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WILL Precision Medicine LEAD TO A HEALTHIER POPULATION?

The dominance of genomics in biomedical research today is driven by scientific theory and opportunity, but it is pushing science dangerously far from proven pathways to widespread health benefits.

Human health and biomedical science have been transformed in tandem over the past two centuries. From around 1850 to 1920, better nutrition and prevention of epidemic infections were the main contributors to massive improvements in life expectancy and reductions in infant and maternal mortality. These challenges have now receded for much of the world. Chronic diseases have become the principal threats to a healthy lifespan, and in the past half century we have seen a second wave of improved health, above all from enormous gains in control of cardiovascular diseases and cancer. Whereas the increase in life expectancy in the industrialized world from about 50 years in 1900 to nearly 70 years in 1950 is well-known, the addition of nearly a decade in life expectancy since 1970 is far less appreciated. But a rich body of theoretical and practical experience on what drove this more recent wave of success yields a clear set of principles that are securely established as foundational concepts in biomedical and related sciences.

What does transformational progress in reducing the burden of chronic disease look like and how did it happen? What can it tell us about the most promising pathways for future population-wide advances in health?

How we got healthier

About two-thirds of all deaths in the United States and most industrialized countries are caused by cardiovascular disease (CVD) or cancer. Although the burden and character of both these disease categories have evolved dramatically in recent decades, for CVD the magnitude of the reduction in incidence (occurrence of new cases, both fatal or nonfatal), prevalence (proportion of the population living with a chronic condition), and death toll in the past 60 years is not widely appreciated. Mortality rates from coronary heart disease (CHD), the most common form of CVD, in the United States peaked in 1968, and have declined by 2%-3% every year since, until the past two years. The total reduction, after adjusting for changes in the age structure of the population, is now over 75%. Though CVD of course remains common, there are at least six hundred thousand fewer CVD deaths per year in the United States as result of this decline, and the total number of deaths averted since 1968 is on the order of twenty million. This unprecedented success in reducing the burden of the leading cause of death in industrialized countries was achieved not by any single intervention, but through advances along multiple pathways: the development of a clear understanding of the etiologic process; determined efforts to create public awareness, especially about the role of diet and physical activity; successful policy interventions to promote such things as low-fat dairy products and removal of trans fats from food items; introduction of safe, cheap, and effective medications to treat causal risk factors such as high cholesterol and blood pressure; and improved treatment of acute cases and advanced disease of the coronary arteries. Rapid declines in mortality from stroke, the other component of CVD, have been even larger than the declines from CHD, and are continuing as well.

Although the magnitude is considerably smaller, progress has now been made in lowering cancer death rates. Age-adjusted total cancer mortality has declined over 30% in the past 25 years in the United States. Reduction in tobacco use is the most important factor, and for men accounts for 40%-50% of the overall decline in all cancer deaths. Male smoking prevalence rates have dropped from 65% to 20% in the past 70 years. Lung cancer mortality has declined 50%

in men since 1991; colon cancer deaths fell by 50% for both sexes; breast cancer deaths in women are now 40% lower. Cervical cancer death rates have declined by 60% since 1975, and prostate cancer mortality has declined by more than 50% since 1994.

Cancer, of course, is a composite of a wide range of tumors, each with distinct causes, natural histories, and challenges to prevention, detection, and treatment. Nonetheless, the main drivers can be identified. The great decline in smoking is responsible for reductions in lung cancer in both sexes and for fewer deaths from laryngeal and likely bladder cancer. Widespread adoption of technologies that permit early diagnosis (for breast and prostate cancer) or detection of premalignant states (cervix and colon) appear to have been the largest contributors to the reductions in mortality of these cancers, but improved surgical techniques and treatment options have probably played a role as well.

Thus modern biomedicine, especially the component focused on prevention, has brought transformational change not only to infectious diseases but to chronic diseases that less than five decades ago posed hopeless challenges. In the course of this transformation, we have accumulated a rich knowledge base of what research, what tools, and what implementation strategies work in reducing the burden of disease and death.

