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EDITORIAL

Why should genomic medicine become more evidence-based?

Muin J. Khoury · Linda A. Bradley

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In this issue of the Journal, Kumar gives an extensive historical account of the evidence-based medicine movement, and posits that modern medicine is rapidly moving from the current paradigm of "evidence-based medicine" towards the paradigm of "genomic medicine" in the 21st century (Kumar 2008). In this editorial, we elaborate on one angle of this transition, namely the necessity for genomic medicine to become more evidence-based. The premature introduction of technologies into healthcare settings could potentially overwhelm the health system financially, legally and ethically. In addition, the lack of coverage and reimbursement policies by governments and health insurers will lead to differential penetration of and access to technologies of unknown benefits, potentially exacerbating health disparities.

The promise of genomic medicine

More than 4 years after the completion of the Human Genome Project, there is palpable enthusiasm about the numerous recent genome discoveries using genome-wide platforms (Topol 2007), and the continued emergence of all the "omic" disciplines, such as proteomics, nutrigenomics and pharmacogenomics (Gupta and Lee 2007). Undoubtedly, these scientific breakthroughs will help unravel biological mechanisms behind drug interactions and nutritional, environmental and lifestyle exposures in the etiology and pathogenesis of numerous common diseases of public health significance (Burke and Psaty 2007). Many scientists are already seeing that these breakthroughs will lead to immediate or near term health applications. In 2006, Dr. Elias Zerhouni, Director of the National Institutes for Health boldly predicted that "comprehensive, genomics-based health care will become the norm, with individualized preventive medicine and early detection of illnesses (Zerhouni 2006)." In 2005, the introduction of cytochrome P450 testing to help providers prescribe selective serotonin reuptake inhibitors (SSRIs) in the treatment of adults with depression has announced the new era of pharmacogenomics worldwide (Amplichip 2007). In September 2007, after the online publication of the first complete sequence of an individual human being (Craig Venter), the researchers predicted that "we have developed a framework that can serve as a model for the development of the emerging field of en masse personalized genomics" (Levy et al. 2007).

Recently, we have seen the emergence of direct-to-consumer advertising for personalized genetic scans of one million or more genetic variants. This testing is based on array technologies developed as research tools for the genome-wide association studies that lead to discovery of genes related to the occurrence of common complex diseases. In fact, at least three companies are currently selling these research tools directly to the public for $1,000 or less (Harmon 2007). One of the websites asserts that this tool "can help you discover how your genes may affect your chances of developing various diseases and conditions, as well as traits such as athletic ability" (23andme 2007). Another claims that the test allows individuals to know their "genetic risk for 18 diseases based on current literature", to investigate the origins of their ancestors, or to compare genomes with friends and family (deCodeME 2007).

M. J. Khoury (✉) · L. A. Bradley
National Office of Public Health Genomics, Centers for Disease Control and Prevention, 4770 Buford Hwy, MailStop K89, Atlanta, GA 30341, USA
e-mail: muk1@cdc.gov

So what's wrong with this picture?

No one can dispute the scientific promise of genomic technologies. However, it is important that discoveries leading to specific testing applications in clinical or population health scenarios should be subjected to rigorous scientific evaluation, like any other scientific breakthroughs (Khoury et al. 2007). In a recent editorial Evans and Khoury (2007) discussed several reasons why genomic medicine has been slow to embrace the principles of evidence-based medicine. First, genetics has by and large focused on rare genetic diseases for which there are an inadequate number of individuals and families to study using randomized clinical trials or large observational studies. Second, genetics has focused on nondirective approaches to communicating information about genetic risks, mostly for highly penetrant conditions for which there may or may not be effective interventions. Third, the rapid advances in genomics makes difficult the conduct and update of evidence-based guidelines, and challenges traditional systematic review methods. Fourth, the concept of "clinical utility" in genetics has been variably defined and measured (Grosse et al. 2006). Overall clinical utility reflects the balance between benefits and harms, whether using the traditional focus on improved health outcomes for individual tested or considering other potential benefits for family members or information for the sake of information ("knowledge is power").

