

Genomics and Medicine: Distraction, Incremental Progress, or the Dawn of a New Age?

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The technology of molecular genetics has profoundly altered the conduct of biomedical research. An entire universe of problems that in the past had been addressed only through conjecture, including whole genome analysis, can now be studied directly. The rapidity and scope of these changes in research capacity have in turn led to speculation that medicine will be radically altered by the application of genomics to everyday practice. To date, gene therapy and several new tests for genetic susceptibility have been successfully implemented, although their impact on medicine as a whole remains very limited and their future contribution is hotly contested. The potential of molecular genetics, like all technology, must be evaluated on the basis of established principles of clinical

and epidemiologic research. The rhetoric of some enthusiasts focuses instead on an optimistic best-case scenario of the future of DNA science, and many of their most far-reaching claims cannot be substantiated on the basis of what is currently known. The tension between the long-term goal of public health and medicine to identify and remove the causes of ill health, in contrast to the development of technological innovations that can cure disease or identify individual susceptibility, emerges as a major theme in this debate.

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Watson and Crick's letter to *Nature* announced the arrival of molecular genetics 50 years ago (1). Molecular genetics, which has been transformed into genomics by the rapid development of the laboratory technology, has now come of age and is ready to take "center stage in clinical medicine," according to some observers (2). Major advances are said to be possible against an array of intractable problems, and we are challenged to find our bearings in a discipline where new operating rules seem to apply.

Physicians and clinical scientists may be caught off guard by the predictions of a major change in direction for medicine. To date, genomics has had so little impact that there is no basis in current experience to envision more than a limited role in the future. While this sort of empirical generalization suffers from a lack of imagination, it is reasonable to ask: Are we really on the threshold of a new era? On what basis will genomics revolutionize medicine? What standard should we use to judge the potential relevance of genomics across the vast expanse of clinical medicine? Will it be equivalent to the public health movement that led to improved sanitation or even the introduction of sterile surgery, antimicrobials, or x-rays? Responses to these questions range from enthusiastic affirmation to deep skepticism. Most of us, in fact, probably oscillate between being overwhelmed with awe and recognition that the practical achievements of genomics are still limited. How do we arrive at a more stable estimate of what DNA science has in store for us?

While it is true that the future may not be a linear projection of the past, the claims of genomics still have to be evaluated on the basis of principles that we currently accept as valid. In this commentary, we suggest how the potential contribution of genomics to medicine and public health might be assessed on the basis of those principles. We further speculate about the broader context that makes the rhetoric of the genomics revolution so compelling and

how rhetorical exchanges about genomics influence our interpretation of its potential impact.

In the early 1980s, polymerase chain reaction, a laboratory technique of sufficient impact to deserve a Nobel Prize, made direct measurement of DNA variants a practical undertaking. With the explosion in technology that followed, molecular genetics has already helped explain many mendelian disorders, some of which are now recognized as being oligogenic diseases (3). Between 1981 and 2001, 1112 disease genes were discovered and 1430 clinical disorders were characterized at the molecular level (4). Before the end of 2001, there were more than 13 000 entries in the catalog of genetic disorders, and a draft of the human genome sequence had been completed. The transfer of this research into practice has now been put on the agenda, and, to begin this discussion, we offer some illustrative examples.

POPULATION SCREENING

Screening for genetic diseases is obviously one of the most useful applications of molecular technology. Antenatal diagnosis has altered the disease patterns in several populations, with the most notable successes involving hemoglobinopathies in Mediterranean countries (5). In Sardinia, for example, screening for thalassemia is widely available, and the number of children born with the condition has dropped from approximately 225 per year to less than a half dozen. For illnesses among adults, however, genetic screening has not yet become part of routine clinical practice. In 1999, Motulsky identified seven genes that might be candidates for use as screening tests in adults in the United States: *HFE*, *APOE4*, *CYP2D6*, *BRCA1*, *BRCA2*, familial adenomatous polyposis, and factor V Leiden (6). Considerable debate persists about the predictive value and the usefulness of the information obtained from these tests, and many ethical, legal, and social issues are still

unresolved (7–9). As yet, screening tests for variants in these genes do not have a place in clinical medicine, and, since 1999, few if any new candidates have come forward with compelling evidence for screening (7).

