

The Intersection Of Biotechnology And Pharmacogenomics: Health Policy Implications

The move toward greater personalization of medicine might conflict with lowering health spending and expanding access to care.

by **Kathryn A. Phillips**

ABSTRACT: Increasing knowledge of the genetic basis of disease is changing the landscape of health care. Two critical aspects are growth in biotechnology and growth in personalized health care, particularly targeting medicines based on genetic information (pharmacogenomics). This paper provides an overview of the health policy implications of the integration of biotechnology and pharmacogenomics. I examine four factors that determine whether relevant technologies will be successfully adopted, using case studies for illustration. Key policy challenges include determining the appropriate role of policy in (1) providing incentives to develop socially beneficial interventions and (2) facilitating development of the evidence base. [*Health Affairs* 25, no. 5 (2006): 1271–1280; 10.1377/hlthaff.25.5.1271]

OUR INCREASING KNOWLEDGE OF THE GENETIC BASIS of disease is changing the landscape of health care in multiple ways.¹ The shift that is under way has important implications across the board—for patients, providers, industry, insurers, and regulatory agencies. Two critical aspects of this shift are (1) growth in biotechnology applications in health care and (2) the move toward personalized health care, particularly medicines based on genetic information (pharmacogenomics, or PGx).

The biotech and PGx sectors are separate but overlapping. This paper focuses only on the overlap. Surprisingly, the link between biotech, PGx, and health policy has been relatively ignored in the literature; for example, a Medline search found no papers covering all three subjects. There have also been relatively few papers on biotech and health policy.²

The overlap of biotech and PGx is a relatively small piece of the market; how-

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ever, it appears that the two will be increasingly intertwined. The biotech sector is growing: 253 biopharmaceutical products are now on the market, and more than 25 percent of new drugs approved by the Food and Drug Administration (FDA) since 2000 have been biopharmaceuticals.³ Biotech products include both drugs that are developed using biological molecules (biopharmaceuticals) and that may have a companion test (or more than one), and tests that are based on molecular information (molecular diagnostics). PGx includes the use of genetics to target drug therapies both to specific types of tumors or viruses and to people's genetic makeup. Although clinical applications of PGx are limited, it is a critical component of the growing trend toward personalized health care, which targets interventions based on people's genetic, clinical, and familial characteristics.⁴

The objective of this study is to examine the factors that determine whether biotech/PGx interventions will be successfully adopted and the implications for health policy (I use the term "biotech/PGx interventions" to indicate that I am referring to either biopharmaceuticals with companion diagnostics or molecular diagnostics). With the developments in biotech and PGx come concerns about their impact on health care outcomes, costs, and policies. Difficult decisions will need to be made about what new technologies will be adopted, how they should be regulated, who will pay for them, and who will have access to them.⁵ In this paper I provide an overview of this rapidly emerging area and relevant health policy issues, instead of simply entering the debate over whether biotech and PGx are truly "revolutionary" or overhyped, or reviewing the PGx field more generally.⁶

Drivers Of Diffusion

This section draws on established frameworks for explaining the diffusion of new technologies as well as a literature review and anecdotal evidence.⁷ I focus here on four major factors that are relevant to the diffusion of biotech/PGx interventions along the continuum from discovery through clinical implementation.

■ **Nature of the disease and the intervention.** A review of the literature and anecdotal evidence suggests that diseases that are life-threatening, that have a large target population or high market-share potential, that require ongoing care or monitoring, or that have strong advocacy groups appear to be more likely to attract industry interest for development of interventions. Biotech/PGx interventions appear to be more successful where there is an urgent need to target medications because of safety or nonresponse problems, where there is a focused and immediate treatment decision to be made and a lack of good alternatives to using targeting, where genetic variation determines a sizable fraction of variability in response, and where there is growth potential for the drug (for example, widespread off-label uses). Early consideration of targeting during the discovery and development stages appears to contribute to diffusion. Successful development of a biotech/PGx intervention typically requires significant knowledge of the relevant disease mechanisms and a strong linkage between the test results and the outcome of interest. Of particular impor-

tance is that an intervention is more likely to be successfully adopted when the relevant test is highly predictive of what treatment should be used versus simply suggesting a possible treatment or dosage.