Meanwhile, back at the bench

Throughout most of this remarkable period of improved public health, the field of genetics functioned within well-defined subdisciplines in such diverse areas as selective breeding of animals and improvement of crop yields, statistical modeling of heredity, and experimental work to understand monogenic disorders. One of the most significant accomplishments early on in genetics was the clear demonstration that most common or complex traits were highly polygenic—that is, they resulted from the combined small effects of many genes. Characterization of the double helix structure of DNA in 1953 and parsing how genes are expressed in terms of molecular function ushered in a new era of intense focus on the molecular pathways that shape the growth and maturation of the organism. In the 1980s the advent of faster, more efficient gene sequencing technology ignited an explosion of new research opportunities, and eventually the transformation of genetics, a reasonably discrete scientific discipline, into genomics, a vastly more open-ended project with its sights set on establishing a precise, mechanistic description of the "fundamental rules of biology"—not only of intergenerational transfer of information via germline DNA, the traditional focus of genetic research, but of the causal sequence underlying virtually all disease processes. The launching pad for this new era was the Human Genome Project, led in its first phase by James Watson, codiscoverer of the double helix. At a projected cost of $3 billion, only the federal government, primarily the National Institutes of Health, could afford such a large and focused endeavor.

This massive project encouraged people in the genomics community to see themselves as transformational actors in all forms of medical research, and to promise equally transformative benefits for health. As NIH proclaims in its mission statement "the goal of NIH research is to acquire new knowledge to help prevent, detect, diagnose, and treat disease and disability." Genomics became key to that mission. In June 2000, at the ceremony hosted by President Bill Clinton announcing the completion of the Human Genome Project, the world was offered the hope that "genome science will revolutionize … the diagnosis, prevention and treatment of most, if not all, human diseases." Twenty years on, the scale of investment, the dynamism within the field, and the far-reaching claims for transformational impact on health and medicine have only accelerated.

Genomics has further matured since 2000, and broadened into an open-ended pursuit spanning domains from how cells regulate metabolic activity to the impact of all environmental exposures that individuals encounter over their lifetime. As a consequence, an enormous growth in resources devoted to research, training, technology development, and implementation, including a substantial de facto reallocation of resources that had been used in traditional biomedical disciplines, has been directed to genomics-oriented biomedicine. NIH, with its $39 billion annual budget, has aggressively promoted this agenda, and currently invests roughly half its resources in genomics-related research. In parallel, NIH spends less and less on research into prevention and public health. In pursuit of the goal to make genomics the basis for a new era of "precision medicine," NIH Director Francis Collins has launched the All of Us research program, with a goal of recruiting one million Americans to have their whole genome sequenced, at a total cost of about $1 billion. NIH continues to advance an undiminished message of promise for this science, as Collins declared in May 2018: "We would expect to see more effective prevention of many diseases, fewer diagnoses of serious illness, and an extension in health span." Genomics science is now being offered as the foundation for a population-based medicine of the future.

Of disease and the genome

We thus appear to be in the early stages of a decisive transition between the multifaceted approach that has yielded such progress over the past two centuries, and the emerging new model driven by genomic sciences and captured by the term "precision medicine." What, then, should we expect from genomics and precision medicine in meeting the enormous chronic health challenges that remain, such as diabetes, dementia, arthritis, renal failure—

and, of course, CVD and cancer? And what about the huge challenges presented by violence and suicide? Based on well-established principles, drawn from the history of biomedicine and public health, are the promissory notes issued by genomics likely to be cashed for value? Does the evidence of success from the first two decades of the genomics era justify the original and continued predictions of transformational progress in population health?

The current undeniable crisis within the health care delivery system notwithstanding, we now stand on a massive edifice of technology and basic biology. We can muster a vast array of effective pharmacologic agents, transplant many solid organs, and perform extraordinarily complex surgical procedures; we can detect and treat many conditions in their earliest stages; we have developed many ways of preventing disease before it starts, especially with the weapons of social policy. At the core of these advances lies a set of principles about what causes disease and how large-scale population-level improvements are achieved.

We appear to be in the early stages of a decisive transition between the multifaceted approach that has yielded progress over the past two centuries, and the emerging new model driven by genomic sciences.

