Realizing the Potential of Pharmacogenomics: Opportunities and Challenges

Report of the
Secretary's Advisory Committee on Genetics, Health, and Society

May 2008

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DEPARTMENT OF HEALTH & HUMAN SERVICES **Public Health Service**

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May 12, 2008

The Honorable Michael O. Leavitt
Secretary of Health and Human Services
200 Independence Avenue, S.W.
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Dear Secretary Leavitt:

On behalf of the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) and in keeping with our mandate to provide advice on the broad range of policy issues raised by the development and use of genetic technologies, I am pleased to submit our report, *Realizing the Potential of Pharmacogenomics: Opportunities and Challenges*. The report explores the potential for pharmacogenomics (PGx) to advance the development of diagnostic, therapeutic, and preventive strategies to improve the safety, effectiveness, and quality of health care. It identifies untapped opportunities and critical barriers associated with PGx research and makes policy recommendations to enhance the development of PGx applications and their integration into clinical practice and public health.

The report is the culmination of 3 years of factfinding, public consultation, analysis, and deliberation by the Committee. Many people shared their knowledge, expertise, and perspectives with us and deepened our understanding of the current scientific, technological, clinical, and policy landscapes and the paths forward for realizing the potential of pharmacogenomics. We are indebted to them for their contributions to the report's development.

We appreciate the opportunity to address this important topic and hope that our input will prove helpful to you and the Department.

Sincerely,

Steven Teutsch, M.D., M.P.H.
SACGHS Chair

Reed V. Tuckson, M.D.
SACGHS Chair Emeritus

About SACGHS

The Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) was first chartered in 2002 by the Secretary of Health and Human Services (HHS) as a public forum for deliberation on the broad range of policy issues raised by the development and use of genetic tests and, as warranted, to provide advice on these issues. The charter sets out the following specific functions of the Committee:

- Assessing how genetic and genomic technologies are being integrated into health care and public health;
- Studying the clinical, public health, ethical, economic, legal, and societal implications of genetic and genomic technologies and applications;
- Identifying opportunities and gaps in research and in data collection and analysis efforts;
- Examining the impact of current patent policy and licensing practices on access to genetic and genomic technologies;
- Analyzing uses of genetic information in education, employment, insurance, and law; and
- Serving as a public forum for discussion of issues raised by genetic and genomic technologies.

Structurally, SACGHS consists of up to 17 individuals from around the Nation who have expertise in disciplines relevant to genetics and genetic technologies. These disciplines include biomedical sciences, human genetics, health care delivery, evidence-based practice, public health, behavioral sciences, social sciences, health services research, health policy, health disparities, ethics, economics, law, health care financing, consumer issues, and other relevant fields. At least two of the members are specifically selected for their knowledge of consumer issues and concerns and the views and perspectives of the general public.

Representatives of at least 19 Federal department or agencies also sit on SACGHS in an *ex officio* (nonvoting) capacity. The departments and agencies are the Department of Commerce, Department of Defense, Department of Education, Department of Energy, Administration for Children and Families (HHS), Agency for Healthcare Research and Quality (HHS), Centers for Disease Control and Prevention (HHS), Centers for Medicare & Medicaid Services (HHS), Food and Drug Administration (HHS), Health Resources and Services Administration (HHS), National Institutes of Health (HHS), Office for Civil Rights (HHS), Office for Human Research Protections (HHS), Office of Public Health and Science (HHS), Department of Justice, Department of Labor, Department of Veterans Affairs, Equal Employment Opportunity Commission, and Federal Trade Commission.

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* The appointments of these SACGHS members had either ended before or had not yet begun at the time the recommendations were finalized. Therefore, they did not participate in the vote on the final recommendations. However, they did participate in the deliberations of the report and draft recommendations.

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* The appointments of these SACGHS members had either ended before or had not yet begun at the time the recommendations were finalized. Therefore, they did not participate in the vote on the final recommendations. However, they did participate in the deliberations of the report and draft recommendations.

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Acknowledgments

The Committee wishes to thank the members of the Secretary's Advisory Committee on Genetics, Health, and Society's (SACGHS) Pharmacogenomics Task Force for their pivotal role in guiding the development of this report. The Task Force was initially chaired by Emily Winn-Deen until June 2006 when her appointment to the Committee ended, at which time Kevin FitzGerald assumed the chair position. The Task Force also included SACGHS members Jim Evans, Andrea Ferreira-Gonzalez, Debra Leonard, Julio Licinio, Steve Teutsch, and Hunt Willard as well as SACGHS *ex officio* agency representatives Greg Feero, National Institutes of Health (NIH); Steve Gutman, Food and Drug Administration (FDA); Alan Guttmacher, NIH; Joseph Hackett, FDA; Muin Khoury, Centers for Disease Control and Prevention (CDC); Tim Leshan, NIH; Rochelle Long, NIH; Liz Mansfield, FDA; Gurvaneet Randhawa, Agency for Healthcare Research and Quality (AHRQ); and Allen Rudman, FDA.

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The Committee also thanks all of the individuals and organizations that responded to the Committee's request for public comments on an earlier draft of the report (see Appendix B for a list of public commenters). These comments greatly enhanced the accuracy and comprehensiveness of the report and the relevance of the recommendations.

The Committee is indebted to Cliff Goodman, Christel Villarivera, Erin Karnes, Lindsey Wu, Charlene Chen, Eric Faulkner, and Amanda Thomas of The Lewin Group for their substantial research, analysis, and writing. SACGHS is also grateful to Sandra Howard and Theresa Lawrence of the HHS Office of the Assistant Secretary for Planning and Evaluation (ASPE) for their support of the project and to ASPE for providing resources for the report's development.

SACGHS wishes to recognize the work of SACGHS staff members. Fay Shamanski served as lead staff member at the start of the project, and Suzanne Goodwin saw the project to completion. Dr. Shamanski and

Ms. Goodwin were responsible for organizing the deliberations of the Task Force and the full Committee and drafting the recommendations. In addition, Yvette Seger and Cathy Fomous provided support and scientific expertise, Joe Milone and Tony Tse assisted in the development of the recommendations, and Sarah Maddox and Tara Hurd helped compile and summarize the public comments. Sarah Carr provided overall guidance to the staff.

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The Committee thanks the NIH Office of Biotechnology Activities, under the direction of Amy Patterson, and the NIH Office of Science Policy, under the direction of Lana Skirboll, for their ongoing support and operational management of SACGHS.

Contents

Preface

The Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) was chartered in 2002 to provide advice to the Secretary of Health and Human Services (HHS) on policy issues raised by the development and use of genetic technologies and their integration into clinical practice and public health. Because the scope of its charge encompasses a broad range of issues, the Committee undertook a prioritization process during its first year to help it focus its work on areas in which policy recommendations will have the greatest impact. The Committee ranked pharmacogenomics (PGx) as a high-priority issue warranting indepth deliberation and analysis because of its potential to affect health care and the important policy issues it raises. The Committee believes that although there are tremendous opportunities in this field, several challenges need to be addressed for the field to advance and to prepare for its appropriate integration into clinical practice and public health.

SACGHS began its deliberations with informational sessions during its June and October 2005 meetings (see Appendices C and D for summaries of these sessions). At the June 2005 meeting, the Committee members learned about the fundamentals of PGx and the state of the field as well as the ethical, legal, and social implications of PGx. Committee members also heard from representatives of the diagnostics and pharmaceutical industries, a public health provider, and a health care provider about their perspectives on PGx. In addition, they were updated on HHS efforts and future directions in PGx by representatives of the Centers for Disease Control and Prevention, Food and Drug Administration (FDA), and National Institutes of Health. Factfinding continued at the October 2005 meeting with an exploration of the economic challenges associated with PGx product development and its integration into clinical practice. The Committee also heard more about the ethical and social issues associated with race and genetics in the study of differential drug response.

To guide its work on PGx, SACGHS assembled a Task Force comprising several Committee members and *ex officios*. As its first task, the Task Force gathered information about Federal efforts to address PGx through a survey of Federal agencies (see Appendix A for descriptions of these Federal activities). The Task Force also reviewed several reports on PGx prepared by other groups. The Task Force used these sources of information, including the presentations, to develop an outline of issues to be discussed in this report.

In early 2006, The Lewin Group (Lewin), through a contract with the Office of the Assistant Secretary for Planning and Evaluation, was commissioned to assist with the report's development. Lewin began its work by preparing a review of the PGx literature. Meanwhile, the Task Force used the presentations and literature review to draft recommendations. The literature review and draft recommendations were reviewed by SACGHS at its June 2006 meeting.

Following the June 2006 meeting, Lewin prepared a first draft of SACGHS's PGx report that incorporated information from the literature review, presentations, Federal efforts survey, and summary of other PGx reports. The SACGHS staff revised the draft recommendations to incorporate input received from the Committee at the June 2006 meeting. The Task Force held a daylong meeting in September 2006 to discuss the draft report and revised recommendations. The draft report and recommendations were further revised to reflect the Task Force's discussion. The next iteration of the draft report and recommendations was reviewed at the November 2006 SACGHS meeting. From December 2006 to February 2007, Lewin conducted interviews with 15 stakeholders with expertise on PGx and related fields to obtain their input

on the November 2006 draft of the report and recommendations. During two conference calls in February and March 2007, the Task Force reviewed a summary of the interview comments and provided guidance to Lewin and the SACGHS staff on how to revise the draft report and recommendations.

In March 2007, the public was invited to provide comments on the draft report. The request was disseminated through the *Federal Register*, the SACGHS Web site, SACGHS listserv, and a targeted mailing, as well as at the Secretary's announcement of the Personalized Health Care Initiative on March 23, 2007. The Committee received 56 responses to this request from a wide range of individuals and organizations (see Appendix B for the list of commenters). The comments were carefully reviewed by the Task Force and the SACGHS staff. In August and September 2007, the Task Force held conference calls to consider whether and how to address each comment. Another iteration of the report was prepared that reflected the Task Force's input and was reviewed at the November 2007 SACGHS meeting. At the November 2007 meeting, SACGHS finalized the recommendations.

This final report reflects the cumulative work of SACGHS, its PGx Task Force, and the Lewin and SACGHS staffs and the insightful comments of the expert presenters, interviewed stakeholders, and the public.

Executive Summary

Pharmacogenomics (PGx) is the study of how individual genetic differences affect drug response. The emerging field of PGx arises from the convergence of advances in pharmacology, genetics, and, more recently, human genomics. Greater understanding of the role of certain drug-metabolizing enzymes has the potential to improve the health of large populations and subgroups. It can provide clinicians with tools to assess risks and benefits associated with using available medicines for particular patients and to select therapies and treatments tailored to each patient. In so doing, PGx should enable direct management of individual patient-drug response for many conditions.

Realizing the benefits of PGx on a large scale remains a long-term goal. Applications of PGx in practice have been notable but few. Nevertheless, current and emerging advances suggest that better targeted, more effective PGx-based treatments have the potential to yield significant gains in personal health, population health, and cost-effective resource allocation.

This report is intended to provide timely, policy-relevant information about PGx to help frame recommendations for the HHS Secretary and other policymakers and stakeholders. It examines the potential for PGx to advance the development of diagnostic, therapeutic, and preventive strategies to improve health. It also explores the opportunities and challenges associated with PGx research, development of PGx applications, and integration of these applications into clinical practice and public health.

A. The Potential of PGx

PGx has drawn great attention for its potential to redirect personal care and public health paradigms in the United States and abroad. It has begun to offer powerful tools for using information about individual genetic variations and drug responses to "personalize" or "customize" health care decisions.[1] Some early applications of PGx include HER2/neu testing of metastatic breast cancer patients to determine responsiveness to Herceptin®, the use of thiopurine 6-mercaptopurine testing to manage the treatment of children with acute lymphoblastic leukemia, and the use of *CYP2C9* and *VKORC1* testing of those at risk for harmful blood clots to guide warfarin dosage.

PGx still is an emerging field, and the instances of PGx being used in practice are few to date. Some in the field consider the early promise of PGx to be largely unfulfilled,[2,3,4,5] although modest benefits are on the horizon.[6] Also, much of the valuable information about PGx is in the form of early scientific discoveries. Although this information has the potential to be useful, its clinical utility is not yet well understood.

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[1] NIH Web site. One Size Does Not Fit All: The Promise of Pharmacogenomics. See http://www.ncbi.nlm.nih.gov/About/primer/pharm.html [accessed December 18, 2007].
[2] Tucker G. Pharmacogenetics ─ expectations and reality. *BMJ* 2004. 329(7456):4-6.
[3] Hopkins MM, Ibarreta D, Gaisser S, et al. Putting pharmacogenetics into practice. *Nat Biotechnol* 2006. 24(4):403-10.
[4] Schmedders M, van Aken J, Feuerstein G, Kollek R. Individualized pharmacogenetic therapy: a critical analysis. *Community Genet* 2003. 6(2):114-9.
[5] Ginsburg GS, Angrist M. The future may be closer than you think: a response from the Personalized Medicine Coalition to the Royal Society report "Personalised medicine: hopes and realities." *Personalized Med* 2006. 3(2):119-23.
[6] Hopkins MM 2006. Op. cit.

Once it becomes more fully realized, PGx may address certain major health needs, including the need to reduce adverse drug reactions (ADRs). Although safe and effective in most instances, current empirical approaches to pharmaceutical therapy contribute to an estimated 3 million incorrect or ineffective drug prescriptions annually.[7] PGx has great potential to increase the safety and effectiveness of drug treatment by identifying those at risk for ADRs and helping physicians prescribe drugs and dosages in ways that are better tailored to expected individual patient responses. Although most of the current attention on PGx focuses on a small number of recent molecular breakthroughs, much of the potential health benefit of PGx resides in some of the longer standing, more widely used products. Indeed, most ADRs, including many that are likely to be influenced by genotype, arise with the use of older drugs.

PGx also may help improve the productivity of the new drug pipeline. The ability of PGx-based diagnostics to identify potentially slow and fast metabolizers of and nonresponders to investigational drugs eventually may improve the efficiency and lower the costs of clinical trials. The use of PGx in clinical trial design and patient accrual could lead to reductions in the time needed to develop a drug, from 10 to 12 years to perhaps as few as 3 to 5 years.[8] The ability to stratify patient groups using biomarkers and genomic data should enable investigators to discern significant treatment effects that otherwise would be diluted in more heterogeneous populations. This ability also should enable development of drugs tailored for patients with "orphan" and other rare conditions as well as for other underserved patient groups. New methods for conducting clinical research (e.g., adaptive clinical trial designs) have emerged and may help improve and accelerate PGx research.[9,10,11,12] Even so, the net impact of these technologies will reflect, in part, what can be highly complex and resource-intensive pathways for developing, validating, and commercializing many of these PGx tests and accompanying therapies.[13]

PGx has the potential to improve management of chronic diseases, which pose the greatest clinical and economic burdens in the United States and elsewhere. The current therapeutic approach for these diseases is to slow their progression and diminish their symptoms. PGx may help improve symptoms and reduce health care costs through more effective treatments and fewer avoidable ADRs. However, PGx also could increase costs if drugs for smaller markets are priced higher to recoup research and development costs or if PGx testing is added to the cost of drug treatment.

Adaptation of regulatory and payment requirements is of particular importance for the future of PGx. The Food and Drug Administration (FDA) is clarifying the pathways for PGx products from concept to market with guidance and other documents pertaining to PGx data collection and submission and drug/diagnostic codevelopment. Moreover, diverse stakeholders are using knowledge gained from the study of ethical, legal, and social issues to improve access to health care services and protect intellectual property (IP) and patient data. It will be important for these stakeholders to continually assess the environment for

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[7] PricewaterhouseCoopers (2005). *Personalized medicine: the emerging pharmacogenomics revolution.* See http://www.pwc.com/techforecast/pdfs/pharmaco-wb-x.pdf [accessed December 18, 2007].

[8] Ibid.

[9] Roden DM, Altman RB, Benowitz NL, et al. Pharmacogenomics: challenges and opportunities. *Ann Intern Med* 2006. 145(10):749-57.

[10] Gunderson KL, Kuhn KM, Steemers FJ, et al. Whole-genome genotyping of haplotype tag single nucleotide polymorphisms. *Pharmacogenomics* 2006. 7(4):641-8.

[11] Kuehn BM. Industry, FDA warm to "adaptive" trials. *JAMA* 2006. 296(16):1955-7.

[12] Scott Gottlieb, M.D., Deputy Commissioner for Medical and Scientific Affairs, Food and Drug Administration. Speech before 2006 conference on adaptive trial design, Washington, DC, July 10, 2006. See http://www.fda.gov/oc/speeches/2006/trialdesign0710.html [accessed December 18, 2007].

[13] Ginsburg GS, Konstance RP, Allsbrook JS, Schulman KA. Implications of pharmacogenomics for drug development and clinical practice. *Arch Intern Med* 2005. 165(20):2331-6.

developing, validating, and delivering PGx diagnostics and therapies to ensure that PGx yields both health and economic benefits.

B. Challenges and Key Considerations

PGx will need to overcome many challenges for its full potential to be realized. As noted earlier, only a small number of PGx products have reached the market to date, and of these, few have been widely adopted into practice. In addition, current third-party payment mechanisms, including Medicare's statutory prohibition against reimbursement for most screening applications, pose barriers to PGx innovation and can discourage the adoption of PGx tests and therapies by health care providers. Also, the current health information technology infrastructure is not well suited for researching PGx technologies and supporting informed use at the point of care. Furthermore, PGx technologies are challenging FDA's regulatory framework. Finally, although PGx offers ways to improve care for broad populations and subgroups, some are concerned that PGx could exacerbate health and health care disparities in underserved populations.

Although the Federal Government and the private sector have helped advance PGx research and development and its integration into clinical practice and public health, there is still much to be done. Key considerations for realizing the potential of PGx include the following:

- **Product development and clinical studies** must be adapted to assess the accuracy and predictive value of PGx-based diagnostics.
- **Clinical trials** must be adapted to determine the safety, efficacy, and effectiveness of PGx-based therapies, including assessment of biological markers, intermediate endpoints, health outcomes, and adverse events (AEs).
- **Regulation** of PGx products that fosters innovation while ensuring patient safety and improved outcomes will require clear and evolving guidance from, and transparent communication among, the Centers for Disease Control and Prevention (CDC), Centers for Medicare & Medicaid Services (CMS), FDA, Federal Trade Commission, and National Institutes of Health (NIH).
- **Coverage and reimbursement** of PGx technologies may be insufficient to support the development and manufacturing costs of these therapies and tests. Demonstration of clinical utility and value will be critical for obtaining coverage and adequate reimbursement.
- **Health information technology infrastructure** must be sufficiently robust, detailed, and interoperable to support PGx research and PGx-based diagnostic and treatment decisions and surveillance.
- **Education and training** for physicians and other clinicians are essential to ensure their competence with PGx technologies and their ability to counsel patients and families and make informed health care decisions.
- **Ethical, legal, and social issues** will continue to arise as advances in PGx result in greater compilation, transmission, and use of genetic and genomic information. These issues must be addressed to ensure equitable access to health services; instill confidence in the public, health care providers, industry, and policymakers; and realize the health and economic benefits of PGx.

C. Recommendations

Pursuant to these key considerations, SACGHS makes the following recommendations.

1. Basic Research

NIH should receive and put more resources into (1) basic research on the biochemical pathways associated with drug metabolism and drug action, the genes and gene variations involved in these pathways, and the functions of these genes related to the safety and effectiveness of drug treatments and diagnostics and (2) nonhypothesis-based approaches to understanding the relationship between genetic variations and individual responses to drugs.

2. Translational Research

As knowledge of the underlying biology accrues, further research will be needed to translate this knowledge into the development of clinically useful PGx products and to assess their clinical validity and clinical utility. HHS agencies should facilitate the development of clinically useful PGx products by investing more resources in all components of translational research (including translating basic research findings into clinical trials and translating clinical research findings into clinical practice, public health, insurance coverage, and health policy).

3. Clinical Research

3A. Where study results will be used to demonstrate safety and efficacy to support a premarket review application, sponsors and researchers should be encouraged to consult with FDA and CMS early in the study design phases. This approach will help ensure that these studies have adequate clinical study designs (e.g., sufficient statistical power) and quality controls in place should the study later be submitted for regulatory review.

3B. As appropriate, NIH should consider making FDA's existing quality-of-evidence standards a component of its assessments of the scientific merits of grant and contract submissions.

3C. In situations where PGx tests are essential to clinical drug use, HHS should require its grantees and contractors to participate in FDA's Voluntary Genomic Data Submission Program during the exploratory phase of drug development and/or the review process for preinvestigational device exemption.

3D. To enable the investigation of biomarkers associated with drug response, HHS should encourage sponsors of federally funded clinical drug trials to obtain appropriate biological samples from research participants. HHS also should develop guidance and standards on how these samples and other participant data will be collected, stored, shared, and used (see also Recommendation 4 in the Research Logistics section of the SACGHS Large Population Studies report).

4. Development of PGx Products

4A. FDA should develop and implement guidance on the codevelopment of PGx drugs and diagnostics. The guidance should clarify the review process for codeveloped PGx products and promote collaboration between drug and diagnostics developers.

4B. FDA's Office of Combination Products should coordinate FDA's review of codeveloped PGx products to minimize delay in approvals and ensure timely access to them.

4C. HHS should engage all stakeholders in identifying and providing incentives to encourage the development of PGx products, especially for smaller patient populations and/or markets.

5. Establishing an Evidence Base

The adoption of PGx technologies will hinge on the availability of evidence of their analytical and clinical validity, clinical utility, cost-effectiveness, and value of PGx. The following steps should be taken to facilitate the establishment of the evidence base and support the integration of PGx technologies into clinical practice and public health:

5A. HHS should identify and address evidence gaps in the analytical and clinical validity, clinical utility, cost-effectiveness, and value of PGx technologies. Progress will require high-quality data resources; improved methodologies in the design, conduct, and analysis of observational studies; and empirical research on the evidence and standards necessary for making decisions for various purposes (e.g., coverage, clinical guidelines, performance metrics, value-driven health care) in various clinical contexts.