■ **Regulation.** Regulation is a key factor in determining the diffusion of new technologies.⁸ The FDA has taken a proactive approach to providing guidance on PGx, because it is hoped that PGx can facilitate both the goal of improving drug safety and effectiveness while streamlining the clinical trials process and expediting drug approvals. The FDA has developed a variety of initiatives, including advisory groups and interagency collaborative efforts; sponsorship of conferences; development of staff expertise; and development of guidance for genomic data submission, new testing approaches, and codevelopment of tests and drugs.⁹

However, the FDA must consider a number of challenges in determining how to regulate biotech/PGx interventions. The agency is under increased pressure to safeguard drug safety because of several recent, highly publicized cases of drug withdrawals after approval.¹⁰ At the same time, the FDA has a role in ensuring that beneficial products are available to consumers. Thus, they are under pressure to address the “pipeline problem,” which is the slowdown in new medical products to the U.S. market, an issue they are addressing through the Critical Path Initiative.¹¹ The FDA must consider the costs and benefits of its regulatory actions and, to the best of its ability, keep regulation “least burdensome” for industry sponsors.¹² Of particular concern for biotech/PGx interventions is the ongoing debate over whether the FDA should more closely regulate diagnostics, which are typically less highly regulated than pharmaceuticals.

■ **Value, coverage, and reimbursement.** There are many challenges to determining the societal value of PGx interventions and, thus, the appropriate policy response. Many of these challenges are technical, such as a lack of data that link interventions to health and economic outcomes. Another challenge is the need to evaluate multifactorial conditions and diagnostic/drug combinations. Still other challenges emerge from the policy context. The value of diagnostics is often harder to measure than the value of drug therapies. For example, payers might be concerned that the up-front costs of testing will be higher than the downstream savings, particularly given the rapid enrollee turnover in many health plans.

For new technologies such as biotech/PGx interventions to be adopted, there must be benefits to the potential users and purchasers. Although numerous observers have discussed the potential benefits of personalized medicine and PGx, there is little empirical evidence supporting such claims: The few cost-effectiveness analyses of PGx interventions that have been conducted show inconclusive results as to whether such interventions are a relatively good value for society.¹³ There are also relatively few mechanisms or incentives to assess economic value from a societal perspective, because agencies such as the FDA and the Centers for Medicare and Medicaid Services (CMS) do not explicitly use cost-effectiveness analyses in their decision-making processes.

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A related issue is coverage and reimbursement policies, which might be considered the ultimate incentive for industry to bring products to market. However, there is much ambiguity about whether biotech/PGx interventions are or will be covered, by whom, and at what rates. The U.S. Department of Health and Human Services (HHS) Secretary’s Advisory Committee on Genetics, Health, and Society has made examination of reimbursement for genetic technologies (including PGx tests) a major priority. The committee has stated that problems with coverage and reimbursement are limiting appropriate access and clinical integration of genetic technologies.¹⁴ Barriers noted include the novelty of many genetic tests, the limited availability of data to support evidence-based coverage decisions, the lack of a process for identifying and addressing gaps in evidence, limitations in Medicare statutes for covering genetic tests, and variability in coverage determinations.

