

The Promise and Perils of Personalized Medicine

A Vimo Research Group™ Report
Expert, Independent and Objective Health Care Analysis

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Introduction

Despite the promise of genetics to alter the medical industry, pharmaceutical companies continue to live and die by blockbuster drugs and the cost of sequencing an individual's DNA is prohibitively expensive for mass market purposes.

Michael Leavitt, current Secretary of Health and Human Services, has made advancing personalized medicine one of his department's top priorities. In a speech to the Personalized Medicine Coalition, Leavitt described a move toward more individually tailored treatments as a transformative shift that could dramatically improve treatment. "Personalized health care," he said, "means knowing what works, knowing why it works, knowing who it works for, and putting that knowledge into practice for patients. Personalized health care brings together our best prospects at the cutting edge of health care. It can help us achieve not only better quality, but better value in health care."ⁱ

Leavitt's vision sounds promising, even inspiring, but it is hardly new. At the end of the last century, the New York Times published an article entitled "Outlook 2000: Economy & Industry; In the Works: Drugs Tailored to Individual Patients."ⁱⁱ The premise of the article was that within a decade, pharmaceutical companies would have moved away from manufacturing blockbuster medications that yield \$1 billion or more in annual revenue and onto more narrowly tailored medications designed for an individual's genetic profile. This article reflected the day's conventional wisdom: Just a year earlier, pioneering geneticist Craig Venter had announced that by 2003, every American would have a credit card containing all of his or her genetic information.ⁱⁱⁱ

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and the cost of sequencing an individual's DNA is prohibitively expensive for mass market purposes.

It would be a mistake to suggest that pharmacogenomics—the science of using genetic information to tailor medical treatments—as well as other aspects of personalized medicine have failed to progress in the intervening decade, however. It cost \$3 billion to create the first human genome sequence and in less than ten years, that price has dropped to \$1 million.^{iv} Individual tests for specific genetic markers can now cost as little as \$199. And pharmaceutical makers have begun to sell treatments targeted at specific populations based on genetics or other factors. For example, cancer drugs including Herceptin and Gleevec are prescribed only to patients with specific genetic profiles.^v Similarly, the heart failure drug BiDil, which failed to gain FDA approval in a general population, was studied in smaller populations and is now approved for treating the disease in “self-identified blacks.”^{vi}

In other words, personalized medicine has not made the great leap forward that many predicted it would make, but has instead made a series of small but meaningful advances that will likely lead to further innovations in the years to come. This slower progress can be traced to two major factors. The first hurdle has been that linking diseases to genes and then developing appropriately tailored treatments has proven to be much more difficult than initially anticipated. Although this has slowed treatment advances, it has improved scientific understandings of genetics and disease.

The second challenge stems from the fragmentation of the health delivery system, and at the moment, this difficulty continues to hamper the advance of personalized medicine. Although personalized medicine offers numerous opportunities to deliver

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better medicine at lower costs, the short-term costs to stakeholders including individuals and pharmaceutical makers discourage the widespread adoption of the early diagnostic tests that could facilitate the growth of personalized medicine.

What is Personalized Medicine?

At its core, the idea behind personalized medicine is that the understanding of an individual's genetic profile opens up opportunities to improve treatments and lower costs. In a speech to the Personalized Medicine Coalition, Health and Human Services Secretary Michael Leavitt described the impending shift as one toward "mass personalization."^{vii} That is, despite the name, personalized medicine will not be characterized by the development of individual drugs for individual people, at least in the foreseeable future. Rather, the shift will be from a one-size-fits-all approach to medicine toward treatments and preventive measures tailored to match the genetic profiles of smaller but significant populations.

The Department of Health and Human Services lists four overarching goals for personalized medicine. These four goals are to:

- Find relationships between genetics and disease that can be put into practice.
- Prevent insurers or employers from using genetic data to discriminate against individuals with pre-dispositions to disease.
- Ensure genetic testing is accurate and useful.
- Create standards to enable data sharing.^{viii}

In practice, the hope is that protections to facilitate genetic sharing will encourage individuals to undergo testing, while better data sharing will improve scientific knowledge and speed research breakthroughs.

