

# How Can We Move Clinical Genomics Beyond the Hype?

## Timely Analysis of Immediate Health Policy Issues

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*“All of the fruits of the tremendous explosion in innovation that’s been occurring in biomedical research – which make the molecular metamorphosis possible – fulfill their purpose only when they are translated into interventions and solutions that are applied to patients.”*

*—Dr. Andrew von Eschenbach, U.S. Food and Drug Administration Commissioner, 2006*

### Introduction

More than a decade after the successful mapping of the human genome, clinical genomics<sup>1</sup> is starting to permeate important parts of patient care and propel ripples throughout the entire U.S. health care system.

Although the field has fallen far short of the transformational therapeutic impact once widely predicted, particularly in regard to common diseases, specific interventions have crossed the divide between rarity and regular use. Genetic testing routinely guides therapy in several common cancers and in HIV disease, and use of costly molecularly targeted anti-cancer drugs is rising sharply. Six in 10 primary care physicians have ordered a genetic test.<sup>2</sup>

Pharmacogenomics, the science of how genetic differences can affect individual drug responses, has become an established part of drug discovery and of the guidance given to physicians on the labels of drugs approved by the Food and Drug Administration (FDA).

Yet while increased adoption is partly due to growing acceptance of useful interventions, it is also due to a porous regulatory structure that allows diagnostic tests of unproven

or no value to be marketed to providers and patients. The result of this policy vacuum is a disturbing paradox. Genomics as a field is beginning to demonstrate its profound potential to improve health and health care. At the same time, the evidence suggests that the current use of clinical genomics tests and therapies often contributes to wasteful spending and even patient harm.

A 2008 article in *Health Affairs* warned that the low threshold for allowing “unsubstantiated [genomic] technologies to enter into practice [has] the potential to overwhelm the health system.”<sup>3</sup> Since then, private-sector efforts to encourage use of clinical genomics have intensified, while efforts to ensure appropriate use have lagged. Evidence-based guidelines for clinicians remain scarce, despite growing efforts to address the problem, and those that do exist can be contradictory. A federal advisory committee that pushed for greater regulation and more reliable data had little impact and was disbanded last year. Meanwhile, government funding for assessment of the evidence on genomic interventions has plunged.

Integrating clinical genomics into routine care poses multiple system

challenges beyond the direct doctor-patient interaction. Health information technology systems typically possess neither the ability to present genomic information in a structured way clinicians can use nor the large data storage capabilities such information demands. Comparative effectiveness research needs to focus on identifiable subpopulations where clinical genomics interventions can have the most powerful impact, but the concept of “identifiable” can raise awkward questions about race and ethnicity.

Finally, the science involved is complicated and often confusing to patients, payers, providers and policymakers alike, making informed decisions that much more difficult.

Controversies over appropriate genetic testing related to the risk of breast cancer have already drawn in all three branches of the federal government and numerous private players. As issues related to clinical genomics become a regular part of access, cost and quality discussions, it is time for a policy community long fluent in the argot of DRGs and billing codes to acquire similar proficiency in the language of DNA and genetic codes. This paper aims to assist that process by examining what

is hype, what is hopeful and what is starting to make a genuine difference in clinical genomics. It also makes specific recommendations about the type of information that would help policymakers, payers, providers and the public make better decisions about the use of clinical genomics.

## The Beginning of the Bench-to-Bedside Journey

When a draft map of the human genome was announced in 2000, followed by a complete map in 2003, breathless predictions of imminent breakthroughs blossomed everywhere from opaque scientific journals to the set of *Oprah*. If the expected clinical cornucopia has not yet materialized, other metrics show substantial results. The \$3.8 billion the U.S. government invested in the Human Genome Project from 1988 through 2003 helped spark \$796 billion in economic impact and \$244 billion in total personal income. In 2010 alone, genomics research and industry activity directly and indirectly supported 310,000 jobs.<sup>4</sup>

The result has been a surge in scientific discovery unparalleled in Western medicine.<sup>5</sup> Consider:

- More than 3,000 genes have been linked to Mendelian (single-gene) disorders.<sup>6</sup>
- Genome-wide association studies, searching beyond single-gene disorders, have found significant correlations between more than 1,200 common genetic variations and 210 traits. These ranged from the clinically important (abdominal aortic aneurysm) to the curious (the ability to smell asparagus in one's urine).<sup>7</sup>
- Different genes code for different enzymes. One family of enzymes, cytochrome P450 (CYP450), has been identified as involved in the metabolism of 90 percent of all drugs.<sup>8</sup> Just one member of this family, CYP2D6, is involved in the metabolism of 100 different drugs, including analgesics, anti-arrhythmics, antidepressants, beta-blockers

and opioid agents.<sup>9</sup>

Genes, chromosomal abnormalities, proteins in the blood and similar indicators are called biomarkers, and they are the key to clinical genomics. For example, certain proteins are associated with more aggressive cancers, while other biomarkers can predict the response to a medication.

In 2003, the FDA began asking companies to voluntarily submit some types of biomarker data related to clinical usage in order to enhance drug safety and effectiveness. In cases where having biomarker information is critical to safe and effective use, the FDA would not allow voluntary submission. The FDA also now requires drug companies to ensure that a companion diagnostic test is approved with the drug approval.

As of June 30, 2011, the agency had approved genomic biomarker information for 76 unique drugs,<sup>10</sup> including the following:

- Twenty-six different genetic biomarkers affecting 18 different therapeutic areas ranging from anti-infectives to psychiatry.
- Common medications used to treat heart disease, depression and pain.
- A preponderance of oncology drugs, with more to come: the oncology drug pipeline contains an estimated 300 Phase II or higher candidates with the potential for testing against a genetic biomarker.<sup>11</sup>

### Precision Labeling for “Precision Medicine”

Language shapes perceptions, but not always accurately. Proponents of “personalized” and “predictive” medicine tend to use those terms within a framework of DNA determinism that pays little more than lip service to individual characteristics unrelated to genetic biomarkers. Yet 40 percent of the factors contributing to premature death among Americans are linked to behavior, 30 percent to genetics, 15 percent to social factors, 10 percent to medical care and 5 percent to environment.<sup>1</sup> A personal genotype remains a much less powerful predictor of future health than a good family history.

