

## P E R S P E C T I V E

**The Health Benefits Of Genomics: Out With The Old, In With The New**

We must dispense with old models of research support and regulatory guidance designed for the pre-Human Genome Project world.

by **Kathy Hudson**

**ABSTRACT:** The disproportionate emphasis on discovery research in genetics and genomics needs to be balanced by new approaches to funding translational research, development of evidence-based clinical guidelines, and robust regulation of genetic tests. These measures will help ensure that patients, providers, and others are better able to discriminate between valid genomic applications that can improve public health and those that are not useful and potentially harmful. Doing so will require that we dispense with models of research support and regulatory guidance designed for the pre-Human Genome Project world, and replace them with policies and programs as innovative as genetics research itself has been. [*Health Affairs* 27, no. 6 (2008): 1612–1615; 10.1377/hlthaff.27.6.1612]

**T**ODAY YOU CAN HAVE one million bits of information mined from your genome or even have the entire three billion DNA letters read and provided to you on a flash drive.<sup>1</sup> But try to present that flash drive to your personal physician, and you're most likely to be greeted with a blank stare. We understand very little of what this sequence means for health and disease. Despite a torrent of funding for basic genetic and genomic discoveries, the much-hyped and much-hoped-for genetic revolution in medicine has not materialized. Muin Khoury and colleagues argue, rightly, that we need to adjust our expectations as well as modernize our approach toward translation of genetics into clinical and public health practice.<sup>2</sup>

The relatively blunt tools of genetics and genomics prior to the Human Genome Project

enabled scientists to harvest low-hanging genetic fruit, ferreting out genes that, when mutated, had a strong and clearly discernible effect on health. These “highly penetrant” gene mutations are responsible for a host of inherited diseases including cystic fibrosis, sickle cell anemia, and Tay-Sachs disease, among others.<sup>3</sup> Because of their strong effects, they were relatively straightforward to identify—they made such a ruckus that they were impossible to miss. And the mass media dutifully trumpeted each new finding, suggesting that the day was imminent when we could “fix” our “bad” genes.

Now, new and more powerful genomic tools such as genome-wide association studies (GWAS) are identifying genetic contributors to common disorders such as diabetes, cardiovascular disease, and prostate cancer.<sup>4</sup> Al-

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*Kathy Hudson (khudson5@jhu.edu) directs the Genetics and Public Policy Center and is an associate professor in the Berman Institute of Bioethics, Institute of Genetic Medicine, and Department of Pediatrics, Johns Hopkins University; she is based in Washington, D.C.*

though this research holds great promise for identifying new targets for prevention and treatment, that promise seems much more distant—temporally and technically—than either its strongest proponents or the media suggest. Association studies will identify the molecular “actors” that play a role in health and disease; however, it is going to take a long time to figure out the twists and turns of the plot. Moreover, GWAS-identified variants have very weak associations with disease. Odds ratios for common genetic variants are generally in the range of 1.1–1.3, a low level of penetrance that makes these variants unlikely to serve as the basis for treatment or prevention.<sup>5</sup>

While weak and often incompletely validated genetic variants make their way into consumer products variously promising to “unlock the secrets of your DNA” or denounced as “snake oil,” is there hope for genomics to provide useful clinical applications in any realistic time frame? Doing so will require that we dispense with old models of research support and regulatory guidance designed for the pre-Human Genome Project world and replace them with innovative policies and programs.<sup>6</sup>

### Out With The Old

The past decade has seen a torrent of funding for basic research that dwarfs the funding for translational research and oversight of genetics and genomics. Consequently, there is no capacity or infrastructure to meet the tsunami of basic research discoveries and move these discoveries rationally into clinical application. In genomics, and more broadly in biomedical research, we need more cost-effective means of evaluating clinical validity and utility. The gold standard of the randomized clinical trial (RCT) may be too expensive and cumbersome for genomic applications, yet we don't want to risk prematurely offering genetic “advice” that turns out to be of questionable clinical value or, worse, may undermine sound medical

counsel.

