Congressional action needed to optimize regulation of genomic tests

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The latest generation of genomic testing offers a chance for significant improvements in patient care, disease prevention, and possibly even the cost-effectiveness of healthcare. A new report recommends that Congress act to incentivize the development of the massive data systems that doctors and regulators will need to make these tests safe and effective for patients.

A team of three leading researchers in law, bioethics, and medical genetics believes the solution lies in bolstering existing regulatory oversight with a systematic, ongoing program of postmarket data collection to continue studying tests after they are in use and resolve lingering questions about the health impact of as-yet-poorly-understood genetic variants.

The Special Report by Barbara J. Evans, Ph.D., J.D. of the University of Houston Law Center, and Wylie Burke, M.D., Ph.D. and Gail P. Jarvik, M.D., Ph.D, both of the University of Washington School of Medicine, appears ahead of print in the May 27 on-line edition of *New England Journal of Medicine*, the leading U.S. journal of original medical research and commentary.

The authors note that modern, genomic-scale tests can generate large numbers of data points for each tested patient, including numerous genetic variants—changes from the expected DNA sequence of an "average" genome.

A genetic variant is said to have clinical validity if its impact on human health is well understood, so that detecting the variant supplies useful information about the patient's health or predispositions to disease. One limit to genomic testing is that the science is still in an early stage of development and the clinical significance of most of the variants these tests detect is not yet known.

Jarvik notes that this "creates a risk that patients will base important medical decisions on diagnoses or predictions that later prove incomplete." For example, a genetic variant that has unknown significance at the time of the test may instead confer a high risk of breast cancer.

The U.S. Food and Drug Administration (FDA) has been grappling with how to regulate these tests. The FDA recently proposed to assess their safety and effectiveness by reviewing whether the test accurately detects a person's variants and whether the results have clinical validity. The FDA has suggested it might base its decisions about clinical validity on high-quality external genetic databases, such as those curated by the National Institutes of Health (NIH) ClinGen program and deposited in its ClinVar database and other FDA-recognized external databases.

Evans, Burke, and Jarvik argue the genomic data resources that will be necessary to assure patients the maximal benefits of genomic testing do not now exist and will have to be built.

"Whole-genome sequencing detects more than 3.5 million variants in a typical person, including 500,000 that are rare or novel. ClinVar, while it is an excellent data resource, currently only has about 77,000 unique genetic variants in it, and many of these are variants of unknown clinical significance," notes Burke.

The President's recent Precision Medicine Initiative proposes to develop

a database reflecting genetic and clinical data for one million volunteers, but even this will not be large enough. Figuring out the clinical impact of a novel gene variant can require data for tens or even hundreds of millions of people.

The researchers' Special Report explores what it will take to develop the needed data resources and recommends an approach—ongoing postmarketing surveillance—that the FDA successfully implemented to improve the safety of approved drugs after a series of serious safety incidents, including those with rofecoxib (Vioxx) during the past decade.

This approach would involve collecting data not just from research settings, as the ClinVar system was originally designed to do, but also from commercial clinical laboratories that administer genomic tests to large, diverse patient populations. The FDA's current medical device regulations—which date back almost 40 years—do not give the agency all the legal powers necessary to implement such a solution. Congress would need to authorize the development of new genomic data systems, as Congress did in 2007 for drugs.

The authors acknowledge that the needed genomic data systems will require significant investments that go beyond what federal funding agencies like the NIH can or should support.

"The United States has a long history, dating back 150 years, of incentivizing private investors to help build our major national infrastructures like the electric power grid and telecommunications network. We as a nation know how to do this," Evans notes.

Developing nationally scaled genomic data systems for patient safety, public health, and scientific advancement, they believe, is our nation's next big infrastructure challenge. The authors call for legislative reforms to enable public-private partnerships and direct private investment and to

enhance appropriate access to the crucial data resources, subject to careful regulatory oversight to protect genetic privacy and engender public trust.

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