As genomic medicine enters the health care mainstream, those in the field should consider a description of their role that recognizes the importance of other approaches. Terms such as “genetically personalized medicine” or “personalized genetic medicine” would make policy discussions about “precision medicine” a great deal more precise.

<sup>1</sup>McGinnis JM, Williams-Russo P and Knickman JR. “The Case For More Active Policy Attention To Health Promotion.” *Health Affairs*, 21(2): 78–93, 2002.

## Genomic Science: Harder Than It First Looks

Almost every cell in the human body contains two copies of the genome, with one each from the father and mother. (Egg and sperm cells contain only one genome copy, while red blood cells have none.) The genome itself is a kind of “book of life” composed of 23 chapters (chromosomes), each containing a thousand or more stories (individual genes), and each of those stories is made up of base-pair DNA “words”—a total of nearly three billion of them.<sup>1</sup>

Rather than being static, though, the genome is dynamic. Genetic code translates into a functional biological effect when the gene is “expressed” as a protein. When this happens, the underlying “genotype” (the total information in the genome) is actualized as a “phenotype” (the manifestation of an individual’s genome, including characteristics ranging from eye color to a disease state).

A cause-and-effect relationship between a specific disease and a specific protein was first established by Linus Pauling and colleagues in a seminal 1949 paper on sickle cell anemia. Pauling confidently predicted “significant progress in the field of medicine as it is transformed from its present empirical form into the science of molecular medicine.”<sup>2</sup> Six decades later, testing for sickle cell disease has improved, but there have been few advances in treating it. Despite the mapping of the human genome, there are three major reasons clinical progress has been so difficult.

- **There is much about the human genome that we still don’t know.** There is roughly a 99.5 percent similarity between the genomes of any two human beings.<sup>3</sup> These remaining differences amount to more than 16 million DNA variants, and although this number is tiny in relative terms, it is these variations that likely contribute to common diseases. Tests that sequence only a part of each genome may miss the bigger picture. Whole genome sequencing has great potential, but given the variation in human genomes, identifying a specific gene variant responsible for a particular condition remains extremely complex.
- **What a disease looks like in the exam room can be very different when seen from a genetic viewpoint.** At a genetic level, the appearance of disease commonality can vanish. For instance, hypertrophic cardiomyopathy—a thickening of the heart muscle—looks like one disease on an echocardiogram, but 20 different genes could be involved. Even untangling complex genetic interactions may not yield much care improvement: “Type 2 diabetes is the most genetically understood and dissected disease out there,” notes James Evans, editor-in-chief of *Genetics in Medicine*. “Yet from a clinical standpoint, the [genetic] information is of questionable utility.”<sup>4</sup>
- **Environmental factors can actually change the way an individual’s genetic code is expressed.** “Why Your DNA Isn’t Your Destiny,” is the way a January 18, 2010 *Time* magazine cover story summarized the impact of epigenetics. Environmental factors can alter the “epigenome” that sits on top of the genome and tells genes to switch on or off. Given the importance of diet and stress in epigenetics, the saying “you are what you eat” may be figuratively true at a molecular level.

Put all this together and the genomic medicine challenge once thought to be like a jigsaw puzzle more closely resembles a Rubik’s cube. Eric Green and Mark Guyer of the National Human Genome Research Institute write, “Our ability to generate [genomic] information has outpaced our ability to analyze it.”<sup>5</sup>

<sup>1</sup> Ridley M. *Genome: The Autobiography of a Species in 23 Chapters*. New York: Perennial, 2000.

<sup>2</sup> Pauling L, Itano H, Singer SJ, et al. “Sickle Cell Anemia, a Molecular Disease.” *Science*, 110: 543–548, 1949.

<sup>3</sup> Levy S, Sutton G, Ng PC, et al. “The Diploid Genome Sequence of an Individual Human.” *PLoS Biology*, 5(10): e254, 2007. Note: Others have used a figure of 99.9 percent similarity.

<sup>4</sup> Evans JP. “Health Care Professionals and Personalized Medicine.” (Paper presented at Personalized Medicine in the Clinic Conference, Phoenix, AZ, March 8, 2010.)

<sup>5</sup> Green ED and Guyer MS. “Charting a Course for Genomic Medicine from Base Pairs to Bedside.” *Nature* 470: 204–213, 2011.

The availability of genetic biomarker data on FDA-approved labels and information on diagnostic tests from organizations such as the National Institutes of Health (NIH) suggest an orderly process of translating research into patient care. The reality is far less systematic.

### Dissemination With and Without Validation

Clinical genomics tests have carved out an increasingly important role in improving the quality of patient care. The tests are now used to make a prognosis, confirm a diagnosis, adjust a medication dose, make

treatment decisions, and monitor therapy. However, two major barriers stand in the way of widespread use: proof of test validity and clinical utility. Test validity—whether a test accurately measures a biomarker—is an issue because current federal regulation only requires that these tests measure what they say they do, not whether what they purport to

measure is of the clinical significance that is claimed. More broadly, the science underlying many studies of genetic biomarker significance has also been challenged.<sup>12</sup> Proven clinical utility matters because physicians won't use a test unless they believe it provides actionable information that can help patients.

