

The New Genomic Medicine

M. Mitchell Waldrop

Earlier this year, almost 50 years to the day after James Watson and Francis Crick first described the DNA double helix, scientists celebrated an equally epochal event: the official completion of the Human Genome Project. They had ample reason to be jubilant. Watson and Crick had given us the *structure* of DNA; now, after 13 years of international effort and an investment of \$2.7 billion, we had its *content*—a 3-billion-character sequence comprising the entire genetic blueprint of a human being.

But then, as the scientists themselves pointed out, this is hardly the time to rest on our laurels. Already, shimmering in the distance, we can begin to see the next milestone: a new “genomic medicine” in which physicians will be able to diagnose and treat each patient’s disorder with molecular precision. Granted, it could still take us a decade or more to get there. “Genomic medicine is an enormous opportunity, and an enormous challenge,” says Timothy Clark, head of bioinformatics at the Cambridge, Massachusetts, biotech firm Millennium Pharmaceuticals. But the first steps are already being taken. Even now, hardly a day goes by that a university or biotech company doesn’t announce the discovery of a gene linked to *this* condition or *that* condition. And the pharmaceutical companies’ development pipeline is full of brand new drugs crafted at least in part with genetic knowledge.

Moreover, when we do get there, the effects on medicine and on the health care system as a whole will be far more profound than most people realize. Indeed, the new genomic medicine is shaping up to be the most potent catalyst for health care transformation since the introduction of antibiotics in the mid-20th century—perhaps even since the germ theory of disease in the 1860s. Nor will the results be limited to new forms of treatment. Along with therapy, genomic medicine will change the nature of drug development, health insurance, and even the relationship between doctor and patient—all in ways the health-care industry is just waking up to.

“It’s only recently that people in the industry have even begun to look at these systemic effects,” says Philip Reilly, CEO of Interleukin Genetics in Waltham, Massachusetts. Just as in the fable of the blind men and the elephant, moreover, the discussion has focused on disjointed bits and pieces of transformation: the Wall Street Journal covers biotech and the pharmaceutical industry, Science and Nature document the latest science; only industry insiders have even begun to delve into the effects on insurance and the doctor-patient relationship. Our goal in this article is to bring those pieces together to provide an overview of the revolution, with all its attendant potential—and danger.

1. Diagnosis and Treatment

One of the most intriguing possibilities is that genomics, will one day reverse the ever-rising spiral of health-care costs, and actually start to drive them lower. Certainly these techniques could eliminate an enormous amount of costly trial and error from medicine, making therapy far safer and more effective than it is today. For example, genomics will allow physicians to identify the exact genetic defects involved in every malignant tumor they see, as well as the exact genetic underpinnings of every case of diabetes, asthma, and so on. Genomics will also reveal how well any given therapy is likely to work for each individual patient—and ultimately lead to pharmaceuticals that precisely target the broken cellular machinery in that patient.

The key is being able to understand and measure human genetic variation among individuals, according to Chris Austin, advanced-research director of the National Human Genome Research Institute in Bethesda, Maryland. “The original genome sequence told us what we have in common,” he says. (Literally: the sequence represented a mix of DNA from many individuals, deliberately chosen to include both sexes and all racial groups.) But the story of health and disease is told mostly in our differences. Why are some of us horribly susceptible to conditions like arteriosclerosis or high blood pressure, no matter how many hours we spend on the treadmill or how much brown rice we consume? Why are others, who appear to have won the genetic lottery, able to smoke two packs a day for decades, and still come out with lungs as clear as a baby’s? Knowing the answer would take a lot of the error out of medicine’s trial and error approach. Such

questions are surprisingly tricky to answer, says Austin, in part because the actual genetic differences involved are surprisingly small. “Between you and me there are only about 3 million genetic differences,” he says—the equivalent of just one spelling variation in every 1000 letters of the genetic code. Or to put it another way, any two human beings are 99.9 percent identical; *all* their differences, whether they be in height, skin color, blood type, athletic ability, disease susceptibility, or anything else, arise from that remaining 0.1 percent. (Actually, that’s true only if you compare women to women or men to men; if you include the X and Y sex chromosomes, the between-gender match falls to only 98.5%—which means that, as jokesters are fond of pointing out, a woman is no more closely related to a man than she is to a female chimpanzee.)