In the middle of the nineteenth century, the great German pathologist and public health advocate Rudolf Virchow declared "mass disease means society is out of joint." A more contemporary framing of that principle would emphasize that like the rest of the animal and plant kingdom, humans' long evolutionary lineage has left us well adapted to life on this planet. As a corollary, the vast majority of health risk, certainly more than 90%, is derived from deleterious environmental exposure over our life course, not information encoded in our DNA. Human genetic adaptability is no match for newly emerging threats to health, as the history of epidemics shows. When a new agent appears on the scene, whether cholera, a new flu virus variant, cigarette smoking, or a huge increase in animal fat consumption, the human genome is unable to prevent the premature deaths of millions of humans. In other words, the human genome does not express itself as a dominant or primary cause of mass disease.

Occasionally, evolutionary forces have conferred new protective adaptations to region-specific epidemics—the role of sickle-cell disease and thalassemia in reducing risk of severe malaria among some African populations is the paradigmatic example here. But the genetic repertoire of our species leaves us susceptible to many noxious exposures that vary with time and place too rapidly for evolutionary forces to react to. Mass disease with a global scope—illnesses that occur in at least 5%-10% of the world's population—almost always occur because of widespread insults that arise external to the organism, whether it be the sanitary conditions in medieval cities that gave rise to plague, or the conditions of trench warfare that contributed to the 1918 flu pandemic. Mass diseases are products of the societies in which we live.

In earlier periods, both insufficient total calories and inadequate sources of specific nutrients were the primary drivers of risk. In the modern era, all too often excessive exposure to substances that are inhaled, ingested, or absorbed through the skin are the fundamental causes of common disease. The transformational events in our progress against chronic disease have been driven by mitigation of those exposures through a familiar litany of interventions such as vaccination, improved diet, and altered behavior. What we have learned about disease, medicine, and population health over the past two centuries tells us that the primary domain of interest for disease prevention consists of external factors, which are products of "sick societies," rather than heritable factors that modify individual-level risk. From this perspective, the prediction that precision genomic medicine will lead to population-wide health demands a sharp break from the source of such benefits in the past.

The introduction of genomics into the mainstream of biomedical research violates another historical precedent. Though technology has clearly played a key role in helping build the current medical armamentarium—from imaging to clinical chemistry to drug development—with rare exception those technological advances emerged from focused research on a disease challenge (vaccines), had self-evident utility at the moment of discovery (the Roentgenogram), or were imported from outside the medical enterprise (lasers, fiber optics). Scientific advances that have led to improved health have nearly always been the result of research that matched technologies to specific human health problems and their clinical solution.

Technology push

The grand theory of human molecular genetics is that the gene is a code that needs only to be deciphered in order to solve the problem of human disease. This theory arose in the 1950s simultaneously with, and reinforced by, the development of modern computer science, with coding of programs at its root. A few decades later, as we have noted, genomics developed as a laboratory-based technology, erupting into widespread use with the development of rapid and accurate sequencing methods. Only then was genomics injected into mainstream biomedicine, and retrofitted to address problems beyond its inherent scope. As applied to clinical medicine, DNA sequencing technology is first and foremost a tool to

study germline errors in the code, preeminently Mendelian (single-gene) traits. The ethos of genetic determinism, and the irresistible allure of technological solutions, have opened the door for the adoption of genomics for the study of conditions where it has no or minimal relevance—namely most, if not all, human diseases. Sequencing (and the rapid acceleration of its throughput) was quickly promoted as a tool for "gene mapping," and thereby attracted much broader research interest. The current wave of large-scale gene-mapping projects has been justified through an appeal to genetic determinism—more causal knowledge self-evidently must lead to solutions. This new causal knowledge would come, in ways we could not foresee, from as-yet-unexplored domains.

When tested, however, these hypotheses have not, to date, been adequately verified. Likewise, the effect of individual genetic variants being sought have been grossly overestimated, in clear contradiction of the established theory of the supposed "polygenic inheritance of complex traits." The outcome was almost preordained—genomic theory emerged without feedback from the clinical or any other empirical setting, and it advanced and captured increasing swaths of biomedical science without evidence of improved population-wide medical advance. Indeed, the more we learn about the genome, the more distant it seems to be from a role as a causative agent in most widespread diseases. We have every reason to believe that the same will be true for those diseases where the etiology remains obscure.