The FDA has generally exercised what it calls "enforcement discretion" in regard to so-called laboratory-developed tests (LDTs). In plain English, the FDA has decided not to regulate them. Historically, LDTs have been simple, well-understood tests designed by pathologists to enable the medical staff to diagnose rare conditions. Nicknamed "home brews," they have a low risk of patient harm. At present, LDTs need only comply with the good manufacturing practices set out in the Clinical Laboratory Improvement Amendments (CLIA).<sup>13</sup> CLIA requires that a lab show it is able to perform the test accurately, not that the test itself is valid.

However, many of today's diagnostic tests are as far from "home brews" as breakfast at a fast food franchise is from Mom's homemade muffins. For example, in vitro diagnostic multivariate indexed assays (IVDMIA) produced by commercial labs examine multiple genes and use complex algorithms to produce a risk score predicting prognosis for a disease or drug response. While test-makers can voluntarily seek FDA approval, perhaps hoping for a marketing advantage, fewer than two dozen of more than a thousand genomic tests on the market have FDA approval.<sup>14</sup>

### *Failing to Protect Patients from Harm*

In an April 2008 report by the Department of Health and Human Services, the Secretary's Advisory Committee for Genetics, Health and Society recommended enhanced oversight of LDTs because of serious cost and quality concerns.<sup>15</sup> One example was inaccurate test results intended to diagnose a serious genetic condition in some individuals with lower back pain. Opponents of more regulation, led by pathologists and clinical labs, warned that greater oversight could delay introduction of innovative new tests, and the FDA in June 2009 settled for publishing suggestions on how labs could voluntarily improve quality.<sup>16</sup>

A year later, the agency altered course, citing "public health concerns" in a Federal Register notice that signaled an intent to regulate. "While the absence of FDA oversight may make it easier for laboratories to develop and offer tests on a rapid timeline...diagnostics critical for patient care may not be developed in a manner that provides a reasonable assurance of safety and effectiveness," the agency wrote.<sup>17</sup> Indeed, a July 2010 article by the FDA commissioner and the NIH director added new problems caused by unreliable LDTs to the Secretary's Advisory Committee's list. The additional issues included:

- Women falsely informed they were negative for the BRCA mutation, which conveys a high risk of breast cancer.
- One woman whose ovaries were removed unnecessarily due to a

false reading on an ovarian cancer test.

- A test for Down syndrome that was discovered to be flawed just days before going to market.<sup>18</sup>

At a March 2011 meeting sponsored by the National Comprehensive Cancer Network, one physician spoke of lung cancer patients routinely receiving "180 or 190" molecular tests despite a "lack of evidence" of the tests' clinical validity.<sup>19</sup> A few months later, a page-one article in the *New York Times* detailed how IVDMIA from respected academic labs produced inaccurate treatment recommendations for cancer patients.<sup>20</sup> As of mid-October 2011, the regulations promised in June 2010 had not yet appeared. Separately, Senator Orrin Hatch (R-UT) is reportedly preparing legislation on this issue.

### *The Direct-to-Consumer Market Draws Attention*

The FDA, Congress and others have paid more attention to the much smaller, direct-to-consumer (DTC) genetic test market, where questions about accuracy and usefulness have generated national publicity and Congressional interest. DTC tests range from the well-established (paternity tests) to the pseudo-scientific (predicting a child's sports abilities) to the debatable (genome-wide scans offering information on everything from ancestral origins to caffeine sensitivity to predisposition to various diseases). Supporters point to the tests' personal utility, while skeptics refer to recreational genomics; the truth may depend on what test is used for what purpose.

## The BRCA Battle: Hope, Hype, Fear, Money, Politics and Science

The economic, clinical, legal and political questions swirling around testing for the BRCA mutations have involved all three branches of the federal government and numerous private players. It's a story that displays both sides of the clinical genomics coin: personalized, predictive, preventive and precise medicine that can also be political, profit- and plaintiff-driven, and perplexing to both patients and professionals. The different actors involved are set forth in italics below.

*Women* who inherit mutations in the Breast Cancer 1 and/or 2 (BRCA1 and BRCA2) genes have about a 50 percent lifetime risk of developing breast cancer and a 40 percent lifetime risk of ovarian cancer.<sup>1</sup> *Men* with one or both mutations run an increased risk for prostate and even breast cancer. Both sexes have a higher risk of pancreatic cancer.

The BRCA genes were cloned at the *University of Utah* in the early 1990s and quickly licensed to and patented by *Myriad Genetics*. An estimated 20 percent of the human genome is patented, and Myriad's patents have been challenged in a long-running lawsuit pitting the *American Civil Liberties Union*, the *Public Patent Foundation* and the *Association for Molecular Pathology* against the *U.S. Patent and Trademark Office*, the *University of Utah Research Foundation* and Myriad. Myriad lost in a lower court in 2010, but the loss was partially reversed in July 2011 by a federal circuit court.<sup>2</sup> That ruling, in turn, is being appealed to the *U.S. Supreme Court*.

### *Deciding Who Gets the Test*

The financial stakes are high. Myriad sells its BRCAAnalysis test for about \$3,300 per patient, and it generates about \$350 million in annual revenues. The *U.S. Preventive Services Task Force* (USPSTF) and the *Centers for Disease Control and Prevention* (CDC) both recommend BRCA testing only for those whose family history indicates increased risk. The USPSTF guidelines include seven different clinical scenarios, but only one in five *primary care physicians* could correctly identify what to do in all of them.<sup>3</sup>

The absence of easy-to-use and reliable decision support is emblematic of the situation for less-publicized interventions. The *Agency for Healthcare Research and Quality* (AHRQ) commissioned research on a Web-based BRCA decision support tool for doctors and patients alike, but it had no money to fund full development. A tool that draws on the AHRQ work is being developed elsewhere drawing on federal funding for breast cancer awareness.