But a more important reason, says Austin, is that it’s actually quite rare to find a gene that is the sole culprit in causing a disease. There are a few; in Huntington’s disease a defective gene produces a protein that forms insoluble clots in certain brain cells, causing dementia, along with a progressive loss of motor control. But far more common are complex disorders that involve multiple genes, each of which only increases our susceptibility. “And that’s a fundamentally different situation,” says Austin, “because there are lots of people running round with bad gene variants who don’t have the disease.” Examples include arteriosclerosis, high blood pressure, schizophrenia, and that poster child for genetic complexity, diabetes, which afflicts 17 million Americans. At least 15 genetic variants have been identified as upping the risk of adult-onset diabetes, and yet none yields the inevitability of Huntington’s. As doctors have been telling us for years, there is also a powerful influence of the environment: diet, exercise and any number of other factors can affect whether the risky genes become active.

Fully sorting out this interplay of multiple genes and the environment, and the contributions of each to health and disease, will take years--if not decades. In the meantime, however, the health-care industry is hardly waiting around. Commercial work in genomics has been rushing ahead more or less independently of the Human Genome Project for years (although the practitioners have eagerly made use of the project’s data as quickly as they could get it.) Much of that effort has focused on one group of genetic markers: those that identify precisely which subclass of disease a patient may have and

determine precisely how he or she will respond to a particular drug.

“Pharmacogenomics,” as the field is known, has gotten the attention of the big pharmaceutical firms, the insurance companies, the regulators at the Food and Drug Administration, and just about everyone else in the health care industry, says Interleukin’s Reilly. The idea has been around for quite awhile, he says, “but the science and technology of it are getting better and better, and people are finally saying that we’re really going to be able to do this.”

Certainly there are any number of biotech firms eager to market the necessary genetic tests. “We can test any set of genes you want, as accurately as you want,” declares Charles Cantor, chief science officer of the San Diego DNA analysis firm Sequenom, Inc. “Biology has never had this kind of data before.” A prime example is the recently developed technology of DNA microarrays, in which a sliver of specially prepared silicon—a “gene chip”—can look for changes in the activity of hundreds of genes at once. Wash one of these chips with a puréed tumor sample, say, and it will respond with a pattern of fluorescent spots that maps the activity of hundreds or thousands of genes at a time. By comparing this pattern with that of a normal cell, a computer can then generate a vividly colored chart that makes it instantly obvious how profoundly disturbed the tumor cells really are—and that can in principle, identify precisely which components of the tumor cells’ regulatory networks are broken. In 2001, for example, Stanford University biologist Patrick O. Brown and his colleagues showed that such a chip could clearly distinguish two types of breast cancer that appear identical under the microscope and had previously been classified as the same cancer. They’re not. Patients with one type respond well to conventional chemotherapy and have a high recovery rate. But patients with the other type, which shows a very different pattern of gene activity, respond not at all. The payoff for such insights, in this and other diseases, is clear: physicians could immediately move non-responsive patients to other kinds of therapy without wasting money, effort, or most important, time.

Still—does all this activity mean that genomic medicine is coming soon to a clinic near you?

Not quite. Yes, genomic medicine has begun to clear some of its first scientific hurdles, particularly in the realm of pharmacogenomics. But, like any other technology, it also faces any number of ethical, legal, economic, and psychological hurdles. “And in my experience,” says Interleukin’s Reilly, “these ‘social’ hurdles are the big ones.”

As patients, for example, you or I (and our doctors) would have an obvious incentive to take advantage of genetic tests if they were available. If nothing else, research tells us that genetics—not environment—is the primary reason our responses are all over the map for certain drugs, including the “statins” used to lower cholesterol, the beta-blockers used to treat congestive heart failure, the bronchodilators used to control asthma, and many others. Genetic variations may also affect our ability to metabolize alcohol, and the compounds in tobacco smoke—which means that genetics could also be a major factor in susceptibility to addiction. In some of these cases, the genetic difference might lie in a “receptor” protein, the gateway molecule that will supposedly allow a particular drug to cross the cell membrane and find its target deep in the interior; if the shape of the receptor isn’t quite what the drug was expecting, then the drug can’t get in, and we might as well have taken a sugar pill. In other cases, the genetic differences might lie in the liver, which harbors a certain set of digestive enzymes that metabolize nutrients and anything else that enters the bloodstream—including drugs. If your enzymes metabolize a given drug faster than expected, it might never have a chance to take effect. If my enzymes metabolize the drug too slowly, it might build up to toxic levels. That’s exactly what seems to be happening with Cipro and related antibiotics, which can sometimes trigger tingling, numbness, or even severe pain in the arms and legs. Such individual differences in metabolic rates are also what make it difficult to get the right dosage with antidepressants like Prozac—which is why Reilly, for one, predicts psychotherapy will be among the first fields to use pharmacogenetic testing routinely.

