GENOMICS

Deflating the Genomic Bubble

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Unrealistic expectations and uncritical translation of genetic discoveries may undermine other promising approaches to preventing disease and improving health.

"Soccer is the sport of the future in America … and it always will be." This oft-quoted epithet poking fun at the promise of the "beautiful game" in the United States can seem uncomfortably apt when applied to genomic medicine. It's now been 10 years since humans deciphered the digital code that defines us as a species. Although it may be hard to overestimate the significance of that achievement, it is easy to misconstrue its meaning and promise. People argue about whether mapping the human genome was worth the investment (*1*–*3*). With global funding for genomics approaching $3 billion/year (*4*), some wonder what became of all the genomic medicine we were promised (*5*). It thus seems an appropriate time to take stock of whence the real benefits from genomic research may come and how best to attain a future in which genomics improves human health.

Recent methodological progress in genomics has been breathtaking. We now regularly assay genomes at millions of loci (*6*), and routine whole-genome sequencing may soon be a reality (*7*). If this trajectory continues, genomic research will illuminate fundamental mechanisms of human disease with a reasonable expectation of practical results (*8*). But claims of near-term applications are too often unrealistic and ultimately counterproductive. From the South Sea and dot-com "bubbles" to the ongoing housing market crisis, the world has seen its share of inflated expectations and attendant dangers. Science is immune to neither.

If we fail to evaluate the considerable promise of genomics through a realistic lens, exaggerated expectations will undermine its legitimacy (*9*), threaten its sustainability, and result in misallocation of resources. Fueling unrealistic expectations for predictive genetic testing and uncritical translation of discoveries may also distract our gaze from other promising approaches to preventing disease and improving health.

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Impediments and Hyperbole

Substantial impediments to realizing many of the claims most frequently heard include the following:

The problem of clinical utility and relative risk. The numerous genetic variants that mediate disease risk typically confer woefully low relative risks (i.e., compared with the much more meaningful absolute risk) and are thus meager in their predictive power (*10*). Their applicability to patient care shows little promise; studies (*11*–*14*) demonstrate that even combining dozens of risk markers provides little clinically meaningful information. In the public health realm, the prospect of effectively stratifying populations as high or low risk, thereby guiding screening, is equally dismal. Given the multifactorial nature of common diseases and the weak predictive properties of genetic-risk alleles, the probability of misclassifying individuals as high or low risk is likely too great to make such an approach feasible in the general population for guiding such things as mammography or colorectal cancer screening (*15*).

The illusion of parsing risk. For common diseases, by definition, we are all at high levels of absolute risk. In this setting, defining precise relative risk on the basis of individuals' genetic information is less meaningful; interventions that lower risk will be useful to everyone, regardless of their relative risk. And for rare diseases, shifting an individual's risk from an already low level may not be very clinically meaningful. For example, the lifetime risk for an individual in the United States to develop Crohn's disease is about 1/1000. How helpful is it for clinicians and patients if that risk shifts to 1/500 or 1/2000?

The difficulty of changing behaviors. The idea that genetic information will promote a healthy life-style has emerged as a dominant claim by those who promote genomic medicine (*16*, *17*). However, there is little evidence that simply telling someone they are at a genetically increased risk for heart disease or diabetes, for example, leads to lasting beneficial changes in diet or exercise habits (*18*, *19*). Altering environments is increasingly recognized as a more effective way of changing those counterproductive behaviors that contribute most to poor health in high-income countries—namely, diet, sedentary behavior, smoking, and alcohol use (*20*).

The paradox of risk information. Even if, despite evidence to the contrary, knowledge of one's genetic status drives behavior change, another problem emerges: for everyone identified at increased risk of a malady, there will be an equal number at decreased risk. Thus, if genetic information were actually found to be uniquely powerful in changing behavior, it could well promote counterproductive behaviors.

The translation of science into the clinic is inherently messy. The public, researchers, and clinicians frequently fail to appreciate that the history of medicine is strewn with ideas once thought promising that did not pan out when scrutinized through the lens of evidence-based medicine (*21*). Hormone replacement therapy, prostate-specific antigen screening, peri–myocardial infarction lidocaine, and many other good ideas, when prematurely implemented, created bubbles of expectation and investment, leaving sponsors disappointed and patients ill-served when reality did not live up to theoretical promise.