### *Legal Issues*

In 2008 an Illinois appellate court ruled in a malpractice case<sup>4</sup> involving BRCA testing that cost concerns are not a defense for recommending against a genetic test. That decision has led some analysts to worry that malpractice fears will prompt unneeded testing. A separate legal and ethical question is whether doctors with a BRCA-positive patient are obligated to contact non-patients who are that patient's relatives.<sup>5</sup>

Meanwhile, the one lawsuit filed in connection with the *Genetic Information Nondiscrimination Act*, passed in 2008 to protect individuals from actions by health insurers or employers, involved a BRCA-positive woman who allegedly lost her position at work after undergoing bilateral prophylactic mastectomy.<sup>6</sup>

### *The BRCA Test in Context*

With all the attention paid to the BRCA mutations, it's easy to forget that they occur in just two out of a thousand women in the general population and account for less than 5 percent of all breast cancers. To put those numbers into context, two hours per week of brisk walking can reduce the risk of breast cancer by nearly 20 percent for the 99.8 percent of women without the BRCA gene.<sup>7</sup>

Perhaps the most important lesson, then, is that clinical genomics interventions should be seen as part of a larger picture. They are a means to an end. Appropriate use adds value and improves care; inappropriate use adds cost and can threaten health.

<sup>1</sup> BRCA1 and BRCA2: Cancer Risk and Genetic Testing. Bethesda, MD: National Cancer Institute, 2009 [www.cancer.gov/cancertopics/factsheet/Risk/BRCA](http://www.cancer.gov/cancertopics/factsheet/Risk/BRCA).

<sup>2</sup> Pollack A. "Ruling Upholds Gene Patent on Cancer Test." *New York Times*, July 29, 2011.

<sup>3</sup> Bellcross CA, Kolor K, Goddard KA, et al. "Awareness and Utilization of BRCA1/2 Testing Among U.S. Primary Care Physicians." *American Journal of Preventive Medicine*, 40(1): 61–6, January 2011.

<sup>4</sup> Downey v. Dunnington SIU. Appellate Court of Illinois, Fourth District, June 13, 2008, [caselaw.findlaw.com/il-court-of-appeals/1411888.html](http://caselaw.findlaw.com/il-court-of-appeals/1411888.html).

<sup>5</sup> Surbone A. "Social and Ethical Implications of BRCA Testing." *Annals of Oncology*, 22(suppl 1): i60–i66, 2011.

<sup>6</sup> Lowe Z. "Woman's Complaint Could Become Test Case for Genetic Discrimination." *Law.com*, June 2, 2010, [www.law.com/jsp/law/LawArticleFriendly.jsp?id=1202469829813](http://www.law.com/jsp/law/LawArticleFriendly.jsp?id=1202469829813).

<sup>7</sup> Breast Cancer. American Cancer Society, February 9, 2011, [www.cancer.org/cancer/breastcancer/detailedguide/breast-cancer-risk-factors](http://www.cancer.org/cancer/breastcancer/detailedguide/breast-cancer-risk-factors).

A study of five companies selling genome-wide scans found they offered information on 213 conditions, with 20 conditions (such as Alzheimer's, heart disease, type 2 diabetes, psoriasis and restless leg syndrome) having the greatest overlap.<sup>21</sup> Different companies use different gene combinations and predictive algorithms. Predictions made by two of the most prominent companies about seven different diseases for five different individuals agreed less than half the time, one study found.<sup>22</sup> A government report called DTC genetic tests "misleading and of little or no practical use to consumers."<sup>23</sup>

Supporters say the tests can motivate consumers to change behavior, although studies of the behavioral impact are equivocal at best.<sup>24</sup> Moreover, the tests' uncertain accuracy also means some consumers will ask their doctor for unneeded additional testing or, conversely, falsely feel protected. In 2010, following publicity about plans to put a genomic test on drugstore shelves, the FDA reasserted its enforcement authority. So far, it has sent letters to 27 DTC companies asking them to demonstrate that their claims meet legal standards.

This regulatory boldness may have been helped by the fact that the DTC market accounts for less than \$20 million in total revenues<sup>25</sup> and involves mainly small companies. By comparison, the larger molecular diagnostics market produces an estimated \$6.2 billion in revenue for clinical laboratories, according to the research firm G2 Intelligence, and has grown rapidly from 14 percent of clinical lab revenues in 2006 to 21 percent in 2009.

### *A Lack of Data*

Unfortunately, the actual usage, cost and growth rate of clinical genomic tests are impossible to independently ascertain. That's because individual genetic tests are not billed as separate items with the Current Procedural Terminology (CPT) codes used for insurance reimbursement. Instead, billing necessitates an idiosyncratic "code stacking" that obscures what was ordered. However, a sweeping update in CPT codes that takes effect in 2012 is expected to include more than 90 gene-specific and genomic procedures in the Tier 1 category of commonly performed tests, with additional codes to be added in 2013. The update will make it much easier for clinicians to order and be reimbursed for common genetic tests and will also generate data on usage. The most recent effort by researchers to even roughly estimate test usage seems to have been 15 years ago, when a mail survey completed by 245 clinical labs reported 175,314 genetic tests during 1996.<sup>26</sup>

There is not even an accurate count of the number of genetic tests available to be billed for. The Secretary's Advisory Committee endorsed a mandatory test registry at the same time it called for increased test regulation. The committee suggested that CDC, CMS or FDA might be an appropriate lead agency to manage the registry.<sup>27</sup> More than three years later, a Genetic Testing Registry is set to be launched shortly; it will be voluntary rather than mandatory and will be managed by NIH, which will phase out its GeneTests site. Meanwhile, the Secretary's Advisory Committee was itself phased out last year when its charter was not renewed.

Registries notwithstanding, integrating clinical genomics into

routine practice remains a challenging task.

### **Putting Clinical Genomics into Practice**

Because clinical genomics can be complex and confusing, dissemination into patient care requires building an infrastructure that allows clinicians to appropriately order, use and be paid for tests and therapies. When a biomarker, a patient population that could be helped and the benefit itself are well-defined, adoption is easier. Today, genetic testing routinely helps define therapeutic choices for some cancers (lung, colorectal, breast and leukemia), heart transplantation and a number of other conditions. In HIV disease, genetic testing to avoid a potentially life-threatening reaction to the drug abacavir has become the standard of care.