5B. HHS should initiate and facilitate collaborations between public (e.g., Agency for Healthcare Research and Quality [AHRQ], Department of Veterans Affairs [VA], CDC, CMS, FDA, NIH, National Institute of Standards and Technology) and private entities (e.g., private health insurance plans, pharmacy benefits managers, health care facilities with electronic medical records, clinical research databases, genetic repositories) to advance the generation and sharing of knowledge on the analytical and clinical validity, clinical utility, cost-effectiveness, and value of PGx technologies.

5C. HHS should encourage and facilitate studies on the clinical validity and clinical utility of PGx technologies and the dissemination of study findings, including negative findings, through publications, meetings, and an information clearinghouse.

5D. HHS should provide mechanisms that promote interactions among basic, translational, clinical, and outcomes researchers for the identification of endpoints and data elements to be measured. The goal of these interactions is to maximize the value and utility of basic and translational research data for downstream assessments of the clinical validity and clinical utility of PGx technologies.

6. Data Sharing and Database Interoperability

6A. HHS should encourage private sector entities (including academic institutions) to share proprietary data voluntarily to advance the development and codevelopment of PGx products. Manufacturers should be encouraged to make their data publicly available to allow others to conduct research and publish such studies.

6B. HHS should work with the private sector to identify obstacles to data sharing and develop solutions to overcome these obstacles (e.g., legal and data confidentiality assurances, IP protections, funding of databases, and health information technology).

6C. HHS should work with other relevant Federal Departments (e.g., VA, Department of Defense [DOD], Department of Commerce) and the private sector to improve data sharing and interoperability among databases. Specifically, HHS should work with existing organizations to create uniform genomic data standards, explore ways to harmonize data analysis methodologies, and develop an infrastructure to enable data exchange. Data sharing and interoperability of research, regulatory, medical record, and claims databases will facilitate the study of the molecular pathogenesis of disease, identification of targets for drug development, validation of PGx technologies, assessment of health outcomes associated with use of PGx technologies, and determination of the cost-effectiveness and economic impact of using these technologies.

6D. FDA should identify, initiate, and facilitate research opportunities and public-private partnerships to encourage the development and codevelopment of PGx products (e.g., through the Critical Path Initiative, The Biomarkers Consortium).

7. Protection of Personal Information

Stronger data security measures will be needed as more PGx researchers access patient data. HHS, through mechanisms such as the American Health Information Community's (AHIC) Confidentiality, Privacy, and Security Workgroup, should develop guidance on how to balance the protection of privacy and confidentiality of personal data with access to these data for PGx research.

8. Population Stratification in Drug Response

8A. FDA should develop guidance that encourages the collection and analysis of genetic and other biological factors that may be better biological predictors of individual differences in drug response than broad categories such as race, ethnicity, and gender.

8B. When drugs are shown to be more or less effective in certain racial and ethnic subpopulations, FDA should encourage manufacturers to conduct additional postmarket studies to identify genetic and other biological, social, behavioral, and environmental markers that may underlie the differential drug effects.

9. Coverage and Reimbursement for PGx Products

9A. CMS should develop a guidance document detailing current Medicare, Medicaid, and State Children's Health Insurance Program coverage and reimbursement of PGx products. CMS also should survey public and private health plans about their decisionmaking processes and coverage policies to help inform its future PGx coverage and reimbursement decisions.

9B. Because the issues identified in the SACGHS Coverage and Reimbursement report are relevant to issues in this report, SACGHS urges HHS to act on the Coverage and Reimbursement report's recommendations.

10. Use of PGx Technologies in Clinical Practice and Public Health

Health care providers need guidance on how to use PGx information when making clinical decisions. The following steps will help ensure that PGx technologies are integrated effectively into clinical practice:

10A. HHS should assist other Federal agencies, State agencies, and private sector organizations in the development, cataloging, and dissemination of case studies and practice models relating to the use of PGx technologies.

10B. HHS should assist professional organizations in their efforts to help their members achieve competence in the appropriate use of PGx technologies. HHS also should encourage and facilitate collaborations between these organizations and the Federal Government around these activities.

10C. As evidence of clinical validity and clinical utility for a PGx technology accrues, HHS should support the conduct of systematic reviews and technology assessments to summarize the evidence base. These systematic reviews and technology assessments should be disseminated to facilitate the development of clinical practice guidelines.

10D. HHS should facilitate the development of evidence-based clinical practice guidelines and dosing guidelines by supporting consensus-building efforts among guidelines developers. These consensus-building efforts should include development of standards that define the minimal levels of evidence required to support guideline decisions. These standards should take into account the clinical contexts (e.g., prevention, diagnosis, treatment) in which the PGx test may be offered.

10E. To inform the development of PGx tests and dosing guidelines, HHS should fund clinical studies that provide evidence on whether PGx information is clinically useful.

10F. The HHS Secretary should encourage organizations to submit clinical practice guidelines on PGx testing to AHRQ's National Guideline Clearinghouse to facilitate dissemination and encourage their implementation and use.

10G. FDA should work with manufacturers to ensure that all relevant PGx information is included in drug labels in a timely manner. When a PGx test is mentioned in a drug label, information should be included about the test's analytical validity, clinical validity, clinical

utility, dosing, AEs, and/or drug selection for clinicians to use when making treatment decisions based on PGx test results. FDA should provide guidance on the standards of evidence that must be met for PGx information to be included in the label.

10H. NIH and FDA should continue expanding the Internet-based DailyMed project, which provides up-to-date, real-time prescription drug label/package insert information to individuals who have Internet access. To ensure that all sectors of the public have access to this information, NIH and FDA should develop additional ways to disseminate this information.

11. Public Education and Engagement

11A. To inform the public about the availability, benefits, risks, and limitations of PGx technologies, HHS should ensure that credible educational resources are widely available through Federal Web sites and other media.

11B. HHS should use existing public consultation mechanisms to stimulate dialog on the potential benefits, risks, and limitations of PGx technologies. This dialog should include an assessment of the public's perceptions of and receptiveness to PGx and the public's willingness to use these technologies and participate in PGx studies.

12. Health Information Technology

The Office of the National Coordinator for Health Information Technology, through the activities of AHIC, should study how clinically validated PGx test results are being incorporated into electronic health records. HHS, in consultation with VA and DOD, also should take steps to ensure that the necessary infrastructure is in place to support the representation of PGx data in electronic health records for use in decision support systems and tools. HHS should explore the development of pilot studies that examine the impact of clinical decision support systems for PGx technologies on clinical practice at the point of care to maximize evidence-based best practices.

13. Enhancing Access to PGx Technologies

HHS should support policies that afford access to PGx technologies in ways that reduce health and health care disparities, improve health care quality, and prevent genetic discrimination. To this end, HHS should continue to encourage and fund research in support of this goal.

14. Consideration and Implementation of Recommendations

The HHS Secretary should take all necessary steps to review and prioritize these recommendations, assess whether and how to implement them, monitor HHS progress, and report back to SACGHS.

I. Introduction

> *"Pharmacogenomics" is the study of how individual genetic differences affect drug response. This definition encompasses interindividual genetic differences such as variation in DNA sequence, gene expression, and copy number related to an individual's metabolism of drugs (pharmacokinetics) or physiological response to drugs (pharmacodynamics).*

The emerging field of pharmacogenomics arises from the convergence of advances in pharmacology, genetics, and, more recently, genomics. *Pharmacogenetics* is generally recognized as the study of how individual genetic differences affect drug response. In contrast, the study of *pharmacogenomics* encompasses the role of the whole genome in pharmacology and drug design.[14,15,16] These two terms often are used inconsistently and interchangeably in the literature.[17,18,19] Many definitions of pharmacogenomics emphasize functional differences mediated by multigene interactions as well as by environmental interactions.[20,21,22,23,24,25] Other definitions broaden pharmacogenomics to include a variety of biomarkers[26] or distinguish pharmacogenetics as the study and pharmacogenomics as the application.[27,28] Some scientists who consider there to be little meaningful difference between the two terms use them interchangeably.

In this report, we use "pharmacogenomics" (PGx) to refer to the study of how individual genetic differences affect drug response. This definition encompasses interindividual genetic differences such as variation in deoxyribonucleic acid (DNA) sequence, gene expression, and copy number related to an

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[15] Shastry BS. Pharmacogenetics and the concept of individualized medicine. *Pharmacogenomics J* 2006. 6(1):16-21.

[16] Secretary's Advisory Committee on Genetics, Health, and Society (2004). *A Roadmap for the Integration of Genetics and Genomics into Health and Society: The Study Priorities of the Secretary's Advisory Committee on Genetics, Health, and Society*. See http://www4.od.nih.gov/oba/SACGHS/reports/SACGHSPriorities.pdf [accessed December 18, 2007].

[17] Khoury MJ. Genetics and genomics in practice: the continuum from genetic disease to genetic information in health and disease. *Genet Med* 2003. 5(4):261-8.

[18] Guttmacher AE, Collins FS. Genomic medicine — a primer. *N Engl J Med* 2002. 347(19):1512-20.

[19] Secretary's Advisory Committee on Genetics, Health, and Society (2004). *Resolution of the Secretary's Advisory Committee on Genetics, Health, and Society on Genetics Education and Training of Health Professionals*. See http://www4.od.nih.gov/oba/sacghs/reports/EducationResolutionJune04.pdf [accessed December 18, 2007].

[20] Goodman C, Faulkner E, Gould C, et al. *The value of diagnostics: innovation, adoption and diffusion into health care*, 2005. See http://www.advamed.org/NR/rdonlyres/61EB858F-EC9E-4FAB-9547-09DABF7D2A72/0/thevalueofdiagnostics.pdf [accessed January 31, 2008].

[21] Shastry BS 2006. Op. cit.

[22] Secretary's Advisory Committee on Genetics, Health, and Society (2004). *A Roadmap for the Integration of Genetics and Genomics into Health and Society: The Study Priorities of the Secretary's Advisory Committee on Genetics, Health, and Society*. Op. cit.

[23] The Royal Society (2005). *Personalised medicines: hopes and realities*. See http://royalsociety.org/displaypagedoc.asp?id=15874 [accessed December 18, 2007].

[24] University of Minnesota, Center for Bioethics, Consortium on Pharmacogenetics (2002). *Pharmacogenetics: ethical and regulatory issues in research and clinical practice.*

[25] Food and Drug Administration (2005). *Guidance for industry: pharmacogenomic data submissions.* See http://www.fda.gov/cber/gdlns/pharmdtasub.htm [accessed December 18, 2007].

[26] PricewaterhouseCoopers (2005). Op. cit.

[27] Council for International Organizations of Medical Sciences (2005). *Pharmacogenetics: towards improving treatment with medicines.* See http://www.cioms.ch/frame_pharmacogenetics_febr_2005.htm [accessed January 23, 2008].

[28] Melzer D, Raven A, Detmer DE, et al. *My very own medicine: what must I know? Information policy for pharmacogenetics*. Cambridge, UK: University of Cambridge, Department of Public Health and Primary Care, 2003.

individual's metabolism of drugs (pharmacokinetics) or an individual's physiological response to drugs (pharmacodynamics). Ultimately, PGx is a subset of a wider discussion of biomarkers and their use in genetic research, clinical practice, and public health. PGx tests, as a particular form of genetic tests, frequently employ high-throughput technologies, such as microarrays or "gene chips," to analyze whole genomes or specific candidate genes or biomarkers for alterations in gene expression affecting drug action or activity. PGx has a significant role in personalized health care, which aims to improve health outcomes, quality of life, and the health care delivery system by delivering patient-specific health care that takes into consideration the individual's genetic risks for particular conditions or diseases and therapeutic responses.[29]

A. Role of PGx in Addressing Unmet Health Needs

Increasing demands for better health and quality of life are prompting changes in the U.S. health care system.[30,31] Although health care needs in the United States are well documented, the means for meeting these challenges vary and have had mixed success.[32,33,34] PGx is a promising, yet still emerging, avenue for addressing a number of these unmet health care needs. As demonstrated in its clinical applications to date, PGx can provide clinicians with tools to help assess the risks and benefits of certain medicines for particular patients and select therapies and treatment plans tailored for those patients.[35,36]

PGx may enable a new paradigm of personalized medicine by delivering the correct drug at the correct dosage to the correct patient at the correct time.[37,38,39] However, PGx is still a nascent area of research, with only a small number of PGx products commercialized to date and many challenges still to address. It remains uncertain whether, when, and to what extent the potential benefits of PGx will be realized on a large scale.

1. Short-Term Benefits of PGx

Incorporating PGx into health care offers the potential to improve patient health and safety through the reduction of adverse drug reactions (ADRs) and enhancement of drug effectiveness. Some already-manifested benefits suggest the possibility of gains in health care quality and health outcomes.

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[31] Cutler DM, McClellan M. Is technological change in medicine worth it? *Health Health Aff (Millwood)* 2001. 20(5):11-29.
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[33] *Crossing the quality chasm: a new health system for the 21st century*. Washington, DC: Institute of Medicine, National Academies Press, 2001. See http://www.nap.edu/books/0309072808/html [accessed December 18, 2007].
[34] *Priority areas for national action: transforming health care quality*. Washington, DC: Institute of Medicine, National Academies Press, 2003. See http://www.nap.edu/books/0309085438/html [accessed December 18, 2007].
[35] Hopkins MM 2006. Op. cit.
[36] Schmedders M 2003. Op. cit.
[37] Melzer D 2003. Op. cit.
[38] Secretary's Advisory Committee on Genetics, Health, and Society (2006). *Coverage and reimbursement of genetic tests and services*. See http://www4.od.nih.gov/oba/sacghs/reports/CR_report.pdf [accessed December 18, 2007].
[39] Ginsburg GS 2006. Op. cit.

a. Improved Patient Health and Safety

Although they are generally safe and effective in most instances, current empirical approaches to pharmaceutical therapy contribute to an estimated 3 million incorrect or ineffective drug prescriptions annually.[40] One study found that approximately 2.2 million people per year in the United States experienced an ADR during a hospital stay or were admitted to the hospital for an ADR. This study also reported that ADRs account for approximately 106,000 deaths per year, which would rank ADRs between the fourth and sixth leading causes of death in the United States, depending on whether liberal or conservative estimates are used.[41] The economic burden associated with drug-related morbidity and mortality is substantial, with annual costs estimated earlier this decade at more than $177 billion.[42,43] ADRs also are the leading cause of market withdrawals of drugs.[44]

Few prescribed medications are effective for all who use them, and most ADRs are caused by an exaggerated effect of a drug on the human body.[45,46] Drug response can be influenced by genetically mediated variations that affect the metabolism, transport, distribution, absorption, and excretion of a drug.[47] Although ADRs can result from a variety of factors, genetic variations of drug-metabolizing enzymes have been highly correlated with ADRs in some instances.[48] One of the most anticipated potential benefits of PGx is the reduction of ADRs. *In vitro* diagnostic tests may be useful in identifying individuals who are more likely to experience ADRs from particular drugs because of genetic variations in drug targets in the body or in the enzymes that metabolize drugs. Achieving even modest reductions in the rate of ADRs could result in substantial improvements in health outcomes and reductions in health care costs.

One group of drug-metabolizing enzymes that figures prominently in contemporary and future PGx applications is cytochrome P450 (CYP450). This enzyme metabolizes many of the most widely prescribed drugs used in the United States, including Adderall® (amphetamine/dextroamphetamine), Coreg® (carvedilol), Effexor® (venlafaxine), Inderal® (propranolol), Paxil® (paroxetine), Prozac® (flouxetine), Risperdal® (risperidone), Strattera® (atomoxetine), Toprol® (metoprolol), Tussionex® (chlorpheniramine and hydrocodone), and Zofran® (ondansetron).[49] A variant of the *CYP2D6* gene, which affects expression of the CYP450 enzyme, is associated with slower metabolism of these drugs and is prevalent at differing rates among various population groups. The *CYP2D6* gene is associated with slower drug metabolism among approximately 5 percent to 10 percent of Caucasians, 1 percent to 3 percent of Hispanics,[50] 2 percent to 5

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[40] PricewaterhouseCoopers (2005). Op. cit.
[41] Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *JAMA* 1998. 279(15):1200-5.
[42] Ernst FR, Grizzle AJ. Drug-related morbidity and mortality: updating the cost-of-illness model. *J Am Pharm Assoc* 2001. 41(2):192-9.
[43] Institute of Medicine Committee on Quality of Health Care in America. To err is human: building a safer health system, Washington, DC: National Academies Press, 2000. See http://www.nap.edu/catalog.php?record_id=9728 [accessed January 23, 2008].
[44] Gut J, Bagatto D. Theragenomic knowledge management for individualised safety of drugs, chemicals, pollutants and dietary ingredients. *Expert Opin Drug Metab Toxicol* 2005. 1(3):537-54.
[45] Nuffield Council on Bioethics (2003). *Pharmacogenetics: ethical issues*. See http://www.nuffieldbioethics.org/fileLibrary/pdf/pharmacogenetics_report.pdf [accessed December 18, 2007].
[46] Phillips KA, Veenstra DL, Oren E, et al. Potential role of pharmacogenomics in reducing adverse drug reactions: a systematic review. *JAMA* 2001. 286(18):2270-9.
[47] The Royal Society (2005). Op. cit.
[48] Phillips KA 2001. Op. cit.
[49] Phillips KA, Van Bebber SL. Measuring the value of pharmacogenomics. *Nat Rev Drug Discov* 2005. 4(6):500-9.
[50] Ibid.

percent of Asians, and 2 percent to 7 percent of African Americans.[51] As is the case with similar genetically determined metabolic traits, conventional racial and ethnic designations are inadequate markers, and differences in drug metabolism among these groups may be more accurately identified with PGx testing.

b. Increased Drug Effectiveness

Varying response rates to drugs pose clinical and economic concerns. Of 14 major drug classes, 7 have shown effective patient response rates of less than 50 percent. Commonly prescribed medications for diseases such as diabetes, depression, and asthma are effective for only approximately 60 percent of patients, and prescribed cancer treatments are effective for only 25 percent of cancer patients.[52,53]

Although current empirical methods of determining the appropriate drug and dosage for particular patients may be adequate and minimally harmful for some drugs, they can be inefficient, expensive, and potentially detrimental to patient health for other drugs. Some PGx products may overcome these negative outcomes by treating patients according to their individual risks for ADRs.[54,55,56]

2. Long-Term Benefits of PGx

Potential long-term benefits of PGx include reducing the burden of disease, improving the economic efficiency of the health care system, and reducing some disparities in health care access and health outcomes.

a. Reduced Burden of Disease

Chronic conditions are a growing concern in the United States. More than 134 million individuals are expected to have a chronic condition by 2020.[57] PGx is emerging as a means for managing variation in individual responses to drugs for chronic and complex conditions.[58,59,60,61,62]

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[51] Bernard S, Neville KA, Nguyen AT, Flockhart DA. Interethnic differences in genetic polymorphisms of CYP2D6 in the U.S. population: clinical implications. *Oncologist* 2007. 11(2):126-35.

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[53] Spear BB, Health-Chiozzi M, Fugg J. Clinical application of pharmacogenetics. *Trends Mol Med* 2001. 7(5):201-4.

[54] Nuffield Council on Bioethics (2003). Op. cit.

[55] Beitelshees AL, McLeod HL. Applying pharmacogenomics to enhance the use of biomarkers for drug effect and drug safety. *Trends Pharmacol Sci* 2006. 27(9):498-502.

[56] Nuffield Council on Bioethics (2003). Op. cit.

[57] Institute of Medicine Committee on Quality of Health Care in America. Crossing the quality chasm: a new health system for the 21st century. Washington, DC: National Academies Press, 2001. See http://www.nap.edu/catalog.php?record_id=10027 [accessed January 31, 2007].

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[59] Hegi ME, Diserens AC, Gorlia T, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. *N Engl J Med* 2005. 352(10):997-1003.

[60] Esteva FJ, Cheli CD, Fritsche H, et al. Clinical utility of serum HER2/neu in monitoring and prediction of progression-free survival in metastatic breast cancer patients treated with trastuzumab-based therapies. *Breast Cancer Res* 2005. 7(4):R436-43.

[61] Szefler SJ, Apter A. Advances in pediatric and adult asthma. *J Allergy Clin Immunol* 2005. 115(3):470-7.

[62] Rotger M, Colombo S, Furrer H, et al. Influence of CYP2B6 polymorphism on plasma and intracellular concentrations and toxicity of efavirenz and nevirapine in HIV-infected patients. *Pharmacogenet Genomics* 2005. 15(1):1-5.

Treatments for many acute and chronic conditions are grossly underutilized: Half of patients with chronic health conditions discontinue their medications after 1 year.[63] Extensive efforts are under way in the United States to enhance disease management, better use existing guidelines, and develop new guidelines to improve the use of effective treatments. Use of PGx test information could complement these efforts by aiding in the selection of medications that are most likely to be effective and well tolerated, which may result in higher compliance rates. These efforts also could yield economic benefits to consumers, payers, and other health care stakeholders.

b. Improved Economic Efficiency of the Health Care System

The current U.S. health care system tends to focus on the short term rather than investing in care that can be economically efficient in the long term. Health care spending continues to increase faster than the economy at large, without concomitant improvements in health care quality. Greater use of validated preventive services and an increase in translational research focused on improving the effectiveness and efficiency of health care delivery could contribute to a more economically efficient system.