Theoretically, personalized medicine could include a wide variety of research efforts from stem cell research to pre-implantation genetic diagnosis (identifying and preventing disease risk during in vitro fertilization) to pharmacogenomic treatments for living patients. This paper focuses solely on the promise and challenges of pharmacogenomic research, defined here as understanding and treating the genetic variations that cause disease rather than the symptomatic conditions of the disease.

Research Challenges

At a conceptual level, pharmacogenomic research seeks to identify genetic variations called single nucleotide polymorphisms (SNPs) that either contribute to disease risk or, in certain cases, directly cause disease. Testing and sequencing the approximately 3 billion base pairs that constitute an individual's DNA is prohibitively expensive for population level research, and as such, research into genomic variations instead focus on identifying and analyzing some fraction of individual SNPs. In the past year, this approach has allowed researchers to identify genetic relationships between individual SNPs and several common cancers as well as coronary artery disease.^{ix}

Indeed, some of this research has already been translated into diagnostic testing. For example, deCODE diagnostics has begun offering a test of the "G" allele of SNP rs10757278 and the 'C' allele in SNP rs1333049, located in the vicinity of the tumor suppressor genes *CDKN2A* and *CDKN2B* on chromosome 9p21" which can uncover as much as a two-fold increase in heart attack risk.^x Similar tests exist to

help physicians gauge how quickly their patients will metabolize common drugs including antidepressants, beta blockers and other common drug classes that are processed in the liver.^{xi} As pharmacogenomic research progresses, the expectation is that similar diagnostic tests—and eventually treatments—will be developed to correlate with reasonably common SNP variations.

This knowledge creation is easier said than done, however. One major roadblock for the progression of personalized medicine has been the complexity of linking diseases to specific SNPs. Although many scientists had initially hoped that single genes would be related to single diseases—that is, diseases would be monogenic—this is generally not the case. While approximately five percent of diseases are monogenic, the remaining 95 percent stem from mutations in a variety of genes, as well as environmental and lifestyle factors.^{xii}

Unlike testing for monogenic diseases, testing for the relationship between multigenic disease and SNPs can be costly and is fraught with the potential for error. For example, recent studies that identified the relationship of certain SNPs to coronary artery disease tested 500,000 SNPs per individual, creating “the potential for false positive results [that] is unprecedented.”^{xiii} This study of coronary artery disease—which used two distinct populations and analyses—uncovered nine statistically significant links between SNPs and heart disease in the first analysis, confirming only three links on the second analysis.^{xiv} Genomic researchers can compensate for this problem by using stringent statistical models that use high threshold significance levels, but this can lead to an increased risk of false negatives (ruling out SNPs that may actually contribute to a condition.) As a result, replicating the results from genomic studies is even more critical than under traditional scientific methods.

This process is further complicated by questions about population selection. The most conclusive link between a SNP variation and coronary disease—the one tested for by deCODE genetics—has been confirmed in several studies of Caucasians, but not in non-white populations. Thus the 9p21.3 SNP variation that increases heart attack risk in Caucasian individuals has been found to not increase this risk for individuals of African descent.^{xv} The reason this relationship appears for whites and not blacks is unclear; for that matter, the reason the SNP variation seems to contribute to heart disease risk in whites is unclear. Nor is there any treatment aimed at the genetic variation itself.

Using race as a proxy for larger genetic variations is, itself, a heavily debated issue for both social and scientific reasons beyond the scope of this paper. In brief, though, it should suffice to note that evolutionary anthropologists have found that far more genetic variation—approximately 94 percent—occurs within the same racial groups rather than between groups, that the variation of genetic traits is gradual rather than distinct, and that different groups have interbred historically, rendering “race” essentially meaningless from an evolutionary perspective.^{xvi}

Simply being able to identify and confirm through several studies a relationship between a SNP and a disease represents the beginning of a shift to the sort of research that would have been fundamentally impossible a decade ago. At the same time, as researchers have begun to advance genomic research, they have found that the basic science is vastly more complicated than anticipated.

Fractured Payment System

Despite the long-term potential of personalized medicine to deliver better medicine at lower costs, the short-term costs of regular genetic testing are exceedingly high for both individuals and pharmaceutical makers.