Beyond an appeal to principles, we now have the accumulated experience of some 25 years of genomic research, with a few projects reaching back as far as the 1970s. Anything approaching a broad summary of this rapidly evolving science is clearly beyond our scope here. However, an empirical basis for our concerns is required, and several conclusions have now achieved general consensus in the academic community. First, however, it is necessary to reaffirm what no one disputes—that adequate support for all branches of science is an essential investment in the infrastructure of modern society. Nor can those investments be limited to science that promises near-term benefits. For genomics at the present, this trade-off was articulated by former National Cancer Institute director Harold Varmus's sentiment that "genomics is a way to do science, not medicine." Second, the advent of genomic technology has already generated a huge array of new tools beyond DNA sequencing that have transformed many lab sciences, and advanced public health, for example contributing crucially to our understanding of the spread of viruses in epidemics and the evolution of drug resistance in microorganisms, to new diagnostic assays, and to immunotherapy for cancer.

Major changes in population health, and extension of healthy years of life, however, belong to a dimension far removed from these incremental, niche advances, as beneficial as they are for many patients.

Four (out of five) reasons why

Enthusiasm for genomics and precision medicine builds on expectations for major scientific and medical progress in at least five major areas.

1. Enabling disease prediction. Although thousands of familial, genetic syndromes had been catalogued in the pre-genomic era, it is now possible to define the DNA sequence variations in great detail, and early success with cystic fibrosis, the so-called BRCA complex related to breast cancer, and Huntington's disease offered the promise of much wider translational success for genomics. As noted, however, for most diseases the impacts for specific genetic factors are small, and studies of unprecedented size were required. Many of these have now been completed—at enormous cost, needless to say—and a robust literature exists for common disorders such as CHD, diabetes, hypertension, obesity, and other metabolic traits.

Focusing on two pressing public health concerns of the moment, CHD and diabetes, we have conclusive evidence regarding risk prediction from DNA markers. Collectively representing cohorts of almost half a million patients, four major studies have now published virtually identical results. As is well known, the odds of dying from CHD is driven by four major risk factors: elevated cholesterol, cigarette smoking, high blood pressure, and diabetes. After accounting for these easily measured traits, DNA markers offer trivial additional information, perhaps identifying 2%-3% of individuals who might be reclassified as low or high risk. The sole response to this information would be adjustment of the dose of a cholesterol-reducing statin at a younger age. Roughly 80%-90% of the risk of the common adult form of diabetes, type 2 diabetes, can be determined from body mass index (BMI; a simple ratio of height to weight), and randomized trials have shown that in almost half of patients type 2 diabetes can be prevented, and indeed normal glucose control restored, with weight loss. Regular fitness activity and cessation of smoking also modify risk. The very large studies already completed demonstrate that virtually no additive predictive information can be derived from more genome-wide searches for additional "risk variants." Similar knowledge has emerged for hypertension, stroke, dementia, and numerous other conditions.

Genetic prediction of cancers similarly struggles with predictors that are too weak in most cases to be useful in clinical practice. For example, in a very large European database in which the average lifetime risk of breast cancer is 5.1%, the risk for women in the top 5% of gene scores is 12%, and in the bottom 25% it was 2.4%. These results have no impact on clinical practice: preemptive invasive procedures cannot be justified for a group of women whose likelihood of not getting breast cancer is 88%, and 2.4% risk is still too high to abandon screening.

2. Providing critical new insights into molecular pathways. The rise of genomics has encouraged the view that once the DNA mutations underlying a trait have been identified, no matter how small, downstream metabolic consequences would be revealed and, along with them, targets for clinical intervention. Efforts to define cell-based pathways using molecular technology have in fact met with some success. We now know, for example, much more about immune function, control of fetal hemoglobin, and lipid regulatory mechanisms, in large part through application of genetic and molecular technology. However, most metabolic networks are so intricate, redundant, and multidimensional that following Ariadne's thread is mere child's play compared with an attempt to move from identifying a mutation to tracing that mutation to a specific physiological outcome. Complexity involved in inference from genotype to organism has been evident for years. In sickle cell anemia, for example, an apparently simple genetic change—the single nucleotide substitution of adenine for thymine in the hemoglobin gene—produces strokes, pulmonary hemorrhage, painful bony crises, and enhanced susceptibility to the pneumococcus bacteria. The linkage of genetic change to clinical manifestation is sufficiently complex that six decades after the underlying molecular basis of the disorder was discovered, we still have no specific therapy for the condition.