Although many applications look biologically promising, recent systematic reviews of the available evidence have been rather disappointing. For example, as part of an evidence-based review, researchers from Duke University reviewed the cumulated evidence regarding whether testing for CYP450 polymorphisms in patients with depression treated with selective serotonin reuptake inhibitors (SSRIs) leads to improved outcomes, and whether test results are useful in decision making (AHRQ 2007). The evidence showed that data on the association between CYP450 genotypes and the metabolism, effectiveness, and side effects of SSRIs in the treatment of depression were mostly derived from heterogeneous studies with small samples. They did not find data on whether CYP450 testing in adults entering SSRI treatment for depression leads to improved clinical outcomes. They also found limitations in the quality of evidence that need to be considered in designing future studies of the validity and utility of CYP450 testing in the treatment of depression with SSRIs (AHRQ 2007). These findings prompted the independent Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group to issue its recommendation of "insufficient evidence" for the integration of this test into routine practice, discouraging its use until further research can close the evidence gap (EGAPP 2007).

The recent availability of testing for one million genetic variants is an extension of some previously promoted genomic profiles [e.g., cardiogenomic or osteogenomic profiles (Haga et al. 2003)]. In 2006, a Government Accountability Office (GAO 2006) investigation of such practices in the United States found major errors, discrepancies and misleading information provided to consumers on web sites offering genomic profiles directly to consumers. Genetic variants with weak or modest effects (odds ratios from 1 to 1.5 that genome-wide association studies are finding for genetic variants associated with common diseases) have limited added value in the prediction and prevention of common diseases unless specific effective interventions can be offered based on such information (Haga et al. 2003). For example, Janssens et al. assessed genetic profiles for risk of type 2 diabetes and showed that weak genetic effects have probably little added value in predicting future disease compared to more conventional tools such as body mass index, family history and other factors (2005, 2006).

In the United States, the US Preventive Services Task Force (USPSTF 2007), a well established independent US body that develops evidence based practice guidelines for primary care, has examined only two genetic topics between 2001 and 2006. The first is *BRCA1* testing in breast and ovarian cancer (USPSTF 2005) and the second is screening for *HFE* mutations to identify individuals at risk for hereditary hemochromatosis in the general population (Whitlock et al. 2006). These two topics were chosen about 10 years after the genes for *BRCA1* and hemochromatosis were discovered in 1994 and 1996, respectively. For *BRCA1*, many years after such tests made their way into practice, the task force found sufficient evidence for a subset of women with the appropriate family history for referral to genetic counseling for decision-making about the possible use of the tests (USPSTF 2005). For *HFE* testing, the task force found sufficient evidence (among others, the uncertain natural history and low penetrance of *HFE* mutations) to recommend against screening in the general population (Whitlock et al. 2006). A major obstacle to the USPSTF decision-making for both *BRCA1* and *HFE* testing was impeded by the slow accumulation of scientific evidence on clinical utility for testing for these conditions.

The way forward

Undoubtedly, scientific progress will continue to occur rapidly in all areas of genomics and related fields, which will help shed light on the biologic processes of human diseases at the molecular, biochemical and physiological levels. We should not be prematurely judging the genomics enterprise as unlikely to lead to health benefits (Holtzman

2000; Buchanan et al. 2006; Chaufan 2007). Nevertheless, just because a scientific finding makes biological sense, does not necessarily imply that it has immediate and inherent value in clinical practice. We believe that genomic medicine must embrace principles of evidence-based medicine, which can only lead to an orderly transition from genomic research to the practice of genomic medicine. This leads to two immediate recommendations. First, we need more investment in translation research, not only discovery research. As described elsewhere (Khoury et al. 2007), there are four overlapping phases of translation research, from gene discovery to demonstration of health impact at the population level. Traditionally, such research has received much less support than discovery research both in genomics and other areas.

In addition, we need increased emphasis on continuous evaluation and synthesis of the evidence for genomic applications in practice based on systematic reviews and evaluative processes such as the Agency for Healthcare Research and Quality Evidence-based Practice Centers (AHRQ 2007) the EGAPP initiative (EGAPP 2007), the Cochrane collaboration (Cochrane 2007). While government agencies and the private sector spend considerable resources in sponsoring discovery research, they do not spend as much on translation research and spend even less on evidence-based reviews, which are a vital form of research. Evidence reviews are crucial in telling us "what we know and what we do not know" at any given point in time about the validity and utility of genomic applications in practice. This information will be crucial to various stakeholders such researchers, test developers, providers, patients, and policy makers.

We should not take shortcuts on the "translation highway" from genome discoveries to population health impact. Concomitant with the current explosion in genomics technologies, we now have a crucial window of opportunity for genomic medicine to embrace evidence-based medicine and use its tools to conduct appropriate research and evaluation of these technologies. We view the rapprochement of genomic medicine and evidence-based medicine as an essential first step to fulfill the promise of genomic medicine in the 21st century.

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