PGx testing for potential ADRs or ineffective drug responses may reduce health care costs over the long term by diminishing the duration and severity of illness and the costs associated with ineffective treatment and avoidable ADRs. PGx testing also could increase economic efficiency by speeding the selection of an effective drug therapy and improving the effectiveness of selected drugs through more appropriate dosing schedules. In addition, PGx testing may help clinicians identify who is the best candidate for a drug, potentially eliminating treatment of those with an unfavorable risk-benefit ratio. [64]

However, even with these potential benefits, payers' willingness to invest in PGx testing may be limited by the short-term costs of PGx adoption and the inability to realize the financial returns due to high rates of enrollee turnover in health care plans. The average consumer likely will experience a net increase in health care costs, particularly in the short term, due to uptake of new PGx drugs and technologies and greater patient cost sharing. Also, PGx testing may not be cost-effective for some conditions that are influenced by more complex, polygenic interactions. Storage of laboratory samples and heritable genetic information for later use could lower some of these costs by eliminating the need for repeated specimen collection and testing.

c. Enhanced Patient Access and Improved Health Outcomes

The current U.S. health care system is poorly suited to deal with fundamental problems of access to appropriate care.[65] Landmark studies conducted by the RAND Corporation demonstrate that patients received only 55 percent of recommended care for their conditions. Statistically significant though clinically moderate differences were seen among various sociodemographic groups (e.g., women vs. men, young vs. elderly adults, blacks and Hispanics vs. whites, high- vs. low-income groups).[66,67]

The causes of disparities in access to health care have far more to do with socioeconomic factors than with a lack of targeted therapies, and interventions directed at addressing these socioeconomic factors will be

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[63] Teutsch SM, Berger ML. Misaligned incentives in America's health: who's minding the store? *Ann Fam Med* 2005. 3(6):485-7.
[64] Garrison LP Jr 2006. Op. cit.
[65] Teutsch SM 2005. Op. cit.
[66] McGlynn EA 2003. Op. cit.
[67] Asch SM, Kerr EA, Keesey J, et al. Who is at greatest risk of receiving poor-quality health care? *N Engl J Med* 2006. 354(11):1147-56.

more successful at reducing these disparities. Even so, PGx applications may help reduce these disparities. Some observers suggest that PGx tools will enable more cost-effective development of drugs by using clinical trial participants who are most likely to respond to investigational drugs and through more targeted indications for clinical use. Doing so may result in greater availability of drugs that otherwise would not have been developed.[68] If this model prevails and adequate payment for these drugs is provided, some underserved populations could experience greater access to safer and more effective drugs. Alternatively, limiting the use of new agents to subgroups rather than making them available to broader populations could result in increased unit drug costs as manufacturers seek to recoup drug development costs, which could reduce their affordability, thereby limiting their availability to more financially privileged persons.

B. Complexity of the Science

PGx involves interindividual genetic variations that result in differences in the function of drug transporters, drug-metabolizing enzymes, and drug targets.[69,70] Genetic variations can be germline (heritable) or somatic (nonheritable). Most PGx research to date has focused on germline variations; however, many clinical conditions arise from somatic variations.[71] The distinction between these two main pathways of genetic variation has implications for PGx research design, clinical and public health impact, and resource allocation.[72]

The scientific goal of PGx is to identify and quantify the association between variations in DNA sequence and variations in the drug response phenotype (i.e., the "genotype-phenotype correlation").[73] As a drug acts on a patient, the patient's body also acts on the drug. The drug must be absorbed, arrive at its site of action, interact with its targets, and be metabolized and excreted. Pharmacokinetics influences the concentration of a drug as it arrives at its target, predominantly through drug-metabolizing enzymes. Pharmacodynamics refers to the factors that influence the response of the target and all the downstream signaling that comes from the target. All of these processes can be subject to clinically relevant genetic variation.[74]

PGx can be used to determine a patient's metabolic response to particular types of drugs, which is influenced by drug-metabolizing enzymes that may be mediated by individual genetic variations (polymorphisms and insertions/deletions). Prominent among these enzymes are CYP450 and its gene variants, particularly *CYP2D6* and *CYP2C19,* which play a role in the metabolism of approximately 25 percent of all prescription drugs.[75]

A prototypical example of applied PGx is a test that predicts patient response to thiopurine 6-mercaptopurine, a mainstay drug used to treat acute lymphoblastic leukemia (ALL) in children. The drug is metabolized by the enzyme thiopurine methyltransferase (TPMT); however, individuals who have a germline variation resulting in low TPMT activity are at increased risk for life-threatening myelosuppression (inhibition of

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[68] PricewaterhouseCoopers (2005). Op. cit.
[69] Evans WE, Relling MV. Moving towards individualized medicine with pharmacogenomics. *Nature* 2004. 429(6990):464-8.
[70] Shastry BS 2006. Op. cit.
[71] National Health Service (2003). *Our inheritance, our future: realising the potential of genetics in the NHS.* See http://www.dh.gov.uk/assetRoot/04/01/92/39/04019239.pdf [accessed December 18, 2007].
[72] Baker SG, Kaprio J. Common susceptibility genes for cancer: search for the end of the rainbow. *BMJ* 2006. 332(7550):1150-2.
[73] In addition to known genetic variations that influence metabolism, there is a risk that there are unidentified variants that could also influence drug metabolism. In other words, PGx testing may not account for all nucleotide changes that could influence metabolism.
[74] Nuffield Council on Bioethics (2003). Op. cit.
[75] Jain KK. Applications of AmpliChip CYP450. *Mol Diagn* 2005. 9(3):119-27.

bone marrow function) when treated with the drug. Due to decreased levels of enzyme production, the concentration of this drug in the bloodstream of these individuals can reach toxic levels. Before scientists learned of this variation and its effect, a child treated for ALL with thiopurine 6-mercaptopurine was at risk for an adverse event leading to destruction of bone marrow and death. Numerous studies have shown a correlation between the *TPMT* genotype and frequency of myelosuppression. PGx testing now allows identification of *TPMT* variants to help guide treatment.[76,77,78]

An application of PGx related to pharmacodynamics is targeting drug therapy on the basis of somatic variations occurring at drug target sites. An example of this type of application is the cancer therapy Herceptin® (trastuzumab).[79] In 25 percent to 30 percent of women with metastatic breast cancer, aberrant expression of *HER2/neu* oncogenes and subsequent overexpression of the HER2 protein are associated with genetic alterations in specific cell types. Immunohistochemistry tests can identify women whose tumors overexpress the HER2 protein, and fluorescent *in situ* hybridization tests can identify women with the *HER2/neu* alteration. Women who test positive for either assay respond better to Herceptin®, allowing targeted drug therapy.

Physicians who prescribe medications understand that variations in drug response are influenced by other factors in addition to genetic variation and complex interactions between biological and environmental factors. These nongenetic factors include age, gender, diet, other underlying medical conditions, and drug interactions. For instance, proper dosing for warfarin, a drug commonly prescribed for those at risk for harmful blood clots, is affected by complex factors that affect proper dosing. If an individual is homozygous for the **3* variant of the *CYP2C9* gene, clearance of the drug is greatly reduced. Warfarin action also is affected by the *VKORC1* gene. The optimal maintenance doses of warfarin can vary depending on whether an individual has two copies of the low-dose *VKORC1* variant or two copies of the high-dose variant. *VKORC1* variants are reported to be responsible for about 30 percent of the variation in the final warfarin dose, and *CYP2C9* is thought to be responsible for about 10 percent.[80] Other nongenetic factors such as age, body surface area, hypertension, heart disease, use of other prescription drugs, renal status, bleeding history, and intake of certain foods that could interfere with warfarin absorption or anticoagulation response also have been shown to have an effect on warfarin dosing and, thus, need to be taken into account when

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[76] Zhan ZP, Yang XY, Liang LQ, Wang YX, Huang M, Lian F. The profile and clinical significance of azathioprine metabolic enzymes activity in rheumatological patients. *Zhonghua Nei Ke Za Zhi* 2006. 45(7):537-9.

[77] Hibi T, Naganuma M, Kitahora T, Kinjyo F, Shimoyama T. Low-dose azathioprine is effective and safe for maintenance of remission in patients with ulcerative colitis. *J Gastroenterol* 2003. 38(8):740-6.

[78] Gisbert JP, Nino P, Rodrigo L, Cara C, Guijarro LG. Thiopurine methyltransferase (TPMT) activity and adverse effects of azathioprine in inflammatory bowel disease: long-term follow-up study of 394 patients. *Am J Gastroenterol* 2006. 101(12):2769-76.

[79] Herceptin® Web site. About Herceptin® & Metastatic Breast Cancer. See http://www.herceptin.com/herceptin/patient/about/herceptin.jsp [accessed December 18, 2007].

[80] Rieder MJ, Reiner AP, Gage BF, et al. Effect of VKORC1 haplotypes on transcriptional regulation and warfarin dose. *N Engl J Med* 2005. 352(22):2285-93.

prescribing the drug and dosage.[81] Much remains to be learned about the application of PGx to warfarin as clinical trials continue.[82,83,84,85]

C. Current State of the PGx Field

In the 1990s PGx innovation promised a new paradigm in health care. Although a small number of important PGx products have reached the market, early expectations for the field have not yet materialized. Although the push for innovation and demand for personalized medicine continue, new products face careful assessments of benefits, risks, and costs. Approaches to regulation and reimbursement will affect how PGx technologies are used. Federal agencies have issued guidance documents to help support industry efforts to incorporate genomic and biomarker information into the drug development process. Similarly, international cooperation has enhanced the interoperability of health information technology (IT) systems and data sharing efforts related to PGx.[86,87]

Although most of the current attention on PGx focuses on a small number of recent molecular breakthroughs, much of the potential health benefit of PGx resides in some of the longer standing, more widely used products. Most ADRs, including many that are likely to be influenced by genotype, arise with the use of older drugs.[88]

The PGx field offers alternatives to traditional models of drug development. The prevailing "blockbuster" model for broad populations, intended to yield annual revenues exceeding $1 billion, is strained due to increases in the costs and duration of the drug development process, rising prices of prominent or truly novel ("breakthrough") drugs, and heightened public awareness of actual or perceived lapses in drug safety.[89]

PGx drug and test combinations are likely to come to market with high sticker prices, although these prices may be offset by downstream reductions in inappropriate drug use, fewer visits to physicians to change medications or adjust dosages, and cost savings realized from decreased ADRs and improved effectiveness. The prospect of higher drug development costs and narrower markets for new drugs could further motivate manufacturers to affix premium prices to these drugs.

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[81] Food and Drug Administration (2007). *Questions and Answers on New Labeling for Warfarin (marketed as Coumadin)*. See http://www.fda.gov/cder/drug/infopage/warfarin/qa.htm [accessed March 5, 2008].

[82] National Institutes of Health (2006). *PRospective Evaluation Comparing Initiation of Warfarin StrategiEs (PRECISE): pharmacogenetic-guided versus usual care.* See http://clinicaltrials.gov/ct/show/NCT00377143?order=1 [accessed December 18, 2007].

[83] National Institutes of Health (2006). *A pharmacogenetic study of warfarin dosing, "The COUMA-GEN Study."* See http://clinicaltrials.gov/ct/show/NCT00334464?order=2 [accessed December 18, 2007].

[84] National Institutes of Health (2007). *Comparison of warfarin dosing using decision model vs. pharmacogenetic algorithm.* See http://clinicaltrials.gov/ct/show/NCT00511173?order=9 [accessed December 18, 2007].

[85] National Institutes of Health (2007). *Study to develop a reliable nomogram that incorporates clinical and genetic information.* See http://clinicaltrials.gov/ct/show/NCT00401414?order=11 [accessed December 18, 2007].

[86] European Medicines Agency (2006). *ICH Topic E 15: definitions for genomic biomarkers, pharmacogenomics, pharmacogenetics, genomic data and sample coding categories.* See http://www.emea.europa.eu/pdfs/human/ich/43798606en.pdf [accessed December 18, 2007].

[87] Food and Drug Administration (2006). *Guiding principles processing joint FDA EMEA voluntary genomic data submissions (VGDSs) within the framework of the Confidentiality Arrangement.* See http://www.fda.gov/cder/genomics/FDAEMEA.pdf [accessed December 18, 2007].

[88] Melzer D, Raven A, Ling T, Detmer D, Zimmern R. Pharmacogenetics: policy needs for personal prescribing. *J Health Serv Res Policy* 2005. 10(1):40-4.

[89] PricewaterhouseCoopers (2005). Op. cit.

Although some PGx products and services are available in the health care market, much of the existing information on PGx has not yet been translated into practical clinical applications. Clinical applications of PGx have been limited by a lack of evidence of clinical validity and clinical utility as well as by other barriers.[90] The paucity of clinically relevant supporting evidence is a major reason why PGx clinical practice guidelines and dosing recommendations have not been developed and why PGx information has not been incorporated routinely into drug labels. Also, current postmarketing surveillance techniques and infrastructure may be inadequate for the collection and analysis of data.[91,92,93] Enhancements in postmarketing surveillance methods can generate information about the benefits, risks, and costs of PGx products. Tracking the impact of PGx on disease burden and quality of life also is needed to inform public health decisions.

D. Purpose and Scope of This Report

This report aims to explore the opportunities for PGx to advance the development of diagnostic, therapeutic, and preventive strategies to improve health. It also explores the opportunities and challenges associated with PGx research, development of PGx applications, and integration of these applications into clinical practice and public health. The report addresses the current, evolving environment for PGx and its potential to inform the decisions of clinicians, policymakers, and other stakeholders. It is intended to provide policy-relevant information about PGx to help frame recommendations for the HHS Secretary and other policymakers and stakeholders.

To highlight the steps in the process from innovation to adoption and diffusion of PGx, this report is organized into three main sections. The first, ***Research and Development***, provides an overview of basic, translational, and clinical research for PGx and describes aspects of the infrastructure needed to promote PGx research and development (R&D). ***Gatekeepers*** describes the roles of four main types of stakeholders involved in facilitating the progression of PGx from R&D to the marketplace. ***Implementation of PGx To Improve Outcomes in Clinical Practice and Public Health*** explores important aspects of the use of PGx in clinical practice and public health settings, including the need for education and IT to support its use. Ethical, legal, and social issues related to PGx are described throughout the report. Although the path from innovation to adoption and diffusion of health care technology is traditionally described as linear, the major phases along this continuum overlap, where information learned in one phase informs a future phase. Also, as PGx technologies are implemented in clinical practice, lessons learned may inform priorities for future R&D. These points of critical feedback also are noted throughout the report.

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[90] Webster A, Martin P, Lewis G, Smart A. Integrating pharmacogenetics into society: in search of a model. *Nat Rev Genet* 2004. 5(9):663-9.

[91] Melzer D 2003. Op. cit.

[92] FDA Web site. About MedWatch. See http://www.fda.gov/medwatch/What.htm [accessed December 18, 2007].

[93] Secretary's Advisory Committee on Genetics, Health, and Society (2006). Transcript of ninth meeting, March 27, 2006. See http://www4.od.nih.gov/oba/SACGHS/meetings/March2006/transcripts/FullDayTranscript03-27.pdf [accessed December 18, 2007].

II. Research and Development

Pharmacogenomics (PGx) has multiple potential roles along the research and development (R&D) continuum, from basic research of biochemical pathways and relevant biomarkers to the development of targeted drugs and diagnostic tests. The following sections describe the potential roles that PGx can play throughout the R&D process; the infrastructure needed to promote and support the use of PGx in R&D; and potential ethical, legal, and social issues (ELSI) arising from PGx-based R&D.

A. Basic Research

Basic research in PGx primarily involves the identification of the biochemical pathways and related biomarkers involved in drug metabolism and drug response. In addition to identifying relevant biomarkers, much basic PGx research is devoted to refining and improving the sensitivity of high-throughput methods for detecting gene expression and drug response.

Genome-wide association studies (GWAS), as well as candidate gene studies, are emerging as useful tools for the discovery of genes associated with variability in drug response. A GWAS is defined as any study of genetic variation across the entire human genome that is designed to identify genes associated with observable traits (such as blood pressure or body weight) or the presence or absence of a disease or condition.[94] Since GWAS collect large volumes of genotypic and phenotypic information, researchers may be able to determine correlations between a certain genetic makeup and a drug response. These correlations may lead investigators to a series of potential genetic targets or "candidate genes" that can be further evaluated for their ability to predict drug response (safety or efficacy) in model systems and clinical trials.

Efforts currently under way to elucidate such associations include the International HapMap Consortium; the Genetic Association Information Network (GAIN); the Genes, Environment and Health Initiative (GEI); The Biomarkers Consortium; and the Framingham Single Nucleotide Polymorphism (SNP) Health Association Resource (SHARe), among others. The International HapMap Consortium aims to develop a human haplotype map (the HapMap) that will elucidate patterns of variation in the human genome.[95,96] GAIN is a public-private partnership of the National Institutes of Health (NIH), Foundation for the NIH (FNIH), Perlegen Sciences, Affymetrix, and Pfizer Global Research and Development to fund whole-genome association studies and genotyping services to aid in the identification of genetic risk factors.[97,98] GEI will provide genotyping facilities, a coordinating center for analytical support, data quality assessment and quality control, logistical management, and support for the investigation of major scientific questions using existing deoxyribonucleic acid (DNA) samples from well-characterized subjects. Data for this research will be made available in the central, controlled-access database established by the National

[94] NIH Web site. Genome-Wide Association Studies (GWAS). See http://grants.nih.gov/grants/gwas/index.htm [accessed December 18, 2007].
[95] International HapMap Project Web site. International HapMap Project. See http://www.hapmap.org/ [accessed December 18, 2007].
[96] The International HapMap Consortium. A haplotype map of the human genome. *Nature* 2005. 437(7063):1299-320.
[97] Foundation for the National Institutes of Health Web site. Genetic Association Information Network. See http://www.fnih.org/GAIN2/home_new.shtml [accessed December 18, 2007].
[98] Perlegen Sciences. Perlegen Sciences News Release, February 8, 2006. Genetic association information network launched: novel public-private partnership created to unravel the genetics of common disease through whole genome association studies. See http://www.perlegen.com/newsroom/pr/2006/2006_02_08_Pfizer_NIH_Press%20Release.pdf [accessed December 18, 2007].

Center for Biotechnology Information (NCBI).[99] Framingham SHARe provides data from 9,000 subjects enrolled in the Framingham Heart Study for use in GWAS to identify critical genetic variations underlying cardiovascular disease and other chronic diseases.[100]

Although GWAS can be a useful tool for PGx research, the associations among loci are complex.[101,102] Uncertainty remains over the robustness of GWAS, including concerns about sample size, collection bias, and the current ability of high-throughput technologies to produce the necessary volume of data.[103,104] Also, although these methods have considerable scientific value, affordable sequencing and storing of whole genomes on a large scale remain far in the future and will require robust information management systems and methods for genomic analysis.[105] Because the sequencing of whole genomes currently is too expensive to perform on a large scale, some observers see a need for more cost-effective genotyping methods in GWAS.[106,107]

Recommendation 1

NIH should receive and put more resources into (1) basic research on the biochemical pathways associated with drug metabolism and drug action, the genes and gene variations involved in these pathways, and the functions of these genes related to the safety and effectiveness of drug treatments and diagnostics and (2) nonhypothesis-based approaches to understanding the relationship between genetic variations and individual responses to drugs.

B. Translational (T1) Research: From Basic to Clinical Research

Translational research can be applied to different phases of R&D. Various models depict translational research as a process occurring in two stages.[108,109,110] The first stage, sometimes referred to as "type 1 (T1) translation," uses findings from basic research, including preclinical studies, to inform the development and testing of an intervention in clinical trials, such as Phase I through III clinical trials. Type 2 (T2) translation involves the translation of clinical research findings into clinical practice, public health, and health policy.[111,112] This section focuses on T1 translation; section E discusses T2 translation.

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[99] NIH Web site. The Genes and Environment Initiative (GEI). See http://www.gei.nih.gov/ [accessed December 18, 2007].
[100] NIH Web site. NHLBI Launches Framingham Genetic Research Study. See http://www.nhlbi.nih.gov/public/may06/feature.htm#fram [accessed December 18, 2007].
[101] Roden DM 2006. Op. cit.
[102] Gunderson KL 2006. Op. cit.
[103] Wang WY, Barratt BJ, Clayton DG, Todd JA. Genome-wide association studies: theoretical and practical concerns. *Nat Rev Genet* 2005. 6(2):109-18.
[104] Farrall M, Morris AP. Gearing up for genome-wide gene-association studies. *Hum Mol Genet* 2005. 14 Spec No. 2:R157-62.
[105] Roden DM 2006. Op. cit.
[106] Gunderson KL 2006. Op. cit.
[107] Goldstein DB. The genetics of human drug response. *Philos Trans R Soc Lond B Biol Sci* 2005. 360(1460):1571-2.
[108] Sussman S, Valente TW, Rohrbach LA, Skara S, Pentz MA. Translation in the health professions: converting science into action. *Eval Health Prof* 2006. 29(1):7-32.
[109] Westfall JM, Mold J, Fagnan L. Practice-based research—"Blue Highways" on the NIH roadmap. *JAMA* 2007. 297(4):403-6.
[110] Ozdemir V, Williams-Jones B, Cooper DM, Someya T, Godard B. Mapping translational research in personalized therapeutics: from molecular markers to health policy. *Pharmacogenomics* 2007. 8(2):177-85.
[111] Sussman S 2006. Op. cit.
[112] Westfall JM 2007. Op. cit.

The Pharmacogenetics Research Network (PGRN) is one program that aims to encourage and accelerate the translation of basic research into clinical research. PGRN is a trans-NIH effort led by the National Institute of General Medical Sciences. This nationwide collaboration of 12 independently funded interactive research groups discovers genetic variations (not limited to SNPs) and studies relationships between these genetic variations and patient-drug responses. PGRN investigators perform genotype-to-phenotype studies, which examine genetic variability in individuals who respond differently to drugs, and phenotype-to-genotype studies, which identify gene variants of pharmacological interest and determine whether they are the cause of variability in patient responses. The identification of genotype-phenotype correlations usually is followed by mechanistic biological studies. A major component of PGRN is the Pharmacogenomics Knowledge Base (PharmGKB), where PGx data collected from studies within and beyond PGRN are stored and made freely available to scientists. With data on more than 10,000 human gene variations that affect drug responses, PGRN enables the scientific community to access a wealth of information on genes, drugs, and diseases.[113]

In addition to PGRN, NIH supports several research efforts, including SNP Typing for Association with Multiple Phenotypes from Existing Epidemiologic Data, the Candidate Gene Association Resource, Enhancing Development of Genome-Wide Association Methods, and the Database of Genotype and Phenotype (dbGaP), that provide genomic information at no cost to qualified investigators. By enabling exchange of existing data through resources such as these, researchers can avoid duplication of efforts.[114,115,116,117]

As described in section F below, Infrastructure Enabling Research and Development, databases and repositories that store PGx data are expected to play a role in translating basic research into clinical research. Such PGx databases and repositories should enable more efficient clinical trial enrollment by selecting participants based on the presence or absence of particular markers and potential responsiveness to an investigational drug.[118]

Recommendation 2

As knowledge of the underlying biology accrues, further research will be needed to translate this knowledge into the development of clinically useful PGx products and to assess their clinical validity and clinical utility. HHS agencies should facilitate the development of clinically useful PGx products by investing more resources in all components of translational research (including translating basic research findings into clinical trials and translating clinical research findings into clinical practice, public health, insurance coverage, and health policy).