A technique that will "knock out" altogether the action of a gene almost invariably does not lead to the expected observable consequence in the organism, and there is as yet little evidence that genome-wide association studies that statistically link multiple genetic sites to "risk markers" for diseases are leading to significant improvement in understanding pathophysiologic processes. The rare successes that have been achieved (for example, identification of an allelic variant in the genetic locus PCSK9 that influences cholesterol metabolism) are still being derived from study populations where the link between risk and genetics (for example, in high-risk families) was already long-established. Living organisms are simply too complex to yield up a set of fundamental laws, and instead reveal more and more intricate processes and networks that wriggle and squirm across time and space, refusing to cast a fixed image.

3. Isolating genetic mutations that predispose patients to severe adverse drug reactions. Pharmaceutical agents are essentially foreign bodies, as far as our species is concerned, that evolution has never been called on to protect us from. It should be unsurprising, then, that many drugs have side effects, as well as some variation in absorption, metabolism, or effect depending on the individual. Genetic predisposition therefore can play a role in modulating person-level response. Some important successes have been achieved, especially in the identification of people at risk for severe adverse reactions. Early in the experience of so-called pharmacogenomic testing, variation in the efficacy of drugs used to prevent blood clots was identified. The added value of characterizing the relevant genes has now been studied in clinical trials. The most important examples are warfarin and clopidogrel, drugs that inhibit clotting by modifying platelet function. Both have significant side effects. Clopidogrel requires further metabolic conversion in the liver to make the active compound, and person-level variation in enzyme function produces the genetic effect. The original molecule was reformulated to avoid this variability in response; the most recent agent to become available, ticagrelor, avoids the between-person variability seen with clopidogrel, and thereby obviates the need for gene testing. Clearly drug companies have great incentive to market their drugs to the widest possible sales base to maximize profits, and want to avoid the step of gene testing if possible. Additional new drugs—the so-called non-vitamin K oral anticoagulants—are now showing promise for patients experiencing serious side effects from warfarin, further limiting the role of gene testing for that drug.

Current use of the new anticoagulants, however, requires conventional assays of platelet function. This return to traditional practice—omitting "gene prediction" and measuring the physiologic variables that are the direct target of the treatment (e.g., serum lipids, blood pressure, blood sugar)—reaffirms our assertion that decision-making for individual patients will continue to be based on biochemical or other basic parameters. The complexities along the pathway from gene to physiologic outcomes are almost always influenced by too many other factors for us to be able to make clinically useful decisions from genetic information.

For other classes of common drugs, even these modest successes have rarely been seen. For example, a very extensive, long-running NIH-funded project on medications used for high blood pressure resulted in genetic scores that at best predicted 1-2 mmHg difference in response between individuals after testing; as above, they merely confirmed that direct measurement of blood pressure after you prescribe the drug will remain the basis of clinical practice. A vast array of other minor findings has been reported, but over time the scenarios we outline here have been repeated: either new agents replaced drugs that required gene testing (including a drug for hepatitis C), or the genetic effect was trivial. Pharmacogenomics overall has therefore not lived up to early expectations. Additional efforts face a stiff challenge to success, for reasons that should now be familiar: links between genomic makeup and patient response to drugs are too complex to have much clinical value, and actual measurement of physiological end points are almost always more informative.

4. Identifying targets for new drugs. At the very earliest stages of the genomic revolution, the pharmaceutical industry and innumerable start-up companies invested heavily in the search for "novel targets" that could be identified through DNA association studies. Though some new agents discovered from genetic research are in clinical trials (for example, a protein inhibitor for elevated triglycerides and an RNAi blocker for fatty liver disease), these efforts have yielded surprisingly little. In fact, a crisis has emerged with a drastic reduction in new drugs coming to market in the past two decades. An important exception relates to drugs influencing immune response, including autoimmune diseases. And there may well be drugs in the pharmaceutical pipeline based on genomic research that could yet translate into useful products.

