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No Shortcuts on the Long Road to Evidence-Based Genomic Medicine

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Rapid advances in genomics

have led to a new era of precision medicine, resulting in a substantial increase in the number of genetic tests available for research and clinical practice. As of April 27, 2017, the Genetic Testing Registry,[1] maintained and updated by the National Institutes of Health, contained information on 49 521 tests conducted at 492 laboratories for 10 733 disease conditions involving 16 223 genes. These tests cover a wide variety of diseases, rare and common, for different types of applications such as diagnosis, treatment, and prevention.

For 2 decades, there have been ongoingdiscussions of the importance of a strong evidentiary foundation for genetic testing. Several advisory groups, including the Task Force on Genetic Testing[2] and the Secretary's Advisory Committee on Genetic Testing,[3] made a number of recommendations to strengthen the evidence base for genomic medicine. The key element of the discussion is the need to have answers to a number of scientific questions that are relevant to establishing the analytic validity of genomic tests (the ability of tests to be accurate), along with clinical validity (showing an association with disease end points)and clinical utility (showing effectiveness in improving health outcomes).[2]

> With the recent proliferation of directto-consumer genetic testing, the need for evidence in genomic medicine is more important than ever.

What Is the Status of the Evidence Base in Genomic Medicine?

Two recent systematic reviews clearly show an insufficient evidence base for largescale implementation of genomic medicine. Phillips et al[4] summarized findings of systematic reviews that evaluated the analyticand clinical validity and clinical utility of genomic tests as compared with alternative nongenetic tests. Of 21 systematic reviews published in 2010 through 2015,13 were cancer focused. All reviews identified potentially important clinical applications of genomics, but most had significant methodological weaknesses that

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precluded any conclusions about clinical utility. These limitations included moderate to substantial risk of bias, lack of assessment of strength of the evidence, and absence of quality assessment criteria. The authors concluded, “we found a very limited body of evidence about the effect of using genomic tests on health outcomes”[4]

Roberts et al[5] published a systematic review exam- iningthe current state ofthe field of implementation science in genomic medicine. In 2014, 283 published articles evaluated implementation of genomic medicine. Most studies described uptake of genomic tests or preferences for use by clinicians and patients. Key study design elements, such as the racial/ethnic composition of study populations, were underreported in studies. Few studies incorporated implementation science theoretical frameworks, sustainability measures, or capacitybuilding measures. Most studies focused on patient factors associated with implementation rather than macro-level factors (eg, health systems, policies, education, financing). Only a few studies attempted to develop and evaluate evidence-based strategies that can improve implementation of genomic medicine. The authors concluded that “the current knowledge base around implementation science to turn the promise of genomic medicine into reality is severely limited”[5]

Moving Forward: A New Evidence Framework?

In March 2017, the National Academies of Sciences, Engineering, and Medicine released a study report titled “An Evidence Framework for Genetic Testing.”[6] A special committee composed of a multidisciplinary group of experts examined the scientific literature to evaluate the evidence base for different types of genetic tests and “to develop a framework for decision making regarding the use of genetic tests in clinical care.”[6] The committee focused on clinical applications and utility of genetic tests and examined how evidence is generated, evaluated, and synthesized. The committee reviewed several available methods for assessing the analytic validity, clinical validity, and clinical utility of genetic tests. These included the Centers for Disease Control and Prevention Office of Public Health Genomics-sponsored ACCE (Analytic Validity, Clinical Validity, Clinical Utility, and Ethical, Legal, and Social Implications) framework[7] and the EGAPP (Evaluation of Genomic Applications in Practice and Prevention) Working Group methods.[8] The committee developed an updated evaluation process for decision making by policy makers and clinicians that incorporates elements from ACCE, EGAPP, and other evaluation methods.

The recommendations ofthe committee reaffirm and extend previous work by outlining 7 evaluation steps: (1) define genetic test scenarios on the basis ofthe clinical setting, the purpose ofthe test, the population, the outcomes of interest, and comparable alternative methods; (2) for each genetic test scenario, conduct an initial structured rapid assessment to determine whether the test should be used in practice or requires additional evaluation; (3) conduct or support evidence- based systematic reviews for genetic test scenarios that require additional evaluation; (4) conduct or support a structured decision process to produce clinical guidance for a genetic test scenario; (5) publicly share resulting decisions and justification about evaluated genetic test scenarios, and retain decisions in a repository; (6) implement timely review and revision of decisions on the basis of new data; and (7) identify evidence gaps to be addressed by research.

Evidence Evaluation Needs Data: No Shortcuts to Conducting Research Studies

Any system of evaluation of genomic medicine is based on data collected by research studies (eg, randomized clinical trials and appropriately conducted observational studies that minimize bias and confounding). However, only a limited amount of this type of research has been conducted; studies that are beyond basic science discoveries (ie, evaluation, implementation, and outcomes research) represent less than 2% of the total published literature in genomics.[9]

To be sure, an increasing number of applications in genomics can save lives and prevent disease today.[10] However, there are no shortcuts to fulfill the ultimate promise of genomics and precision medicine in improving health and preventing disease. Some approaches can accelerate this process, includingcollaboration, data sharing, public and clinician education, policy approaches, use of electronic health records, rapid reviews, and new models for a learning health system that integrates genomics with other evidence- based health services. With the recent proliferation of direct-to- consumer genetic testing, the need for evidence in genomic medicine is more important than ever. For genomic medicine to improve population health, rigorous evidence is needed to evaluate the analytic validity, clinical validity, and clinical utility of genetic tests and howto implement genomics in clinical settings.

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