Those same genetic tests will also help doctors identify which of us is most likely to suffer side effects from a particular drug—“side effects,” in this case, meaning much more than an upset stomach. According to the *Journal of the American Medical Association*, adverse reactions to FDA-approved drugs that were correctly administered by licensed physicians occur at the rate of 2.2 million cases per year in the United States,

with more than 100,000 of those cases ending in death. That makes the innocent-sounding “side effects” the fifth leading cause of death, right after heart disease, cancer, stroke, and pulmonary disease, and just ahead of accidents. Obviously, anything that could lower those figures would save a great deal of human suffering, not to mention cost.

On the other hand, patients (and their doctors) will have to balance any possible benefits from the genetic tests against their cost and their reliability, which can be low. Even though a test might detect the presence of a given genetic variant very accurately, admits Sequenom’s Cantor, “How accurately can you predict the outcome? That’s tougher.” Just as in disease susceptibility, the instances where drug response is determined by a single gene are in the minority. Indeed, drug response can be just as much a complex, multi-gene process as diabetes, and just as much influenced by an individual’s environment and life experience. That’s one big reason why the insurance industry has been leery of paying for genetic testing. And until the tests’ reliability improves—which it undoubtedly will, in time, as researchers learn more about the basic genetics—that attitude is unlikely to change.

2. Drug development.

Meanwhile, the big pharmaceutical companies, or “pharmas,” are finding pharmacogenetics be an exceptionally tricky balancing act. “My experience is that the scientists in the big pharmas love it, and the marketing people hate it,” says Reilly.

On the one hand, the pharmas have often, and with some justice, been accused of cultivating a Hollywood-like addiction to “blockbusters”: drugs like Prozac or Viagra that can be sold at a premium to millions of people. Occasionally, as in a recent article in the *Wall Street Journal*, they’ve even been accused of undermining the development of pharmacogenomic tests for those blockbusters, on the grounds that screening out even few percent of potential customers would cost them millions. And whatever the truth of that allegation, it is true that the Pharmas have little incentive to offer genetic testing for drugs already on the market—not when they’re desperately trying to recoup an average investment of \$800 million for every drug that actually makes it that far.

On the other hand, it's not clear how long the FDA will sit still for that attitude once reliable tests are actually available, since it means deliberately selling drugs to at least some people in the overall patient population for a particular drug who won't benefit from it. What the pharmas really need is to get that \$800 million figure way down—which is why there's a very different attitude in the laboratories, where company researchers see that genomics could speed the process of developing new compounds. For one thing, says Millennium Pharmaceuticals' Clark, genomics has already opened up a whole new world of possibilities. "In past decades, there were only about 500 cellular proteins used as drug targets in the entire industry." But now, he says, thanks to the Human Genome Project, "we've essentially done a survey of all the 30,000-plus genes in the body. So even if only a small fraction of those are potential drug targets for drug development, we're talking about thousands of new targets."

Furthermore, genetic testing could allow researchers to sidestep problems with a new drug early in the development cycle. To take a hypothetical example, let's say that the researchers at MegaPharmaCo come up with a new drug that drastically slows the progress of dementia in Alzheimer's patients. Unfortunately, clinical trials show that, in a small number of individuals, the drug also seems to trigger life-threatening heart arrhythmias. Today, since the Food and Drug Administration would never approve such a drug, MegaPharmaCo would have no choice but to write off its sunk costs and start looking elsewhere—which is a classic example of where that \$800-million-per-marketable-drug figure comes from: roughly \$720 million, or 90%, is the cost of other drugs that washed out along the way. With the right genetic tests, however, MegaPharmaCo could identify the vulnerable individuals ahead of time and eliminate them from the clinical trials. Result: the large majority of Alzheimer's sufferers get a better life, MegaPharmaCo gets a new moneymaker instead of an expensive failure—albeit a moneymaker that will have to bear a clear warning on the label about who should not take it—and the upward pressure on drug prices eases a notch.

