ACMG releases report on incidental findings in clinical exome and genome sequencing

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The American College of Medical Genetics and Genomics (ACMG) released the widely-anticipated "ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing" report at its 2013 Annual Clinical Genetics Meeting today in Phoenix. The ACMG Annual Clinical Genetics Meeting is one of the largest gatherings of medical and health professionals in genetics in the world.

As exome and genome sequencing become more commonly used in medical care, doctors will increasingly be able to learn about genetic changes that increase an individual's risk for developing an unrelated disease. In the past, these incidental genetic findings (unrelated to the condition for which the patient was tested) were seldom provided to the patient.

The ACMG has now created a set of recommendations addressing incidental findings and a minimum list of conditions, genes, and variants that are recommended to be returned whenever clinical sequencing is performed. The ACMG now recommends that for the conditions on the list, the laboratory should return the incidental findings to the doctor ordering the sequencing, and those doctors should manage this information with the patient in the context of that patient's clinical presentation and family history.

Incidental, or secondary, findings, are health-related interpretations of a patient's genetic code that are unrelated to the primary reason for

ordering the testing. For example, if an exome or genome sequence were ordered to help diagnose a cardiac condition, there would exist the possibility of finding a different gene that indicated a predisposition for cancer. If the cancer risk were reported to the ordering clinician as an incidental finding, the clinician and patient could explore whether to increase medical surveillance in a way that could catch a cancer earlier and reduce mortality in that patient.

The extensive 27-page report was developed through a year-long consensus process by a Working Group comprised of medical and laboratory geneticists from leading institutions and outside reviewers. The process produced recommendations that were ultimately reviewed and approved by the ACMG Board of Directors, which is comprised of board-certified clinical and laboratory medical genetics healthcare professionals. The report includes detailed recommendations as well as the background and rationale for these recommendations.

Dr. Wayne Grody, FACMG, president of the ACMG said, "This Report is tremendously important because it begins to standardize the process by which the comprehensive power of genomic sequencing can be tailored to optimally benefit patients when clinically important findings not directly related to the primary reason for ordering the test are revealed. We recommend that labs performing clinical exome and genome sequencing recognize and report significant mutations for the serious diseases specified in the Report."

The ACMG report generated a short list of well-understood conditions/genes/variants for which the possibility exists of medical intervention with high benefit to those carrying the variants if they are detected presymptomatically.

Robert C. Green, MD, FACMG, a medical geneticist at Brigham and Women's Hospital and Harvard Medical School, co-chaired the Working

Group and was lead author of the Report. "The genome has an extraordinary potential for providing health-related information about both rare and common conditions, but it has been difficult to draw a line and suggest that one set of findings should be part of the medical report and another set should not," said Dr. Green. "In these recommendations, despite a scarcity of clear scientific evidence, we have identified a small number of conditions, genes and variants through consensus that are likely to have a positive impact upon the health of patients and their families if identified incidentally."

Leslie G. Biesecker, MD, FACMG, co-chair of the Working Group, chief of the Genetic Disease Research Branch at the National Human Genome Research Institute said, "The implications of the ACMG recommendations are that as clinical sequencing becomes more widespread, a small percentage of families that are sequenced, perhaps not more than 1-2%, will learn unexpected but potentially life-saving information about an illness they may have never suspected they were at risk for. Thus, these recommendations are an innovative approach to addressing one of the most difficult problems in genomic medicine and to help transition us toward new models of delivering genomic information."

The report concludes: "In summary, the Working Group has recommended that when a report is issued for clinically indicated exome and genome sequencing, a minimum list of conditions, genes and variants should be routinely evaluated and reported to the ordering clinician who can place them into the context of that patient's medical and family history, physical examination and other laboratory testing." It further stated, "The Working Group recognizes that this list should, and will, evolve as further empirical data are collected on the actual penetrance of these variants, and on the health benefits and costs that might follow from their disclosure as incidental findings."

More information: The Recommendations will be published at www.acmg.net and in a forthcoming edition of *Genetics in Medicine*, the peer-reviewed journal of the ACMG.