GENE THERAPY

Gene therapy symbolizes the great hope for the breakthrough achievements now possible with genomics. The treatment of severe combined immunodeficiency disorder and hemophilia provide concrete examples of the potential for modern molecular biology to change the course of a fatal illness (10, 11). But the benefits of gene therapy have not been durable in patients with hemophilia A, and 2 of the 10 children with severe combined immunodeficiency disorder who received gene therapy developed leukemia caused by the retroviral vector, leading to the suspension of all similar trials. Together with the publicity surrounding earlier flawed gene therapy trials, this experience provides a cautionary tale in bringing this new technology to patients.

PHARMACOGENOMICS

From an evolutionary point of view, one of the areas most likely to benefit from genetics is drug therapy. For many millennia, our ancestors were hunter–gatherers, and variants in genes that code for drug receptors and drug metabolizing enzymes arose without the selective pressure of modern pharmaceutical companies. In 2002, U.S. sales of drugs were \$154 billion (12). This epidemic of licit drug use creates the potential for interactions between new drugs and ancient genes. Important instances in which pharmacogenetic information can reduce toxicity and potentially improve outcomes already exist (13–15). Molecular biology and genetics have also produced startling insights into pathophysiology as the basis for new therapy. We now know the structure and function of the Philadelphia chromosome in chronic myelogenous leukemia, we have a specific inhibitor of this tyrosine kinase, and we know many of the genetic variations that confer resistance to this new drug (16–18). Compared with the chemotherapeutic model in which we give the most toxic drugs at the highest possible doses to kill the cancer, this therapy is nontoxic and represents an astonishing achievement. Whether it will be possible to develop a similar approach to the treatment of other cancers remains unknown.

GENOMICS AND COMMON DISEASE

When we turn to treatment and prevention for common illness, genomics enters more difficult terrain. Two thirds of the deaths in the United States are attributable to cardiovascular diseases or cancer. To date, both association studies and genome-wide scans have identified only weak and inconsistent genetic signals for the underlying conditions, such as hypertension and diabetes (19–21). Once the relevant genes are characterized, sequence variation as-

sociated with these quantitative traits has often been extraordinarily complicated, even for well-defined phenotypes (22). It is still not known whether single nucleotide polymorphisms in coding regions or other types of sequence variants account for most of the genetic effects that distinguish individuals from one another. Even without that knowledge, we can assume that, for complex phenotypes with a genetic architecture that involves dozens if not hundreds of loci, many variants will be involved and they will be sorted into individual packages with as much variety as personality and physiognomy.

Yet, to change the practice of medicine, genomics will have to offer solutions to the problems posed by common complex disorders. Gene therapy is out of the question. The small individual effect of each of the variants will not justify interventions that are expensive, difficult to develop and administer, and potentially risky. Theoretically, genetics could play a role in prevention by offering more accurate assessment of individual susceptibility. Hopes for the revolutionizing effect of genomics have, therefore, been pinned on the gene chip or affordable ways to sequence each patient's genome, leading to tailored therapy (7). The steps required to bring these diagnostic devices into clinical practice would include replication of findings linking genetic variants to risk in several populations; proof that their use improves detection or the approach to treatment; and evidence that genetic tests add new information not already available from the history, physical, and laboratory examination. The basic principles of clinical epidemiology cast doubt on the "gene-tailored" strategy for common disease, however. Screening and intervention for risk factors, such as smoking and hypertension, have been successful because they identify the direct cause, which can then be eliminated. Even though risk factor assessment is not a good individual predictor, intervening in broad categories of patients is effective because it is practical and safe. Risk stratification uses an intermediate step to identify those at highest risk, and its success then depends on the diagnostic accuracy of the test (23). Unless the susceptibility genotypes are common and have a moderately large relative risk, they will be of limited use in this process (23). Even under generous assumptions, for example, of sensitivity and specificity in the range of 60%, a relative risk of 2, and an expected incidence of 20%, predictive value will be far too low to be clinically useful (for example, 15%). Many persons would be labeled high risk when they will remain free of disease, and many cases of disease will be missed. Furthermore, risk will have to be summarized as the combination of many polymorphisms. To the clinician, genetic susceptibility will look like the panoply of symptoms for hypothyroidism in the elderly—common in patients but only slightly more so than in persons without the condition—yielding weak predictive value (23, 24).

