FROM BIRTH TO DEATH AND BENCH TO CLINIC

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CHAPTER 29

Personalized Medicine and Genomics

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personalized medicine and genomics

by Anne-Marie Laberge and Wylie Burke

Framing the Issue

Clinicians seek to provide health care that is tailored to the individual, and patients wish to receive such care. Choices about medications, surgery, prevention, and other medical interventions ideally take into account the unique circumstances and preferences of each patient. The term "personalized medicine" captures this shared goal. To achieve patient-centered care, clinicians need to know the personal circumstances of their patients—their occupations, family relationships, and medical histories—and to engage in shared decision-making, to ensure that patient values and perspectives are properly weighed in clinical decision-making.

In the wake of the Human Genome Project, genetic tests are increasingly seen as the key to dramatic improvements in clinicians' ability to individualize health care. Tests to identify susceptibilities to common diseases like cancer and diabetes may provide a guide to preventive care. Pharmacogenomics—the use of genetic tests to identify likely responses to drugs—may help to achieve safer and more effective drug therapy. These potential benefits of genomic research have received considerable scientific, media, and commercial attention. In two prominent initiatives, the Personalized Medicine Coalition (www.personalizedmedicinecoalition.org) and the Department of Health and Human Services Secretary's Personalized Health Care Initiative (www.hhs.gov/myhealthcare), the term "personalized medicine" refers specifically to genetically based health care.

Complexities in Genetically-Based Health Care

The idea of using genetic risk information to individualize health care is intuitively appealing. And successful examples of this approach are already entering clinical practice. For example, genetic tests can identify rare individuals who have a high risk for certain cancers, leading to specific recommendations for screening and medical treatments to reduce cancer risk. A few pharmacogenomic tests are also being used in clinical practice, and several more appear promising. For example, genetic testing is used to identify the breast cancer patients who are most likely

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HIGHLIGHTS

- The term "personalized medicine" traditionally refers to health care that is tailored to the individual, but recently, it has been used to refer specifically to genetically-based health care.
- Using genetic risk information to motivate healthy behaviors could in principle lead to important health gains, but research suggests that risk information (genetic and non-genetic) is not highly motivating.
- Most genetic risks are modest, so genetic testing may have limited value in individualizing health care.
- Even when risk prediction is clinically useful, genetic risk may not be—some of those with a genetic risk will never develop disease, while others without genetic risk factors may develop disease due to other risks, such as environmental exposures.
- Pharmacogenomics—using genetic tests to determine likely drug response—is perhaps the most promising example of genetically-based health care.

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to benefit from the drug Herceptin. A genetic test can also determine the initial dose of mercaptopurine, used to treat leukemia and autoimmune diseases, to avoid severe side effects in individuals who are genetically susceptible to developing them (see box, *Better Drugs Through Genetics*). In addition, genetic testing may help to identify important differences among patients with a given disease. For example, a test that measures gene expression in breast cancer tissue can be used to predict which women have the highest risk of cancer recurrence and therefore will benefit most from chemotherapy.

However, some cautions are in order for genetically-based health care. The use of genetic tests for prevention assumes that individuals who learn more about their personal risk of disease will be motivated to modify their behavior or comply with a medical intervention to prevent the diseases for which they are at risk. This expectation will undoubtedly prove correct some of the time. For example, women who perceive themselves to be at high risk for breast cancer are more likely to get regular mammography screening. Using genetic risk information to motivate healthy behaviors could in principle lead to important health gains—but research to date suggests that risk information (genetic and nongenetic) is not, as a rule, highly motivating. Although anxiety and other adverse psychosocial effects could also occur, these effects have generally been smaller than expected even for highly predictive genetic tests. There also is a concern, however, that those who get normal test results will be falsely reassured and then fail to follow basic screening and healthy lifestyle recommendations.

Equally important, using risk information to direct clinical care is not always a good idea. Some health care is beneficial for everyone and should not be limited to high risk groups: for example, we recommend that all women have regular cervical cancer screening (the Pap test), even though women vary in their risk to develop the disease. Similarly, all smokers benefit from quitting, even though some have a higher risk than others for lung cancer, heart disease, and other complications of smoking. The use of genetic risk information would not replace population screening advice, especially if other health determinants are of greater importance in the likelihood of developing disease (like exposure to or infection with human papillomavirus for cervical cancer, or smoking for lung cancer).

Better Drugs through Genetics? The Promise of Pharmacogenomics

Perhaps the most promising example of genetically based health care is pharmacogenomics. There is considerable variation in how people respond to drugs. Variants in the genes involved in drug processing and response are an important contributor to this variation. Pharmacogenomic testing can sometimes help to improve drug treatment. For example, a genetic test can identify the patients who are at high risk for severe complications from mercaptopurine, a drug used to treat leukemia and autoimmune diseases. Testing can help clinicians to adjust drug doses appropriately.

Even with pharmacogenomics, however, some caution is in order. Variants in certain genes involved in drug processing (from the CYP450 gene family) have been associated with changes in the breakdown of an important category of antidepressants, the selective serotonin reuptake inhibitors (SSRIs, the most famous of which is Prozac). The idea of using pharmacogenomic testing prior to SSRI use has received a lot of favorable attention, but a recent systematic review of medical studies found no evidence that SSRI drug efficacy or frequency of adverse events was associated with these genetic variants, or that these genetic variants can help guide patient management.