Still, as one overview put it, "The number of genomic markers in clinical practice is very small. The number of markers to guide treatment decisions is even smaller."<sup>28</sup> There is an almost complete lack of evidence from traditional randomized controlled trials, forcing reliance on other forms of evidence. Over the past five years an estimated two dozen clinical genomics evidence reviews have been funded by agencies such as CDC, CMS and AHRQ (including through its USPSTF), yet very few have been able to unequivocally determine clinical utility, even for interventions that have made their way into practice.<sup>29</sup>

Meanwhile, the funding for new research dwarfs the monies available to translate existing research into improved care. Consider the following examples:

- Less than 3 percent of genomics articles in the peer-reviewed literature between 2002 and 2006 included information on translating research into practice.<sup>30</sup>
- Just 1.8 percent of grants in cancer genetics for 2007 by the National Cancer Institute went to translational research, and a scant 0.6 percent of publications on the topic dealt with translational issues.<sup>31</sup>
- The federal office overseeing the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group—a national effort to apply evidence-based medicine to genomics—recently had its budget cut by 90 percent. Funding for CDC’s Office of Public Health Genomics plummeted from \$12.3 million in fiscal year 2010 to an expected \$797,000 in fiscal year 2012.

NIH recently announced plans for a National Center for Advancing Translational Sciences that includes genomic medicine, but its impact is unclear. In contrast, the influence of the private sector continues to grow.

### *Contradictions and Confusion*

One of the most influential private-sector voices is the Blue Cross and Blue Shield Association’s Technology Evaluation Center (TEC), whose recommendations go to health plans serving 100 million members. From 1997 through 2010, the TEC evaluated 24 genomic tests and therapies, including specific interventions and broad topics such as genetics in prostate cancer. About two-thirds of evaluations related to oncology.<sup>32</sup> Large commercial

insurers also review selected tests and drugs.

It is not surprising that different groups reach different and even contradictory conclusions. In 2007, with much fanfare, the FDA approved a genetic test for sensitivity to warfarin, a commonly used and clinically important blood thinner. However, in 2009, CMS reviewed the science and professional group recommendations and decided Medicare would not cover the test’s use. On the other hand, even before testing for the KRAS mutation to guide colorectal cancer therapy was embraced by the FDA, some private payers decided to reimburse for it.<sup>33</sup>

Another example involves breast cancer. The Blue Cross TEC determined that Oncotype Dx, one of two major genetic tests that can guide breast cancer therapy, met its evidence standards, but the similar MammaPrint test did not. Yet the MammaPrint test was FDA-approved, while Oncotype Dx was never submitted for FDA approval. (As noted earlier, FDA approval is not required.) Meanwhile, CDC’s EGAPP Work Group concluded there was evidence for both tests, but not enough to make a recommendation.<sup>34</sup> Randomized trials are underway, but test usage continues to grow in the meantime. The company making Oncotype Dx says 50,000 patients got the test in 2009 at a retail cost of about \$4,000 per patient.<sup>35</sup>

A national survey of randomly selected primary care physicians found that 60 percent had ordered one of four common genetic tests, either for breast or colon cancer or for Huntington’s or sickle cell disease, and 74 percent had referred a patient for genetic testing.<sup>36</sup> The latter two tests are for well-defined single-gene disorders. The former

two tests, while widely used, have a less solid evidence base. Though patients expect their doctors to be able to explain the rationale and workings of genetic tests,<sup>37</sup> they’re likely to be disappointed. While 98 percent of physicians agree that genetic testing is useful in guiding drug therapy, just 10 percent feel adequately informed about using it.<sup>38</sup> Even where evidence is available, it has not been utilized.<sup>39</sup> Patients and providers alike guess at which interventions are investigational and which are not. One large Blue Cross plan has posted its genomic medicine coverage policies online, but it is an exception.<sup>40</sup>

As expensive anti-cancer medicines that provide substantial benefit to a small but genetically identifiable subpopulation become more common, the clinical and cost consequences of reimbursement decisions will rise. For instance, a recent study of a drug that targets the enzymes involved in blood clotting (apixaban) was hailed as “one of the most significant advances in cardiovascular medicine in the last five years” for its impact on mortality and complications.<sup>41</sup> Yet when it comes to getting these types of medications into regular use, researchers recently concluded that “no medical literature exists suggesting how to formally integrate [pharmacogenomic] information into the formulary decision process” used by hospitals, medical groups and health plans.<sup>42</sup>

### *Guidelines and Infrastructure Building*

One solution is to improve guideline development and dissemination to practitioners. Prominent efforts include those of the Clinical Pharmacogenetics Implementation Consortium, affiliated with NIH; the

American Society of Clinical Oncology; and the National Comprehensive Cancer Network. A few large health systems, such as Intermountain Health Care, are trying to build guidelines related to clinical genomics interventions into their electronic medical records (EMRs).

A *JAMA* commentary called for the genomics community to reach out to clinicians with “unambiguous evidence that links the use of genomic information to improved patient-centered health outcomes, particularly for common conditions.”<sup>43</sup> In the meantime, the for-profit sector is building its own implementation infrastructure:

- McKesson, the giant pharmaceutical distributor, is creating electronic guidelines, billing codes and a database to track insurer payment policies. CVS-Caremark and Medco, two of the largest pharmacy benefit managers, are similarly involved in making it easier for providers to order and be paid for genetic interventions.
- DNA Direct, a Medco subsidiary,<sup>44</sup> provides a “turnkey” service to health plans and hospitals. There is a well-defined menu of genetic tests, phone and Web-based advice for professionals and patients, and guidance on what actions to take based on test results.
- Navigenics, with roots in DTC testing, is targeting primary care physicians in a partnership with national concierge medicine company MDVIP (a subsidiary of Procter & Gamble).

