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Medical Genetics: Translating Genes Into Health®

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Kathy Hudson, PhD
Chief of Staff
Office of the Director
National Institutes of Health
1 Center Dr. Room #103
Bethesda, MD 20892

Dear Kathy,

The American College of Medical Genetics (ACMG) is pleased to have this opportunity to comment on the NIH and FDA plans to develop a *Genetic Test Registry*. The American College of Medical Genetics represents more than 1500 biochemical, clinical, cytogenetic, medical and molecular geneticists, genetic counselors and other health care professionals committed to the practice of medical genetics in the United States, most of whom are Board certified by the only board of the American Board of Medical Specialties (ABMS) that is specific to this area of medical practice, the American Board of Medical Genetics (ABMG).

The ACMG engages in activities that advance the practice of medical genetics, ranging from promulgating laboratory and practice guidelines to advocating for fair health policies; increasing access to genetic services and improving the public's health; and promoting development and implementation of methods to diagnose, treat and prevent genetic disease. We have given considerable thought to the plans of NIH and FDA to develop and implement a "genetic test registry". As such, we offer the following comments for your consideration.

The ACMG recognizes that there are significant problems with a relatively small number of genetic tests. However, we are very concerned any time that genetics is separated from and treated differently than other specialties of medicine. We've spent many decades trying to minimize perceptions of genetic exceptionalism, only to find that it is now being imposed through federal involvement in the clinical practice of genetic medicine. While we appreciate the need to provide useful information to providers and the public on genetic tests, the potential for programs such the Genetic Test Registry (GTR) to cause more problems than are fixed is significant.

***General Comments***

ACMG acknowledges that there is a relatively small subset of "genetic tests" for which there are justifiable concerns about test quality, safety, and



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effectiveness. However, we are not convinced that the GTR as currently described is the most effective way to address those concerns given the potential roles of the Federal Trade Commission and States Attorney's General in protecting the public from consumer fraud. Further, we have concerns about the potential for harms to result from the type of information proposed for the GTR for many genetic tests and how it is used. Lastly, it is concerning that the GTR is controlled by two federal agencies, one of which has a regulatory role, which sets up an adversarial relationship with the provider community. Because the program has significant potential to negatively impact the practice of medicine and medical genetics as well as the public, it would have been preferable to have developed this program as a public – private partnership.

ACMG is concerned about the overly broad definition of genetic tests that is used for the GTR. Overly broad definitions of genetic tests have contributed to the long-standing problems in developing viable oversight of the tests that really raise concerns. While there may be analytical similarity among the many uses of molecular diagnostics, the pre- and post-analytic issues attendant to heritable disease trait testing are very different from those for acquired somatic diseases. Genetic counseling isn't an issue for traits that aren't inherited. Somatic disease genetic tests for cancer and leukemia have been developing in relatively well controlled environments for over 30 years that are very different from those of heritable disease tests. The National Cancer Cooperative Study Group system that includes groups such as the Children's Oncology Group, Cancer and Leukemia Group B, and others has closely associated the clinical and research community with the regulatory and reimbursement sectors and managed to avoid many of the issues facing heritable disease genetics. While one could argue that better information on any laboratory test is valuable to providers and the public, it is important to consider what is unique about genetic tests that justifies separating them from other areas of laboratory medicine.

Many of our concerns stem from issues associated with rare and orphan diseases. The overwhelming majority of heritable disease genetic tests are for rare and orphan diseases for which the evidence bases and the statistical power of classical calculations of test performance characteristics are weak. Of particular concern is the bias that is inherent in the ascertainment of patients in clinical settings. Unless the test has been offered in newborn screening and diagnostic and follow-up data collected from patients identified by screening, our knowledge of the genetic disease will be limited.

The GTR announcement suggests that the performance characteristics of all genetic tests should be formally determined. There is a point, however, at which this information becomes part of the practice of medicine. Formal calculations of clinical validity and utility are based on specific intended uses of tests and even with a single test, clinical validity and utility will vary with the presentation of the patient. The more pathognomonic features of a condition that are present in a patient the higher apparent validity and utility will be. This doesn't preclude using a test in a patient with some, but not all, features of a condition as one moves through a differential diagnosis. It would be concerning if the public used the generic information in the GTR to second guess clinical decisions or to forego them. Rare Mendelian diseases will have seemingly weak test

performance characteristics, despite the strength of the genetic factors. Laboratories will only have limited data of their own to document the clinical performance of their tests so all will have to develop the same evidence base to document many of the features of a test. It would be more useful if some of the features of a genetic test were developed centrally with individual laboratories supplementing that with information unique to their test. In fact, general information about the scientific validity of a test could be more useful to the public in understanding whether a test has clinical validity.

It is our understanding that the former "GeneTests" web site will become the backbone of the proposed registry. With the transfer of control of the former GeneTests laboratory testing web site listings to this program, NIH acquires a product with a widely respected 'label'. It is concerning that the data proposed to be in the registry will be voluntarily deposited without external review. ACMG is concerned that poorly vetted information could misinform providers and place patients at risk. Registry information provided through NIH and FDA will be presumed to be accurate and actionable. However, the disclaimers required for information that has not been independently reviewed seem likely to lead to confusion among users.

There are significant differences between the means by which drugs for orphan diseases are regulated *vs*. the way devices for rare and orphan disease testing are regulated. Developing useful information for the range of users described in the program announcement will impose a significant unfunded mandate on clinical laboratories, whether the program is voluntary or not. While NIH may have funded some of the studies through which the initial validity of tests was established, they long ago required that clinical testing not be funded through grants. Support for well organized clinical investigation involving genetic diseases has been poor. Hence, evidence bases have been local and their statistical power has been weak. A program that allows data to be brought together to inform test performance more broadly could be more useful than one that provides information based on weak local evidence.

In summary, ACMG is concerned that information that hasn't been independently reviewed that is made available to the public and providers has the potential to cause harm. We welcome the opportunity to work with NIH to develop a program that ensures the accuracy of the information being promulgated. It could be initiated by focusing on the genetic tests for which concerns have been raised. Rare disease diagnostic tests require a different approach. General information about how one develops test performance data for rare diseases and the allowances that are made with regard to test performance data should be developed before individual test data is made widely available to avoid misunderstandings by patients and payers in order to ensure that access to tests is maintained.

We appreciate the opportunity to comment on the proposal to develop a Genetic Test Registry. We are available to this evolving program for additional information if needed and look forward to working with you in the future.

Sincerely,

Bruce Korf, MD, PhD
President

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