Evaluating Genetic Risk for Breast Cancer

Most genetic risks for disease pose only a modest risk, making genetically-based risk prediction imprecise. For example, many women have a change (mutation) in the TGFB1 gene, which is associated with a small increase in breast cancer risk: a woman with this gene mutation would have a 12.8–14% lifetime risk of breast cancer, as compared to an average risk of 12%. Prevention strategies—including mammography and regular breast exams—are the same whether or not a woman has the gene mutation. So whether knowing about the variant would help is not clear because it would not change a woman's health care and might cause her to worry unnecessarily.

This genetic risk is markedly different from the highly publicized risks associated with the BRCA1 and BRCA2 genes; women with BRCA mutations have a 50–85% lifetime risk of breast cancer—sufficiently high to merit taking actions that would not be recommended to the average woman, such as preventive removal of the breasts or ovaries and the use of magnetic resonance imaging for breast screening (which costs about ten times more than mammography). But BRCA mutations are also rare: they occur in less than one in 500 individuals in the population.

Putting Genetic Risk in Perspective

Even when risk prediction is clinically useful, genetic risk may not be the best risk information to use. Other risk factors, like occupational exposures, cholesterol level, or body weight may be more important in determining the best health care for a particular patient.

As they make health care decisions, patients and clinicians will need to take into account the limitations in risk prediction. Some individuals with a genetic risk factor will never develop the disease in question, while others who lack the genetic risk factor may develop the disease due to other risk factors—just as some individuals with high cholesterol never develop heart disease, while others with normal cholesterol levels do. In particular, risk prediction for common diseases is imprecise because most genetic risks are modest (see box, *Evaluating Genetic Risk*).

Genetic factors can decrease, as well as increase, risk. A given individual might have higher risk based on some genetic factors, and lower risk based on others. Although researchers are now beginning to examine the combined impact of multiple genetic risk factors, we still know very little about how these different genetic risks influence each other and how they interact with environmental factors: some might have additive or synergistic effects, some might cancel each other, some might have an effect only when other risk factors are present, and some might have independent effects. When researchers estimate the likely effect of testing for many different genetic risk factors, they predict that most people will be found to have middle range risks, from a little below to a little above average. So for most people, genetic testing may have limited value in individualizing health care.

Personalization: Relationships, Not Technology

Genomic research offers clinicians new techniques for risk assessment and disease classification. However, the scope of this new testing paradigm remains to be determined. Calling it "personalized medicine" may be something of a misnomer if it creates the impression that genetic tests will make health care more personal. The fundamental basis of personalized health care—and what patients value most—are relationships with health care providers who know them, value their per-

RESOURCES

Web sites

- www.dnapolicy.org – the Genetics and Public Policy Center. Includes news and events, issue briefs, polls and social science research, and publications.
- www.geneticalliance.org – the Genetic Alliance. Includes resources and publications on policy issues, Wiki informational tools, podcasts, and news.
- www.gene-watch.org – the Council for Responsible Genetics. Includes reports and issue briefs on the Council's Programs, a bookstore, and the magazine *GeneWatch*.
- www.geneticsandsociety.org – the Center for Genetics and Society. Includes a newsletter, publications, and a blog.

Recent news

- Olivia Judson, "Testing Genes, Solving Little," *New York Times*, August 17, 2008.
- Jeanne Lenzer, "Direct to Consumer Genetic Testing: Knowing Me, Knowing You," *British Medical Journal*, April 21, 2008.
- Rick Weiss, "Genetic Testing Gets Personal," *Washington Post*, March 25, 2008.
- Melissa Healy, "Genetic-Testing Consumers Have Tools but Little Guidance," *Los Angeles Times*, March 24, 2008.
- Jeremy Manier, "Genetic Link Found to Some with Autism," *Chicago Tribune*, January 10, 2008.

Further reading

- W. Gregory Feero, Alan E. Guttmacher, and Francis S. Collins, "The Genome Gets Personal—Almost," *Journal of the American Medical Association*, March 19, 2008.
- Kenneth Offit, "Genomic Profiles for Disease Risk: Predictive or Premature?" *Journal of the American Medical Association*, March 19, 2008.
- David J. Hunter, Muin J. Khoury, and Jeffrey M. Drazen, "Letting the Genome Out of the Bottle—Will We Get Our Wish?" *New England Journal of Medicine*, January 10, 2008.
- Wylie Burke and Bruce M. Psaty, "Personalized Medicine in the Era of Genomics," *Journal of the American Medical Association*, October 10, 2007.
- A. Janssens et al., "The Impact of Genotype Frequencies on the Clinical Validity of Genomic Profiling for Predicting Common Chronic Diseases," *Genetics in Medicine*, August 2007.


See legislation appendix


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spective, and engage in shared decision-making about health care choices.

Genetic tests should be seen as the latest set of tools to assist clinicians and patients in the decision-making process. Some genetic tests will undoubtedly play an important role in identifying individuals with high risks for preventable disease, or in refining clinical diagnoses. However, genomics may have a limited role in disease prediction for most patients. Pharmacogenomic testing may have wider use, but much research remains to be done. Irrespective of the number of genetic tests that prove clinically useful, genomic research will continue to provide essential new information about how and why diseases occur. This research is likely to lead to important leaps forward in prevention and treatment for all patients.