Integrating genetic data into care management faces practical problems beyond guideline development and

reimbursement. For instance, biomarker information in drug interaction databases provides value only if the patient’s genetic information is known. Kaiser Permanente and the University of California–San Francisco have genotyped 100,000 Northern California Kaiser enrollees under an NIH grant to link that data electronically to health surveys, other biological data and disease registries.<sup>45</sup> (Kaiser is also part of a larger pharmacogenomics evaluation effort by the 15-member HMO Research Network.) The Department of Veterans Affairs recently announced the “Million Veteran Program,” an effort to consolidate genetic, military exposure, health and lifestyle information in a single database in order to study correlations between genetic variations and disease.

Separately, a national collaborative led by the Coriell Institute for Medical Research is trying to determine whether patient-friendly genetic information, including genetic counseling, will lead individuals with chronic disease to change their behavior.<sup>46</sup> Scalability may be an issue: there are only about 2,000 certified genetic counselors in the nation.

Integrating genetic data into an EMR for routine therapeutic use poses another challenge. Few systems have the capability to process or structure genetic data; even at academic medical centers, clinicians often must enter genetic data manually. Moreover, storage requirements for a patient’s entire genome will be orders of magnitude larger than traditional biomedical information. Experts estimate that just one genome could consume 370 GB, although the ability to focus on desired variants

could shrink those requirements considerably.

### *Genomic Therapy Goes Direct-to-Consumer*

As with diagnostic tests, treatment options based on genetic test results have a direct-to-consumer (DTC) component that skirts traditional gatekeepers. The following are just a few examples:

- PatientsLikeMe, a social media site, enables tracking of genetic variables, treatment choices and patient-reported outcomes for ALS.
- Genomera, a start-up, plans to use “crowd-sourced health science” to enable patients to carry out genomic research.
- Cancer Commons, an open-science initiative, helps patients individualize treatment based on their tumor’s genomic subtype and then rapidly disseminate what they’ve learned to professionals and other patients.
- N-of-One and other consultants offer to help patients find customized, genetic cancer-fighting therapies.

The extent to which these diverse activities will contribute to value-enhancing use as opposed to just increasing volume and costs remains to be seen. The key is whether clinical genomics continues to be treated as a separate phenomenon or is recognized as one more technology, albeit a potentially extraordinary one, to be integrated into the health care system.



## Race, Ethnicity and Genetics: A Difficult Mix

Race and ethnicity can complicate even ordinary clinical encounters; adding in genetics can make those conversations even more awkward. After all, it was not that long ago that genetic pseudo-science was widely used to label some groups as intrinsically inferior.

There are two separate issues involving race and ethnicity. The first is scientific: To what extent should clinical genomics guide treatment of different racial and ethnic groups? The second is economic: How should we ensure access by traditionally underserved racial and ethnic groups?

The science is complicated by code words. A recent journal article referred to a study showing an increased risk of a potentially fatal adverse reaction in “Asian patients” taking carbamazepine, an anticonvulsant and mood stabilizer.<sup>1</sup> The plain meaning refers to anyone from an Asian nation, but in the United States the word is used to refer to certain Asian subgroups. But genetic homogeneity is linked to geographically distinct populations and an ancestrally shared gene pool. “Asian” appearance can be misleading. The carbamazepine study was conducted in Taiwan with Han Chinese patients.<sup>2</sup> Koreans, in contrast, tend to have the Alatic genetic makeup of the Mongolian region.

Sometimes, research can help resolve the racial and ethnic jumble. The blood thinner warfarin is one of the most frequently prescribed drugs in the world, but too low or high a dose can have serious consequences. Three different groups—Whites, Blacks and East Asians—have different probabilities of genetic warfarin sensitivity. Without more information, these racial differences potentially complicate a dosing algorithm. However, an 11-nation study was able to identify a single VKORC1 polymorphism correlated to sensitivity across all racial groups, enabling one dosing algorithm for the drug.<sup>3</sup> (Age, sex and vitamin K intake can also influence warfarin dose-response.)

Sometimes, the way to avoid racial or ethnic concerns may be to screen everyone. For instance, a lawsuit that followed the death of a Black football player with sickle cell trait prompted the National Collegiate Athletic Association to recommend screening all Division I athletes for this condition. However, the universal screening remains controversial.<sup>4</sup>

But sometimes there are simpler ways to deal with these complicated genetic scenarios. With sickle cell screening for athletes, for example, critics say the problem is not a genetic trait, but dangerously high-stress training methods. With both warfarin and carbamazepine, extra watchfulness for an adverse reaction immediately following the first dose can be just as effective as, and much less costly and complicated than, pre-dosage genetic testing.

### Uncomfortable Science

Beyond the practical implications, individuals and ethnic groups may be uncomfortable with science that singles them out. The BRCA genes are more frequently found in Ashkenazi (Eastern European-origin) Jews than in the general population, but Jewish groups remain uncomfortably aware that the false idea of a Jewish “race” has been a staple of anti-Semites.

Many African Americans had similarly mixed feelings when in 2005 the FDA approved BiDil, a combination of vasodilators to treat heart failure, as the first racially targeted drug. The idea of a race-based therapy was controversial,<sup>5</sup> but in the case of BiDil the argument eventually became moot. The drug’s maker had tested it on self-identified Black people, but not on any comparison population, in order to gain a new indication that would extend the drug’s patent life.<sup>6</sup> BiDil was removed from the market in early 2008 after sales plummeted due to lower-priced generics.

