Introduction
In 1999 Francis Collins published a foundational document of precision medicine entitled “Medical and Societal Consequences of the Human Genome Project,” (1) which made predictions about the ways the human genome would be used to predict, prevent, and treat disease in 2010. In 2000, he suggested that “Over the longer term, perhaps in another 15 or 20 years, you will see a complete transformation in therapeutic medicine” (2).

The vision described in the article became the aspirational template for the precision medicine movement (Figure 1). We have passed the 2010 deadline and are rapidly approaching 2020, yet the “complete transformation in therapeutic medicine” has not occurred. Using the framework of the predictions made nearly 20 years ago, we argue that the foundational assumptions of precision medicine are unsound.

The terms precision medicine and personalized medicine have been used interchangeably to refer to the view that incorporating information encoded in the human genome as the dominant factor in the prediction, diagnosis, and treatment of human disease will lead to marked improvements in human health. Recently, some precision medicine advocates have recommended expanding the scope of precision medicine to incorporate inputs beyond the genome (3), but because precision medicine has been nearly synonymous with genomics, the emphasis on the genome is our focus (4).

A genetic revolution in medicine?
Disease with a genetic component. Precision medicine asserts a tight linkage between individual variability in DNA sequence and disease causation. For rare diseases, DNA testing for most common classes of drugs. Trials of pharmacogenomic dosing of warfarin, in which “precise” dosing is needed to balance the antithrombotic effect of the drug against the risk of severe bleeding, have shown no benefit of such testing (9). By contrast, trials of a one-size-fits-all pill containing aspirin, a statin, and an antihypertensive — the very antithesis of precision medicine — for the prevention of cardiovascular disease have shown effectiveness (10).

The polyclonal and adaptive nature of most malignancies makes demonstrating improved overall survival across a broad array of cancers challenging. A multicenter randomized trial of treatment based on tumor sequencing compared with conventional cancer treatment showed no advantage of sequencing (11), and the most recent findings of the large (6,000 patients screened thus far) NCI-MATCH (National Cancer Institute–Molecular Analysis for
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Two assumptions are embedded in this scenario: that high-relative-risk groups will be discovered through genetic testing and that genetic data will change behavior. The first assumption, as noted above, has generally not been supported, and no gene has been discovered since 1999 that conveys a relative risk of six for lung cancer. The second assumption, that communicating genetic risk estimates will change behavior, is not supported by a meta-analysis of 18 studies (15). Thus, a fourth foundational idea, that genetic knowledge will change behavior, is also not supported by evidence, though this lack of evidence has done little to stem the tide of direct-to-consumer genetic testing.

Gene therapy. For many years the clinical application of gene therapy was stalled, though recent trials have shown promising results in several rare diseases. These successes are impressive, but their costs are enormous, and it is unclear how it will be possible to fund such therapy. The idea, expressed at the dawn of the genomic era, that gene therapy was also a possibility for the treatment of common diseases, has largely been abandoned. Thus, a fifth foundational idea central to precision medicine, that gene therapy might have implications for common diseases, has not so far been supported.

Understanding the basic biologic defect and treat with drug therapy. As the expected value of many GWAS has failed to materialize, the argument for the value of human genomics has shifted from disease prediction and prevention to the use of gene variants to increase understanding of disease biology for translation into drug therapy. The hidden assumption is that the host genome is the driver of every cellular event. But the genome is as much acted upon as it is actor, and the trigger for gene action is frequently an environmental stimulus, making the environment the primary cause, not the gene.

Unfortunately, the pharma pipeline has not been filled by GWAS-identified targets (16). Even where the study of genes has led to novel compounds, as with PCSK9 inhibitors, the clues have come from rare families identified on the basis of their clinical picture and not from GWAS conducted on large samples of the population (17). The new, genetically driven drugs for cystic fibrosis parallel the situation in cancer, in that they have modest effects but huge costs (18). Thus, a sixth tenet of precision medicine has yet to bear fruit, particularly for common complex diseases that occur later in life.

Summary: what is success?
The promises of precision medicine are to dramatically change patient care via individually tailored therapies and, as a result, to prevent disease, improve survival, and extend healthspan (19).

However, nearly two decades after the first predictions of dramatic success, we find no impact of the human genome project on the population’s life expectancy or any other public health measure, notwithstanding the vast resources that have been directed at genomics. Exaggerated expectations of how large an impact on disease would be found for genes have been paralleled by unrealistic timelines for success, yet the promotion of precision medicine continues unabated.
In light of the limitations of the precision medicine narrative, it is urgent that the biomedical research community reconsider its ongoing obsession with the human genome and reassess its research priorities including funding to more closely align with the health needs of our nation. We do not lack for pressing public health problems. We must counter the toll of obesity, inactivity, and diabetes; we need to address the mental health problems that lead to distress and violence; we cannot stand by while a terrible opiate epidemic ravages our country; we have to prepare conscientiously for the next influenza pandemic; we have a responsibility to prevent the ongoing contamination of our air, food, and water. Topics such as these have taken a back seat to the investment of the NIH and of many research universities in a human genome–driven research agenda that has done little to solve these problems, but has offered us promises and more promises.

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