commentary

Evidence based medicine meets genomic medicine

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When asked to summarize a preacher's sermon on the subject of sin, a young man thought for a minute and said, "He's against it." Our attitude in the medical profession toward Evidence Based Medicine (EBM) typically demonstrates about the same level of nuance and complexity (we are for it!). After all, it is obvious that EBM is a force for good in our field and is what separates us from magicians, faith healers, and snake oil salesmen. But it is instructive to realize that it was only 35 years ago that the seminal book by Archie Cochrane, *Effectiveness and Efficiency: Random Reflections on Health Services* was published, igniting the EBM movement. Indeed, the term "Evidence Based Medicine" was not commonly used until the 1990s,[1,2] highlighting the surprising fact that the medical community has consciously and methodically embraced EBM for only a relatively short time.

Our particular field, medical genetics, has been even tardier in embracing the rigorous precepts of EBM, for reasons both sound and otherwise. But we are now entering a new era in which genome-based information will permeate every facet of health care and disease prevention, from cardiology to oncology and nutritional interventions. The prescription of medications for countless disorders may be guided by genetic information, and genomic profiles will increasingly be used to guide prevention strategies. In the midst of these changes it is critical that our field enthusiastically embrace EBM, to "sort the wheat from the chaff." In the United States, although several groups have occasionally addressed issues related to genetics and genomics (such as the US Preventive Services Task Force[3] and the Cochrane Collaboration[4]), the only sustained effort to address EBM in a genetic context is the Centers for Disease Control and Prevention's EGAPP initiative (Evaluation of Genomic Applications in Practice and Prevention; http://www.egappreviews.org/about.htm). EGAPP seeks to establish an independent, systematic, evidence-based process for assessing genetic tests and other applications of genomic technology as these procedures transition from research to clinical and public health practice. Several advisory committees to the government have encouraged this kind of initiative, including the Secretary's Advisory Committee on Genetics, Health, and Society.[5]

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It is in this light that we publish, in this issue of *Genetics in Medicine*, an EGAPP report[6] that focuses on evidence-based criteria for the application of emerging genetic data in the clinic setting, and the evidence review on which the EGAPP statement is based.[7] The reports focus on an area of active inquiry, press coverage, and frequent (perhaps overly) optimistic claims: pharmacogenomics (PGx). Specifically, they address whether genetic analysis of cytochrome P450 polymorphisms can be a useful tool to guide management of adults with depression who are treated with selective serotonin reuptake inhibitors (SSRIs). The EGAPP working group[6] and Thakur et al.[7] methodically scrutinize the current evidence and existing gaps behind this potential application of pharmacogenomics, and both find insufficient evidence to support the current use of CYP450 testing for adults beginning SSRI treatment for nonpsychotic depression.

These sober and timely analyses will be seen as disappointing to some, but should not necessarily be construed as invalidating the rationale behind pharmacogenomically guided prescription of SSRIs. Nor should they discourage future studies of other emerging topics in medical genetics. Rather, these reports offer vital information by simply telling us that PGx guidance of SSRI use in the treatment of depression is not yet ready for prime time. They offer added value by pointing to gaps in the evidence that require attention before such genomic applications in health care are embraced. Indeed, several other EGAPP reports addressing various topics (including genetic testing for colorectal cancer and the use of cardiogenomic profiles in the prediction and prevention of coronary artery disease, as well as other pharmacogenomic applications) are currently underway, and we look forward to their results.

It may well be that ongoing trials that examine outcomes of clinical utility and cost-effectiveness will eventually vindicate a PGx approach to the use of SSRIs and many other agents. But, as scientists, we must guard against the temptation to embrace new practices because they seem so "right" or simply because they are biologically plausible. The history of medicine is strewn with the corpses of good ideas (and trusting patients) because seemingly great ideas did not bear up under close scrutiny. Twenty years ago when one of us (J.E.) was a medical resident, the practice of extracranial-intracranial arterial bypass surgery was touted as an effective method for treating or preventing strokes in people with carotid artery atherosclerosis. After all, it seemed perfectly logical that bypassing an obstructed internal carotid artery could only benefit the patient. Hard data showed us otherwise, and this practice has been appropriately abandoned.[8] The broader lesson is important: theoretical underpinnings and laboratory-based rationales, even in support of a logical idea, are insufficient to support

implementation in the clinical arena—rigorous outcome data are required. Indeed, an excessive reliance on "common sense" is at times the enemy of a deeply rational understanding of our world. As illustration, we defy anyone to watch a sunset and innately feel that the sun isn't spinning around the earth rather than the other way around.

There are several reasons why medical genetics has been slow to embrace EBM. First, our field has so far focused on rare diseases, and the number of patients, quite simply, is often not sufficient to allow adequately powered studies (or to make funding of such studies feasible). Moreover, medical genetics has traditionally focused on diagnosis and not on interventions, where EBM usually holds sway. Finally, medical geneticists are highly mechanistically oriented and, as such, are perhaps not as readily influenced by the practical questions upon which EBM studies typically focus. Thus, the medical genetics community has been late in embracing EBM. But if our field is truly to rise to the fore and realize its potential to inform far-flung fields of medicine, it is imperative that we proceed on a firm evidence base. This is particularly crucial in an era when genetics will increasingly address significant public health issues; genomic-based interventions must demonstrate their added value when compared with more conventional nongenetic approaches.

An enthusiastic embrace of EBM is not to imply that it will be sufficient for answering all our questions. Medical and public health practitioners, at least for the foreseeable future, will be confronted daily with questions for which there are simply no "gold-standard" answers. Prospective randomized controlled trials are expensive, and the questions must be of sufficiently broad interest to justify their funding. Moreover, there are issues for which randomized controlled trials would be needless, unethical,[9] or impossible (try designing a placebo-controlled, double-blinded study to address the effects of daily alcohol intake on coronary artery disease). Indeed, it is the very limits of EBM that ensure that the "Art" of medicine will remain a key part of our profession. The astute clinician must have knowledge of the evidence that exists and the wisdom to understand how to apply this necessarily limited body of data to the care of the individual patient. The reports in this issue of *Genetics in Medicine* are important steps along this path as we seek to understand how to integrate rapid advances in genomics to health care and disease prevention.

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