The conclusion that race-based drugs are only a marketing conceit, however, has also turned out to be premature. Recall that race and ethnicity can sometimes be a proxy for ancestral geography. Two recent papers in the journal *Nature* found a unique gene structure in African Americans. The researchers plan to pursue similar research with regard to Latinos, who have a mix of European, American Indian and African ancestry.<sup>7</sup>

Scientific and socioeconomic concerns can overlap. For example, the Northwest-Alaska Pharmacogenomics Research Network is conducting pharmacogenomic research in American Indian, Alaska Native and rural Pacific Northwest populations with the aim of identifying genetic differences and also of ensuring that those populations have access to interventions based on those differences. Researchers have also noted ways in which discrimination and other environmental stresses among low-income populations can have epigenetic effects.

Studies have examined the use of genetic testing by physicians serving primarily minority populations (who are significantly less likely to order a test),<sup>8</sup> the use of BRCA testing by Hispanic and Black women at high risk (which has increased, but is still significantly lower than among non-Jewish White women),<sup>9</sup> and the accuracy of a BRCA-carrier prediction tool among minorities (which generally works well for African Americans, Asian Americans and Hispanics, but has room for improvement with non-Hispanics).<sup>10</sup>

Unfortunately, unfair profiling by race remains a danger in the brave new world of clinical genomics, and the old categories of haves and have-nots have not disappeared. As one study put it, “Access and knowledge barriers continue to limit the use of this technology to the wealthy, the well-insured and the medically well-informed.”<sup>11</sup>

<sup>1</sup> The article referred to Stevens-Johnson syndrome among those taking carbamazepine. See Mrazek DA and Leerman C. “Facilitating Clinical Implementation of Pharmacogenomics.” *Journal of the American Medical Association*, 306(3): 304–305, 2011.

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<sup>3</sup> Limdi NA, Wadelius M, Cavallari L, et al. “Warfarin Pharmacogenomics: A Single VKORC1 Polymorphism is Predictive of Dose Response Across 3 Racial Groups.” *Blood*, 115(18): 3827–3834, 2010.

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<sup>5</sup> Carlson RJ. “The Case of BiDil: A Policy Commentary on Race and Genetics.” *Health Affairs (Web Exclusive)*, October 2005.

<sup>6</sup> Wolinsky H. “Genomes, Race and Health.” *EMBO Reports*, 12(2): 107–109, February 2011.

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<sup>8</sup> Shields et al.

<sup>9</sup> Levy DE, Byfield SD, Comstock CB, et al. “Underutilization of BRCA 1/2 Testing to Guide Breast Cancer Treatment: Black and Hispanic Women Particularly at Risk.” *Genetics in Medicine*, 13(4): 349–355, 2011.

<sup>10</sup> Huo D, Senie RT, Daly M, et al. “Prediction of BRCA Mutations Using the BRCAPro Model in Clinic-Based African American, Hispanic and Other Minority Families in the United States.” *Journal of Clinical Oncology*, 27(8): 1184–1190, 2009.

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## The Promise of Clinical Genomics

The buzz of excitement surrounding clinical genomics is similar in some ways to the early enthusiasm for computers in medicine. Both are technologies intuitively perceived to possess enormous power to change care for the better. Both have birthed snappy sound bites: “paper kills,” in the one case, or personalized, predictive, and precision medicine, in the other. And both have attracted true believers whose enthusiasm can sometimes lead them to blur the distinction between what is doable today and what might be possible tomorrow. As with health information technology, the rapid dissemination of clinical genomics technology is strongly backed by businesses that stand to reap significant profits from increased adoption. Although there is nothing inherently wrong with their advocacy, it should be recognized as such.

Those similarities should sound a warning about realistic expectations. As the tools of DNA discovery enter mainstream medicine, clinical genomics is following the same path as other innovations: sometimes underused, because of a lack of understanding or reimbursement; sometimes appropriately used and reimbursed; sometimes overused or misused because of patient or provider enthusiasm, legal pressure or other factors; and sometimes used entirely appropriately to significantly improve patient care.

The challenge is to ensure that as clinical genomics grows in importance, it meets the same evidence standards as other interventions. For example, clinical genomics advocates routinely assert

that biomarker-guided therapy might eliminate expensive and harmful adverse drug reactions.<sup>47</sup> However, were that proposition to be presented seriously to patient safety experts, there would be hard questions about the proportion of adverse reactions attributable to genetic causes in the first place, the type of patient data and information systems needed to implement this solution, and the probability that less costly and complicated interventions could accomplish at least as much a great deal more quickly.

### *Policy Changes to Improve Value*

For policymakers, payers, providers and the public, the overarching imperative is for improved transparency of information. This includes:

1. **Data on evidence.** A recent *JAMA* commentary noted “the thin line between hope and hype in biomarker research.”<sup>48</sup> Right now, there are large gaps in knowledge, either because questionable studies or a lack of data entirely. Dissemination of information on genomics in practice is impeded by having information scattered across multiple websites. Government- and privately funded technology assessments often fail to coordinate methodologies and targets of inquiry.
2. **Data on implementation.** NIH could demonstrate that its forthcoming Genetic Testing Registry will serve constituencies beyond clinical laboratories by making available comprehensive information to researchers and clinicians. The government could also fund more reliable research examining the benefits, harms and economic impact of genomic

interventions in actual practice. At present, the medical literature is largely filled with anecdotes that provide little useful policy guidance.

3. **Data on regulatory actions.** The FDA could finally regulate LDTs as promised, report on what LDT tests have been approved, and initiate post-marketing surveillance on their safety. FDA data on pharmacogenomic information available to prescribing physicians could also be examined, since the agency’s pronouncements on these issues can be contradictory and confusing.<sup>49</sup>
4. **Data for payment.** Public and private payers could be clearer about what evidence they require. Medicare now pays for genomic interventions on the basis of ad hoc decisions. The Medicare Payment Advisory Commission could provide Congress with objective advice about how this technology should be implemented. Evidence-based criteria will become critical with the proliferation of expensive medications targeting small subgroups of patients, particularly those with cancer and other serious diseases.
5. **Data for consumers.** Congress and federal agencies could give the public information and tools it needs to make good decisions about a technology that often raises uncomfortable ethical, clinical and economic questions. For instance, prenatal genetic testing is becoming easier and much less expensive, as is testing newborns for possible predisposition to a long list of diseases that may or may not be clinically relevant. Given the

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risks and benefits of clinical genomic tests set forth in this paper, government and private payers alike could focus more closely on consumer education and protection.