■ **Ability to integrate diagnostics and pharmaceuticals.** All of the factors described above are influenced by another major shift in the health care landscape: the increasing integration of diagnostics and pharmaceuticals. Because the promise of PGx is greater ability to appropriately identify individuals for treatment, the importance of diagnostics is ascending. However, the diagnostics and drug industries have historically been largely separate, with different cultures, business models, and regulatory mechanisms.¹⁵ With the emergence of codeveloped products, new development and regulatory models will be needed. Other challenges include the prevailing investment and reimbursement models that often place a lower value on diagnostics, ambiguity regarding intellectual property, lack of samples for testing and validating biomarkers, and lack of demonstrated clinical utility.¹⁶

Case Study: Herceptin

Herceptin (trastuzumab) is a genetically engineered humanized monoclonal antibody that was developed after the discovery of the human epidermal growth factor receptor-2 protein (HER2/neu). Because of its dependence on identifying HER2 status prior to use, Herceptin has been a much-cited example not only of a biotech drug but also of personalized medicine.

■ **Success story.** The story of HER2 testing and Herceptin illustrates a fast and successful adoption of a biotech/PGx intervention. The FDA approved Herceptin in 1998 through its fast-track process, and since then the drug has helped launch Genentech as a leader in biotech drugs. Sales of Herceptin have continued to grow rapidly: It is among the top twenty best-selling biotech drugs, with sales of \$747 million and a growth rate of 56 percent during 2004–05.¹⁷

Many factors contributed to the success of Herceptin. The drug targets a life-threatening disease for which there are few alternative treatments, and clinical tri-

als showed a clear survival benefit. There is a direct relationship between the biomarker and drug response, and there was early consideration of the need for a diagnostic test. There also was a strong patient advocacy effort to gain approval for the drug.¹⁸ The FDA approved Herceptin and a test for HER2 jointly, with reviews occurring in parallel, coordinated labeling for the two products, and the approvals issued in the same week. HER2 testing and Herceptin have been recommended by major professional organizations and are covered by major payers.¹⁹

■ **Future challenges.** The story of Herceptin, however, is also emblematic of future challenges, particularly payers' ability to cover high-cost drugs and the difficulties in developing appropriate diagnostics. Herceptin costs around \$3,000 monthly.²⁰ The cost-effectiveness analyses conducted to date are inconclusive, given the drug's high cost and that the impact on median survival is estimated to be only a few months. For example, Elena Elkin and colleagues reported results of \$125,000 per quality-adjusted life year (QALY) gained, which is more costly than the \$50,000 threshold often used to determine a socially efficient intervention.²¹ Also, the costs of Herceptin have escalated after evidence emerged suggesting that Herceptin can be used more widely to treat early, nonmetastatic breast cancer.²² Other countries did not issue fast-track approval of Herceptin; for example, the United Kingdom did not approve the drug until almost two years after the United States did because of uncertainty about the benefits of the drug relative to its costs.²³

The story of Herceptin illustrates that a technical challenge will be to determine the most appropriate companion test and coordinate its development and approval. There are several HER2 tests, and debate continues over which test is most appropriate.²⁴ The FDA was able to coordinate the simultaneous approval of Herceptin and a relevant test, although it recognized that efforts need to continue to streamline the process. To this end, the FDA has developed a concept paper that addresses the approval pathway for a drug combined with a diagnostic genomics test.²⁵

■ **Other new oncology drugs.** Herceptin is only the tip of the iceberg for new oncology treatments, a major area of focus for biotech companies. Oncology is in the midst of a major shift to subtyping of disease based on genetics, thus opening the door to targeted therapies and the use of PGx tests—for example, UGT1A1 testing for irinotecan (Campostar) and BCR-ABL testing for imatinib mesylate (Gleevec). However, other therapeutics have proved to be more difficult to target, and thus the commercial success of Herceptin may prove to be an anomaly. The example of gefitinib (Iressa), a drug for non-small cell lung cancer, serves as a warning sign that the ability to target a drug to those who can most benefit from it will become increasingly urgent. Iressa was developed and approved for use without a diagnostic test to identify responders. Subsequent evidence showed little benefit from Iressa except in specific subgroups, and the company has essentially withdrawn it.²⁶ A test has been developed that might remedy this problem, although it remains to be seen whether the drug can be rescued.²⁷