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[113] NIGMS Web site. Pharmacogenetics Research Network. See http://www.nigms.nih.gov/Initiatives/PGRN/ [accessed December 18, 2007].
[114] NHLBI Web site. STAMPEED. See http://public.nhlbi.nih.gov/GeneticsGenomics/home/stampeed.aspx [accessed December 18, 2007].
[115] NHLBI Web site. CARe: Candidate-gene Association Resource. See http://public.nhlbi.nih.gov/GeneticsGenomics/home/care.aspx [accessed December 18, 2007].
[116] NHLBI Web site. ENDGAME: Enhancing Development of Genome-Wide Association Methods. See http://public.nhlbi.nih.gov/GeneticsGenomics/home/endgame.aspx [accessed December 18, 2007].
[117] NHLBI Web site. dbGAP: NHLBI DNA Resequencing and Genotyping Program. See http://www.nhlbi.nih.gov/resources/res-databases/dbgap.htm [accessed December 18, 2007].
[118] PricewaterhouseCoopers (2005). Op. cit.

C. Clinical Research

Clinical drug trials traditionally involve the random assignment of sufficient numbers of study participants with a particular condition to either the investigational drug group or control group to detect statistically significant differences in drug response between the two groups. It is typical to enroll large numbers of subjects to ensure that any statistically significant results represent a true treatment effect. Some study participants with a given condition may be less genetically predisposed than others to respond to the investigational drug, however. Applying PGx to clinical trials can enable more targeted selection of subjects and smaller trials by identifying those subjects who are more likely to respond to a drug based on their genotype.[119,120] Thus, PGx may be a means for applying more precise and effective inclusion and exclusion criteria in clinical trials, resulting in smaller, more efficient, and safer clinical studies.[121,122]

Investigators also can genotype subjects recruited for Phase I trials to identify gene variants that are linked to drug metabolism. Identifying polymorphisms in the drug target gene during Phase I and II trials and linking them to adverse drug reactions (ADRs) or variations in drug response then can be used to screen out subjects who are likely to experience ADRs in Phase III clinical trials.[123]

Although PGx-informed clinical trials can be more efficient, some note their potential limitations. These trials are most feasible when dealing with common polymorphisms. It may be difficult to ascertain sufficient cases of homozygous-mutant or -deficient subjects in a reasonable length of time for genetic variants that occur at low rates.[124]

Claims of cost savings associated with PGx-informed clinical trials also should be carefully reviewed. Although use of PGx in clinical trial design could increase the efficiency of new drug development and reduce potential harms to subjects, reductions in drug development time and costs have yet to be demonstrated. PGx-informed clinical trials could become costly if, for example, larger numbers of subjects are needed in early-phase trials to identify relevant PGx variants. Larger sample sizes also may be needed in later stages to identify ADRs, given that many ADRs occur infrequently.[125] Ultimately, the cost of using PGx in drug development would likely be offset by downstream savings resulting from reductions in inappropriate drug use, fewer health care provider visits to change medications or adjust dosages, and decreased ADRs.[126]

The use of PGx in the development of new drugs will require flexible study designs that are informed by PGx data as they become available. Adaptive clinical trials are emerging as an example of such a flexible approach to clinical trial design. Compared with nonadaptive clinical trials in which subject selection and related study design aspects are determined in advance, data from adaptive clinical trials are analyzed periodically and used to modify the trial design as needed. Adaptive clinical trial designs aim to be iterative

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[119] Ibid.
[120] Sadee W. Pharmacogenomics: the implementation phase. *AAPS PharmSci* 2002. 4(2):E5.
[121] Emilien G, Ponchon M, Caldas C, Isacson O, Maloteaux JM. Impact of genomics on drug discovery and clinical medicine. *QJM* 2000. 93(7):391-423.
[122] Issa AM 2002. Op. cit.
[123] Ibid.
[124] Garrison LP Jr, Veenstra DL, Carlson RJ, Carlson JJ, Meckley LM. *Backgrounder on pharmacogenomics for the pharmaceutical and biotechnology industries: basic science, future scenarios, policy directions – final report.* University of Washington, Department of Pharmacy, Pharmaceutical Outcomes Research & Policy Program, 2007. See http://depts.washington.edu/porpp/documents/University%20of%20Washington%20Backgrounder%20on%20Pharmacogenomics--February%202007.pdf [accessed December 18, 2007].
[125] Nuffield Council on Bioethics (2003). Op. cit.
[126] Ibid.

and flexible and to have the ability to be fine-tuned throughout the drug development process, potentially leading to more efficient and precise identification of effective treatments.[127]

Rather than selecting from a cross-section of the general population, in an adaptive clinical trial, outcomes from early phases of the trial can be used to adjust and narrow the sample in subsequent stages to include only subjects with a greater probability of having a positive outcome. The ability to identify critical biomarkers during the drug development process allows investigators to predict more accurately who these positive responders are likely to be.[128,129] Emerging data from an adaptive trial also can be used to decide whether to stop a trial, modify treatment allocation, or drop or add treatment arms.[130]

Clinical trial sponsors hope adaptive trial designs will establish drug safety and effectiveness better and faster and with smaller sample sizes, while decreasing study participants' exposure to less effective or harmful treatments. Other benefits include the ability to observe positive treatment responses sooner and avoiding ethical dilemmas that cause clinicians and subjects to balk at traditional randomization to treatment arms.[131] Moreover, in clinical trials that contain substudies of biomarker validation, adaptive trial designs may provide an opportunity to complement and expand on more traditional therapeutic dose monitoring approaches to biomarker validation.[132,133]

The reauthorization of the Prescription Drug User Fee Act (PDUFA) is a significant step toward developing the necessary infrastructure for using adaptive trial designs in drug development. Under PDUFA IV, the Food and Drug Administration (FDA) will develop guidance on testing, detecting, and preventing safety problems through enriched clinical drug trial designs.[134,135] FDA representatives also note that adaptive clinical trials can play a role in the Agency's Critical Path Initiative.[136]

Although using adaptive trial designs has clear benefits, experts in industry and academia note potential pitfalls. Controversy exists over the use of adaptive design in later trials, particularly Phase III trials, which have less statistical efficiency and results that can be difficult to interpret. Adaptive trial designs often are not used in Phase III trials because interim results are not confirmative and can be misleading. Adaptive trial designs also can be logistically complicated and complex to run, requiring a robust and integrated data system to manage information on drugs and trial participants. Some observers are concerned that these trials could result in unintentional unblinding of the subjects' treatment arm assignment and bias because of preferential selection of trial participants.[137]

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[127] Kuehn BM 2006. Op. cit.
[128] Ibid.
[129] Scott Gottlieb, M.D., Deputy Commissioner for Medical and Scientific Affairs, Food and Drug Administration 2006. Op. cit.
[130] American Statistical Association (2005). Critical Path Initiative: what it means for pharmaceutical industry statisticians. FDA/Industry Workshop, September 14-16, 2005. See http://www.amstat.org/meetings/fdaworkshop/presentations/2005/G1_Offen_Critical%20Path.ppt [accessed February 28, 2007].
[131] Scott Gottlieb, M.D., Deputy Commissioner for Medical and Scientific Affairs, Food and Drug Administration 2006. Op. cit.
[132] National Institute of Allergy and Infectious Diseases (2007). *Comments on realizing the promise of pharmacogenomics: opportunities and challenges* (public comment draft).
[133] Albers LJ, Ozdemir V. Pharmacogenomic-guided rational therapeutic drug monitoring: conceptual framework and application platforms for atypical antipsychotics. *Curr Med Chem* 2004. 11(3):297-312.
[134] Food and Drug Administration (2007). *The future of drug safety – promoting and protecting the health of the public: FDA's response to the Institute of Medicine's 2006 report*. See http://www.fda.gov/oc/reports/iom013007.pdf [accessed December 18, 2007].
[135] Prescription Drug Use Fee Act. *Fed Regist* 2007. 72(9):1743-53.
[136] Food and Drug Administration (2006). *FDA and the Critical Path Institute announce Predictive Safety Testing Consortium*. See http://www.fda.gov/bbs/topics/news/2006/NEW01337.html [accessed December 18, 2007].
[137] Kuehn BM 2006. Op. cit.

In addition to adaptive trial designs, other types of study designs should be considered when conducting clinical research. Biological correlative trials, which involve prospectively defined protocols using archival biological samples from existing clinical trials and observational and/or epidemiological studies, also may be useful in developing evidence-based PGx associations; however, this approach has not been adequately validated.[138]

Regardless of how clinical trials are conducted, for tests subject to FDA review, sponsors need to ensure that studies are designed to meet FDA quality-of-evidence standards. In recognition of the need to encourage and assist sponsors of PGx research, FDA has issued guidance documents on the use of PGx data during the drug development process and has made recommendations to sponsors seeking FDA approval for PGx tests. One such guidance document, *Guidance for Industry: Pharmacogenomic Data Submissions,* was issued specifically to facilitate the use of PGx data in drug development and to support the voluntary submission of genomics data.[139] FDA evidence standards and PGx-related guidances are discussed in greater detail in Chapter III. Gatekeepers.

Recommendations 3A, 3B, 3C, and 3D

3A. Where study results will be used to demonstrate safety and efficacy to support a premarket review application, sponsors and researchers should be encouraged to consult with FDA and CMS early in the study design phases. This approach will help ensure that these studies have adequate clinical study designs (e.g., sufficient statistical power) and quality controls in place should the study later be submitted for regulatory review.

3B. As appropriate, NIH should consider making FDA's existing quality-of-evidence standards a component of its assessments of the scientific merits of grant and contract submissions.

3C. In situations where PGx tests are essential to clinical drug use, HHS should require its grantees and contractors to participate in FDA's Voluntary Genomic Data Submission Program during the exploratory phase of drug development and/or the review process for preinvestigational device exemption.

3D. To enable the investigation of biomarkers associated with drug response, HHS should encourage sponsors of federally funded clinical drug trials to obtain appropriate biological samples from research participants. HHS also should develop guidance and standards on how these samples and other participant data will be collected, stored, shared, and used (see also Recommendation 4 in the Research Logistics section of the SACGHS Large Population Studies report).

D. Development of PGx Products

This section discusses the application of PGx to new and existing drugs, drugs found to be ineffective for their initial target population during drug development, and drugs withdrawn from the market. It also discusses the development of PGx diagnostic tests and codevelopment of PGx drug-diagnostic combinations.

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[138] 21st Century Medicine (2007). *Comments on realizing the promise of pharmacogenomics: opportunities and challenges* (public comment draft). See http://www4.od/nih.gov/oba/sacghs/reports/pgx_publiccomments.pdf [accessed April 21, 2008].

[139] Food and Drug Administration (2005). *Guidance for industry: pharmacogenomic data submissions*. See http://www.fda.gov/cber/gdlns/pharmdtasub.htm [accessed December 18, 2007].

1. PGx Test Development

Although both types of testing involve an individual's genome or gene products, the broader concept of *genetic testing* differs from the more specific concept of *PGx testing*. Genetic testing is performed primarily to diagnose or determine a person's genetic risk of developing a condition or disease. PGx testing is a particular form of genetic testing used to inform therapeutic decisions such as whether to use particular drugs and at what dosages. Most genetic testing, including PGx testing, is performed as an in-house service by clinical laboratories, although some genetic tests are marketed as *in vitro* diagnostic (IVD) test kits.

As with any diagnostic test, PGx tests vary in their sensitivity, specificity, and predictive power. The clinical validity of these tests depends on these parameters.[140] PGx studies that test for SNPs require population sample sizes large and diverse enough to obtain statistically significant results in different substrata of the population.[141,142] In particular, sample sizes to validate a PGx test should be sufficiently large to measure and compare drug responses between different genotypic groups.[143,144]

A key concern related to the development of PGx tests is projecting market utilization of the test and the accompanying return on investment. This concern, of course, is linked to the anticipated use of the therapies whose prescriptions will be informed by the PGx test result. Individualized drug therapies may be cost-effective only for certain combinations of disease, gene, drug, and test characteristics and should be evaluated accordingly.[145] Clinicians and health care payers will use identified risk factors and other patient information to focus the use of such tests on patients who are likely to benefit from having their test results. This will be particularly true for expensive tests or those resulting in expensive therapies.[146] Demand may be high for tests that are developed to inform therapeutic decisions for common, chronic diseases, especially if more patient-years of unnecessary or ineffective treatment can be avoided with PGx testing and personalized treatment.[147]

As is the case for new drugs, gene patents will strongly influence the development of PGx products. Protecting gene patents is important for pharmaceutical and biotechnology companies because it enables these entities to recoup their R&D investments.[148] There is uncertainty in the United States about what is a legally patentable material or method. Most PGx tests for which patents have been filed are based on the identification of a small number of SNPs that relate to various drug responses. It is unclear whether such gene variants can be patented.[149] Most patent claims likely will focus on methods of testing, treatments arising from testing, and novel dosages. Intellectual property (IP) rights also will be an issue in the process of PGx test development. For example, if development of a PGx test requires access to DNA sequences, a company developing such a test may need to obtain a license from the patent holder, adding to R&D costs.

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[140] Robertson JA, Brody B, Buchanan A, Kahn J, McPherson E. Pharmacogenetic challenges for the health care system. *Health Aff (Millwood)* 2002. 21(4):155-67.
[141] The Royal Society (2005). Op. cit.
[142] Kirchheiner J, Fuhr U, Brockmöller J, Pharmacogenetics-based therapeutic recommendations – ready for clinical practice? *Nat Rev Drug Discov* 2005. 4(8):639-47.
[143] Katz DA. From bench to bedside: a diagnosis framework for pharmacogenetics research. *Mol Genet Metab* 2002. 77(1-2):57-60.
[144] Kirchheiner J 2005. Op. cit.
[145] Veenstra DL, Higashi, MK, Phillips KA. Assessing the cost-effectiveness of pharmacogenomics. *AAPS PharmSci* 2000. 2(3): E29.
[146] Flowers CR, Veenstra D. The role of cost-effectiveness analysis in the era of pharmacogenomics. *Pharmacoeconomics* 2004. 22(8):481-93.
[147] Veenstra DL 2000. Op. cit.
[148] Nunnally AC. *Intellectual property perspectives in pharmacogenomics*. WilmerHale, 2005. See http://www.wilmerhale.com/publications/whPubsDetail.aspx?publication=952 [accessed October 22, 2007].
[149] Barton JH. Patents, genomics, research, and diagnostics. *Acad Med* 2002. 77(12 Pt 2):1339-47.

In addition, the issue of who will be granted patent rights could be particularly complex when multiple entities are involved in the development of a diagnostic test.[150]

2. Codevelopment of Drugs and Diagnostic Tests

Drug development and diagnostic development traditionally have been carried out separately by different manufacturers. PGx codevelopment refers to the contemporaneous, linked development of drugs and PGx tests in which drugmakers would investigate various biomarkers during the early stages of drug development, resulting in a validated biomarker that can be identified with a diagnostic test.[151] FDA would review the two products simultaneously, potentially accelerating the FDA approval process. Exhibit 1 describes the review process for the breast cancer drug Herceptin® and its diagnostic tests.

Exhibit 1. The Case of Herceptin®

Herceptin®, marketed by Genentech, is a monoclonal antibody indicated for about a quarter of breast cancer patients who have a genetic abnormality that leads to overexpression of the HER2 protein. During product development, Genentech and FDA noted that appropriate treatment with Herceptin® required a diagnostic test to identify HER2-positive individuals. Genentech initially collaborated with Dako Corporation to provide such a test. The two manufacturers simultaneously filed applications for coordinated use of the drug and an immunohistochemistry test, which measures the level of expression of the HER2 protein in tumors. The two products gained FDA approval in late 1998. After Herceptin® was on the market, Genentech found that the medical community remained uncertain about when it was appropriate to test patients for the HER2 protein. Further research found that a test method based on fluorescence *in situ* hybridization (FISH), which detects the underlying gene alteration in the tumor cells by measuring the number of copies of the *HER-2/neu* gene,[152] also could select those patients who would benefit from Herceptin®.[153] Genentech worked with the diagnostic firm Vysis (later acquired by Abbott Laboratories) to gain FDA approval of a FISH test and applied to FDA to change the label for Herceptin® to include FISH testing as an alternative.[154] Initial results indicate that FISH was the preferred method, but results have been mixed about which is the better testing method.[155,156]

In many cases, a biomarker is not identified until later in the drug development process, precluding this sort of simultaneous review. In such cases, a PGx test is developed after the drug has proceeded through its development and review processes, and the original drug label may be modified to include information about the PGx test. Parallel development of drugs and diagnostics is a relatively new aspect of drug development and calls for careful coordination. Incentives for pharmaceutical companies to search for relevant biomarkers and develop a companion test may include increased use of the drug if greater

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[150] Nuffield Council on Bioethics (2003). Op. cit.

[151] Food and Drug Administration (2005). *Drug-diagnostic co-development concept paper* (draft). See http://www.fda.gov/cder/genomics/pharmacoconceptfn.pdf [accessed December 18, 2007].

[152] In tumor cells that are HER-2-positive, there are two or more copies (i.e., gene amplication) of the *HER-2/neu* gene per chromosome 17.

[153] Ross JS, Fletcher JA, Bloom KJ, et al. HER-2/neu testing in breast cancer. *Am J Clin Pathol* 2003. 120 Suppl:S53-71.

[154] Herceptin® Web site. Herceptin® product insert. See http://www.gene.com/gene/products/information/pdf/herceptin-prescribing.pdf [Accessed December 18, 2007].

[155] Klein P, Anderson S, Genentech Inc., Laboratory Corporation of America. FISH analysis identifies HER2+ patients missed by immunohistochemistry. *Proc Am Soc Clin Oncol* 2002. 21:abstr 1944.

[156] Hofmann M, Stoss O, Gaiser T, et al. Central HER2 IHC and FISH analysis in a trastuzumab (Herceptin®) Phase II monotherapy study: assessment of test sensitivity and impact of chromosome 17 polysomy. *J Clin Pathol* 2007. [Epub ahead of print].

effectiveness can be demonstrated in a subgroup of patients.[157] For example, the HIV/AIDS drug Selzentry® (maraviroc) was proven safe and effective in a subpopulation of HIV/AIDS patients with a certain HIV substrain identified through PGx testing. It likely would not have been approved by FDA for use in the general population in the absence of the PGx test.[158,159,160] Also, as highlighted by the case of Herceptin®, codevelopment can result in expedited drug approvals. Other examples of successful parallel development efforts are Erbitux® (cetuximab), Vectibix® (panitumumab), and Gleevec® (imatinib) and their corresponding diagnostic tests.[161,162,163,164]

Codevelopment of PGx products offers several potential advantages over sequential development. For instance, with sequential development, scientific and/or technological issues for one product may have substantial implications for the other. In addition, clinicians may be more likely to use a diagnostic test if it is developed in conjunction with clinical trials for the indicated drug. Parallel development also may diminish the need for postapproval label changes, potentially reducing the administrative burdens of FDA and drug manufacturers and avoiding unnecessary confusion of clinicians.[165] The FDA Office of Combination Products (see Chapter III. Gatekeepers) can facilitate codevelopment of drugs and their companion tests by coordinating their approval.

There has been some resistance by the pharmaceutical industry to take on such codevelopment.[166] One reason is that use of a PGx companion test may segment the market for a drug into parts too small to be profitable. Furthermore, ambiguity remains about FDA's regulatory intentions with regard to laboratory-developed tests (LDTs), which have not been subject to the same level of FDA review as IVD test kits sold to clinical laboratories. However, FDA's 2006 draft guidance on IVD multivariate index assays may help clarify this ambiguity (see Chapter III. Gatekeepers).[167]

Recent industry efforts show support for the concept of codevelopment. Several pharmaceutical and diagnostic companies have forged cooperative relationships to identify valid biomarkers, which could lead to the development of PGx tests. For example, Roche Diagnostics Corporation and Eli Lilly and Company reportedly are collaborating to validate biomarkers with the goal of selecting patients who could benefit from Gemzar® (gemcitabine), a drug approved for non-small cell lung, pancreatic, metastatic breast, and ovarian cancers, or other drugs.[168] Collaborations such as these are likely to be important for the growth and advancement of the PGx field.

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[157] Garrison LP Jr 2007. Op. cit.

[158] Hamilton DP. *Personalized medicine takes a (tiny) step forward*. Venture Beat, 2007. See http://venturebeat.com/2007/08/08/personalized-medicine-takes-a-tiny-step-forward/ [accessed December 18, 2007].

[159] Maraviroc (Selzentry, Celsentri) (2007). HIV InSite. See http://hivinsite.ucsf.edu/InSite?page=ar-06-01 [accessed December 18, 2007].

[160] Food and Drug Administration (2007). *Accelerated approvals under 21 CFR 314 subpart H (drugs) & 21 CFR 601 subpart E (biologics)*. See http://www.fda.gov/cder/rdmt/accappr.htm [accessed December 18, 2007].

[161] Food and Drug Administration (2004). *FDA approves Erbitux for colorectal cancer*. See http://www.fda.gov/bbs/topics/NEWS/2004/NEW01024.html [accessed December 18, 2007].

[162] The Healthcare Sales & Marketing Network (2006). *Dako receives FDA approval for use of EGFR pharmDx™ with Vectibix™*. See http://salesandmarketingnetwork.com/news_release.php?ID=2014028&key=Amgen [accessed December 18, 2007].

[163] Food and Drug Administration (2006). *PMA final decisions rendered for September 2006*. See http://www.fda.gov/cdrh/pma/pmasep06.html [accessed December 18, 2007].