Developing the evidence base and educating doctors, patients and payers on how to use the evidence will take time, patience and money.

The disbanding of a citizen advisory committee that consistently pushed the Department of Health and Human Services for greater oversight is disturbing. “Medicine is no longer able to simply adopt every new change or technology that comes down the pike,” says Robert Davis, a senior Kaiser Permanente researcher. “There is increasing awareness that

things that are ‘obviously’ better... may have unanticipated costs and real medical harms that should make us all demand a higher level of evidence before we adopt change.”<sup>50</sup>

As clinical genomics moves from bench to bedside and becomes a significant component of the U.S. health care system, it is advice well worth following.

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## About the Author and Acknowledgements

Michael L. Millenson is the president of Health Quality Advisors LLC, the Mervin Shalowitz, MD Visiting Scholar at Northwestern University’s Kellogg School of Management and a senior policy consultant to the Urban Institute. The author thanks Bob Berenson and two anonymous peer reviewers for their enormously helpful comments and suggestions and Juliana Macri for her editorial and research assistance. This research was funded by the Robert Wood Johnson Foundation.

## About the Urban Institute

The Urban Institute is a nonprofit, nonpartisan policy research and educational organization that examines the social, economic and governance problems facing the nation.

## Notes

<sup>1</sup> This paper uses clinical genomics as an umbrella term, with the understanding that distinguishing among genetics, genomics, proteomics, epigenetics and other possible categories is more important in a scientific paper than in a policy overview.

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<sup>3</sup> Khoury MJ, Berg A, Coates R, et al. "The Evidence Dilemma in Genomic Medicine." *Health Affairs*, 27(6): 1600–1611, November/December 2008.

<sup>4</sup> *Economic Impact of the Human Genome Project*. Columbus, OH: Battelle Technology Partnership Practice, May 2011, [www.battelle.org/publications/humangenomeproj.pdf](http://www.battelle.org/publications/humangenomeproj.pdf).

<sup>5</sup> Feero WG, Gutmacher AE and Collins FS. "Genomic Medicine—An Updated Primer." *New England Journal of Medicine*, 362: 2001–2011, 2010.

<sup>6</sup> *OMIM—Online Mendelian Inheritance in Man*. Washington: National Center for Biotechnology Information (NCBI), [www.ncbi.nlm.nih.gov/omim](http://www.ncbi.nlm.nih.gov/omim).

<sup>7</sup> Hindorf LA, Junkins HA, Hall PN, et al. "A Catalog of Published Genome-Wide Association Studies." Washington: Office of Population Genomics, 2011, [www.genome.gov/gwastudies](http://www.genome.gov/gwastudies).

<sup>8</sup> Maréchal JD, Kemp CA, Roberts GCK, et al. "Insights into Drug Metabolism by Cytochromes P450 from Modeling Studies of CYP2D6-Drug Interactions." *British Journal of Pharmacology*, 153: S82–S89, 2008.

<sup>9</sup> Caraco Y. "Genes and the Response to Drugs." *New England Journal of Medicine* 351(27): 2867–2869, 2004.

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<sup>12</sup> See the following two sources. Ioannidis JPA and Panagiotou OA. "Comparison of Effect Sizes Associated with Biomarkers Reported in Highly Cited Individual Articles and in Subsequent Meta-Analyses." *Journal of the American Medical Association*, 305(21): 2200–

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<sup>13</sup> The Clinical Laboratory Improvement Amendments of 1988 were passed by Congress in response to public concern over false-negative Pap smear readings from clinical labs. Information on FDA use of those provisions can be found at: [fda.gov/MedicalDevices/DeviceRegulationandGuidance/IVDRegulatoryAssistance/ucm124105.htm](http://fda.gov/MedicalDevices/DeviceRegulationandGuidance/IVDRegulatoryAssistance/ucm124105.htm).

<sup>14</sup> Personal communication with Elizabeth Mansfield, director of the personalized medicine staff, U.S. Food and Drug Administration, 15 July 2011.

<sup>15</sup> "U.S. System of Oversight of Genetic Testing: A Response to the Charge of the Secretary of Health and Human Services." Bethesda, MD: Secretary's Advisory Committee on Genetics, Health, and Society, April 2008, [oba.od.nih.gov/oba/SACGHS/reports/SACGHS\\_oversight\\_report.pdf](http://oba.od.nih.gov/oba/SACGHS/reports/SACGHS_oversight_report.pdf).

<sup>16</sup> Chen B, Gagnon M, Shahangian S, et al. "Good Laboratory Practices for Molecular Genetic Testing for Heritable Diseases and Conditions." *MMWR*, 58(RR06): 1–29, 2009.

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<sup>44</sup> DNA Direct is not involved with PBM activities. Medco itself recently agreed to be acquired by ExpressScripts, but the combination of the two PBMs had not been approved as this was being written.

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<sup>49</sup> A widely quoted statistic used by FDA officials and by others quoting the agency is that "about 10 percent of labels for FDA approved drugs contain pharmacogenetic information." However, the FDA's own website lists just 76 drugs with biomarker information, much fewer than 10 percent of all approved drugs. Having genetic information in the label could be a description of the clinical pharmacology, not of a drug characteristic actionable in clinical practice.

<sup>50</sup> Personal communication with Robert Davis, MD, MPH, director of research, Center for

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