Actually, that example is not so hypothetical. This kind of genetic testing would have saved GlaxoSmithKline a lot of grief a few years ago when it was forced to withdraw alosetron, the first drug approved for irritable bowel syndrome, after a small number of

users developed life-threatening complications. (Following intense lobbying by desperate patients, the FDA has allowed the drug back on the market, but only when used at much lower initial dosages, and with intensive monitoring—precautions that might also be made unnecessary by genetic screening.) Stories like may even be enough to get the attention of the marketing departments, says Reilly: “I see the Pharmas fighting pharmacogenomics until they realize that it can help them rescue a drug that might have been rejected. How this will all shake out over time is far from clear. It may be that improvements in our understanding of cellular networks will make for drugs that are more and more precisely targeted, so that each one meets the needs of a smaller and smaller population of patients. Of course, it’s an interesting question whether the development costs of these niche drugs will ever fall far enough that a small population could afford them. But if that did happen, it would certainly spell the end of the blockbuster drug. Or would it? “The blockbuster drug model won’t go away,” argues Jeffery Augen, director of IBM’s bioinformatics unit—“but it will change. When you target diseases at the molecular level, addressing the underlying mechanism, you may find differences and commonalities that weren’t obvious before. So you may end up with one compound that treats multiple diseases. In fact, there are already drugs on the market that have different targets. An example are the Cox-2 inhibitors, which are very potent against inflammation—but only because they interfere with the growth of capillaries, which means that they may be also inhibitors for cancer growth.”

The upshot: we can expect Big Pharma to embrace genomics slowly, after they’ve had a chance to calibrate the intrinsic trade-offs. And over time, we can hope genomics can begin to reverse the rise in drug costs. “I have certainly made the argument that it will,” says Reilly. “But I don’t know the time frame. In the next three years? Absolutely not. In the next 10 years? Maybe.”

3. Insurance.

Beyond diagnostic genetic testing is the largely unexplored realm of predictive testing: genetic assessments that will one day tell us not just what we have now, but what may lie in our medical future. Eventually, such tests could finally force the health care system to

get serious about delaying, or even preventing things like heart disease or diabetes, instead of always waiting until we get sick. And as a side effect, genomics will likely transform the insurance industry—which, after all, lives and dies by evaluating risks—beyond recognition.

For the time being, the “payers”— insurance companies, managed care companies, Medicare, Medicaid, and the like—find the whole notion of predictive genetic testing to be something of a nightmare. “I think the issue is too new, and the insurance industry is barely grappling with it,” says Murali Prahallad, Sequenom’s business development manager. In fact, adds Prahallad, who has worked closely with the industry, “a lot of insurers seem to be banking on the idea that testing will be made illegal, or will be so ethically abhorrent that it will just go away.”

Of course, it won’t go away. The science is too powerful and the human desire to know the future too great. But the industry’s wish is understandable. On the one hand, genetic testing is already a political lightning rod: the same genetic data that could help us stay healthier, through better treatment plans and preventative measures, could also make us a higher insurance risk, not to mention a greater employment risk. Thus the widespread anxiety over genetic discrimination, and the laws that have been passed in many states to prohibit it. But on the other hand, insurance can’t work as a business unless higher risks are covered by higher premiums. So how can the payers *not* take genetic data into account? And conversely, what are they supposed to do in the not-too distant future, when individuals can get themselves tested in private, and then sign up for a policy knowing a few nasty little facts about their genomes that the insurance company doesn’t know?

“We’re talking about the fundamental principles of how we assign risk,” says Prahallad, “How industry deals with that is a huge open question.”

The end result won’t be business as usual. But what will the business model look like? Prahallad offers one scenario. “I would start with two presumptions: first, that no one should be denied coverage on genetic basis; and second, that no one should be forced to have a genetic test in order to qualify. Then I, as an applicant, have two choices. A). I don’t

take the test, in which case I go into a risk pool just as today, on the basis of age and so forth. But I would also have to certify that I don't know of any genetic conditions that affect my health. What I know, the insurance company knows; I won't try to game the system. Or B). I submit to test, and get assigned to a genetic risk class. If I'm low risk, that's not a problem; maybe I even get a lower premium."