Case Study: CYP450 Tests

Numerous companies have developed tests for CYP450 mutations, and they are widely used by industry during the drug discovery and development phases as well as being available directly to consumers via the Internet. However, the visibility of CYP450 testing was raised substantially with FDA approval of the AmpliChip CYP450 test in 2004. Its approval has been called a “milestone” in personalized medicine, and it received widespread attention in the industry and lay press.²⁸ This chip tests for genetic mutations in two common drug-metabolizing enzymes (CYP2D6 and CYP2C19) that are relevant to many commonly used drugs such as antidepressants and cardiovascular drugs.²⁹

■ **Slow adoption and future challenges.** Despite widespread interest in CYP450 tests, adoption into clinical practice has been slow, and its story portends future challenges, particularly the barriers imposed by lack of evidence of clinical utility, the complexities of drug response, and lack of coverage for tests used for screening purposes. A major challenge to adoption of CYP450 tests is the lack of evidence about their clinical utility and how to use the tests in clinical practice. It has been difficult to determine when testing would be useful for many reasons, including the multifactorial nature of drug response, lack of evidence linking mutations to important clinical outcomes, and variability both across and within drug classes.³⁰ Furthermore, since a single CYP450 mutation is unlikely to be responsible for drug response, P450 tests are typically not “gatekeeper” tests that determine the use or nonuse of a drug, such as HER2 testing for Herceptin.

■ **Regulatory approaches.** The AmpliChip illustrates how regulatory approaches are evolving in response to these new tests. Roche initially planned to market the test to laboratories as a reagent for use in “home-brew” tests, which are exempt from premarket review. However, the FDA determined that the AmpliChip would need more extensive FDA review.³¹ Thus, the experience of AmpliChip demonstrated that the FDA would indeed approve such tests and that it might require a higher level of review. The approval did open the door for other companies to obtain approval for CYP450 tests, and thus the market is expected to grow.³²

■ **Insurance coverage.** CYP450 tests illustrate how perceptions of value will play a large role in the adoption of new technologies. Payers have typically been reluctant to provide coverage for tests that are used for population screening to predict future risk because of ambiguity about the usefulness of the information provided and the costs involved in screening large populations when there may be few direct or immediate benefits.³³ Conversely, payers have been more likely to provide coverage for tests that are used for diagnosis and immediate therapeutic decisions. For example, Medicare covers diagnostic tests but not screening tests (with the exception of legislatively mandated changes such as coverage for mammography). In the case of HER2 testing, testing is considered diagnostic and thus appears to be widely covered. In contrast, P450 tests could be used for both screening and diagnosis, and results can be relevant to current or future drug response; thus, the benefits

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might not be immediate. For these reasons, insurance coverage of tests such as AmpliChip appears much more limited.³⁴

■ **Costs versus benefits.** Lastly, CYP450 tests illustrate that innovative approaches will be needed to assess the value of such tests. A particular difficulty is that CYP450 tests are relevant to a range of conditions and drugs, and thus it is unusually difficult to sort out the costs and benefits. For example, there is no one source of comprehensive information on the relationship of key mutations such as CYP2D6 to metabolism, drug response, and clinical outcomes. Therefore, such data have to be cobbled together from various sources. In particular, the lack of clinical outcome data makes it problematic to assess value.³⁵

■ **Future challenges.** In contrast to HER2 and Herceptin, CYP450 tests illustrate the saga of a new technology where the factors identified that influence diffusion are not aligned. There are many challenges to such tests, including the lack of demonstrated clinical utility and value and the resultant lack of payer coverage. The story of AmpliChip might not portend the experience that other CYP450 tests will encounter, because other tests might be able to overcome these challenges. However, it does illustrate the policy challenge of determining who will conduct and pay for clinical utility studies. A particularly thorny issue is that no one manufacturer of such tests has the intellectual property necessary to provide the financial incentive to conduct such studies.

