

The Genome Gets Personal—Almost

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IT'S THE "YEAR OF PERFECT VISION," 2020. AMY, AGE 21 YEARS, visits with her physician and elects to have complete genome sequencing. At a follow-up visit, Amy chooses to learn of her genetic risk factors for heart disease, diabetes, breast cancer, and colon cancer. Amy's physician provides her with risk scores for those disorders, and with suggestions for lifestyle modifications. Specifically, Amy is alerted to her particularly high risk of developing type 2 diabetes, and her physician recommends a rigorous program of diet and exercise that had been shown in a controlled study to delay or prevent disease onset. The next year, Amy develops mild asthma and her physician selects an optimal therapy based on Amy's genetic profile. Five years later, Amy informs her physician that she and her husband are planning to start a family, and they request information regarding the risk of having a child affected by a serious genetic disease, based on their genome sequence data. She learns that both she and her husband are carriers for the recessive lethal childhood disorder spinal muscular atrophy, and they seek further counseling. When Amy turns 40, she begins colorectal cancer screening based on her higher-than-average risk factors, and at age 45 a precancerous polyp is detected in her colon and is successfully removed.

Only a few years ago, this scenario of personalized medicine in routine clinical care would have seemed wildly optimistic. But Amy's access to complete genome sequencing is actually scientifically plausible and technically feasible today—admittedly at very high cost, given that a commercial entity offers to sequence any individual's genome for approximately \$350 000.¹ On the other hand, the ability to interpret Amy's DNA sequence accurately, and the rigorous testing of interventions to show how best to utilize this information to prevent or treat disease, still requires a great deal of intense research effort. It should not be assumed that those steps will be quick or easy.

The field of human genome research is in a rapid discovery phase. Completion of the Human Genome Project in 2003,² the Phase I HapMap project in 2005,³ and the first phase of the Encyclopedia of DNA Elements (ENCODE) project in 2007⁴ have provided scientists with a wide array of research tools to apply to important medical issues, while simultaneously deepening the understanding of the architecture and function of the genome. The recent initiation of the second phase of the

ENCODE project,⁵ the "1000 Genomes" project,⁶ and initiatives to bring full genome sequencing costs below \$10 000⁷ promise to accelerate knowledge generation further.

Perhaps the most breathtaking recent advances relevant to personalized medicine come from the current explosion of genome-wide association studies. These studies are based on the ability to search the genomes of large numbers of individuals in an unbiased way for statistical associations between the most common form of genetic variation, single nucleotide polymorphisms (SNPs), and the occurrence of disease. Unthinkably expensive as recently as 2004, genome-wide association studies have been made possible through the availability of HapMap data³ and the ability to genotype individuals rapidly and accurately at hundreds of thousands of SNPs on miniaturized gene chips for less than \$1000 per person. In the past year, genome-wide association studies yielded highly robust information on scores of new genetic markers for common chronic disorders including diabetes,⁸ heart disease,⁸ Crohn disease,⁹ and several common cancers.^{10,11} Flowing from each of these discoveries is the potential for new targets for drug development, as well as the development of enhanced tests for screening, diagnosis, and prognosis of common chronic disease.

The majority of genetic risk factors discovered through genome-wide association studies make only modest independent contributions (each increasing the risk by 10% to 40%) to an individual's risk of disease. Many markers have yet to be discovered. For some known markers much remains to be learned about their contribution to the incidence of disease. Despite the profusion of these discoveries in the last year or two, it is apparent that for many disorders a large "heritability gap" exists; ie, the genetic risk factors discovered to date using genome-wide association study approaches explain only a small proportion of the observed heritability. It is also clear that some of these markers occur in regions of the genome that seem to be devoid of actual genes—the most notable example is a region on chromosome 8 that has been strongly linked in several studies to the risk of developing prostate cancer.¹²

Clinical application of these markers for preventive medicine is currently limited by several factors: (1) lack of information on how the prevalence and risk contribution of these markers vary across population groups; (2) limited data on how the inheritance of multiple markers affects an individu-

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al's risk for various diseases; (3) fragmentary information on how most genetic risk factors interact with environmental factors; and (4) a paucity of studies on common diseases that test the effect of interventions based on genetic risk factors.

Despite these limitations, a variety of companies have recently begun to offer direct-to-consumer testing of individual SNPs associated with specific disorders, including type 2 diabetes, breast cancer, and atrial fibrillation. Several companies now offer genome-wide scans, incorporating more than 500 000 markers, for approximately \$1000. Some of these services promise to educate the purchaser on topics ranging from ancestry to behavioral characteristics to cardiovascular disease risk.¹³ Understandably, these early applications of risk assessment have encountered skepticism regarding the correlation between their stated or implied benefits and their actual clinical utility.¹⁴

There has also been considerable recent activity in pharmacogenetics and pharmacogenomics bearing on personalized medicine. For example, the US Food and Drug Administration recently altered the labels of both warfarin and carbamazepine to incorporate language encouraging health care professionals to consider pharmacogenetic testing prior to prescribing these drugs in certain situations. A recent trial demonstrated the successful use of pharmacogenomic testing to reduce the incidence of hypersensitivity reactions in patients with HIV infection who were prescribed abacavir.¹⁵ Several large trials are under way to examine the usefulness of testing for variants in genes affecting warfarin metabolism as part of an algorithm for dose selection to reduce serious bleeding events. In the realm of advanced molecular diagnostics, prognostic tests for breast cancer recurrence based on tumor gene expression arrays are now in wide use.¹⁶