The fifth reason

5. Unlocking at long last the secrets of cancer, which after all, according to the current dominant theory, is a genetic disorder. Despite years of intense, well-funded research, progress toward effective treatment, let alone cure, of most cancers remains an elusive goal. To oversimplify the general proposition, harmful DNA mutations at least at some stage may drive the growth of tumor cells, and ultimately the metastases that prove fatal. Identifying "driver mutations" and blocking their effects could thus possibly offer cures. Unfortunately, the results across all these hope-filled propositions have, in sum, been dismal. From a historical perspective genomics is a young science, and the unexpected will occur with time. However, for some hypotheses, accumulating research is asymptotically approaching a null result.

The dominant theory in cancer biology remains gene-centric: either somatic mutations, occurring in the absence of known external cause, allow a clone of cells to escape from normal control of cell replication and death, or pathologic mutations in some less-defined way act at the earliest stages to drive growth and metastasis of tumor cells. Whereas it is incontrovertible that carcinogenic agents of diverse types, including viruses, ionizing radiation, and aromatic hydrocarbons, do cause pathologic mutations, a vigorous debate continues within oncology as to whether this is actually the process that triggers and sustains cancer development. For example, recent work demonstrates that normal tissue adjoining tumors harbors the same mutations as the tumors themselves; conversely, tumors transplanted from one model organism to another usually do not survive. In other words, the mutations themselves are clearly not the sole actors, or perhaps not even the causal driver, of tumor growth. Thus, a complementary "field theory" has been proposed that emphasizes tissue-level factors, particularly cell-to-cell communication. Recent experimental evidence now conclusively shows that at least some of these abnormal functional states, which cannot be explained in terms of mutations, must exist for tumors to propagate locally and, more importantly, to metastasize. Though this brief summary hardly does justice to a complex, rapidly evolving field, we hope it begins to communicate why large-scale sequencing projects of tumors have not delineated clear causal pathways, and more importantly why agents developed to block driver mutations have usually not met expectations, or, if they succeed, seem to act through entirely unexpected and independent mechanisms.

Despite these unresolved questions, substantial success has been achieved with several classes of new antitumor drugs. The drug imatinib mesylate, marketed as Gleevec, has been widely celebrated in this regard. Although it is the sole example in current use of target-selective therapy, it has led to lasting remission for some two thousand patients in the United States per year with chronic leukemia, without the debilitating side effects of chemotherapy. But Gleevec's success may be (and so far has been) hard to repeat: it works on a specific causal chromosomal abnormality of the sort that is uncommon in most cancers. Moreover, life-long therapy is required at an approximate average cost of $1 million per patient.

There is as yet little evidence that genome-wide association studies are leading to significant improvement in understanding pathophysiologic processes.

Biomarker-driven molecular research, leading to development of antibodies on the cell surface of individual tumors, has also met with substantial success. For example, a panel of genetic tests for individual tumors that allows better matches for drug therapy has entered the clinical arena. Immunotherapy, an important example of the transition from molecular research to translation—especially the so-called check point inhibitors—can specifically target solid tumors in about 15% of patients, although these are not genetic targets. An increasing, but small, proportion of patients with melanomas have attained durable long-term remission with a combination of new genetic/immunotherapies.

But the central theory of cancer as a genetic disorder, with its corollary that the ability to identify unique driver mutations will lead to therapies that can block their action, has not been verified. Instead, it has become a piece of a much more complex puzzle. Whereas any research toward safe, effective antitumor drugs is of enormous value, when

entered onto the balance sheet of factors that account for the 30% decline in cancer rates achieved in the past several decades, the contribution of new curative agents developed through molecular techniques to improvements in health on a scale measurable in population-level statistics remains, at best, somewhere in the range of 2% or less. New knowledge will increase this contribution, yet predictions of a truly transformative role for treatment of advanced cancer lack empirical justification. Most invasive solid tumors have remained stubbornly resistant to curative or durable palliative therapy. At the same time, two new immunizing agents against viruses established to cause cancer in the past few decades—the human papilloma virus that causes cervical cancer, and the hepatitis B virus that underlies most cases of hepatocellular carcinoma—promise, if widely used, to virtually eradicate these two cancers without regard to genomic variability, potentially saving more than a million lives a year worldwide.