Given these hurdles to practical application, why has genomics been the recipient of such hyperbole? Impatience for practical applications from genetic advances is understandable. To be sure, there is much room for improvement in modern medicine: Screening programs

are inherently inefficient given the need to test entire populations, drugs have widely variable efficacy, and diseases strike capriciously. But there are other drivers of inflated expectations (*22*). Researchers gain funding, jobs, and fame, while pressure to commercialize their work adds fuel to the tendency to oversell (*23*, *24*). In a distressing way, biomedical research is often viewed by governments as primarily an engine of economic growth (*25*) and, only secondarily, as an engine of scientific and medical progress. Further pressure results from retail marketing of genomic information, such as direct-to-consumer genetic testing. As boundaries between private and public efforts erode, academic endeavors are increasingly subject to market forces that demand quick payoffs. Finally, the press plays an obvious role in creating unrealistic hopes (*24*). Collectively, these factors contribute to heightened expectations; left unchallenged, they take on a momentum that is hard to unseat.

Realistic Promises

Harold Varmus observed that the full potential of a DNA-based transformation of medicine will be realized only over the course of decades (*8*). We agree; the true promise of genomics is to help lay bare the mechanisms of human disease. Genes responsible for most Mendelian disorders will soon be identified. Genome-wide association studies are illuminating loci that contribute to common disease, and novel drug targets are being identified that will ultimately lead to new therapies. But the timeline for translation of such discoveries will be long.

Pharmacogenomics (PGx; the study of influence of genetic variation on drug response) may represent a near-term payoff of genomic research for carefully selected treatments and could enhance the safety and utility of treatments used for serious disorders (*26*, *27*). But it is unrealistic to expect PGx to revolutionize the use of all (or perhaps even most) drugs, given that much variability in efficacy is not genetically determined (*28*). Indeed, the most powerful predictor of drug efficacy is whether a patient takes the drug, highlighting the importance of human behavior in health outcomes.

If properly harnessed and based on evidence, appropriate risk assessment could aid in clinical decision-making (*29*). The ability to make diagnoses, especially for disorders that result from disruption of a single gene, will provide tangible benefit in the near term. Enhanced diagnostic capacity promises to spare both anxiety and money, ending the cruel "diagnostic odyssey" of families who go for years without a definitive diagnosis. But we should not overestimate the value of diagnosis or risk stratification. Without effective interventions, a diagnosis is only a dimly realized, partially fulfilled hope.

Couples will be empowered to make informed reproductive decisions, as preconceptual screening, augmented by robust genomic analysis, allows them to learn whether they are carriers of disease-related genes. Newborn screening will also benefit as medically actionable conditions are identified. Such advances hold great promise if the information so gathered is useful, cost-effective, and welcome (since not all parents may welcome such information).

So how do we avoid inflating an unsustainable genomic bubble but still realize the true—and considerable—promise of the "genomic revolution"? Solutions range from the political to the personal, from short term to long term. We offer a short list of recommendations as a starting point for debate, aimed at deflating the genomic bubble and realizing the field's long-term promise:

1. Reevaluate funding priorities. A sober assessment of disease etiology suggests that funding priorities may be mismatched to the potential for practical benefit. Much morbidity and premature mortality in high-income countries results from smoking, sedentary behavior, and excessive food and alcohol consumption (*30*, *31*). It is likely that common diseases arising from these behaviors can be reduced by behavioral change (*32*, *33*), but our knowledge of how to effect such change across populations is limited. Yet, U.S. National Institutes of Health and Department of Energy spending on genomics vastly exceeds the budget for behavioral and social science research (*4*, *34*). Given that even a small improvement in our ability to alter behaviors could yield major benefits, we suggest a reappraisal of the apportioning of funds to promote the promise of improved human health.

2. Foster a realistic understanding among the scientific community, the media, and the public of the incremental nature of science and need for statistical rigor. Scientists can start this process by making responsible claims and by advocating that reporters and editors do the same.

3. Maintain focus on developing high-quality evidence before integrating good ideas into medical practice. Develop novel ways of assessing evidence so as not to delay implementing promising modalities.

We believe that genomic discovery and resultant applications will provide great benefits to human health. Ours is not a call to gut existing research or too rigidly tie funding to the degree of disease burden. Indeed, the nature of scientific progress is arguably not optimized by a rigid allocation of resources to purely practical need. But failing a (desirable but unlikely) massive expansion of total funding for all types of research, a realistic view of the promise of genomics and an appropriate prioritization of research funding are vital to realizing that future. The pursuit of our common goal—improved human health—demands that we take a hard look at disease causation and order our priorities accordingly.

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