Health Policy Implications

This review has identified several key factors that influence the diffusion of biotech/PGx interventions and their health policy implications. The case studies illustrated how biotech/PGx interventions can be successfully adopted—or not adopted—depending on whether those factors are in alignment. Some of these factors are inherent aspects of the intervention or disease and thus less amenable to policy interventions—for example, whether there is a clear link between genetic variability and drug response and the size of the affected populations. However, other factors clearly can be modified through policy levers such as FDA regulation and CMS coverage and reimbursement decisions.

■ **Role of policy in providing incentives?** One question is the appropriate role of health policy in providing incentives for the development of socially beneficial medical interventions. One key aspect of this question is who the driver of innovation will be and to what extent regulatory agencies such as the FDA should facilitate innovation (a “carrot” approach) or strengthen regulation (a “stick” approach). Although there has been general consensus that the pharmaceutical industry as a whole has been slow to embrace PGx because of concerns over the potential impact

to the “blockbuster model” that has dominated the industry, some observers now feel that this is starting to change, as the industry has more success stories such as Herceptin. As noted, the FDA has played an active role in facilitating PGx interventions, although it remains to be seen whether the agency will gravitate toward stronger incentives and stricter requirements to use PGx data. Others have suggested that health care payers will begin to advocate more strongly for approaches that target drugs to specific populations because of concerns over drug safety, effectiveness, and costs. Thus, there are multiple incentives and several drivers behind biotech/PGx adoption, and the appropriate role for health policy will be an evolving question.

■ **Role of policy in providing evidence of value?** Another health policy question will be to determine the appropriate role for policy in facilitating or providing evidence of societal value. As noted above, there is a dearth of relevant data, even very basic data such as how many diagnostics are being used and by whom. Many issues need to be examined, including the cost and use of these new technologies, whether there is equal access to new technologies for underserved populations, how patients and providers value the benefits of these technologies, the risk-benefit trade-offs, and how research findings can be translated into practice. To illustrate, there is little publicly available evidence as to whether uninsured or disadvantaged women are equally like to receive HER2 testing or Herceptin, even though without these data, the true societal impact cannot be assessed.³⁶

■ **Need for an evidence base.** One step forward would be the development of an evidence base that can further identify the factors that influence adoption and that provides evidence on clinical utility and risk-benefit trade-offs. Because no single U.S. agency is devoted to technology assessment, such efforts have to be developed from various groups such as the Centers for Disease Control and Prevention (CDC), the National Institutes of Health (NIH), and private foundations. One example is the CDC’s recent establishment of the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) project.³⁷

OUR INCREASED KNOWLEDGE OF THE GENETIC BASIS of disease offers much potential to improve health care. However, it also raises many issues about translation from research into clinical practice and health policies. The move toward greater personalization of medicine might directly conflict with two other major concerns in the United States: growing spending on health care and pharmaceuticals, and access to care for underserved populations. Difficult decisions will need to be made about which new technologies will be adopted, how to regulate them, who will pay for them, and who will have access to them. It will be important to separate the hype about these new approaches from their actual risks and benefits. Health policy has an important role to play in achieving these goals.

