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NEWS RELEASE

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Exome Sequencing Provides New Approach to Diagnosis of Rare Genetic Disorders

New Genetic Test Leads to Life-Saving Treatment for One Little Boy, Reports *Genetics in Medicin*e

PHILADELPHIA, Pennsylvania – December 20, 2010 | A genetic testing approach called exome sequencing—which provides a clinically practical alternative to whole-genome sequencing—led to correct diagnosis and life-saving treatment in a child with a previously unknown genetic disease, reports an upcoming paper in Genetics in Medicine, the official peer-reviewed journal of The American College of Medical Genetics (ACMG). The journal is published by Lippincott Williams & Wilkins, a part of Wolters Kluwer Health.

"We are now entering an era in which comprehensive genomic analysis at the nucleotide level, such as whole-exome sequencing, has been added to the clinician's armamentarium," write Howard J. Jacob, Ph.D., and colleagues of the Medical College of Wisconsin, Milwaukee, in a commentary accompanying the new clinical report. "Our view from the bedside was that exome sequencing enabled us to offer a treatment based on a diagnosis rooted in natural disease history and laboratory science." Dr. Jacob is Director of the Human and Molecular Genetics Center at MCW.

Exome Sequencing Allows Diagnosis of Mysterious Genetic Disorder

Elizabeth A. Worthey, Ph.D., and Alan D. Mayer, Ph.D., led an interdisciplinary team investigating a serious and mysterious illness in a young boy. Beginning at age 15 months, the child developed an "unusually aggressive" form of inflammatory bowel disease that did not respond to the usual treatments.

Testing showed numerous abnormalities of the child's immune system, but none that pointed to any specific diagnosis. "Over a 3-year period, there were more than 100 surgical procedures, clinical consultations with physicians from around the world, innumerable informal discussions, weekly clinical care meetings, and informal e-mail consultations with world-leading experts," the authors write. "Despite these measures, we enjoyed little strategic success."

Finally, they tried a new approach: whole-exome sequencing. As an alternative to sequencing of all of an individual's genes (genome), exome sequencing focuses on the protein-coding region (exome). This limited range of target genes provides a feasible approach to identifying the gene responsible for an unknown disease.

Of more than 16,000 gene variants identified by exome sequencing, about 1,500 were previously unknown. Through a process of elimination, medical geneticists identified the most likely culprit: a mutation of the gene XIAP, which plays a critical role in the inflammatory process and programmed cell death (apoptosis).

Other XIAP mutations have been linked to a rare but potentially fatal blood disease called hemophagocytic lymphohistiocytosis (HLH)—which can be successfully treated by bone marrow transplantation. Because the doctors considered their patient to be at high risk of developing HLH, they performed a hematopoietic progenitor cell transplant using unrelated donor cord blood as the blood stem cell source. Within a few weeks, the donor cells engrafted, providing the patient with normally functioning XIAP genes.

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After recovering from the transplant procedure, the child was at last able to eat and drink normally, with no return of bowel disease. Doctors are confident that the transplant will prevent HLH—and hopeful that it will keep his inflammatory bowel disease from returning as well.

The results demonstrate the power of exome sequencing to make diagnoses that would be practically impossible using conventional genetic tests. Although exome sequencing is very expensive, the cost is decreasing rapidly, while the knowledge needed to interpret the results continues to increase.

"The tools available to make this diagnosis have evolved so rapidly that they were not available when the child first presented 4 years ago," Dr. Jacob and colleagues write. They believe that, in the not-too-distant future, exome or even genome sequencing may even replace current single-gene test approaches. The authors emphasize that such approaches raise a host of new ethical considerations, including the need for careful informed consent.

Based on lessons learned from their experience, the team at the Human and Molecular Genetics Center are developing new strategies and policies to guide their approach to similar cases in the future. Dr. Jacob and co-authors conclude, "We are confident that genomic sequencing will have a growing role in establishing the correct diagnosis for patients and, most importantly, improving outcomes."

Note to reporters: Interviews with the lead authors available upon request by contacting Kathy Beal, Public Relations Director for the ACMG: phone 301-238-4582 or e-mail kbeal@acmg.net

About Genetics in Medicine
Genetics in Medicine (www.geneticsinmedicine.org) is the official peer-reviewed journal of The American College of Medical Genetics. The journal is published by Lippincott Williams & Wilkins, a part of Wolters Kluwer Health, a leading provider of information and business intelligence for students, professionals, and institutions in medicine, nursing, allied health, pharmacy and the pharmaceutical industry.

About the American College of Medical Genetics
Founded in 1991, the ACMG (www.acmg.net) provides education, resources and a voice for the medical genetics profession. To make genetic services available to and improve the health of the public, the ACMG promotes the development and implementation of methods to diagnose, treat and prevent genetic disease. Members include biochemical, clinical, cytogenetic, medical and molecular geneticists, genetic counselors, and other health care professionals committed to the practice of medical genetics. Genetics in Medicine, published monthly, is the official journal of the ACMG.

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