[164] Food and Drug Administration (2005). *PMA final decisions rendered for June 2005*. See http://www.fda.gov/cdrh/pma/pmajun05.html [accessed December 18, 2007].

[165] Food and Drug Administration (2005). *Drug-diagnostic co-development concept paper* (draft). Op. cit.

[166] Wechsler J. Drug development linked more closely to diagnostics. *Pharm Technol* 2004. 28(10):28-36.

[167] Evans BJ. Distinguishing product and practice regulation in personalized medicine. *Clin Pharmacol Ther* 2007. 81(2):288-93.

[168] Marchant J. Innovations in diagnostics: next generation molecular and point-of-care diagnostics driving personalized healthcare. *Reuters Business Insight* 2006.

FDA is encouraging new product codevelopment through its release of guidelines and concept papers that clarify some of the regulatory issues involved in the codevelopment of drugs and PGx diagnostic tests, including a concept paper on drug-diagnostic codevelopment, which is currently under revision.[169,170,171] Other efforts by organizations such as the American Association for Cancer Research, National Cancer Institute (NCI), NIH, and The Biomarkers Consortium also have advanced the drug-diagnostic codevelopment process.[172,173,174,175]

Recommendations 4A and 4B

4A. FDA should develop and implement guidance on the codevelopment of PGx drugs and diagnostics. The guidance should clarify the review process for codeveloped PGx products and promote collaboration between drug and diagnostics developers.

4B. FDA's Office of Combination Products should coordinate FDA's review of codeveloped PGx products to minimize delays in approvals and ensure timely access to them.

3. Using PGx To "Rescue" Drugs

PGx may provide an avenue for "rescuing" or reintroducing drugs that were found ineffective during drug development or were withdrawn from the market due to serious ADRs. Drugs that failed to demonstrate a treatment effect in a heterogeneous sample could be further developed with a subset of the sample that responded well to the drug.[176,177,178,179] *Posthoc* analysis of the clinical trial data could identify these positive responders, and subsequent genotyping of these subjects could uncover a biomarker that helps predict response. DNA samples from clinical trial participants are one source of data that could be used for this type of PGx research.[180,181]

PGx data also may reveal links between ADRs and specific genetic variations that are identifiable through testing. The availability of such information would allow identification of patients at risk of experiencing an

[169] Food and Drug Administration (2005). *Guidance for industry: pharmacogenomic data submissions.* Op. cit.
[170] Food and Drug Administration (2005). *Drug-diagnostic co-development concept paper* (draft). Op. cit.
[171] Food and Drug Administration (2006). *Draft guidance for industry and FDA staff: pharmacogenetic tests and genetic tests for heritable markers*. See http://www.fda.gov/cdrh/oivd/guidance/1549.pdf [accessed December 18, 2007].
[172] Foti M. Written testimony submitted to the House Appropriations Subcommittee on Labor, Health and Human Services, Education and Related Agencies. American Association for Cancer Research (2007). See http://www.aacr.org/home/public--media/public-policy--legislative-affairs/testimony/the-house-appropriations-subcommittee-on-labor,-health-and-human-services,-education-and-related-agencies-(2007).aspx [accessed December21, 2007].
[173] Wechsler J. *Regulatory beat: Critical Path Initiative tops FDA priority list for 2006*. BioPharm International (2006). See http://www.c-path.org/Portals/0/CP031406/printCont.pdf [accessed December 18, 2007].
[174] Food and Drug Administration (2006). *Critical Path opportunities initiated during 2006.* See http://www.fda.gov/oc/initiatives/criticalpath/opportunities06.html [accessed December 18, 2007].
[175] Food and Drug Administration (2005). Genomics at FDA: presentations from FDA, DIA, PhRMA, BIO & PWG workshop on *Applications and validation of genomic biomarkers for use in drug development and regulatory decisionmaking*. See http://www.fda.gov/CDER/genomics/biomarkers.htm [accessed December 18, 2007].
[176] Shah J. Economic and regulatory considerations in pharmacogenomics for drug licensing and healthcare. *Nat Biotechnol* 2003. 21(7):747-53.
[177] Nuffield Council on Bioethics (2003). Op. cit.
[178] PricewaterhouseCoopers (2005). Op. cit.
[179] Robertson JA 2002. Op. cit.
[180] The Royal Society (2005). Op. cit.
[181] Parent A, Noiseux M, Côté G. *Potential for pharmacogenomics science and technology in Canada: pharmaceutical mirage or oasis?* Science-Metrix, Canadian Biotechnology Secretariat (2004). See http://www.science-metrix.com/pdf/SM_2003_015_IC_Pharmacogenomics_Potential_Canada.pdf [accessed January 31, 2007].

ADR before the drug is prescribed. If the drug had been withdrawn from the market due to ADRs, the PGx data could potentially provide the necessary evidence to support its reintroduction. Lotronex® (alosetron), a medication developed by GlaxoSmithKline to treat irritable bowel syndrome, is an example of a drug that FDA reexamined. Soon after receiving FDA approval, it was withdrawn from the market after some patients experienced ADRs, including serious intestinal complications.[182,183] In 2004, FDA allowed it to be placed back on the market given certain conditions, including that postmarket analyses be conducted to determine whether any cytochrome P450 (CYP450) enzymes are responsible for the drug's metabolism.[184]

Some speculate that withdrawn drugs are unlikely to be reintroduced unless PGx data show improvements in the risk-benefit ratio.[185] Drug developers also are unlikely to pursue reintroduction if the drug's patent has expired or if there is an alternative treatment that does not require PGx testing. Drug developers may be motivated to use PGx to develop new but similar drugs or to rescue drugs in cases where no alternative treatments are available.[186,187]

4. Application of PGx to Existing Drugs

PGx tests that help predict drug response and ADRs have the potential to improve the safety and efficacy of existing drugs. For example, warfarin, an anticoagulant taken by more than a million people in the United States, requires accurate dosing to avoid serious complications such as hemorrhaging. Current dosing decisions for the drug are based on limited knowledge of patient characteristics, which explain only a small percentage of the variability in response. Studies suggest that polymorphisms in the *CYP2C9* and *VKORC1* genes may explain some of the interpatient variation in response to warfarin treatment.[188,189,190,191] Development of a PGx test for the *CYP2C9* and *VKORC1* variants has been suggested as a means to identify those who may be at a higher risk of warfarin-associated bleeding. Diagnostic manufacturers stand to benefit from investing in PGx research on existing drugs if the research identifies genetic variants that can predict drug response and leads to the development and marketing of a clinically useful test.[192]

The application of PGx to existing drugs may not always add value. For example, 43 SNPs previously had been shown to be associated with patients' response to the statin class of lipid management drugs. However, after further examination, only two of the original 43 SNPs were shown to have a statistically significant association, and the result applied to only one of the statins. Moreover, the effect is of minor clinical significance (approximately a 3-percent decrease) and is smaller than the known effects of age and

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[182] Nuffield Council on Bioethics (2003). Op. cit.
[183] Shah J 2003. Op. cit.
[184] Food and Drug Administration (2004). *Update on risk management activities for Lotronex (alosetron hydrochloride)*. See http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4040B1_16_FDA-Tab-1.pdf [accessed on December 18, 2007].
[185] Shah RR. Can pharmacogenetics help rescue drugs withdrawn from the market? *Pharmacogenomics* 2006. 7(6):889-908.
[186] Shah J 2003. Op. cit.
[187] Nuffield Council on Bioethics (2003). Op. cit.
[188] Sconce EA, Khan TI, Wynne HA, et al. The impact of CYP2C9 and VKORC1 genetic polymorphism and patient characteristics upon warfarin dose requirements: proposal for a new dosing regimen. *Blood* 2005. 106(7):2329-33.
[189] Rieder MJ, Reiner AP, Gage BF, et al. Effect of VKORC1 haplotypes on transcriptional regulation and warfarin dose. *N Engl J Med* 2005. 352(22):2285-93.
[190] Li T, Lange L, Li X, et al. Polymorphisms in the VKORC1 gene are strongly associated with warfarin dosage requirements in patients receiving anticoagulation. *J Med Genet* 2006. 43(9):740-4.
[191] Food and Drug Administration (2005). Transcript of Monday, November 14, 2005 meeting of the Clinical Pharmacology Subcommittee of the Advisory Committee for Pharmaceutical Science. See http://www.fda.gov/ohrms/dockets/ac/05/transcripts/2005-4194T1.pdf [accessed December 18, 2007].
[192] Nuffield Council on Bioethics (2003). Op. cit.

gender.[193] Where a drug's potential ADRs are considered minor compared with other medical risk factors, it may be in a patient's best interest to take the drug without PGx testing. If the drug results in an ADR, then the patient can be prescribed an alternative drug or have the dosage adjusted.[194]

Although adding indications for existing drugs is less costly and time consuming than developing new drugs, conducting PGx research on existing drugs is still a costly venture.[195] Pharmaceutical companies are likely to consider multiple factors when deciding whether to fund PGx research on existing drugs, including a drug's patent status, the feasibility of developing a PGx test and its potential clinical value, and the potential for return on investment.[196] A pharmaceutical company may have a financial incentive to pursue PGx research on one of its drugs if it could result in an extension of its patent life. For example, PGx could lead to the identification of new indications for existing drugs, subpopulations for which an existing drug is more beneficial, or new dosing or drug release profiles for those with particular PGx test results.[197] Each of these possible outcomes could extend the market life and profitability of a drug by offering some measure of additional market exclusivity (i.e., under which identical generic products could not be approved or cleared by FDA). Delaying the market entry of generic competitors may be an incentive for a company to invest in PGx research on an existing drug.[198] However, this exclusivity would have little practical impact unless it involved a new dosing formulation or strength, especially if physicians could prescribe old forms of the drug for the new indications. As such, there may be little financial incentive for a pharmaceutical company to invest in PGx research for an existing drug that is no longer under patent or under circumstances where additional patent protection is likely to be limited.[199]

5. PGx and Small Target Populations

PGx may enable more drugs to be developed and brought to market if subgroups of patients who will benefit from the drug can be identified.[200] PGx may provide a way to identify these subgroups, bolstering the case for the development of drugs that previously may have been abandoned.

PGx-based drugs are well positioned to benefit from the Orphan Drug Act of 1983, whose purpose is to encourage the development of drugs for patient populations that are likely to be too small (fewer than 200,000 individuals) to generate sales large enough for drugmakers to recoup their investment. Orphan drug development is encouraged through multiple incentives, including 7 years of exclusive marketing rights for the drug manufacturer, tax credits for the cost of clinical research, grants to support research on new treatments for rare diseases, FDA user fee waivers, and occasional expedited FDA review for market clearance or approval (orphan drugs must still demonstrate that they are safe and effective, however). This law has been very successful, leading to FDA approval of more than 200 orphan drugs, with hundreds more in the R&D pipeline. The provisions of the Orphan Drug Act are largely favorable for PGx-based drugs because they may have a large clinical impact on a small target population, may be intended for patients

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[193] Thompson JF, Man M, Johnson KJ, et al. An association study of 43 SNPs in 16 candidate genes with atorvastatin response. *Pharmacogenomics J* 2005. 5(6):352-8.
[194] Ibid.
[195] PricewaterhouseCoopers (2005). Op. cit.
[196] GlaxoSmithKline (2007). *Comments on realizing the promise of pharmacogenomics: opportunities and challenges* (public comment draft). See http://www4.od/nih.gov/oba/sacghs/reports/pgx_publiccomments.pdf [accessed April 21, 2008].
[197] Issa AM. Pharmacogenomic profiling in postmarketing surveillance: prospects and challenges. *Pharmacogenomics* 2003. 4(5):647-55.
[198] GlaxoSmithKline (2007). Op. cit.
[199] Government Accountability Office (2006). *New drug development: science, business, regulatory, and intellectual property issues cited as hampering drug development efforts.* Report to Congressional requesters. GAO-07-49. See http://www.gao.gov/new.items/d0749.pdf [accessed December 18, 2007].
[200] GlaxoSmithKline (2007). Op. cit.

with diseases lacking any effective treatment, and may be validated by clinical trials involving smaller numbers of subjects than typically would be enrolled.[201,202]

The targeted-population route to gain market entry, especially for drugs that otherwise would not have been classified as orphan products, may be attractive to companies if PGx can lower clinical trial costs by targeting investigational therapies in smaller, shorter clinical trials. Such developments, however, may not be in keeping with the intent of the Act and may prompt greater FDA scrutiny of orphan drug applications in the future.[203,204] It is not clear whether FDA would recognize a PGx-based drug as an orphan product if it confers a large benefit to an orphan-size population but only a modest benefit or no benefit to a much larger population.

Similar to the Orphan Drug Act, the Humanitarian Device Exemption of the Safe Medical Devices Act of 1990 offers incentives for the development of orphan devices, including PGx test kits, that have a target population of fewer than 4,000 persons. Products meeting the definition of a humanitarian use device (HUD) are exempt from the effectiveness requirements of the Federal Food, Drug, and Cosmetic Act.[205,206] The purpose of this exemption is to recognize that some conditions (e.g., certain genetic conditions) are so rare that it would be difficult for companies to enroll sufficient numbers of clinical trial subjects. Among other requirements, sponsors of FDA-approved HUDs must demonstrate that there is no comparable device available and ensure that the HUD is overseen by an institutional review board. Also, the price for the HUD cannot exceed the total cost of R&D, fabrication, and distribution.

The target population thresholds for orphan drugs and HUDs differ markedly. The target market population for an orphan drug must be fewer than 200,000 persons, whereas the target population for an HUD must be fewer than 4,000. Consequently, for some smaller genomically defined subpopulations, the regulatory landscape could favor the development of PGx drugs but not their companion PGx diagnostics. The benefits of codevelopment of PGx drugs and tests are described elsewhere in this chapter. Policy options that have been suggested for addressing the population threshold differences between orphan drugs and devices include expanding the scope of the Orphan Drug Act and raising the current population threshold for an orphan device to match the population threshold for an orphan drug.[207,208] If these solutions are not feasible, however, other incentives—legislative or other means—may need to be identified.

Recommendation 4C

4C. HHS should engage all stakeholders in identifying and providing incentives to encourage the development of PGx products, especially for smaller patient populations and/or markets.

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[201] Lesko LJ, Woodcock J. Pharmacogenomic-guided drug development: regulatory perspective. *Pharmacogenomics J* 2002. 2(1):20-4.
[202] Shah J 2003. Op. cit.
[203] Loughnot D. Potential interactions of the Orphan Drug Act and pharmacogenomics: a flood of orphan drugs and abuses? *Am J Law Med* 2005. 31(2-3):365-80.
[204] Wood AJ. A proposal for radical changes in the drug-approval process. *New Engl J Med* 2006. 355(6):618-23.
[205] US Congress. House of Representatives. 1990. *Safe Medical Devices Act of 1990*. 101st Cong., 2d sess., HR 3095. See http://thomas.loc.gov/cgi-bin/bdquery/z?d101:HR03095:@@@D&summ2=1&|TOM:/bss/d101query [accessed December 28, 2007].
[206] Food and Drug Administration (2006). *Humanitarian Device Exemption (HDE) regulation: questions and answers.* See http://www.fda.gov/cdrh/ode/guidance/1381.pdf [accessed December 18, 2007].
[207] Collins FS, Green ED, Guttmacher AE, Guyer MS. A vision for the future of genomics research. *Nature* 2003. 422(6934):835-47.
[208] Food and Drug Administration (2006). *The Orphan Drug Act (as amended)*. See http://www.fda.gov/orphan/oda.htm [Accessed December 18, 2006].

E. Translational (T2) Research: From Development to Clinical Practice and Public Health

The scientific complexity of PGx affects the prospects for innovation, adoption, and diffusion of PGx-based health care. Despite the large and growing body of information on the genetic basis of variable drug responses, most of this scientific knowledge has yet to be translated into clinical practice and public health. Converting PGx science into useful tests will entail establishing the analytical validity, clinical validity, and clinical utility of the test and understanding the ELSI aspects of its use.[209]

Converting scientific discoveries to patient health care poses challenges. First, discerning the links between genes and disease pathology for the purposes of informing drug discovery requires extensive biological, functional, and pathway analyses. Second, associations among a genetic marker, disease, test result, treatment, and health outcomes can be confounded by an individual's age, gender, weight, comorbidities, other genetic characteristics, health-related behaviors, environmental factors, compliance with treatment plans, and drug-drug interactions.[210] Third, sensitivity, specificity, predictive values, and other measures of accuracy need to be well characterized and clinically defined to ensure correct interpretation of test results. Fourth, the clinical utility of a PGx test depends on the timing and nature of its application (e.g., therapy selection, dosing or therapy monitoring). Finally, the information yielded must be linked to a clinical decision and action. Taken together, these challenges can make it difficult for regulators, payers, clinicians, and patients to discern the utility of a PGx test.[211,212]

1. Analytical Validity, Clinical Validity, and Clinical Utility

For the successful adoption of PGx into clinical practice and public health, a PGx test should demonstrate analytical validity, clinical validity, and clinical utility. *Analytical validity* is a measure of how accurately and consistently a test detects the presence of a specific genotype.[213,214,215] *Clinical validity* refers to the accuracy with which a test detects or predicts a given phenotype (clinical disorder or outcome).[216,217,218] *Clinical utility* refers to the net balance of risks and benefits associated with using a test in routine practice, including its ability to inform clinical decisionmaking, prevent adverse health outcomes (e.g., morbidity, mortality),

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[209] Burke W, Atkins D, Gwinn M, et al. Genetic test evaluation: information needs of clinicians, policy makers, and the public. *Am J Epidemiol* 2002. 156(4):311-8.
[210] The Royal Society (2005). Op. cit.
[211] Secretary's Advisory Committee on Genetics, Health, and Society (2006). *Coverage and reimbursement of genetic tests and services*. Op. cit.
[212] Califf RM. Defining the balance of risk and benefit in the era of genomics and proteomics. *Health Aff (Millwood)* 2004. 23(1):77-87.
[213] Gwinn M, Khoury MJ. Epidemiologic approach to genetic tests: population-based data for preventive medicine. In: Khoury MJ, Little J, Burke W, eds. *Human genome epidemiology: a scientific foundation for using genetic information to improve health and prevent disease*. Oxford, England: Oxford University Press, 2003.
[214] Burke W 2002. Op. cit.
[215] CDC Web site. Evaluation of Genetic Testing. ACCE: A CDC-Sponsored Project Carried Out by the Foundation of Blood Research. See http://www.cdc.gov/genomics/gtesting/ACCE.htm [accessed December 18, 2007].
[216] Gwinn M 2003. Op. cit.
[217] Burke W 2002. Op. cit.
[218] CDC Web site. Evaluation of Genetic Testing. ACCE: A CDC-Sponsored Project Carried Out by the Foundation of Blood Research. Op. cit.

and predict outcomes considered important to patients and their families.[219,220,221,222] Assessment of clinical utility should account for the availability of resources and patient preferences and moral values.[223]

Analytical validity must be established before clinical validity and clinical utility can be demonstrated. However, it still is critical to establish clinical validity and clinical utility even after analytical validity is shown.[224] If a test is analytically accurate but would not be applicable or effective in practice, it may not improve the delivery of health care.

As in other types of tests, higher sensitivity and specificity of PGx tests increase confidence in clinical decisions based on test results.[225] For example, tests with low sensitivity (which generate more false-negative results) can fail to identify a greater number of patients at high risk for an ADR or who would benefit from a potentially effective treatment. If the ADR is serious or if the treatment is the only one effective for a disease with high mortality or morbidity rates, then a PGx test with low sensitivity poses great risk. PGx tests with low specificity (which generate more false-positive results) can incorrectly identify a greater number of patients as being at high risk for an ADR, which may cause those patients to forgo effective treatments. Tests with low specificity also can incorrectly identify patients as likely responders to a treatment, which may lead to unnecessary use of an ineffective treatment and a missed opportunity to pursue alternative, potentially beneficial treatments.

A PGx test's predictive value will vary with the complexity of its target. Complex tests that look for multigenic interactions and metabolic pathways can be more predictive than a PGx test for a single gene.[226,227] Furthermore, the predictive value of a test may not be static; as tests incorporate new knowledge about the etiology of a disease and the associated genetic loci, they may become more accurate.[228]

The clinical outcomes of PGx testing depend on how the test results affect clinician and patient treatment decisions, the effectiveness of the indicated treatment, potential drug interactions, patient compliance, and other factors. Health care providers will need to consider PGx test results alongside these factors to guide treatment.[229,230]

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[219] Gwinn M 2003. Op. cit.
[220] Burke W 2002. Op. cit.
[221] Grosse SD, Khoury MJ. What is the clinical utility of genetic testing? *Genet Med* 2006. 8(7):448-50.
[222] CDC Web site. Evaluation of Genetic Testing. ACCE: A CDC-Sponsored Project Carried Out by the Foundation of Blood Research. Op. cit.
[223] Secretary's Advisory Committee on Genetics, Health, and Society (2007). *U.S. system of oversight of genetic testing: a response to the charge of the Secretary of Health and Human Services* (public comment draft). See http://www4.od.nih.gov/oba/SACGHS/reports/SACGHS%20Draft%20Report%20on%20the%20Oversight%20of%20Genetic%20Testing%2011-5-2007.pdf [accessed January 23, 2008].
[224] Ibid.
[225] Katz DA 2002. Op. cit.
[226] The Royal Society (2005). Op. cit.
[227] Ingelman-Sundberg M, Oscarson M, McLellan RA. Polymorphic human cytochrome P450 enzymes: an opportunity for individualizing drug treatment. *Trends Phamacol Sci* 1999. 20(8):342-9.
[228] Yang Q, Khoury MJ, Botto L, Friedman JM, Flanders WD. Improving the prediction of complex diseases by testing for multiple disease-susceptibility genes. *Am J Hum Genet* 2003. 72(3):636-49.
[229] Burke W 2002. Op. cit.
[230] Melzer D 2003. Op. cit.