With both monogenic as well as multigenic diseases, research and treatments have not progressed as quickly as previously hoped for a second set of reasons: Despite the long-term potential of personalized medicine to deliver better medicine at lower costs, the short-term costs of regular genetic testing are exceedingly high for both individuals and pharmaceutical makers.

For pharmaceutical makers, a better understanding of genetics comes with the promise of facilitating research and drug development, but with the potential drawback of eliminating the blockbuster drug. In the short-term, better genetic testing will help doctors and pharmaceutical makers understand who should take a particular medication or receive a specific treatment. Such testing could improve drug response, reduce adverse reactions, and increase the speed at which individuals receive the appropriate treatments, all of which could improve treatment and lower overall health care costs.^{xvii}

This would make for good medicine, but not necessarily good business. For most conditions, doctors have few options but to prescribe a potential treatment for any patient with a condition and hope it works. If genetic testing demonstrates that the drug will only work in one in five patients with a specific mutation, a pharmaceutical maker has lost eighty percent of its potential market.^{xviii} Although improved diagnostics can help pharmaceutical makers rescue failed drugs—a point that will be discussed in more detail in the next section—diagnostics for blockbuster medications could be disastrous financially.

Further hampering investment is the poor reimbursement rate for diagnostic tests.^{xix} As a general rule, diagnostic and preventive genetic screenings are not well-reimbursed by insurers, and because of this, most pharmaceutical companies and other investors are hesitant to sink much money into genetic screenings.

Without protections for genetic data, it may be unrealistic to think that individuals will pay for tests on their own. Beyond the direct costs of any genetic testing, knowing one's genetic profile can lead to more problems than solutions for several reasons. In part, this is because diagnostic testing has outpaced treatment options. A woman can find out if she carries a gene that will give her a dramatically increased chance—as high as an 85 percent lifetime chance—of developing breast cancer.^{xx} Her options, however, are limited to increasing the frequency of cancer screenings or prophylactic surgery.

Furthermore, and perhaps more importantly, federal laws do not yet prohibit third parties from sharing genetic data.^{xxi} At the moment, a third party testing company can sell a person's genetic data to advertisers, insurers or anyone else who cares to purchase it.^{xxii} Although it may seem unlikely that a testing company would risk the fallout of selling genetic data, the threat to an individual can be significant. By undergoing testing, a woman might find out that she has a high predisposition to cancer, few options to avoid the disease, and that—in the absence of strong privacy protections for genetic tests—she may now have more difficulty finding a job or health insurance to allow her to pay for the cancer therapy she will almost certainly need.

Because there are few incentives for any patient to undergo genetic testing, there is a lack of good data for pharmaceutical researchers to use to develop tailored

treatments. But because there are few personalized treatment options, individuals have little reason to want genetic tests—and given the lack of privacy protections, good reason to want to avoid them.

Discussion

Despite these challenges there are several reasons to think that pharmacogenomic research will continue to progress. First, while identifying relationships between genes and diseases has proven to be significantly more difficult than expected, this genetic research has not been a dead end. Not only do scientists have a better understanding of genetics in general, but pharmacogenomic research has led to improved diagnostics and several early, tailored medicines including BiDil, the drug aimed at African American heart failure patients, and the breast cancer medication Herceptin.

These advances not only represent initial pharmacological breakthroughs, but they demonstrate a regulatory willingness on the part of the FDA to grant approval for medicines aimed at smaller parts of the population.

These treatments also represent business opportunities. While targeting treatments to genotypes could undermine the market for blockbuster drugs, in the case of medications such as BiDil, finding a targeted therapeutic group—in this case, “self-identified Blacks,” an approval that has not come without controversy—has allowed pharmaceutical researchers to rescue a previously failed medication. Indeed, approximately 80 percent of drugs that reach the clinical trial stage fail, contributing significantly to the costs of drugs for all stakeholders.^{xxiii}

This early acceptance of tailored treatment should encourage investment into further pharmacogenomic research. Additionally, consumer driven health care—by eliminating some of the fragmentation of the payment system and encouraging preventive treatment—should help drive some early testing that will facilitate future research and breakthroughs. In addition, the House of Representatives overwhelmingly passed legislation to prevent employers or insurers from using genetic data to make coverage or hiring decisions. But as of November 2007, more than six months after passing in the House, the bill has yet to be voted on in the Senate.^{xxiv}

