The rules remain the same for genomic medicine

The case against "reverse genetic exceptionalism"

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Developments in genomics continue at a breathtaking pace. Over the past few years, we have seen our capacity to analyze the human genome, gene expression, proteomics, and epigenomics increase by orders of magnitude. The advent of microarray analysis has made simultaneous genotyping of 1 million sites in a person's genome a routine matter, global expression patterns in any given tissue can be readily ascertained by similar technology, and because of the rapid emergence of "next-generation" sequencing platforms, affordable whole exome and whole genome sequencing are now realities.

A plethora of genome-wide association studies have provided the first wave of new knowledge from these robust analytic techniques, shedding light on the fundamental underpinnings of a host of diseases[1] and identifying hundreds of genes that play a role in entities ranging from breast cancer to eye color. The power of such studies lies primarily in their ability to identify novel genetic loci that are involved in disease pathogenesis, but whose roles could not have been predicted by our (typically slight and hard won) biochemical and physiological understanding (i.e., from a candidate gene approach). The loci so identified reveal new and promising drug targets and will surely point the way toward a more thorough understanding of both rare and common diseases. Such progress promises eventually to contribute greatly to patient care and the alleviation of myriad disorders. However, the key word is "eventually."

Perhaps in keeping with the breakneck pace of progress in basic genomics, we are impatient to apply such advances to patient care and disease prevention. From academics to private enterprise, numerous endeavors have sprung up to offer genotyping and whole genome sequencing directly to the individual. Indeed, we may well be on the brink of an era in which many individuals will obtain genetic information outside of the confines of traditional health care. The urge to capitalize on our burgeoning ability to probe the genome is understandable. Current medical practice is often an inefficient process, with available therapies working in only a subset of individuals and optimal approaches identified only through trial and error. Great individual and public-health benefits could be realized if drug treatment and disease prevention were better tailored to individual susceptibilities.

Nevertheless, a premature embrace of genetics in health care and disease prevention runs the risk of practicing what we term "reverse genetic exceptionalism" (rGE). Genetic exceptionalism (GE), of course, is the practice of treating genetic information differently from other medical information. That we might do so is understandable: many of us see our genomic data as somehow different than the results of our knee x-ray or our hemoglobin level. Although both types of information are private and should be protected, the sheer amount of information implicit in our genetic code, not to mention its rather frightening fixity, might reasonably mandate some special consideration in terms of privacy and regulation of access. Thus, GE makes sense in some circumstances—as, for example when genetic risks related to mental illness or other behavioral conditions have the potential to stigmatize individuals or groups.[2] We have, therefore, argued that recognition of some degree of GE is appropriate, not unlike the special protection now accorded to psychiatric records in the medical record.[3] The promise of improved health care and disease prevention through genomics, however, is based primarily on risk information that is little different from other common health measures. The wave of new genetic tests made possible by genome-wide association studies, for example, will at best offer predictions about future risk that are comparable in scope with cholesterol or blood pressure measurements.

Several attributes of medical genetics may have fostered GE. Our field has frequently focused on rare disorders for which evidence is hard to marshal. In addition, the lack of good therapeutic interventions has made it impossible to ask for evidence of improved health outcomes for many genetic conditions. However, these realities have also been used to create a pass for the field of genetics, seemingly excusing it from the demand for rigorous evidence of improved health outcomes when it comes to care and prevention of disease—and threatening to relegate our field to an evidence-free ghetto. This is what we call rGE, a practice which could block the promise of genomic medicine.

A sober analysis of the current landscape must temper our enthusiasm for an overly quick embrace of personalized genomics. Although it may ultimately be broadly transformative for patient care or public health, we need to beware of rGE: the vast majority of genomic polymorphisms, which confer increased risk of disease, are of decidedly modest impact, with typical relative risks of <1.5,[4] severely constraining their applicability to individual patient care[5] or the parsing of populations to inform screening programs.[6] For common diseases, even a substantially reduced degree of risk will not obviate current public health recommendations related to healthy lifestyle or screening, and for rare disorders, even a substantial change in relative risk results in only a small shift in absolute risk, undermining the utility of such information. Moreover, there is little evidence thus far that genetic information will be uniquely effective in inducing long-term beneficial behavioral changes. Finally, for every individual found to be at increased risk of, say, heart disease, another will be found to be at reduced risk—making genetic information and its impact on behavior a decidedly double-edged sword.

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To be sure, there are promising advances in the realm of genomic medicine, which will likely be applied to patients and populations in the near term. Gene expression panels are already transforming the assessment of cancer prognosis. Pharmacogenomic approaches to the use of selected agents such as abacavir,[7] tamoxifen,[8] warfarin,[9] and clopidogrel[10] are already have (or may soon) become standard of care. Risk panels using multiple variants with small effect may eventually emerge as a useful tool for guiding prevention. In the long–term, genetic medicine holds great promise for delineating the underpinnings of human health and disease and will assuredly make great contributions to medical practice and the field of public health. But, the excitement and novelty, which justifiably surround the field of genomics, should not obscure the fact that the rules of evidence-based medicine have not changed. Good ideas alone, no matter how attractive, are insufficient to guide the practice of medicine. Along with the power to help comes an equally profound power to harm[11] (or at a minimum, waste precious resources).

These are both exciting and challenging times. Along with our new ability to analyze the entire genome of an individual in one fell swoop comes the sobering realization that whole genome analysis represents the first test in the history of medicine, which is guaranteed to produce abnormal results in all who are tested. As we move forward and strive to apply genetic advances to the benefit of patients and the health of individuals, we must maintain an unwavering focus on demanding evidence of clinical utility for genomic modalities and not succumb to the lure of rGE.

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