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NOTES

1. F.S. Collins et al., "A Vision for the Future of Genomics Research," *Nature* 422, no. 6934 (2003): 835–847.
2. T. Nagle et al., "The Further Evolution of Biotech," *Nature Reviews Drug Discovery* 2, no. 1 (2003): 75–79; and H.I. Miller, "As Biotech Turns 20...", *Nature Reviews Drug Discovery* 1, no. 12 (2002): 1007–1008.
3. G. Walsh, "Biopharmaceuticals: Recent Approvals and Likely Directions," *Trends in Biotechnology* 23, no. 11 (2005): 553–558.
4. R. Snyderman and Z. Yoediono, "Prospective Care: A Personalized, Preventative Approach to Medicine," *Pharmacogenomics* 7, no. 1 (2006): 5–9.
5. H. Varmus, "Getting Ready for Gene-based Medicine," *New England Journal of Medicine* 347, no. 19 (2002): 1526–1527.
6. P. Nightingale and P. Martin, "The Myth of the Biotech Revolution," *Trends in Biotechnology* 22, no. 11 (2004): 564–569.
7. See D.M. Berwick, "Disseminating Innovations in Health Care," *Journal of the American Medical Association* 289, no. 15 (2003): 1969–1975; J.A. Robertson et al., "Pharmacogenetic Challenges for the Health Care System," *Health Affairs* 21, no. 4 (2002): 155–167; Lewin Group, "The Value of Diagnostics: Innovation, Adoption, and Diffusion into Health Care," July 2005, <http://www.advamed.org/publicdocs/thevalueofdiagnostics.pdf> (accessed 10 August 2005); Burrill and Company, *The Burrill Personalized Medicine Report* (San Francisco: Burrill Media Group, 2005); S.B. Haga and W. Burke, "Using Pharmacogenetics to Improve Drug Safety and Efficacy," *Journal of the American Medical Association* 291, no. 23 (2004): 2869–2871; K.A. Phillips and S.L. Van Bebbber, "Measuring the Value of Pharmacogenomics," *Nature Reviews Drug Discovery* 4, no. 6 (2005): 500–509; K.A. Phillips, S.L. Van Bebbber, and A.M. Issa, "Priming the Pipeline: A Review of the Clinical Research and Policy Agenda for Diagnostics and Biomarker Development," Solicited Report to the U.S. Food and Drug Administration (2005); and K.A. Phillips and S.L. Van Bebbber, "Regulatory Perspectives on Pharmacogenomics: A Review of the Literature on Key Issues Faced by the United States Food and Drug Administration," *Managed Care Research and Review* 63, no. 3 (2006): 301–326.
8. Berwick, "Disseminating Innovations in Health Care."
9. See Food and Drug Administration, Center for Drug Evaluation and Research, "Genomics at FDA," <http://www.fda.gov/cder/genomics/default.htm> (accessed 1 May 2006).
10. K.A. Phillips et al., "Reframing the Debate on Drug Withdrawals: Improving Drug Safety by Improving the Evidence Base" (Unpublished manuscript, 2005).
11. FDA, *Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products*, March 2004, <http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.pdf> (accessed 7 June 2006).
12. Phillips et al., "Priming the Pipeline."
13. K.A. Phillips and S.L. Van Bebbber, "A Systematic Review of Cost-Effectiveness Analyses of Pharmacogenomic Interventions," *Pharmacogenomics* 5, no. 8 (2004): 1139–1149.
14. U.S. Department of Health and Human Services, *Coverage and Reimbursement of Genetic Tests and Services: Report of the Secretary's Advisory Committee on Genetics, Health, and Society*, February 2006, http://www4.od.nih.gov/oba/sacghs/reports/CR_report.pdf (accessed 7 June 2006).
15. D.W. Feigal and S. Gutman, "Drug Development, Regulation, and Genetically Guided Therapy," in *Pharmacogenomics: Social, Ethical, and Clinical Dimensions*, ed. M.A. Rothstein (Hoboken, N.J.: John Wiley and Sons, 2003), 99–108.
16. Phillips et al., "Priming the Pipeline."
17. D.P. Hamilton, "Genentech's Profit Jumps 64 Percent on Strong Cancer-Drug Sales," *Wall Street Journal*, 11 January 2006.
18. R. Bazell, *Her-2: The Making of Herceptin, a Revolutionary Treatment for Breast Cancer* (New York: Random House, 1998).
19. See Aetna, "Clinical Policy Bulletin no. 0313: Herceptin (Trastuzumab)," 16 May 2006, <http://www.aetna>