The complex information needs of clinicians pose a challenge on two fronts. First, there is little evidence to date of the clinical utility of most PGx tests.[231] The scarcity of evidence is due to such factors as a limited understanding of how genetic and nongenetic factors interact to contribute to clinical outcomes, a lack of prospective randomized controlled trials that evaluate PGx tests, and the challenge of demonstrating that PGx testing has incremental benefit compared with standard or usual health care. Second, most health care providers have not been trained in how to interpret available PGx information.[232] The PGx information currently in drug labels appears to be inadequate for guiding treatment decisions and dosing recommendations and is based on PGx test results that largely are not yet available.[233]

Not only is it difficult to generate evidence of clinical validity and clinical utility for a PGx test, but also there is little motivation to do so and considerable confusion about what constitutes a demonstration of clinical validity and clinical utility. FDA, for example, does not evaluate clinical validity or clinical utility *per se* but rather assesses the safety and effectiveness of a device.[234] These parameters generally are tied to an assessment of the analytical and clinical performance of the device. Furthermore, although, for example, a 10-percent tumor response to chemotherapy may be a promising short-term outcome for certain cancers and sufficient for FDA approval or clearance, it may be less compelling for clinicians and payers interested in knowing whether the chemotherapy affects survival.

There is a growing need to evaluate the clinical accuracy and value of PGx technologies. Greater collaboration and interaction among basic, translational, clinical, and outcomes researchers may help identify common and measurable endpoints and data elements that could be used to assess the clinical validity and clinical utility of PGx tests. For example, the addition of a field to the ClinicalTrials.gov database that identifies which studies are collecting germline and/or tissue-specific (e.g., tumor) DNA would indicate a valuable source of data for clinical validity and clinical utility studies.

In addition to evidence of the clinical performance and impact of PGx tests, payers and others involved in making resource allocation decisions need more information on the cost-effectiveness of PGx products. Cost-effectiveness analysis is used to quantify the incremental (difference in) cost per incremental unit of effectiveness achieved with a PGx test vs. standard health care. Although sometimes controversial, cost-effectiveness analyses can help guide decisions about how finite funds are best spent for improving health. To date, little research has been conducted on the cost-effectiveness of PGx interventions.[235] Of the PGx pharmacoeconomic analyses that have been done, most are regarded as exploratory or inconclusive.[236, 237,238]

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[231] Webster A 2004. Op. cit.

[232] University of Minnesota, Center for Bioethics, Consortium on Pharmacogenetics (2002). Op. cit.

[233] Phillips KA 2005. Op. cit.

[234] For FDA, the term "effectiveness" means that based on information provided, "it can fairly and responsibly be concluded by qualified experts that the device will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling of the device" (FFDCA, section 513(a)(3)(A)). This is informally interpreted as "Do the performance data provided adequately support the intended use claimed by the sponsor?" Elsewhere in this report, the term "effectiveness" is used as a measure of how well the test performs in "real-world" clinical settings, and "efficacy" is used for outcomes seen in controlled research settings.

[235] Phillips KA 2004. Op. cit.

[236] Dervieux T, Bala MV. Overview of the pharmacoeconomics of pharmacogenetics. *Pharmacogenomics* 2006. 7(8):1175-84.

[237] Phillips KA, Van Bebber SL. Regulatory perspectives on pharmacogenomics: a review of the literature on key issues faced by the United States Food and Drug Administration. *Med Care Res Rev* 2006. 63(3):301-26.

[238] Phillips KA 2004. Op. cit.

Recommendations 5A, 5B, 5C, and 5D

The adoption of PGx technologies will hinge on the availability of evidence of their analytical and clinical validity, clinical utility, cost-effectiveness, and value of PGx. The following steps should be taken to facilitate the establishment of the evidence base and support the integration of PGx technologies into clinical practice and public health.

5A. HHS should identify and address evidence gaps in the analytical and clinical validity, clinical utility, cost-effectiveness, and value of PGx technologies. Progress will require high-quality data resources; improved methodologies in the design, conduct, and analysis of observational studies; and empirical research on the evidence and standards necessary for making decisions for various purposes (e.g., coverage, clinical guidelines, performance metrics, value-driven health care) in various clinical contexts.

5B. HHS should initiate and facilitate collaborations between public (e.g., Agency for Healthcare Research and Quality [AHRQ], U.S. Department of Veterans Affairs [VA], Centers for Disease Control and Prevention [CDC], Centers for Medicare & Medicaid Services [CMS], FDA, NIH, National Institute of Standards and Technology) and private entities (e.g., private health insurance plans, pharmacy benefits managers, health care facilities with electronic medical records, clinical research databases, genetic repositories) to advance the generation and sharing of knowledge on the analytical and clinical validity, clinical utility, cost-effectiveness, and value of PGx technologies.

5C. HHS should encourage and facilitate studies on the clinical validity and clinical utility of PGx technologies and the dissemination of study findings, including negative findings, through publications, meetings, and an information clearinghouse.

5D. HHS should provide mechanisms that promote interactions among basic, translational, clinical, and outcomes researchers for the identification of endpoints and data elements to be measured. The goal of these interactions is to maximize the value and utility of basic and translational research data for downstream assessments of the clinical validity and clinical utility of PGx technologies.

2. Current Initiatives in Health Outcomes Research for PGx

AHRQ and CDC are well positioned to coordinate the evidence-based translation of genetic tests and genomic applications from research to clinical practice and public health. CDC's National Office of Public Health Genomics initiated the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) project in 2004. Through the work of the independent EGAPP Working Group, this pilot project is using knowledge from existing U.S. and international assessment processes to examine evidence on the readiness of genetic tests for translation into clinical practice and public health. PGx tests for CYP450 and *UGT1A1* have been a recent focus of EGAPP assessment efforts.[239]

One evidence report published in November 2006 assessed evidence on whether CYP450 polymorphism testing in adults entering selective serotonin reuptake inhibitor (SSRI) treatment for nonpsychotic

[239] CDC Web site. Evaluation of Genomic Applications in Practice and Prevention (EGAPP): Implementation and Evaluation of a Model Approach. See http://www.egappreviews.org/workingrp/topics.htm [accessed December 18, 2007].

depression leads to improvement in outcomes and whether testing results are useful in medical, personal, or public health decisionmaking. The investigators reported a lack of high-quality clinical studies examining CYP450 polymorphism testing for treating depression and mixed evidence regarding the association between CYP450 genotypes and SSRI metabolism, efficacy, and tolerability in the treatment of depression. The report found no evidence as to whether testing leads to improved outcomes; whether test results are useful for medical, personal, or public health decisionmaking; or whether there are direct or indirect harms associated with testing or with subsequent management options. The investigators called attention to the need for good-quality data for addressing these questions.[240,241] In the absence of supporting evidence, the EGAPP Working Group concluded that CYP450 testing for patients beginning SSRI treatment should be discouraged until further clinical trials are completed.

A review team has completed another more targeted evidence report on *UGT1A1* testing in colorectal cancer patients treated with irinotecan. Publication of the *UGT1A1* evidence report is planned for 2008 and will include recommendations of the EGAPP Working Group. Ten other PGx-related tests are currently under consideration for review.

In addition to EGAPP, CDC created the Human Genome Epidemiology Network (HuGENet), which assesses "the impact of human genome variation on population health and how genetic information can be used to improve health and prevent disease."[242] Its reviews highlight the current state of epidemiologic and clinical knowledge about particular human genetic variations and describe gaps in current knowledge that may warrant additional research.[243] HuGENet reviews relevant to PGx include a meta-analysis of studies on the association between CYP450 and breast and ovarian cancer.[244,245]

Other Federal efforts that likely will contribute to the evidence base for PGx include AHRQ's Developing Evidence to Inform Decisions about Effectiveness (DEcIDE) Network and the Centers for Education and Research on Therapeutics (CERTs). The DEcIDE Network conducts accelerated practical studies for which randomized controlled trials would not be feasible or timely or would raise ethical concerns. Research performed by this network focuses on the outcomes, safety, comparative effectiveness, and appropriateness of health care products and services, including PGx-based drugs.[246] Similarly, the CERTs demonstration program focuses on advancing the use of therapeutics (i.e., drugs, medical devices, biological products) through research and education efforts.[247]

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[240] Agency for Healthcare Research and Quality (2007). *Testing for cytochrome P450 polymorphisms in adults with non-psychotic depression treated with selective serotonin reuptake inhibitors (SSRIs)*. Evidence Report/Technology Assessment #146. AHRQ Publication No. 07-E002. See http://www.ahrq.gov/clinic/tp/cyp450tp.htm [accessed December 18, 2007].

[241] Agency for Healthcare Research and Quality (2007). *Testing for cytochrome P450 polymorphisms (CYP450) in adults with non-psychotic depression prior to treatment with selective serotonin reuptake inhibitors (SSRIs)*. See http://www.ahrq.gov/clinic/tp/cyp450tp.htm [accessed December 18, 2007].

[242] CDC Web site. Welcome to HuGENet. See http://www.cdc.gov/genomics/hugenet/default.htm [accessed December 18, 2007].

[243] CDC Web site. HuGE reviews. See http://www.cdc.gov/genomics/hugenet/reviews.htm [accessed December 18, 2007].

[244] Agency for Healthcare Research and Quality (2007). *Genomic tests for ovarian cancer detection and management.* See http://www.ahrq.gov/clinic/tp/genovctp.htm [accessed December 18, 2007].

[245] Ibid.

[246] AHRQ Web site. DEcIDE Network & CERTs. See http://effectivehealthcare.ahrq.gov/aboutUs/generate.cfm [accessed December 18, 2007].

[247] Agency for Healthcare Research and Quality (2007). *Centers for Education and Research on Therapeutics: Overview*. AHRQ Publication No. 07-P000-EF. See http://www.ahrq.gov/clinic/certsovr.htm [Accessed December 18, 2007].

F. Infrastructure Enabling Research and Development

Integration of PGx into R&D will require an infrastructure that supports the sharing of data and the interoperability of databases and data repositories. To maximize their value, these databases and repositories will need to be integrated and linked to clinical data sources.[248,249]

1. Data Sharing

Advances in PGx research have led to the creation of public and proprietary databases and data repositories for storing, retrieving, and analyzing genetic and genomic data. These databases range from data sets containing data collected by pharmaceutical companies during clinical trials to large population-based publicly accessible genomic databases.[250,251] With some 65 biotechnology companies and a majority of large pharmaceutical companies worldwide currently investing in PGx-related technologies and more than 260 noncommercial research institutions also exploring PGx, the number of data sets containing PGx information is believed to be large.[252] Use of these databases as research tools could lead to the identification of new drug targets, improved assessment of drug response and treatment, increased drug safety and efficacy, and reductions in certain health care costs.[253,254,255]

Researchers have called for the sharing of and open access to genotypic data in research databases and repositories and corresponding drug-response phenotypic data from clinical data sources.[256,257] Moreover, investigators who draw on information from large public PGx databases increasingly are encouraged to return enriched data (e.g., data from clinical trials) to these databases.[258] Some researchers suggest that establishing and running open "personalized medicine" databases containing group and individual patient genotypic and drug-response phenotypic data could lead to a significant return on investment via reduced ADRs and improved pharmacotherapy.[259]

Several federally funded efforts are under way to facilitate data sharing. The NIH-funded PharmGKB, described above, is a shared, Web-based central repository of PGx data from PGRN research and the research community at large.[260] In the short term, PharmGKB aims to serve as a resource to facilitate basic PGx research. In the long term, PharmGKB is expected to have an impact on the delivery of health care and serve as a resource for researchers, health care providers, pharmacologists, policymakers, and the public. To meet these goals, PharmGKB supports research projects in multiple areas. For example, the Pharmacogenetics

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[248] Goldman BR. Pharmacogenomics: privacy in the era of personalized medicine. *NW J Tech Intell Prop* 2005. 4(1):83-99.
[249] Gurwitz D, Lunshof JE, Altman RB. A call for the creation of personalized medicine databases. *Nat Rev Drug Discov* 2006. 5(1):23-6.
[250] Nuffield Council on Bioethics (2003). Op. cit.
[251] Vyas H, Summers R. An information-driven approach to pharmacogenomics. *Pharmacogenomics* 2005. 6(5):473-80.
[252] Hopkins MM 2006. Op. cit.
[253] Regnstrom K, Burgess DJ. Pharmacogenomics and its potential impact on drug and formulation development. *Crit Rev Ther Drug Carrier Syst* 2005. 22(5):465-92.
[254] Altman RB, Klein TE. Challenges for biomedical informatics and pharmacogenomics. *Annu Rev Pharmacol Toxicol* 2002. 42:113-33.
[255] Joly Y, Knoppers BM. Pharmacogenomic data sample collection and storage: ethical issues and policy approaches. *Pharmacogenomics* 2006. 7(2):219-26.
[256] Gurwitz D 2006. Op. cit.
[257] Vyas H 2005. Op. cit.
[258] Joly Y 2006. Op. cit.
[259] Gurwitz D 2006. Op. cit.
[260] NIH Web site. Pharmacogenetics Research Network. See http://www.nigms.nih.gov/Initiatives/PGRN [accessed December 18, 2007].

Ontology Project aims to develop standardized mechanisms and taxonomies for organizing, annotating, and indexing PGx data to assist researchers in integrating genotype-phenotype information.[261] Another NIH-funded database, the single nucleotide polymorphism database, represents the largest public repository of SNP data in the world. These data come from multiple sources, including individual laboratories, large sequencing centers, and industry.[262] NCI's Cancer Biomedical Informatics Grid (caBIG) is another effort that links researchers, physicians, and patients throughout the cancer community to collect and disseminate data on cancer and health care.[263]

Some observers call for reciprocity between researchers and pharmaceutical companies. However, industry is unlikely to share what it considers to be proprietary data without some assurances that patents and data it has specified as confidential are protected before restatement or publication. Companies may seek legal arrangements to retain the right to pursue and market any product resulting from the research when agreeing to share IP.

Generally, the Federal Government discourages users of its public databases from seeking patents on findings or products derived from shared data. According to NCBI, data submitted to dbGaP, which archives and distributes findings from GWAS studies, are considered to be precompetitive and are not protected by patents.[264] The NIH policy that supports the development of GWAS encourages patents for downstream discoveries but discourages patenting of early information that could slow future research.[265]

Some companies are becoming more aware of the potential benefits of data sharing.[266] In February 2007, Novartis Pharmaceuticals Corporation made the results of its genomic analysis of type 2 diabetes available at no cost on the Internet. The public availability of these data was a result of negotiations between Novartis and two academic institutions that the company worked with to identify genetic variants that influence the risk of type 2 diabetes. This arrangement allowed Novartis and the academic institutions to collaborate without competing with each other on patent issues. Given the magnitude of data, Novartis views this partnership as an opportunity to "lure in researchers who identify leads from the data." If researchers find results to help treat or cure diabetes, Novartis hopes that they will want to collaborate with the company on the development of a corresponding drug.[267] Pfizer, Perlegen, and Affymetrix, along with Abbott Laboratories, recently formed the similar GAIN partnership with NIH. This collaboration, which also will include other stakeholder partners (e.g., private foundations, advocacy groups), intends to provide open, equal access to data from whole-genome association studies using samples from existing case-control studies of patients with common diseases.[268]

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[261] PharmGKB Web site. The Pharmacogenetics and Pharmacogenomics Knowledge Base. See http://www.pharmgkb.org/index.jsp [accessed December 18, 2007].
[262] Vyas H 2005. Op. cit.
[263] NIH Web site. Cancer Biomedical Informatics Grid (caBIG). See http://cabig.cancer.gov/index.asp [accessed December 18, 2007].
[264] NIH Web site. About dbGaP. See http://www.ncbi.nlm.nih.gov/entrez/query/Gap/gap_tmpl/about.html [accessed December 18, 2007].
[265] NIH Web site. Genome-Wide Association Studies. Op. cit.
[266] Pincock S. Pharma goes open access: Novartis shares diabetes genomic data, and experts say there's more to come. *The Scientist* 2007. See http://www.the-scientist.com/news/home/52891/ [accessed December 18, 2007].
[267] Ibid.
[268] Foundation for the National Institutes of Health Web site. Genetic Association Information Network. Op. cit.

Recommendations 6A and 6B

6A. HHS should encourage private sector entities (including academic institutions) to share proprietary data voluntarily to advance the development and codevelopment of PGx products. Manufacturers should be encouraged to make their data publicly available to allow others to conduct research and publish such studies.

6B. HHS should work with the private sector to identify obstacles to data sharing and develop solutions to overcome these obstacles (e.g., legal and data confidentiality assurances, IP protections, funding of databases, and health information technology).

2. Linking Databases

Efforts to collect, store, model, and link genomic, molecular, cellular, clinical, and public health data are still at an early stage.[269,270] At present, separate funding streams, stakeholder groups, administrative protocols, and organizational cultures are hindering the sharing and linking of these data. Variations in data format variations among the various databases also make it difficult to integrate and exchange data.[271] Furthermore, although advances in health information technology promise to connect research databases and clinical records, this data-intensive enterprise is years away from being fully adopted into day-to-day clinical practice and clinical information systems. Groups such as the American Health Information Community (AHIC), a Federal advisory body that is developing recommendations on standards for interoperable integration of genomic test information into electronic health records, are working to address issues of data standardization, interoperability, clinical decision support, and patient confidentiality and privacy concerns.[272] Integration of PGx and clinical information likely will prompt ELSI concerns, such as informed consent and data protection, that may affect the willingness of patients, clinicians, and health care managers to participate in PGx research and apply this information in clinical practice.[273]

Recommendation 6C

HHS should work with other relevant Federal Departments (e.g., VA, U.S. Department of Defense, U.S. Department of Commerce) and the private sector to improve data sharing and interoperability among databases. Specifically, HHS should work with existing organizations to create uniform genomic data standards, explore ways to harmonize data analysis methodologies, and develop an infrastructure to enable data exchange. Data sharing and interoperability of research, regulatory, medical record, and claims databases will facilitate the study of the molecular pathogenesis of disease, identification of targets for drug development, validation of PGx technologies, assessment of health outcomes associated with use of PGx technologies, and determination of the cost-effectiveness and economic impact of using these technologies.

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[269] Hoffman MA. The genome-enabled electronic medical record. *J Biomed Inform* 2007. 40(1):44-6.
[270] Altman RB 2002. Op. cit.
[271] Vyas H 2005. Op. cit.
[272] DHHS Web site. Electronic Health Records Workgroup. See http://www.hhs.gov/healthit/ahic/healthrecords/ [accessed December 18, 2007].
[273] Joly Y 2006. Op. cit.

3. Collaborations

Collaborations among U.S. and international researchers, clinicians, industry, and governments are essential to advancing PGx research and the development and codevelopment of PGx products. Several institutions are dedicated to enhancing collaboration among researchers in the field of genomics.

The Public Population Project in Genomics is an international consortium for the development of infrastructure to merge and compare results from population-based genomic studies. Its goal is to generate large, well-characterized data sets from population samples to assist the biomedical community in identifying the genetic and environmental interactions responsible for disease.[274]

The Biomarkers Consortium is a U.S. collaboration that aims to harmonize basic and translational research and develop safe and effective medicines and treatments for use in clinical practice. Founding members include FNIH, FDA, NIH, the Pharmaceutical Research and Manufacturers of America, CMS, and the Biotechnology Industry Organization.[275]

FDA's Critical Path Initiative aims to encourage public and private sector collaborations toward the development of PGx products. The initiative sponsors the Critical Path Opportunities Report and List, which describes new scientific discoveries and how they can be used to improve the test accuracy of newly developed medical products.[276] Collaborations resulting from this initiative should help promote the sharing of research and clinical data for use in PGx research. The Critical Path Institute (C-Path), an independent, nonprofit institute, aims to support FDA's Critical Path Initiative by addressing the scientific, safety, and educational aspects of drug development. With input from FDA, industry experts, and academia, C-Path has created several research initiatives, including Cancer Biomarkers, Collaborative Cardiovascular Drug Safety and Biomarker Research, Rare/Orphan Diseases, and Predictive Safety Testing Consortium, as well as an educational partnership with the University of Arizona.[277] Additional funding from Congress may be required to further develop and implement these and other partnerships identified by the Critical Path Initiative.[278]

Recommendation 6D

FDA should identify, initiate, and facilitate research opportunities and public-private partnerships to encourage the development and codevelopment of PGx products (e.g., through the Critical Path Initiative, The Biomarkers Consortium).

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[274] P^{3}G Public Population Project in Genetics Web site. About P^{3}G. See http://www.p3gconsortium.org/about.cfm [accessed December 18, 2007].
[275] The Foundation for the National Institutes of Health Web site. The Biomarkers Consortium – About Us. See http://www.biomarkersconsortium.org/index.php?option=com_content&task=section&id=5&Itemid=39 [accessed December 18, 2007].
[276] FDA Web site. FDA's Critical Path Initiative. See http://www.fda.gov/oc/initiatives/criticalpath/ [accessed December 18, 2007].
[277] The Critical Path Institute Web site. The Critical Path Institute: Overview. See http://www.c-path.org/Projects/Overview/tabid/223/Default.aspx [accessed December 18, 2007].
[278] Nuffield Council on Bioethics (2003). Op. cit.

G. Ethical, Legal, and Social Issues in Research and Development

PGx R&D raises several ELSI concerns. This section discusses issues related to the protection of personal health information, informed consent, population stratification in drug response, and liability.

1. Protection of Personal Health Information

PGx research involves the collection of biological samples, demographic data, and medical records. Participation in PGx research and the sharing of genomic information may put research subjects at risk for unauthorized disclosure and use of their data. As genomic research expands toward population-based studies, the risks involved with the storage of large-scale sequencing information will multiply. Maintaining the confidentiality of these data is essential.[279,280,281] However, data protections must be weighed against constraints on data access that would impede beneficial research and applications.

To minimize the risks of participating in PGx research and improve the confidentiality of genomic data, researchers often "anonymize" or code biological specimens before sharing them with others. The National Bioethics Advisory Commission defines anonymized specimens as those that lack identifiers and therefore cannot be linked to an individual. In contrast, coded specimens are those that receive a code when given to an investigator but can still be traced to a particular individual using a code key.[282] Access to coded samples can be critical in PGx research, where genetic information from biological samples may need to be linked to clinical outcomes to understand how genetic variation affects drug response.