Hope and hype are difficult to separate and harder still to temper. The Evaluation of Genomics Applications in Practice and Prevention (EGAPP) Working Group set up by the Centers for Disease Control and Prevention (CDC) has embarked on an ambitious project to do just that: review the scientific evidence and make recommendations about the clinical use of a limited set of genetic tests.<sup>7</sup> One of the first products of this exemplary ef-

fort was a review of the clinical validity of variants in cytochrome P450 (CYP450) to guide treatment, drug choice, and dosage for certain antidepressants.<sup>8</sup>

Even with a steady supply of EGAPP-like evidence reviews and a steady supply of evidence-based guidelines, dissemination and adoption of these guidelines is likely to

be a slow and imperfect process. For example, although health care provider and laboratory guidelines for cystic fibrosis (CF) carrier testing were adopted in 2001, there is continuing disagreement in the laboratory community as to how many and which mutations to include in a test panel, as well as inconsistent practices among providers ordering CF screening tests.<sup>9</sup>

### In With The New

The EGAPP process gives us a model for identifying and evaluating the evidence required to demonstrate clinical validity and utility for genetic tests, and to discriminate between valid, useful genetic tests and interventions and those that are unproven or possibly even harmful. But the slow pace at which these reviews operate and the limited number of tests and conditions currently under review argue for a much faster, more streamlined process for understanding which tests are ready for prime time and under what circumstances. Integration of these evidence-based guidelines into clinical decision-support tools embedded in electronic medical records could facilitate appropriate ordering and interpreta-

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tion of genetic tests.<sup>10</sup>

These reviews need to be accompanied by regulatory approaches that employ a risk-based paradigm that doesn't sweat the small stuff, but still keeps unsafe tests out of the marketplace and closely polices the claims made by testing companies about their wares. For example, although the results of the EGAPP review determined that CYP450 testing for depression treatment was not yet ready for clinical use, and these findings were well publicized, companies continue to advertise CYP450 testing for this purpose.<sup>11</sup>

For well over a decade, expert government advisory groups have recommended enhancements in the oversight of genetic tests, but the Centers for Medicaid and Medicare Services (CMS)—which by historical accident is oddly responsible for clinical laboratory oversight—alternately has indicated that the agency is working on regulatory changes, or that the current system is sufficient and no changes are needed.<sup>12</sup> Health and Human Services (HHS) Secretary Michael Leavitt in 2007 asked yet another expert advisory committee to recommend how best to regulate genetic tests. In April 2008 the committee delivered a comprehensive and reasonable set of recommendations; in the four months since, there has been radio silence from HHS, leaving most observers to conclude that these recommendations merely will join others on the shelf.<sup>13</sup>

Where the CMS has been positively obstructionist, at least the Food and Drug Administration (FDA) has signaled interest in ensuring the safety and effectiveness of some novel entrants to the genetic testing market.<sup>14</sup> However, instead of carving out a small subset of tests for oversight, the FDA needs a more holistic approach and should deploy a tiered review process for all laboratory-developed tests (LDTs). FDA review should focus on “high-risk” tests, meaning those that address serious disease and that yield therapeutically actionable information. Additionally, the FDA should consider strategies that allow preliminary approval based on limited evidence coupled with postmarket development of evidence of clinical validity and utility.

The Secretary's Advisory Committee on Genetics, Health, and Society recommendation to develop a mandatory genetic testing registry also is a critical step toward improving oversight, particularly for tests that will not undergo FDA review. Under such a registry, companies selling genetic tests would be required to submit data on the tests' analytical and clinical validity to such a registry. Data would be available to health care providers and the public, to inform their decisions about whether a test is appropriate.

Finally, the Federal Trade Commission must take action to stop false and misleading claims made by purveyors of genetic tests directly to consumers. These claims serve only to confuse the public to the detriment of their pocketbook—and, potentially, their health—and to undermine public confidence in genetic medicine.

In addition to ensuring that tests themselves are safe, we need to ensure that genetic test results are safe from misuse. The recent enactment of the Genetic Information Nondiscrimination Act (GINA)—which will be fully implemented by the end of 2009—makes it illegal for health insurers and employers to use genetic information in coverage or employment decision making.<sup>15</sup> However, as GINA goes into effect, we need aggressive and robust training and education to make sure that patients, health care providers, researchers, and others fully understand what protections GINA does and does not provide.

Needless to say, all of these suggestions presuppose a funding environment where disproportionate emphasis on discovery research is balanced by funding for translational research to establish the validity and utility of new genetic tests, development and dissemination of health professional guidelines, and effective regulation of genetic tests.

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## NOTES

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