- .com/cpb/data/CPBA0313.html (accessed 7 June 2006).
20. For example, the unit price given for one vial (typically a twenty-eight-day supply) of 440 mg Herceptin (trastuzumab) at one online prescription pharmacy, RxUSA, <http://www.rxusa.com/cgi-bin2/db/db.cgi>, is \$2,844.06 (accessed 7 June 2006).
 21. E.B. Elkin et al., "HER-2 Testing and Trastuzumab Therapy for Metastatic Breast Cancer: A Cost-Effectiveness Analysis," *Journal of Clinical Oncology* 22, no. 5 (2004): 854–863.
 22. "Herceptin and Early Breast Cancer: A Moment for Caution," *Lancet* 366, no. 9498 (2005): 1673.
 23. R. Lewis et al., *A Rapid and Systematic Review of the Clinical Effectiveness and Cost-Effectiveness of Trastuzumab for Breast Cancer*, 4 October 2001, <http://www.nice.org.uk/download.aspx?o=29275> (accessed 1 May 2006).
 24. F. Lewis et al., "Testing for HER2 in Breast Cancer," *Histopathology* 45, no. 3 (2004): 207–217.
 25. FDA, "Drug-Diagnostic Co-Development Concept Paper," April 2005, <http://www.fda.gov/cder/genomics/pharmacoconceptfn.pdf> (accessed 1 May 2006).
 26. FDA, "FDA Statement on Iressa," 17 December 2004, <http://www.fda.gov/bbs/topics/news/2004/new01145.html> (accessed 1 May 2006).
 27. See Genzyme Genetics, "Genzyme Launches Exclusive Lung Cancer Test," Press Release, 27 September 2005, <http://www.genzymegenetics.com/about/news/GENZ%20PR-092705.asp#TopOfPage> (accessed 7 June 2006).
 28. Burrill and Company, *The Burrill Personalized Medicine Report*.
 29. K.A. Phillips et al., "Potential Role of Pharmacogenomics in Reducing Adverse Drug Reactions: A Systematic Review," *Journal of the American Medical Association* 286, no. 18 (2001): 2270–2279; and Phillips and Van Bebber, "Measuring the Value of Pharmacogenomics."
 30. Blue Cross Blue Shield, *Special Report: Genotyping for Cytochrome P450 Polymorphisms to Determine Drug-Metabolizer Status*, Assessment Program vol. 19, no. 9 (December 2004), http://www.bcbs.com/tec/vol19/19_09.pdf (accessed 7 June 2006).
 31. S. Gutman, "OIVD Requests a Meeting with Roche Diagnostics regarding the AmpliChip CYP450 Microarray," 8 July 2003, <http://www.fda.gov/cdrh/oivd/letter-roche2.html> (accessed 7 June 2006).
 32. See FDA, "FDA Clears First of Kind Genetic Lab Test," Press Release, 23 December 2004, <http://www.fda.gov/bbs/topics/news/2004/new01149.html> (accessed 1 May 2006).
 33. B. Carlson, "Payers Move Slowly on Test Coverage Decisions," *Biotechnology Healthcare* (August 2005): 31–39.
 34. CIGNA, "CIGNA HealthCare Coverage Position: Drug Metabolizing Enzyme Genotyping Systems (AmpliChip)," 15 June 2005, http://www.cigna.com/health/provider/medical/procedural/coverage_positions/medical/mm_0381_coveragepositioncriteria_AmpliChip.pdf (accessed 7 June 2006); Aetna, "Clinical Policy Bulletin 0715: Pharmacogenetic Testing," 10 March 2006, <http://www.aetna.com/cpb/data/CPBA0715.html> (accessed 7 June 2006); and Blue Cross Blue Shield, *Special Report*.
 35. Phillips and Van Bebber, "Measuring the Value."
 36. K.A. Phillips, "Personalized Medicine for Colorectal and Breast Cancer Screening and Treatment: An Integrated and Interdisciplinary Approach to Translating Genetic Information into Clinical Practice and Health Policy" (Working paper, available from the author, 2006).
 37. See CDC, "Evaluation of Genomic Applications in Practice and Prevention (EGAPP): Implementation and Evaluation of a Model Approach," 31 May 2006, <http://www.cdc.gov/genomics/gtesting/egapp.htm> (accessed 7 June 2006).