Existing technical approaches may not be sufficient to preserve the confidentiality of genomic information, because an individual could be identified from very few SNPs.[283] Researchers have demonstrated that, in some instances, information considered to be "deidentified" can be "reidentified" using readily available information. Continued efforts are needed to improve the coding and encryption of data, particularly as more sophisticated means arise to overcome these protections. However, stronger privacy protections could impede appropriate data access and the ability to notify participants about aggregate research findings.[284,285]

Various technical, social, and legal methods of preventing the misuse of confidential information have been proposed and/or implemented. For example, the Health Insurance Portability and Accountability Act of 1996 Privacy Rule establishes Federal privacy protections for individually identifiable health information held by health plans, health care clearinghouses, and health care providers that conduct certain transactions electronically, many of which may be involved in or be sources of data for PGx research.[286]

The 2006 National Human Genome Research Institute Workshop on Privacy, Confidentiality and Identifiability in Genomic Research emphasized the importance of striking a balance between "protecting

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[279] PricewaterhouseCoopers (2005). Op. cit.
[280] University of Minnesota, Center for Bioethics, Consortium on Pharmacogenetics (2002). Op. cit.
[281] Rothstein MA, Epps PG. Ethical and legal implications of pharmacogenomics. *Nat Rev Genet* 2001. 2(3):228-31.
[282] National Bioethics Advisory Commission (1999). *Research involving human biological materials: ethical issues and policy guidance*. See http://bioethics.georgetown.edu/nbac/hbm_exec.pdf [accessed December 18, 2007].
[283] Lin Z, Owen AB, Altman RB. Genetics. Genomic research and human subject privacy. *Science* 2004. 305(5681):183.
[284] University of Minnesota, Center for Bioethics, Consortium on Pharmacogenetics (2002). Op. cit.
[285] Joly Y, Knoppers BM, Nguyen MT. Stored tissue samples: through the confidentiality maze. *Pharmacogenomics J* 2005. 5(1):2-5.
[286] Goldman BR 2005. Op. cit.

and respecting" the privacy and confidentiality of subjects' data while fostering efficient access to their data for genomic research. Several approaches to protecting the identity of subjects were suggested, such as limiting the amount of genomic information released from each sample, statistically degrading or scrambling data before they are released, removing identifying data prior to coding the information, and using controlled data-release arrangements whereby parties must commit to protecting privacy and confidentiality before being granted access.[287] Some observers suggest that the combination of a national biobank along with laws and policies for preventing misuse of data could help reduce the risk of confidentiality breaches while enabling researcher access to large volumes of data.[288] Still, public and policymaker skepticism regarding the security of data in a national biobank needs to be addressed. Others suggest the use of "honest broker" systems for the protection of privacy. These systems are intended to prevent researchers from tracing identifiable research data back to subjects.[289] Currently, AHIC is developing recommendations regarding the protection of personal health information that seek to balance the needs of appropriate information protection and access to electronic health records.

Recommendation 7

Stronger data security measures will be needed as more PGx researchers access patient data. HHS, through mechanisms such as AHIC's Confidentiality, Privacy, and Security Workgroup, should develop guidance on how to balance the protection of privacy and confidentiality of personal data with access to these data for PGx research.

2. Informed Consent

PGx may raise special concerns related to informed consent. For instance, clinical practice guidelines or payment policies (e.g., in the form of prior authorization or utilization review) may call for PGx testing as a prerequisite for treatment. Individuals might object to having to consent to testing to gain access to a treatment.[290] This issue also can arise when PGx testing is a condition of enrollment in the clinical trial of an investigational drug. Although not an issue in healthy volunteer studies, subjects in patient studies may feel compelled to consent to genotyping to gain access to the study agent.

Informed consent also can be a challenge when coded specimens are used. In recent years, informed consent requirements for the use of coded specimens have varied under two different regulations intended to protect individuals participating in clinical research. U.S. Department of Health and Human Services (HHS) Protection of Human Subjects regulations (also known as the Common Rule), which are contained in Title 45 Code of Federal Regulations (CFR) Part 46 and administered by the Office for Human Research Protections (OHRP), protect the rights and welfare of human subjects involved in research conducted or supported by HHS. A second set of regulations contained in Title 21 CFR Parts 50, 56, and 812 applies to clinical investigations of products regulated by FDA. FDA and HHS human subjects protection regulations differ in several significant ways.

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[287] National Human Genome Research Institute (2006). Summary of the NHGRI workshop on privacy, confidentiality and identifiability in genomic research. October 3-4, 2006. See http://www.genome.gov/19519198 [accessed December 18, 2007].
[288] University of Minnesota, Center for Bioethics, Consortium on Pharmacogenetics (2002). Op. cit.
[289] Gilbertson JR, Gupta R, Nie Y, Patel AA, Becich MJ. Automated clinical annotation of tissue bank specimens. *Medinfo* 2004. 11(Pt 1):607-610. See http://pcabc.upmc.edu/publications/Medinfo2004_5711Gilbertson.pdf [accessed December 18, 2007].
[290] The Royal Society (2005). Op. cit.

Under HHS regulations, research using anonymized samples is not considered to be human subjects research. Therefore, the requirements of 45 CFR Part 46, including the informed consent requirements, do not apply. In 2004, OHRP issued guidance stating that research using coded human specimens also is not considered human subjects research if (1) the specimens are not collected specifically for the proposed research through interaction or intervention with living individuals and (2) the investigator(s) cannot readily ascertain the identity of the living individuals to whom the specimens pertain because procedures are in place that prohibit the release of the code key to the investigator(s) until the individuals are deceased.[291]

In contrast, the definition of a human subject under FDA regulation of IVD device studies is more stringent than the Common Rule and includes any individuals whose specimens could be traced to them. As such, informed consent is required before specimens can be used in FDA-regulated research, and waivers are permitted only in research involving emergency or life-threatening situations. The discrepancies between these two policies have had ramifications for the translation of PGx discoveries into clinically useful treatments, since differing informed consent requirements have been applied at different points along the R&D continuum.[292]

Various groups have called for a more uniform approach to the regulation of human subjects research.[293] In a 2006 guidance, FDA announced that it would allow the use of coded specimens if researchers elect to implement a set of voluntary privacy protections described in the guidance.[294] This policy brings FDA's regulatory approach more in line with that of OHRP, although it does not completely harmonize them.

HHS agencies are aware of the inconsistencies in Federal policies governing clinical research. Currently, NIH has dedicated resources to harmonize Federal policies and address issues related to the protection of human research subjects. For example, the Clinical Research Policy Analysis and Coordination Program was established in 2004 as part of the NIH Roadmap to promote the coordination of clinical research policies such as those involving human biological materials and data.[295] These activities reflect an ongoing effort to create an overarching ethical and legal framework for such research.

Achieving the appropriate level of informed consent is an important consideration in PGx research; broad consent may lead to uninformed decisions, whereas narrow consent can hinder research. Additional guidance may be needed to help investigators design consent processes that maximize the benefits of research while preserving adequate levels of choice.

3. Population Stratification in Drug Response

Most available diagnostics and drugs are developed on the basis of their clinical performance in subgroups of the general population that have certain risk factors or indications. Clinical trials often include diverse populations, which enables data on drug response to be collected from the various groups that might later

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[291] DHHS Web site. Guidance on Research Involving Coded Private Information or Biological Specimens. See http://www.hhs.gov/ohrp/humansubjects/guidance/cdebiol.htm [accessed December 18, 2007].

[292] Evans BJ, Meslin EM. Encouraging translational research through harmonization of FDA and common rule informed consent requirements for research with banked specimens. *J Leg Med* 2006. 27(2):119-66.

[293] National Bioethics Advisory Commission (2001). *Ethical and policy issues in research involving human participants.* See http://bioethics.georgetown.edu/nbac/human/oversumm.pdf [accessed December 30, 2007].

[294] Food and Drug Administration (2006). *Guidance on informed consent for in vitro diagnostic device studies using leftover human specimens that are not individually identifiable. Guidance for sponsors, institutional review boards, clinical investigators and FDA staff.* See http://www.fda.gov/cdrh/oivd/guidance/1588.html [accessed December 18, 2007].

[295] NIH Web site. Research Policy Analysis & Coordination Program Overview. See http://crpac.od.nih.gov/about.asp [accessed December 18, 2007].

be prescribed the drug. Current drug development and use in current clinical practice, however, typically do not consider how interindividual genomic variations alter drug response.

The premise of individualizing drug treatment involves stratification of these diverse populations into smaller subpopulations that may be predisposed to ADRs based on their genomic profiles.[296] Although genetic characteristics can vary by racial or ethnic origin,[297] such divisions sometimes are based on ethnic, racial, or other demographic information instead of more precise selection criteria.

The use of concepts such as race and ethnicity in the context of health care is controversial.[298] For instance, in an action drawing considerable national interest, FDA approved BiDil® (hydralazine and isosorbide dinitrate) in 2005 for the treatment of heart failure in self-identified African American patients.[299,300] This approval continues to generate controversy. Some researchers have questioned the validity of the analyses showing differences in drug response between African American and other patients with heart failure and the motivations of BiDil's® developers and manufacturer. Because of these suspicions, some individuals have recommended that physicians prescribe the drug as they see fit regardless of a patient's race, whereas others continue to argue the merits of basing prescriptions of BiDil® on self-identification as an African American.[301,302] Individuals of various ethnic and racial backgrounds participating in the Communities of Color and Genetics Policy Project community dialogs have argued that, even though avoiding genetic discrimination is a top priority, it is acceptable for genetic technologies to be approved for specific racial and ethnic populations if supported by evidence.[303] Lower than expected uptake of BiDil® and difficulty obtaining reimbursement underscore uncertainties and risks that may be associated with targeted therapies (see Exhibit 2 below).

Given the considerable genetic variation within conventional or self-identified racial and ethnic groups, attempts to use racial or ethnic designations as proxies for genetic variation are likely to be scientifically suboptimal and medically impractical.[304,305] Such attempts can result in imprecise prescription guidelines and reinforce a public view of biologically defined races.[306,307] As such, genotypic information should be taken into account along with other relevant patient information when prescribing medications.

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[296] University of Minnesota, Center for Bioethics, Consortium on Pharmacogenetics (2002). Op. cit.

[297] For example, there is a high prevalence of the gene for the CYP2D6 enzyme among Ethiopian and Saudi Arabian populations that results in markedly increased metabolism of many medicines, whereas 7 percent of Caucasians have a genetic variant that results in reduced activity of this enzyme. See: McLellan RA, Oscarson M, Seidegård J, Evans DA, Ingelman-Sundberg M. Frequent occurrence of CYP2D6 gene duplication in Saudi Arabians. *Pharmacogenetics* 1997. 7(3):187-91.

[298] Weber W. Pharmacogenetics. New York, NY: Oxford University Press, 1997.

[299] Meadows M. *FDA approves heart drug for black patients*. FDA Consumer Magazine, 2005. See http://www.fda.gov/fdac/features/2005/505_BiDil.html [accessed December 18, 2007].

[300] Kahn J. Genes, race and population: avoiding a collision of categories. *Am J Public Health* 2006. 96(11):1965-70.

[301] Sankar P, Kahn J. BiDil: race medicine or race marketing? *Health Aff (Millwood)* 2005. Suppl Web Exclusives:W5-455-63.

[302] Puckrein G. BiDil: from another vantage point. *Health Aff (Millwood)* 2006. 25(5):w368-74.

[303] Fleck L, Castillo J, Krouse F, et al. *Communities of color and genetics policy report: summary dialogue report.* See http://www.sph.umich.edu/genpolicy/current/reports/summary_dialogue_report.pdf [accessed December 18, 2007].

[304] Lee SS. Racializing drug design: implications of pharmacogenomics for health disparities. *Am J Public Health* 2005. 95(12):2133-8.

[305] Shanawani H, Dame L, Schwartz DA, Cook-Deegan R. Non-reporting and inconsistent reporting of race and ethnicity in articles that claim associations among genotype, outcome, and race or ethnicity. *J Med Ethics* 2006. 32(12):724-8.

[306] Nuffield Council on Bioethics (2003). Op. cit.

[307] University of Minnesota, Center for Bioethics, Consortium on Pharmacogenetics (2002). Op. cit.

Exhibit 2. The Case of BiDil®

A recent high-profile example of racially based prescribing is FDA's approval of BiDil® for the treatment of heart failure in self-identified African American patients. This approval was based mainly on results of the African American Heart Failure Trial (A-HeFT) involving self-identified African American enrollees.[308] Since it was approved, only about 1 percent of the 750,000 African Americans with heart failure have received prescriptions for BiDil®. This development is reportedly due to the unwillingness of health plans to pay for the drug, which is estimated by VA to cost between $1,382 and $2,765 annually per patient. Instead, many health plans pay for the two inexpensive generic drugs that make up BiDil®, even though dosing the two generic drugs to match the levels in BiDil® poses challenges to patient compliance. Because of the lower than expected sales of the drug, NitroMed (manufacturer of BiDil®) reported in January 2008 that it would be discontinuing sales and promotional activities for BiDil®. It plans to keep BiDil® available and on the market for patients while it develops a once-a-day formulation, BiDil XR® (BiDil® is currently dosed three times daily). The company expects to file a new drug application for BiDil XR® in 2010, following finalization of the formulation in 2008 and completion of bioequivalence trials in 2009.[309]

Racially based prescribing could have negative effects on the development and uptake of PGx products. For instance, it could lead to the preferred development of medicines for certain patient populations over other populations if particular patient groups are likely to respond better to an investigative therapy or if wealthier countries are expected to have a more lucrative market for a new therapy compared with poorer countries. These scenarios raise concerns about the equity of drug development, including the distribution of benefits and risks among various population groups.

As with BiDil®, it is becoming increasingly common for pharmaceutical companies and academic groups to carry out clinical trials in self-defined ethnic groups as a way to extend their drug patents. Recent reports indicate that similar race-specific trials have been conducted for the cancer drug Iressa® (gefitinib) and the statin drug Crestor® (rosuvastatin).[310] A review of claims and abstracts of patent applications since 1976 shows a fivefold increase in the use of racial categories in gene-related patents.[311] This type of IP protection could lay the foundation for commercial ventures in which companies market PGx products to specific social groups based on the prevalence of certain genetic variations in these groups. In the case of BiDil®, NitroMed's patent for the drug's use in the general population would have expired in 2007 had the manufacturer not obtained an extension for use of the drug in African American patients. Because of the patent extension, NitroMed now has a monopoly on the BiDil® market until 2020.[312]

Although some industry observers believe that market segmentation is financially advantageous, others view population-targeted medications as having a negative economic impact on the drug market. One developer reportedly abandoned an acne drug after learning that FDA approved it with the requirement that prospective users be tested for an ADR-associated enzyme deficiency, thereby decreasing the drug's market size.[313]

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[308] Meadows M 2006. Op. cit.
[309] NitroMed Web site. NAACP and NitroMed Announce Partnership to Narrow Disparities in Cardiovascular Healthcare. See http://phx.corporate-ir.net/phoenix.zhtml?c=130535&p=irol-newsArticle&ID=795741&highlight [accessed December 18, 2007].
[310] Herper M. Race-based medicine arrives. Forbes 2005. See http://www.forbes.com/home/healthcare/2005/05/10/cx_mh_0509racemedicine.html [accessed December 18, 2007].
[311] Kahn J. Patenting race. *Nat Biotechnol* 2006. 24(11):1349-51.
[312] Ibid.
[313] Pollack A. A special drug just for you, at the end of a long pipeline. *The New York Times*. November 8, 2005.

Racially based prescribing also may result in potential bias toward particular racial or ethnic groups if perceived or actual affiliation with that group is used as a proxy for a genetic profile. Aside from implications for equity, this may be scientifically unjustifiable, since not every member of a group will have the genetic variant in question. One study reported that 2 percent of Ashkenazi Jews in the Metropolitan Washington, DC, area carried a mutation in their *BRCA1* and *BRCA2* genes, conferring a 56-percent risk of breast cancer and 16-percent risk of ovarian cancer by age 70.[314] Although none of the study participants were identifiable, the local population of Ashkenazi Jews was identified as having a particularly high risk of cancer relative to the general population. Such findings could lead to misinformed actions by employers, health care payers, and the public, with negative implications, since every person carries roughly the same number of genetic mutations that could lead to disease. Certain population groups such as Finns, Icelanders, Ashkenazi Jews, and Mormons may be at a greater risk for potential bias because they are convenient populations to study (because of their identifiability as a genetically linked population, availability of accurate genealogical records, commitment to public health, and/or awareness of potential medical and public health benefits of genetic research).[315,316]

FDA has provided guidance on the standardized collection of race and ethnicity information in clinical trials.[317] When analyzing clinical trial data, it is important to specify how race or ethnicity was determined since inconsistent determinations can lead to erroneous conclusions.[318] Although FDA requires the collection of race and ethnicity data for statistical and reporting purposes, it may be less appropriate to do so for scientific and medical research that seeks to better understand the biological bases of health problems.[319]

Recommendations 8A and 8B

8A. FDA should develop guidance that encourages the collection and analysis of genetic and other biological factors that may be better biological predictors of individual differences in drug response than broad categories such as race, ethnicity, and gender.

8B. When drugs are shown to be more or less effective in certain racial and ethnic subpopulations, FDA should encourage manufacturers to conduct additional postmarket studies to identify genetic and other biological, social, behavioral, and environmental markers that may underlie the differential drug effects.

[314] Struewing JP, Hartge P, Wacholder S, et al. The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. *N Engl J Med* 1997. 336(20):1401-8.
[315] Lehrman S. Jewish leaders seek genetic guidelines. *Nature* 1997. 389(6649):322.
[316] Tryggvadottir L, Sigvaldason H, Olafsdottir GH, et al. Population-based study of changing breast cancer risk in Icelandic BRCA2 mutation carriers, 1920-2000. *J Natl Cancer Inst* 2006. 98(2):116-22.
[317] Food and Drug Administration (2005). *Guidance for industry: collection of race and ethnicity data in clinical trials.* See http://www.fda.gov/cber/gdlns/racethclin.htm [accessed December 18, 2007].
[318] Shanawani H, Dame L, Schwartz DA, Cook-Degan R. Non-reporting and inconsistent reporting of race and ethnicity in articles that claim associations among genotype, outcome, and race or ethnicity. *J Med Ethics* 2006. 32(12):724-8.
[319] Haga SB, Venter JC. Genetics. FDA races in wrong direction. *Science* 2003. 301(5632):466.

4. Liability Concerns for PGx Drug and Diagnostics Developers

Pharmaceutical companies may be subject to liability for ADRs that occur. The risk of liability may be further aggravated by promotional practices not supported by adequate clinical studies. Tort law provides incentives for manufacturers to conduct PGx research and include PGx information on drug labels.[320,321] All 50 States have adopted some form of the learned intermediary doctrine, which transfers key duties for drug safety from the manufacturer to physicians on the basis of the premise that the physician's prescribing decision ultimately controls the risk to which a patient is exposed.[322,323,324] In many States, listing a risk on a drug label is sufficient to shift liability for that risk from the manufacturer to physicians.[325]

PGx test developers and clinical laboratories that offer PGx tests as a service also face potential liability risk if the test results are incorrect or misinterpreted. As the demand for more rapid turnaround of PGx test results increases and if FDA's regulatory oversight of LDTs is strengthened, more PGx tests are likely to be offered as IVD test kits. These potential changes could expose companies that manufacture, distribute, or interpret genetic tests to greater product defect liability.[326]

[320] Rothstein MA. Liability issues in pharmacogenomics. *Louisiana Law Review* 2005. 66(1):117-24.
[321] Marchant GE, Milligan RJ, Wilhelmi B. Legal pressures and incentives for personalized medicine. *Future Medicine* 2006. 3(4):391-7.
[322] Calabro S. Breaking the shield of the learned intermediary doctrine: placing blame where it belongs. *Cardozo Law Review* 2004. 25:2241-316.
[323] Restatement (Second) of Torts §402A, cmt. k (1977).
[324] Kane DS. Annotation: construction and application of the learned intermediary doctrine, 57 A.L.R. 5th 1, §2A (1998) updated through 2004.
[325] Evans BJ. Finding a liability-free space in which personalized medicine can bloom. *Clin Pharmacol Ther* 2007. 82(4):461-5.
[326] Ossorio PN. Product liability for predictive genetic tests. *Jurimetrics J* 2001. 41:239-60.

III. Gatekeepers

The pathway of a PGx product from its initial development to its successful use in clinical practice is influenced by multiple agents. Some of these agents function as gatekeepers, in that they can enable, halt, or redirect the course of a technology. This chapter describes four main gatekeepers relevant to the current and future use of PGx: industry, the Food and Drug Administration (FDA), the Centers for Medicare & Medicaid Services (CMS) and other payers, and developers of clinical practice guidelines and other clinical standards.

Because PGx research and development often is a global endeavor, PGx researchers, product developers, and health care providers may encounter additional gatekeepers in other countries. Although international gatekeepers also can influence the pathway of a PGx product, they are not a focus of this chapter. However, their role in enabling, halting, or redirecting the course of a PGx technology can be significant and can potentially complicate and delay the PGx research, development, and clinical implementation process.

A. Industry

Pharmaceutical, biotechnology, and diagnostics manufacturers are important gatekeepers for PGx because their perceptions of opportunities, risks, and return on investment influence whether and how they will pursue the development, approval, and marketing of new PGx products. By investing in research and engaging with other stakeholders in efforts related to PGx, industry gatekeepers have been and are likely to continue to be influential in advancing the PGx field.

1. Use of PGx in Drug Development

One of the main concerns of industry and others with a stake in innovation is that using PGx to target products to particular population subgroups could lower revenues and decrease returns on investments in drug development.[327] This approach runs counter to the current dominant "blockbuster" strategy of marketing drugs for use in broad populations, with targeted annual sales of $1 billion or more.[328] For PGx to be widely adopted as a drug development tool, pharmaceutical companies may have to employ new financial strategies that adapt to and capitalize on smaller target markets.[329]

Despite the financial risks inherent in developing products that could result in narrowed markets, industry has begun to incorporate PGx into the drug development process. In parallel, FDA has taken steps to encourage industry's investment in PGx by providing support for more informed development of PGx products. In addition to recent guidance documents pertaining to PGx data submissions and diagnostic tests, FDA efforts include forming advisory groups, forging interagency collaborations, and sponsoring conferences and symposia.[330] The Orphan Drug Act of 1983 provides even more incentives for PGx drug development for rare diseases. This act is described in more detail in Chapter II. Research and Development.