Acknowledging that genetic epidemiology is still a developing field, the available empirical data support the argument against a clinical role for susceptibility testing for

chronic disease. In a recent review of 603 disease associations ascribed to 268 genes, Hirschhorn and colleagues identified only 6 that were positive in 75% of studies (21). From this review, they conclude that “clinical applications of genetic associations should not be considered until the degree of certainty far exceeds the level currently achieved.” Given that a screening and intervention strategy requires even more stringent evidence in the form of net benefit, as well as unresolved societal issues, they argue that the accumulated experience should “raise a loud cautionary alarm: . . . Because of the scientific and ethical uncertainties, a ‘DNA chip’ that can determine crucial genotypes and accurately predict future health is unlikely to become a widespread and useful screening tool in the near future, even if concerns regarding reproducibility can be resolved.” Further investment in “whole genome” genetic analysis as a way to predict someone’s future diseases should wait until we have positive examples of how this information will be useful.

The primary disease-producing forces are rooted in our technologically based lifestyle and the resulting patterns of consumption, behaviors, and environmental exposures. Given universal exposures and virtually universal susceptibility, the conventional approach to common-source epidemics is still the most effective way to control cardiovascular diseases and cancer. It is inefficient to design tailored interventions for the vast array of individual susceptibility profiles in the population, and adherence in the absence of social reinforcement will be even more difficult. The rise and fall of mortality rates from coronary disease in the 20th century demonstrate the power of interventions that address population risk and drug classes that treat risk factors based on phenotype. While cures may become available for a few rare disorders, outcomes for the broad syndromes to which we are all in some degree susceptible will only be minimally improved through genetic screening. Genomic applications in clinical medicine, like all molecular genetics, will be useful only as diagnostic tests for mutations in genes with high penetrance or for diseases with a large genetic component (23).

SCIENCE AS A CULTURAL ARTIFACT

A prediction from today’s limited supply of examples is itself a risky undertaking. One of the most disorienting aspects of the current debate about genomics, in fact, is the mixture of rhetorical and factual claims—one that often fails to distinguish between the urge to answer fundamental questions and a plan to advance the goals of medicine. The resulting tension between theory and practice is not new. Medicine is a pragmatic undertaking, from beginning to end. Like all fields that rely on technology, medicine is interested in what works. But reliance on pragmatism as the sole strategy severely limits what can be accomplished since the creative energy of theoretical science is required for the development of the new knowledge that is to be

applied. Likewise, medicine does not shape its own agenda based on broad philosophical questions but, rather, responds to the illnesses or epidemics with which patients present. As a consequence, while the search for new and better treatments is pragmatic, medicine has to rely on the resources of the culture in which it is embedded, with all its particular strengths and limitations, to guide that search. The practical tools are then developed as these intellectual resources are brought to bear on the everyday problems of health and disease. In an earlier era, the natural world was imbued with divine purpose. At that time, the Catholic Church, at least in the West, determined how the religious worldview was used to fashion pragmatic solutions, and it gave authority to magical thinking as well as empirical observation. Since science succeeded God as the source of philosophical authority, technology has become the instrument we use to solve practical problems, and its application proceeds under the assumptions that dominate the fashions of science.

In the last century, physics occupied the place of “high science,” providing the dominant philosophical structure and taking its authority from the promise to unify our understanding of all forces operating in the universe. One of the most important goals was to gain control over boundless sources of energy. The fundamental questions could best be pursued using immense, expensive technologies, such as the cyclotron and the Hubble telescope. Only a few such instruments are affordable. Structurally, this scientific activity becomes concentrated in a multinational conglomerate that in turn concentrates much of the authority to define the key questions and, thus, the next generation of answers.

