



American College of Medical Genetics

Medical Genetics: Translating Genes Into Health®

September 21, 2011

Amy Patterson, M.D.
Associate Director of Science Policy
Office of Biotechnology Activities
National Institutes of Health
6705 Rockledge Dr., Suite 750
Bethesda, MD 20892

Dear Dr. Patterson,

The American College of Medical Genetics (ACMG) welcomes the opportunity to comment on the Genetic Testing Registry's (GTR) assessment of time and cost burdens to laboratories that voluntarily submit data to the GTR. The ACMG is a medical specialty association whose members include clinical geneticists and clinical genetics laboratory directors in the United States who are board-certified in the specialty of medical genetics. Included in the mission of ACMG are: to promote and provide medical genetics education; to increase access to medical genetic services and integrate genetics into patient care; to advocate for and represent providers of medical genetics services; and to define and promote excellence in medical genetics practice and the integration of translational research into practice.

The ACMG remains concerned that the GTR has the potential to make data available to the public that is inaccurate and that the work associated with providing data is considerably greater than that which is described in the document on which comment was solicited.

A significant number of laboratories offer testing in a large number of genes. However, testing in a gene doesn't correlate with the number of tests that a laboratory might offer. Many tests vary by intended uses and it is true that the parameters of clinical validity and utility will vary with intended use. As such, there are probably many more tests being offered than is predicted. We would expect that many labs could be expected to provide data on considerably more than 100 targeted tests. Further, we anticipate the availability of a number of multigene panels that will be tested by Next Generation Sequencing methods to increase this year and that the transition to NGS for many of the nonspecific phenotypes such as autism spectrum disorders and intellectual disability to transition from oligonucleotide/SNP arrays to NGS which didn't seem readily applicable to

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the types of data being solicited nor the role of bioinformatics in this type of laboratory work. There are also situations of laboratory test use that are considered more in the practice of medicine than they are as classical laboratory tests. This becomes very apparent again in the area of calculating clinical validity and utility. Patients don't necessarily present with a classical set of phenotypes that could be considered pathognomonic of a specific clinical diagnosis for which a consistent determination of clinical validity and utility could be defined. Unfortunately, a significant number of patients don't present with classical phenotypes. As one moves through a differential diagnosis list for a particular patient, the clinical sensitivity of a test will likely be dropping as one moves to less and less likely diagnoses. This feature of genetic test performance could lead to information being made available to the public that is deceptive with regard to any one individual's clinical indications for testing. For instance, for a test related to identification of deletion associated with the deletion 22q syndrome, a patient presenting with classical DiGeorge syndrome could have a clinical sensitivity of 70% or so while testing a patient presenting with an isolated conotruncal abnormality such as a tetralogy of Fallot may only have a clinical sensitivity of detection of deletion 22q of 1-3%.

Given the inherent variability in the clinical aspects of test performance (e.g., clinical sensitivity and specificity as well as predictive values) it will be critical that the information being provided through a resource such as the GTR be acknowledged as being generalized so those seeking information about genetic tests don't expect that what is provided is directly applicable to their situation.

ACMG remains willing to provide any technical and/or clinical assistance to the GTR developers.

Sincerely,

A handwritten signature in black ink that reads "Michael S. Watson". The signature is written in a cursive style and is positioned above the typed name.

Michael S. Watson, PhD, FACMG
Executive Director