On the road taken

Many observers will no doubt find this account overly pessimistic. Numerous success stories have been omitted. The advances enabled by the advent of genomic technology are far-reaching and of great scientific importance. Whole subdisciplines, from human evolutionary history to epidemic surveillance and vaccine preparation for conditions such as Ebola and influenza, have indeed been transformed. But a key distinction is that these advances are due to the power of genomics when applied to *agents* of human disease, not to the disease *host*. Many infectious organisms must take advantage of molecular targets on the surface of cells or be targets for "killer" white cells. Thus an understanding of species-specific susceptibility to bacteria or viruses—for example, pneumococcus or Ebola—can be very informative in vaccine preparation. Distinguishing molecular signatures of pathogens within a species has made outbreak investigation much more precise. But *human* genomics and precision medicine have not transformed human health. Nor, in our view, is there a basis from which to argue that they will do so—certainly not in any foreseeable future.

Meanwhile, the opportunity costs are enormous. To help bring them into focus, we offer a somber, indeed heart-breaking story that has played out in one of the oldest—and thereby most mature—experiments to employ genomics as a tool to improve human health. The Pima Indians of the Sonoran Desert in central Arizona were deprived of irrigation water from the Gila River around 1900 when it was diverted upstream by commercial farmers. Isolated, and confronted with famine, they became dependent on food subsidies from the US Department of Agriculture, and adopted a diet low in nutritional value but high in calories. In the following decades an epidemic of obesity of unprecedented magnitude swept the reservation. The prevalence of type 2 diabetes rose to 50%, and even adolescents with the disease have now required dialysis for renal failure. In the 1970s, NIH established a research institute in nearby Phoenix to search for the unique genetic factors that predisposed the Pima to this crippling disease and use this knowledge to cure or prevent the disease. Despite five decades of research no important genetic mutations were identified, and the sum of available evidence showed that those susceptibility loci that could be isolated were no different, and no more common, in the Pima than in the majority US population.

The depths of the intellectual poverty of this long-running experiment can be summarized by the following quotation, posted as a "research advance" by the Phoenix group on the website of the director of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) in 2016: "In a prospective study conducted between 1965 and 2007, NIDDK investigators followed children from Arizona's Gila River Indian Community for development of type 2 diabetes. They found that BMI and impaired glucose tolerance were strong predictors of type 2 diabetes, but other components of the metabolic syndrome were not." It should be noted here that the scientific observations highlighted in this "advance" was known to the Ayurvedic medical tradition in India in the fifth century BCE, and was certainly common knowledge in the modern era by the seventeenth century. Yet even today this genomic research continues along the line explored for so many years among Pima populations. The rationale for an NIDDK project started in 2015 states: "When it comes to kidney disease … years of exposure to diabetes may change the way the body reads its DNA, increasing the risk of kidney disease … being exposed to high blood sugars or high blood pressure may cause people who have a genetic susceptibility to have kidney disease in the future."

About 10 years ago the Gila community broke off collaboration with NIDDK and mounted its own preventive campaigns based on weight control and increasing physical activity. The risk of hyperbole notwithstanding, this unhappy saga ranks with the Tuskegee Experiment as another egregious project where the natural history of a fatal illness in a vulnerable population was allowed to run its course, under the careful observation of government-funded scientists, in pursuit of a narrow, unjustified hypothesis, built on notions of genetic determinism and race-based susceptibility, while available preventive or curative alternative interventions were ignored or actively shunned.