Biology has succeeded physics as the “the queen of the sciences,” and genomics is rapidly becoming the primary way in which biology engages with the everyday practical world. The Human Genome Project has succeeded in focusing public attention and established the validity of the underlying principles of genomics. As with physics, the “science of fundamental questions” also presents itself as the arbiter of practical solutions: “Genomics, which has quickly emerged as the central basic science of biomedical research, is poised to take center stage in clinical medicine as well” (2). Knowledge about biological chemistry and pathways can now lead directly to new diagnostic tests and improved therapies and, thereby, to improved health and longer life. What is still absent, however, is a step-by-step analysis of how such a future might arise based on the principles of clinical epidemiology and prevention science—in other words, how this translation might occur.

Molecular research has long been privileged as basic science, while population and clinical studies are regarded as the poor intellectual cousins. A survey of the advances in biomedicine does not, however, suggest that this valorization scheme reflects the public health impact of those disciplines. The most important event in medicine in the industrialized world in the last half century has been the

decline in cardiovascular diseases, which has reduced the number of deaths in the United States alone by 600 000 yearly. Molecular biology contributed little to that success. Prevention, pharmacology, and intervention procedures provided the foundation for these improvements in patient care (25). We have now seen a substantial downturn in lung cancer mortality, with more modest declines in death rates from breast and prostate cancer. The sequencing of the human genome and the capacity to type large numbers of genetic variants will not necessarily change the way new therapies are discovered.

There are, in addition, unattractive features of the genomics movement that cannot be ignored. In the public mind, as well as for many health professionals, genomics gives undeserved attention to the idea of discrete causes and the silver bullet. It also reinforces various simplistic and “scientistic” notions, such as genetic determinism and the existence of races as important structural elements of the human population. Little progress has been made toward protecting privacy or limiting the risk for stigmatization. The intense commercialization of genomics has led to absurd practices, such as the patenting of genetic information. As it focuses more on individual risk, genetic medicine becomes less practical for low-income countries (5).

Despite these caveats, there is no doubt that DNA science will continue in an incremental fashion to make important contributions to health and well-being. But at full maturity, will the record of success resemble the current state of affairs in gene therapy or the programs for thalassemia control in Sardinia? The answer any of us might give to that question depends in large degree on how our belief system is structured. Molecular genetics, which has deeply influenced the philosophical framework of biology, often assumes that the primary threats to health are programmed in our DNA rather than our social environment, with disease being transmitted through abnormal physiology rather than food, air, microorganisms, and our place in the social hierarchy. Within the belief system of physics as “high science,” one measure of progress was the continued growth of the nonhuman energy that could be put to work for the average citizen. But instead of control over infinite sources of energy, we are facing grave peril from the irreparable damage to our ecosystem caused by the excessive consumption of the precious energy sources we do have. Despite this undeniable reality, we persist in the belief that we can fix with technology what unrestrained consumption made possible by technology has broken. Genomics may similarly hold the potential to advance the claims of a science belief system over the pragmatic needs of the long-term movement toward prevention through creation of a healthier environment as the most effective means to control common disease.

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Finally, to hinder the description of illness in literature, there is the poverty of the language. English, which can express the thoughts of Hamlet and the tragedy of Lear, has no words for the shiver and the headache. It has all grown one way. The merest school-girl, when she falls in love, has Shakespeare or Keats to speak her mind for her; but let a sufferer try to describe a pain in his head to a doctor and language at once runs dry. There is nothing ready made for him. He is forced to coin words himself, and, taking his pain in one hand, and a lump of pure sound in the other (as perhaps the people of Babel did in the beginning), so to crush them together that a brand new word in the end drops out. Probably it will be something laughable.

Virginia Woolf
On Being Ill
Ashfield, MA: Paris Pr; 2002.

Submitted by:
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