The question is how deal with high-risk individuals. Since they will be covered under this scenario (it will be illegal to deny them coverage, remember), it will be in the payers' interest to move them into an aggressive preventative regimen. Let's say a new genetic test reveals that a 40-year-old employee of a Fortune 500 company is at high risk of developing a deadly form of prostate cancer by the time he's in his 50s. The company's health plan immediately puts him on schedule of frequent screening, plus regular treatments with genetically targeted drugs that will delay the onset of his particular kind of tumor for decades—until long after he has died from other causes. The regimen is pricey. But it costs a fraction of what the plan would have to pay to treat a life-threatening cancer.

In addition, it might also be in the payers' interest to undertake a little wholesale industry restructuring, so that the risks could be pooled in novel ways. For example, a good life insurance purchaser is a bad retirement insurance purchaser, and vice versa; if both were handled through the same company—as they rarely are today—there might be creative new ways to bundle the risks. By extension, the age of genomic medicine might ultimately force the industry to bundle *all* forms of insurance: health, disability, retirement, unemployment, life—the works.

4. The doctor-patient relationship

What will genomic medicine feel like on the receiving end? When we walk through that clinic door in 2013, or in 2023, what kind of experience will we have?

Well, it's clear enough that the experience could be profoundly different from what we're used to—although it's considerably less clear what those differences will be.

On the one hand, for example, it's conceivable that "personalized" genomic medicine could have the paradoxical effect of turning the clinic into a depersonalized assembly line. In this scenario, we'd walk in and get hooked up to a machine. The machine would give us an automated DNA scan. Computers would generate an automated diagnosis. We'd walk out clutching a computer-generated treatment plan—all without once discussing our problems with a human being. This transformation, which would bring medicine into line with, say, banking, could take awhile; when it comes to information technology, the health-care system is light years behind almost any other sector of the economy. But genomics may force the issue. And so will cognitive overload. After all, human doctors are having enough trouble keeping up with medical progress as it is. As the impending explosion of genetic data combines with an multiplication of treatment options, they will find it impossible: the sheer quantity of things the doctor needs to keep in her brain will exceed the capacity of that organ. The current expedient—"subspecialty" care, in which each doctor focuses on a smaller and smaller portion of the patient—won't be practical. So the ancient goal of "finding a good doctor" will no longer be viable; the new goal will be finding a good *health care system*—one that most definitely includes those state-of-the-art facilities for testing, diagnosing, and data analysis.

On the other hand, one could argue that many managed-care clinics are pretty factory-like already; genomics could hardly make them worse. And in any case, it's just as conceivable that genomic medicine will be *more* personalized than it is now, in the sense of offering much more room for individual patient involvement. Thanks to Internet, for example, it's no longer unusual to see patients sitting in doctor's waiting room holding a fistful of printouts: stacks of downloaded research articles about their own conditions, and the gamut of treatment options, from conventional to bizarre. It's a practice some physicians encourage, and others despise. (It may be true, as former House Speaker Newt Gingrich once said, that we'll soon see the day when many patients know more about their specific condition than their doctors—but there will also be quite a few patients who only think they know more.)

Nonetheless, patient activism is here to stay, and the growing emphasis on predictive genomics is only going to reinforce it. In this changing environment, we can expect to see

a substantial shift in the roles of the various health-care professions. Least affected will be surgeons, radiologists, nurses, and the like—specialists licensed to perform specialized procedures. But for general practitioners and all the other the clinicians who interact with the person rather than with the organs, says Sequenom’s Cantor, “The physician as wise counselor pretty much disappears.” These folks may find themselves acting more and more like—well, tech support: specialists who advise patients on choices and consequences as they struggle to cope with a vastly complex biological system and an exploding array of treatment and prevention options. That, in turn, will force physicians to put a lot more emphasis on communication and teaching skills—talents the medical profession largely ignored in its late 20th century incarnation.

Genomics is both an opportunity and a challenge. The changes it brings will make us all uncomfortable in different ways—intellectually, financially, emotionally, ideologically. But the one thing none of us can do is ignore it. We need to understand how genomics will make the world a different place. And for all of us, the greatest challenge is to feel the shape of the beast: the whole elephant, not just head, trunk, legs or tail.

#####