Given the current focus of policy makers and health care payers on containment of health care costs and on evidence-based medicine, a major roadblock, ie, evidence of benefit, limits the adoption of any new technology into mainstream medicine. The challenges personalized medicine faces in this area are not unique. Various respected evidentiary review bodies (including the Centers for Disease Control and Prevention's Evaluation of Genomic Applications in Practice and Prevention and the US Preventive Services Task Force) are struggling to make clinical recommendations regarding applications of personalized medicine, given the relative absence of well-performed clinical studies. Some have identified this lack of evidence as the Achilles heel of personalized medicine and have proposed strategies to address the issue.¹⁷

Another obstacle to widespread application of personalized medicine is fear of genetic discrimination, which is creating difficulties in conducting genetic research studies. Policy discussions over more than a dozen years have led to the conclusion that federal legislative protection is urgently needed, but the legal solution to this problem currently languishes in Congress as a result of a hold by one senator.^{18,19}

Ultimately, the translation of advances in genome research to routine patient care will require an educated population and

educated health care professionals. This barrier should not be underestimated. Numerous organizations including the National Institutes of Health (NIH) have programs designed to increase genetic literacy among the general population, beginning at the level of secondary education. But there is no comprehensive, coordinated national program designed specifically to enhance the public's understanding of the concepts of personalized medicine. Health professional education regarding genomic medicine has also been a component of programs at the NIH and is the central focus of the National Coalition for Health Professional Education in Genetics.²⁰ However, competing educational priorities and a lack of familiarity with basic principles of genetics make it challenging to engage health care professionals in the area of genomic medicine.

There are many rapid advances in personalized medicine to celebrate. But if the goal is to empower Amy and many others like her to take full advantage of these discoveries, it is far too early to declare victory. A great deal of complex, groundbreaking, and multidisciplinary research is still needed before personal genomics reaches the mainstream of medicine.

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REFERENCES

1. Knome Inc Web site. <http://www.knome.com/>. Accessed February 15, 2008.
2. Finishing the euchromatic sequence of the human genome. *Nature*. 2004; 431(7011):931-945.
3. A haplotype map of the human genome. *Nature*. 2005;437(7063):1299-1320.
4. Birney E, Stamatoyannopoulos JA, Dutta A, et al. Identification and analysis of functional elements in 1% of the human genome by the ENCODE pilot project. *Nature*. 2007;447(7146):799-816.
5. Researchers expand efforts to explore functional landscape of the human genome [press release]. <http://www.genome.gov/26023194>. Released October 9, 2007. Accessed February 15, 2008.
6. Kaiser J. DNA sequencing: a plan to capture human diversity in 1000 genomes. *Science*. 2008;319(5862):395.
7. Archon Genomics X Prize Web site. <http://genomics.xprize.org/>. Accessed February 15, 2008.
8. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature*. 2007;447(7145):661-678.
9. Mathew CG. New links to the pathogenesis of Crohn disease provided by genome-wide association scans. *Nat Rev Genet*. 2008;9(1):9-14.
10. Easton DF, Pooley KA, Dunning AM, et al. Genome-wide association study identifies novel breast cancer susceptibility loci. *Nature*. 2007;447(7148):1087-1093.
11. Zanke BW, Greenwood CM, Rangrej J, et al. Genome-wide association scan identifies a colorectal cancer susceptibility locus on chromosome 8q24. *Nat Genet*. 2007;39(8):989-994.
12. Gudmundsson J, Sulem P, Manolescu A, et al. Genome-wide association study identifies a second prostate cancer susceptibility variant at 8q24. *Nat Genet*. 2007; 39(5):631-637.
13. 23andMe Web site. <https://www.23andme.com/>. Accessed February 15, 2008.
14. Hunter DJ, Khoury MJ, Drazen JM. Letting the genome out of the bottle—will we get our wish? *N Engl J Med*. 2008;358(2):105-107.
15. Mallal S, Phillips E, Carosi G, et al. HLA-B*5701 screening for hypersensitivity to abacavir. *N Engl J Med*. 2008;358(6):568-579.
16. Harris L, Fritsche H, Mennel R, et al. American Society of Clinical Oncology 2007 update of recommendations for the use of tumor markers in breast cancer [published online October 22, 2007]. *J Clin Oncol*. <http://jco.ascopubs.org/cgi/content/abstract/JCO.2007.14.2364v1>. Accessed February 19, 2008.
17. Khoury MJ, Gwinn M, Yoon PW, et al. The continuum of translation research in genomic medicine: how can we accelerate the appropriate integration of human genome discoveries into health care and disease prevention? *Genet Med*. 2007; 9(10):665-674.
18. Hudson KL. Prohibiting genetic discrimination. *N Engl J Med*. 2007;356(20): 2021-2023.
19. Genetics benefits at risk. *Nature*. 2008;451(7180):745.
20. National Coalition for Health Professional Education in Genetics Web site. <http://www.nchpeg.org/>. Accessed February 15, 2008.