We wonder if the story of the Gila River Indian Community, writ large, will be the outcome of the headlong rush toward precision medicine across the entire spectrum of biomedicine. In the cancer realm, for example, consider that fatty liver from obesity is now becoming a major cause of liver cancer in some countries—yet another widespread example

of sick societies. Or pancreatic cancer, whose etiology has been an enigma, and for which early detection and effective treatment remain elusive goals—yet very recent evidence suggests fungal infection from the gut could play a major role. A similar causal pathway emerged between the Helicobacter pylori bacterium and stomach cancer, and treatment of this type of bacteria has had an important impact on peptic ulcer disease, and may yet influence the risk of stomach cancer. Preventive interventions for more cancers are almost certainly possible. The search for environmental causes of cancer proceeds apace, but the effort remains modest compared with the work expended on searching for genomic correlates. We have learned the importance of radiation, microorganisms, toxic chemicals, and lifestyle factors such as obesity, and (for breast cancer) age at first birth, but we still have much to learn about the nongenetic causes of cancer. Implementation of modalities to prevent and detect premalignant lesions—as with colonoscopy—could achieve much less costly and more rapid downturns in cancer mortality than are likely to result from the long road to curative therapies derived from molecular research, which are often applied near the end-stage of disease.

Progress is also being observed in two other significant chronic disease challenges. There is a growing awareness that vascular disease has been underappreciated as a cause of dementia, and improving heart health is now accompanied by a welcome decline in incidence of dementia in the elderly. Type 2 diabetes is a major global threat to health, moving rapidly to nonindustrialized countries. As noted, whereas obesity accounts for 70%-80% of risk, and reversing the obesity epidemic has thus far proven difficult, type 2 diabetes incidence rates appear to have leveled off or declined in many countries. Randomized trials have demonstrated that weight loss of as little as 15 pounds can lead to a 40% reduction in onset of type 2 diabetes in high-risk patients, and return 40% of patients with recent onset of the disease to nondiabetic status. Policy to influence food production and sales, as well as eating patterns, is in its infancy and can boast only modest success, but that is clearly the only solution to the challenge of obesity and type 2 diabetes. It goes without saying that the opioid epidemic in the United States, which has cost 770,000 lives since 1999 and reduced overall life expectancy, is a poster child of a social disease whose amelioration will not be driven by precision genomic medicine.

We do not believe genomics and precision medicine will transform biomedicine and population health. Though the history of science will have the final word on this era, we believe that large segments of the biomedical community, supported by tens of billions of public dollars, are in effect headed down the wrong road, if not into a cul-de-sac. To understand this assertion, it is essential to recognize the distinction between "transformational change" and "widespread niche advances." The concern that we have addressed here lies singularly with population health, with benefits accruing to millions. Scientific understanding of both the reasons for enormous gains in population-wide health, and the origins of disease, are being largely displaced by a reductionist, technology- and theory- (and career- and profit-) driven approach to health and medicine that remains largely unproven (and wildly expensive). Of course we want to explore and pursue many new research avenues, but the powerful legacy of genetic determinism and the devotion to technological solutions have narrowed the scope of research aimed at improving population health, and thus narrowed and reduced the benefits that biomedical science could and should be providing, right now.

Ironically, two decades into the genomics revolution life expectancy in the United States has declined for three consecutive years, the reduction in cardiovascular disease rates has leveled off, and a surge of opioid deaths has devastated many communities. These adverse events have no direct relationship to genomics or precision medicine, but just as clearly we have not observed the promised bonus of "more effective prevention of many diseases, fewer diagnoses of serious illness, and an extension in health span." We could, of course, be accused of making a grossly premature judgment. Two decades is a reasonable interval, however, in which at a minimum to demonstrate proof-of-concept, and we see no evidence of that modest milestone having been reached. More to the point, we argue that "genes as a cause" and precision medicine as the "cure" violate basic precepts of health and medicine. Biomedical science should be reoriented and reprioritized to expand its scope in accord with what we actually know about health and disease, and to expand the benefits of science for all.

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Recommended reading

Ronald Bayer and Sandro Galea, "Public Health in the Precision-Medicine Era," *New England Journal of Medicine* 373, no 6 (2015): 499–501.

D. Muñoz and T. J. Wang, "The Polypill Revisited: Why We Still Need Population-Based Approaches in the Precision Medicine Era," *Circulation* 140, no. 22 (2019): 1776–1778.

Nigel Paneth and Michael J. Joyner (eds.), "The Precision Medicine Bubble," special issue of *Perspectives in Biology and Medicine* 61, no. 4 (2018).