (EBG): "Phenylalanine Hydroxylase (PAH) Deficiency Diagnosis and Management: A 2023 Evidence-Based Clinical Guideline of the American College of Medical Genetics and Genomics (ACMG)," in its official journal, *Genetics in Medicine.*

Evidence-Based Clinical Guidelines are extremely important in healthcare because they help provide a framework for caring for an affected patient and can improve shared decision-making. The relevant body of scientific evidence is systematically reviewed and synthesized to form a pillar from which expertise and patient values are applied to guide the recommendation development process. This comprehensive EBG comes on the heels of ACMG's 2023 Systematic Evidence-Based Review (SER) on the treatment of phenylalanine hydroxylase (PAH) deficiency, encompassing phenylketonuria (PKU) and hyperphenylalaninemia (hyperPhe).

Senior author Jerry Vockley, MD, PhD, FACMG explained the importance of this new ACMG EBG, "The new guideline for treatment of phenylalanine hydroxylase deficiency, previously referred to as PKU, is a milestone in synthesizing our understanding of the disease. Many uncertainties in clinical practice from the retired guideline are now clearer, providing the opportunity for better care for patients. Specifically, the recognition of new data supporting that blood phenylalanine should be kept below 360 µmol/L (micromolar) lifelong provides the necessary support for use of modern pharmacotherapeutics across the age span of patients."

There were several topics covered in a 2014 ACMG practice guideline titled "Phenylalanine Hydroxylase Deficiency: Diagnosis and Management" (but developed using a different EBG methodology) that were deemed to have inadequate evidence or required additional analyses, and thus were reassessed in the 2023 SER and addressed in this recently released EBG. Key recommendations from the 2014 ACMG guideline that were not supported by strong evidence but are strongly

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supported in this new ACMG EBG include (1) treatment for PAH deficiency should be lifelong for individuals with untreated phenylalanine (Phe) levels >360 µmol/L, (2) individuals with lifelong Phe levels <360 µmol/L have better intellectual outcomes than those who do not, (3) achieving Phe levels <360 µmol/L prior to conception is strongly recommended to prevent pregnancy complications and negative outcomes for the offspring, and (4) genetic testing for PAH variants is recommended at birth to confirm diagnosis and guide therapy.

The new ACMG Evidence-Based Clinical Guideline also includes detailed sections on Implementation Considerations, Research Priorities, and Economic Considerations. It states, "The economic burden of PAH deficiency on healthcare systems underscores the importance of cost-effectiveness analyses and evidence-based decision making in determining coverage policies and reimbursement structures. By evaluating the long-term benefits and cost savings associated with early intervention and comprehensive management of PAH deficiency, policymakers can make informed decisions regarding healthcare coverage that optimize health outcomes and resource allocation."

According to MedlinePlus, PKU occurs in about 1 in 25,000 newborns. ACMG President Susan Klugman, MD, FACMG, FACOG said, "Phenylketonuria is a prototypic disorder for many aspects of genetics and medicine in general. Its history is significant as it was the first genetic disorder to be universally screened for in newborns and is considered one of the first known treatable genetic disorders. It is therefore appropriate that phenylalanine hydroxylase (PAH) deficiency, including PKU and hyperphenylalaninemia (hyperPhe), is one of the first topics addressed by ACMG's SER/EBG team. The guideline discusses the diagnosis and management of PAH deficiency from the newborn period to adulthood and including pregnancy. It is humbling to realize that PKU management could be considered as the start of precision medicine."

Lead Author Wendy E. Smith, MD, FACMG said, "It is exciting to have continually improving evidence to support care guidelines for a rare diagnosis like PAH deficiency. This is a testament to the dedication of the entire community of providers, patients and families to continually strive to improve treatment options and outcomes."

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About the American College of Medical Genetics and Genomics (ACMG) and ACMG Foundation

Founded in 1991, the American College of Medical Genetics and Genomics (ACMG) is a prominent authority in the field of medical genetics and genomics and the only nationally recognized medical professional organization solely dedicated to improving health through the practice of medical genetics and genomics. The only medical specialty society in the US that represents the full spectrum of medical genetics disciplines in a single organization, the ACMG provides education, resources and a voice for more than 2,600 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. *Genetics in Medicine* and the new *Genetics in Medicine Open,* a gold open access journal, are the official ACMG journals. ACMG's website, www.acmg.net, offers resources including policy statements, practice guidelines, and educational programs. The ACMG Foundation for Genetic and Genomic Medicine works to advance ACMG educational and public health programs through charitable gifts from corporations, foundations and individuals.

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