Banking on these protections and the rise in consumer interest, a number of new companies have begun to offer direct-to-consumer DNA tests that allow consumers to purchase tests that identify risks for specific diseases. By some estimates, the potential market for genetic testing is \$12.5 billion, and although these tests are not yet comprehensive, they do offer early test subjects the opportunity to learn more about their disease profile risks.^{xxv}

Regardless of the popularity of these tests, pharmaceutical and scientific research into the genetic basis of diseases should continue unabated. The most promising avenue for pharmacogenomics involves monogenic diseases such as Huntington's Disease since the association between the gene and disease is clear. For many diseases or traits, however, the link to a single genetic mutation, or even several mutations, may be much less clear. Even 23andMe, one of several new companies offering direct-to-consumer DNA testing, acknowledges that for a trait like height, despite apparent links between a number of genetic variations and height, "The

most conclusive study to date pinpointed an individual gene that influences the trait, but it accounts for only a centimeter of a person's stature.^{xxvi}

Ultimately, eliminating some of the fragmentation in health financing and increasing privacy protections will hasten genetic research. But whether or not this research will fundamentally transform the practice of medicine will depend on the ability of geneticists to uncover meaningful associations between genes and traits, rather than genes that contribute to only a small fraction of an individual's constitution.

ⁱ Leavitt, Michael. "Remarks Prepared for the Honorable Mike Leavitt, Secretary of Health and Human Services, on Personalized Medicine Coalition." September 19, 2007. <http://www.hhs.gov/news/speech/2007/sp20070919a.html>.

ⁱⁱ Pollack, Andrew. "Outlook 2000: ECONOMY&INDUSTRY; In the Works: Drugs Tailored to Individual Patients." *New York Times*. Dec. 20, 1999. <http://query.nytimes.com/gst/fullpage.html?res=9A07E5DB1130F933A15751C1A96F958260>.

ⁱⁱⁱ Duncan, David Ewing. "Welcome to the Future: With a little help from Google, secretive Silicon Valley startup 23andme is betting you'll want to Web-surf your own DNA. But is the science ready?" *Portfolio*. November 2007. <http://www.portfolio.com/news-markets/national-news/portfolio/2007/10/15/23andMe-Web-Site>.

^{iv} Ibid.

^v The Deloitte Center for Health Solutions and Deloitte Consulting LLP. "Targeted Therapies: Navigating the Business Challenges of Personalized Medicine." January/February 2007.

^{vi} Temple, Robert and Norman L. Stockbridge. "BiDil for Heart Failure in Black Patients: The U.S. Food and Drug Administration Perspective." *Annals of Internal Medicine*. Jan. 2, 2007. Pages 57-62.

^{vii} Leavitt, Michael. "Remarks Prepared for the Honorable Mike Leavitt, Secretary of Health and Human Services, on Personalized Medicine Coalition." September 19, 2007. <http://www.hhs.gov/news/speech/2007/sp20070919a.html>.

^{viii} "Personalized Health Care for Informed and Effective Choices." Department of Health and Human Services. <http://www.hhs.gov/myhealthcare/goals/index.html#Goal1>. Accessed November 16, 2007.

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^x deCODE Diagnostics Website. <http://www.decodediagnostics.com/MI-faq.php>. Accessed November 21, 2007.

^{xi} "FDA Clears First of Kind Genetic Lab Test." *FDA News*. December 23, 2004. <http://www.fda.gov/bbs/topics/news/2004/new01149.html>

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^{xiii} Hunter, David J. and Peter Kraft. "Drinking from the Fire Hose—Statistical Issues in Genomewide Association Studies." *New England Journal of Medicine*. 357:5. August 2, 2007. 436-439.

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About Vimo

Vimo is the nation's first integrated comparison-shopping portal for healthcare products and services. On January 24, 2006 we launched a website that allows businesses and consumers to research, rate and purchase health insurance plans and Health Savings Accounts (HSAs), and choose doctors from across the country. Vimo brings together a variety of private and public data sources so that shoppers can find a physician and compare hospital prices for medical procedures. Vimo users can read and post reviews about any of the services or products available.