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[327] Robertson JA 2002. Op. cit.
[328] Bartfai T 2004. Op. cit.
[329] PricewaterhouseCoopers (2005). Op. cit.
[330] Rados C. *Advisory committees: critical to the FDA's product review process*. Food and Drug Administration, FDA Consumer Magazine, 2004. See http://www.fda.gov/fdac/features/2004/104_adv.html [accessed December 18, 2007].

2. Development of PGx Diagnostics

Developers of PGx tests perceive certain incentives and disincentives to innovation in the PGx field, which are shaped by the current regulatory and reimbursement environments. Currently, diagnostic tests are not reimbursed based on the clinical value they provide (i.e., the ability to identify patients who are most likely to respond to or least likely to suffer side effects from a drug). Instead, new diagnostic tests are reimbursed at levels comparable with similar existing tests. As observed in a recent report prepared for the pharmaceutical industry, "[t]he current reimbursement system for diagnostics diminishes the incentive to discover and develop these applications from the point of view of the diagnostic manufacturer."[331] Current reimbursement mechanisms that do not account for test value may provide PGx test developers with insufficient incentive to conduct research to identify PGx biomarkers and corresponding novel tests and little incentive to gather evidence of clinical utility.

In addition to reimbursement considerations, the extent of patent protections may affect incentives for PGx test developers. Strong patent protection for PGx tests may bolster financial incentives by preventing competitors from entering the market for sufficient time to allow test developers to realize profits.[332]

3. Codevelopment of PGx Diagnostics and Drugs

Many diagnostics companies perceive strong incentives to form partnerships with pharmaceutical companies to produce drug-diagnostic combination products based on the use of biomarkers. Pressure from payers also may encourage the codevelopment and comarketing of drugs and diagnostic tests. Given that PGx-related drugs are likely to be expensive, payers may want a reliable, clinically useful diagnostic test to be available simultaneously with the drug so that the drug is prescribed to patients who stand to benefit.

Collaborative arrangements are becoming more common, and it is anticipated that the number of combination products submitted for FDA review will increase.[333] FDA's 2005 concept paper on drug-diagnostic codevelopment outlines key considerations for industry regarding drug-diagnostic combinations. FDA recommends that industry sponsors contact the agency early to determine whether a product is likely to be part of a combination and, if so, whether sequential or simultaneous review of both the drug and diagnostic components is most appropriate.[334] FDA plans to develop draft guidance on drug-diagnostic codevelopment that builds on this concept paper. The release of FDA guidelines and concept papers clarifying issues involved in codevelopment may reduce some of the uncertainty of pharmaceutical companies regarding parallel development of drug and diagnostic tests.

Although codevelopment offers potential benefits for the pharmaceutical industry, its risks are apparent.[335] The availability of a highly specific diagnostic test still narrows a target market for a drug. In the absence of such a test, however, high levels of demand for a drug can be maintained through effective marketing. Codevelopment also could increase the costs and time involved in bringing new therapies to market. Pharmaceutical companies undertaking parallel product development would be responsible for the development of the diagnostic test or would collaborate with a diagnostic manufacturer. These additional

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[331] Garrison LP Jr 2007. Op. cit.
[332] Garrison LP Jr 2006. Op. cit.
[333] Food and Drug Administration, Office of Combination Products (2003). *Annual report to Congress*. See http://www.fda.gov/oc/combination/Congressreport.pdf [accessed December 18, 2007].
[334] Food and Drug Administration (2005). *Drug-diagnostic co-development concept paper* (draft). See http://www.fda.gov/cder/genomics/pharmacoconceptfn.pdf [accessed December 18, 2007].
[335] Diller W. Roche's challenging biomarker strategy. *In Vivo: The Business and Medicine Report* 2004. 53-65.

costs to industry may pose disincentives, particularly for drugs that are narrowly targeted to specific patient subgroups and for which a price premium may be difficult to achieve. Depending on the particular product, the cost of developing the diagnostic test could be relatively low compared with the cost of drug development.

Industry's perceptions of the role of PGx in drug development and codevelopment are still evolving. Continued promulgation of guidance and other clarification from FDA, along with growing experience in developing these products, may help reduce uncertainty.

B. FDA

Through its market approval function, FDA serves as a gatekeeper of new health care technologies. FDA's range of regulatory oversight affecting PGx uptake includes manufacturing practices, conduct of clinical trials, review of safety and efficacy data, market clearance and approval, and postmarketing surveillance. Without FDA approval or clearance for a particular indication, patients in the United States cannot make use of a product unless they participate in a clinical trial (also subject to FDA regulatory oversight) or gain off-label access. PGx faces some of the same challenges as other regulated technologies and certain unique ones.[336]

FDA and product makers interact frequently, especially leading up to key points in the product life cycle. Section 1 below outlines FDA's main roles pertaining to PGx products, including the agency's charge to assess the safety and effectiveness of new products and its guidance documents for industry and other stakeholders. CMS also has a role in regulating the laboratories that perform PGx testing. Its regulatory responsibilities are described in section C below, CMS and Other Third-Party Payers.

1. FDA Regulation of PGx Products

Regulatory oversight of PGx testing is subject to a key distinction—whether it is done in the form of a *product* or a *service*. A PGx test sold as an *in vitro* diagnostic (IVD) test kit is regulated as a medical device. Regulation of medical devices is primarily the responsibility of FDA. A PGx test provided as a laboratory service is considered a laboratory-developed test (LDT). The laboratory performing the test generates information—not a product—that is used to make patient health care decisions. Although FDA has affirmed its statutory authority to regulate LDTs, the extent of FDA's authority in this area is under debate, and FDA currently is not regulating LDTs because of resource constraints.[337] Regulation of clinical laboratories performing both LDTs and IVD tests is primarily the responsibility of CMS, which gets its regulatory authority from the Clinical Laboratory Improvement Amendments of 1988 (CLIA). LDT ordering is regulated at the State level.[338] This section focuses on FDA's regulatory responsibilities regarding PGx products; CMS's role in regulating clinical laboratories is described in section C below.

Within FDA, responsibilities for regulating health care products fall under the Center for Drug Evaluation and Research (CDER), the Center for Devices and Radiological Health (CDRH), and the Center for Biologics Evaluation and Research (CBER). With regard to PGx diagnostics and drugs, the CDRH Office of In Vitro Diagnostic Device Evaluation and Safety is responsible for regulating diagnostics, whereas

[336] Melzer D, Detmer D, Zimmern R. Pharmacogenetics and public policy: expert views in Europe and North America. *Pharmacogenomics* 2003. 4(6):689-91.
[337] Secretary's Advisory Committee on Genetics, Health, and Society (2007). Op. cit.
[338] 21 CFR 809.30(f).

pharmaceuticals generally are regulated by CDER. In 1991, intercenter agreements were drafted among CDER, CBER, and CDRH to facilitate regulation of combination products, including PGx.[339,340] In response to the increasing prevalence and complexity of these products, FDA established the Office of Combination Products (OCP) in 2002. One purpose of OCP is to foster collaboration among relevant FDA centers and offices involved in regulating combination products.[341] Although OCP has a broad coordinating function, primary authority for regulating any given combination product rests with the individual FDA center that is assigned jurisdiction over the product (typically CDRH or CDER).[342]

a. Product Submission and Review Process

FDA regulates the market entry of new IVDs via four pathways: (1) premarket notification, otherwise known as the 510(k) pathway; (2) premarket approval application (PMA); (3) class I exempt; and (4) humanitarian use devices (HUDs). HUDs are pursued infrequently since they are subject to special, rigorous regulatory requirements.

The 510(k) premarket notification process is for moderate-risk IVDs for which there is a legally marketed predicate device. A *predicate device* is one that was cleared through the 510(k) pathway, exempted from the 510(k) pathway, legally marketed prior to enactment of the Medical Device Amendments (also called preamendment devices), or originally placed on the U.S. market as a class III device but later classified as a class I or II device.[343,344] To determine whether a new test is substantially equivalent to a predicate device, FDA may request clinical results demonstrating that the new diagnostic poses no more risk than a predicate device. FDA also requires submission of data indicating effectiveness.

Truly novel IVDs are subject to the more rigorous PMA process, which is based on a review of evidence showing that the device is safe and effective for its intended use. For IVDs, safety is based not on contact of a device with the patient but on the impact that the information generated by the device has on patient management (e.g., potential harm from false-positive or false-negative results). Since PMAs are intended to apply to truly new devices that have no predicate, their effects on human health may not be as well understood as devices that qualify for the 510(k) pathway. As such, the evidence collection and review processes for these technologies often are more resource intensive and time consuming. PMAs also require a review of manufacturing processes, inspections of manufacturing facilities, audits of clinical study sites, and comprehensive reviews of premarket data.

In addition to the standard 510(k) and PMA processes, the FDA Modernization Act of 1997 amended existing regulations by way of a provision referred to as the "Evaluation of Automatic Class III Designation," which created the *de novo* 510(k) process. This provision applies to low- or moderate-risk devices that are designated as class III after they are found not substantially equivalent to a predicate device. Under this

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[339] Taulbee P. FDA proposes streamlining intercenter agreements on combo products. *The Gray Sheet* October 9, 2006. 32(041):14.

[340] As described in the October 2, 2006, *Federal Register*, FDA proposed the idea of eliminating the intercenter agreement between CBER and CDER, indicating that this agreement became outdated in 2003 when regulatory jurisdiction for several therapeutic biological products was transferred from CBER to CDER. The notice was open for public comment until December 1, 2006, and no final decisions have yet been issued regarding the agreement.

[341] Food and Drug Administration, Office of Combination Products (2003). *Annual report to Congress*. Op. cit.

[342] FDA Web site. Overview of the Office of Combination Products. See http://www.fda.gov/oc/combination/overview.html [accessed December 18, 2007].

[343] The Medical Device Amendments to the Federal Food, Drug, and Cosmetic Act became effective May 28, 1976.

[344] FDA Web site. Premarket Notification 510(k). See http://www.fda.gov/CDRH/DEVADVICE/314.html [accessed December 18, 2007].

process, 510(k) applicants with devices meeting these criteria may request a *de novo* downclassification of the device to class I or class II. If FDA approves such a request, the device may be marketed without obtaining a PMA and may serve as a predicate device for future applications.[345,346] The Factor V Leiden test is an example of a device approved via a *de novo* 510(k), and it subsequently served as a predicate device for the Factor II genotyping kit.[347] This classification process may be relevant for other low- or moderate-risk PGx tests entering the market.

Class I-exempt IVDs are not subject to either the 510(k) pathway or the PMA process, but their manufacturers are required to register their establishments, list their devices with FDA, and meet good manufacturing practices (GMP) requirements (a few class I devices are exempt from GMP requirements). The products also must be suitable for the intended use, adequately packaged, and properly labeled. Most analyte-specific reagents (ASRs) are classified as class I exempt. ASRs are the active ingredients used by clinical laboratories for developing LDTs. ASRs include antibodies, receptor proteins, nucleic acid sequences, and other biological or chemical reagents used to identify or quantify substances in biological specimens.[348] In addition to the requirements listed above, ASR manufacturers must restrict the sale of these reagents to laboratories designated as "high complexity" under CLIA.

HUDs are for rare diseases or conditions (affecting fewer than 4,000 individuals per year) that are allowed humanitarian device exemptions. They are subject to institutional review board approval and have restrictions on their use, cost, and labeling but are exempt from having to demonstrate effectiveness.

FDA also regulates the labeling of diagnostics and therapeutics that are marketed in interstate commerce. Drug labels describe the approved indications for use and may specify dosing, contraindications, or other important instructions. Product labels provide clinicians with information about the approved use of a product. The role of labels in informing clinical practice, including some inherent strengths and weaknesses of current labeling practices and recent FDA guidance pertaining to labeling of PGx products, is described in Chapter IV. Implementation of PGx To Improve Outcomes in Clinical Practice.

b. Laboratory-Developed PGx Tests

As described above, ASRs are the active ingredients used in LDTs. LDTs also have been referred to as "in-house tests" or "homebrew tests" (although these terms are no longer in favor). Most ASRs are produced by diagnostics manufacturers and categorized by FDA as class I-exempt devices. Manufacturers of class I-exempt ASRs sold to laboratories are subject to registration with FDA and compliance with GMP and labeling requirements. The smaller number of ASRs that FDA designates as class II and class III devices, such as those involved in blood screening, are subject to more rigorous premarket review requirements. Laboratories that manufacture ASRs for their own internal use are not subject to these FDA regulations.

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[345] FDA Web site. Premarket notification 510(k): Special Considerations. See http://www.fda.gov/cdrh/devadvice/314c.html [accessed December 18, 2007].

[346] Food and Drug Administration, Center for Devices and Radiological Health (1998). *New section 513(f)(2) – evaluation of automatic class III designation, guidance for industry and CDRH staff.* See http://www.fda.gov/cdrh/modact/clasiii.pdf [accessed December 18, 2007].

[347] Mansfield E, O'Leary TJ, Gutman SI. Food and Drug Administration regulation of *in vitro* diagnostic devices. *J Mol Diagn* 2005. 7(1):2-7.

[348] Gutman SI. FDA's role in the regulation of *in vitro* diagnostic. Presentation May 10, 2003. Food and Drug Administration, Center for Devices and Radiological Health, Office of In Vitro Device Evaluation and Safety (2003). See http://www.fda.gov/cdrh/oivd/presentations/051003-gutman-1.html [accessed October 23, 2007].

In contrast to their ingredient ASRs, LDTs traditionally have not been regulated by FDA. Laboratories performing LDTs must report results with the standard disclaimer "This test was developed and its performance characteristics determined by [laboratory name]. It has not been cleared or approved by the FDA."

Although compliance with CLIA and Federal Trade Commission (FTC) regulations entails certain burdens, launch of a PGx test in the form of an LDT has the advantage of a more rapid road to market than launch of the test as an IVD test kit or system that would be subject to FDA premarket clearance or review. Disincentives for developing PGx tests subject to the 510(k) or PMA processes may result in attempts to market IVD test kits/test systems as ASRs.

The Food, Drug, and Cosmetic Act, as amended by the Medical Device Act and Safe Medical Devices Act of 1990, enables FDA to have regulatory oversight over all LDTs and their components. However, aside from the ASR oversight noted above, the agency has elected *not* to exercise this authority. Some observers argue that doing so would encroach on the practice of medicine (i.e., physicians prescribing tests and using the results for clinical decisionmaking), which is beyond FDA's authority. Others express concern that extending FDA oversight to LDTs may slow test development and diminish the availability of these tests.[349,350,351] On the other hand, some argue that FDA regulation of tests marketed as diagnostic test kits, but not tests marketed as laboratory services, constitutes an inappropriate double standard. According to the latter view, genetic tests, including some with limited predictive validity, escape having to demonstrate effectiveness.[352] Still others consider the two separate pathways to be appropriate.[353]

One guidance and one draft guidance, issued in September and July 2007, respectively, pertain to ASRs and the new category of IVD multivariate index assays (IVDMIAs) and clarify FDA's regulation of diagnostic testing conducted by clinical laboratories, including LDTs. These guidances suggest a shift within FDA toward expanding regulation of a small but important and growing number of tests, exposing them to FDA's high standards of safety and effectiveness.

Guidance for Industry and FDA Staff; Commercially Distributed Analyte-Specific Reagents (ASRs): Frequently Asked Questions clarifies the definition of an ASR. This guidance states that single ASRs that are (1) combined or promoted for use with another product such as other ASRs, general purpose reagents, controls, laboratory equipment, software, etc., or (2) promoted with specific analytical or clinical performance claims, instructions for use in a particular test, or instructions for validation of a particular test using the ASR, are considered by FDA *not* to be ASRs and, thus, not exempt from premarket notification requirements.[354] The guidance addresses industry's marketing of increasingly complex combinations of ASR-based products under the less demanding requirements of single ASRs rather than as test kits. Indeed, there has been an increase in LDTs for simultaneous detection of multiple genetic variants. A related concern involves claims of multiple functions for a single ASR when marketing it to a laboratory.[355,356]

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[349] Borchardt PE. Pharmacogenomics: an in-house advantage? *Drug Discov Today* 2006. 11(1-2):1-3.
[350] Merrill RA. Genetic testing: a role for FDA? *Jurimetrics J* 2000. 41:63-6.
[351] Secretary's Advisory Committee on Genetics, Health, and Society (2007). Op. cit.
[352] Holtzman NA. FDA and the regulation of genetic tests. *Jurimetrics J* 2000. 41:53-62.
[353] American Clinical Laboratory Association (2007). *Comments on realizing the promise of pharmacogenomics: opportunities and challenges* (public comment draft). See http://www4.od/nih.gov/oba/sacghs/reports/pgx_publiccomments.pdf [accessed April 21, 2008].
[354] Food and Drug Administration (2007). *Guidance for industry and FDA staff: commercially distributed analyte specific reagents (ASRs): frequently asked questions.* See http://www.fda.gov/cdrh/oivd/guidance/1590.pdf [accessed December 18, 2007].
[355] Genetics and Public Policy Center Web site. Center Sees "New Era in Oversight" of Genetic Tests in Two New FDA Draft Guidances. See http://www.dnapolicy.org/news.release.php?action=detail&pressrelease_id=56 [accessed December 18, 2007].
[356] Gibbs JN. Regulations & standards: the past, present, and future of ASRs. Medical Devicelink (2003). See http://www.devicelink.com/ivdt/archive/03/11/012.html [accessed December 18, 2007].

Draft Guidance for Industry, Clinical Laboratories, and FDA Staff: In Vitro Diagnostic Multivariate Index Assays sets premarket and postmarket regulatory requirements for certain LDTs that combine values of multiple variables in an algorithm to generate a single result to guide diagnosis and treatment. The draft guidance states that IVDMIAs will be actively regulated as medical devices and classified according to their intended use and level of control needed to ensure their safety and effectiveness.[357] In February 2007, FDA cleared the first IVDMIA. MammaPrint® is a microarray gene expression profiling test intended to help clinicians more accurately predict whether an existing, early-stage breast cancer will metastasize.[358,359] Currently, it is unclear what proportion of PGx tests, or algorithms that include PGx test results, will fall into the IVDMIA category (see Exhibit 3 below).

Exhibit 3. The Case of Onco*type* DX®

Onco*type* DX® (sold by Genomic Health) is an example of a diagnostic test that would likely be categorized as an IVDMIA. This test is designed to predict the risk of recurrence in women with early-stage breast cancer and could help clinicians individualize patient treatment plans. It is reported to be more effective than other tests that predict risk based on the size and grade of the tumor.[360] Although Onco*type* DX® has not yet been approved by FDA, it is already covered by some health plans.[361,362]

The test is being used in the **T**rial **A**ssigning **I**ndividua**L**ized **O**ptions for Treatment (**Rx**) (TAILORx), a prospective cohort study sponsored by the National Cancer Institute that was launched in May 2006. TAILORx uses Onco*type* DX® to measure the expression of 21 breast tumor genes to estimate subjects' cancer recurrence risk. Patients with low recurrence scores (<11) experience good outcomes with hormonal therapy alone, and patients with high recurrence scores (>25) benefit from chemotherapy and hormonal therapy, but there is uncertainty about the added value of chemotherapy in patients with midrange (i.e., 11-25) recurrence scores.[363] TAILORx investigates the benefit of adding chemotherapy to standard hormonal therapy for patients with midrange scores. Given the toxicity of chemotherapy, reducing unnecessary treatment could improve the quality of life of breast cancer survivors.[364]

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[357] Food and Drug Administration, Center for Devices and Radiological Health, Office of In Vitro Diagnostic Device Evaluation and Safety (2007). *Draft guidance for industry, clinical laboratories, and FDA staff: in vitro diagnostic multivariate index assays*. See http://www.fda.gov/cdrh/oivd/guidance/1610.pdf [accessed December 18, 2007].

[358] FDA Web site. FDA Clears Breast Cancer Specific Molecular Prognostic Test. See http://www.fda.gov/bbs/topics/NEWS/2007/NEW01555.html [accessed December 18, 2007].

[359] Agendia Web site. About MammaPrint. See http://usa.agendia.com/en/about_mammaprint_2.html [accessed December 18, 2007].

[360] NIH Web site. Personalized Treatment Trial for Breast Cancer Launched. See http://www.nih.gov/news/pr/may2006/nci-23.htm [accessed December 18, 2007].

[361] Association for Molecular Pathology (2005). *Comments on NHIC on the LCD for the Oncotype DX test*. See http://amp.org/PRC/OncotypeDX.doc [accessed December 18, 2007].

[362] Harvard Pilgrim Health Care, 2005. *TA 6.35 Oncotype DX recurrence score assay for predicting breast cancer recurrence.* See http://www.harvardpilgrim.org/pls/portal/docs/page/providers/medmgmt/statements/oncotypedx_policy7.05.pdf [accessed December 18, 2007].

[363] Sparano JA. The TAILORx trial: individualized options for treatment. *Commun Oncol* 2006. 3:494-6.

[364] Paik S, Tang, G, Shak S et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. *J Clin Oncol 2006*. 24(23):3726-34.

Whereas most ASRs are designated as class I devices, which are usually exempt from premarket review, most IVDMIAs are subject to the higher evidence requirements of class II or class III devices. The draft guidance makes it clear that the type of premarket notification process that will be required will be based on the intended use of the IVDMIA:

> *We believe most IVDMIAs will be either class II or III devices, although it is possible that an IVDMIA for a low-risk indication could be class I. For example, a device intended as an indicator of a patient's risk of cancer recurrence may be a class II device (e.g., devices classified under 21 CFR 866.6040, Gene expression profiling assay for breast cancer prognosis), while the same device intended to predict which patients should receive chemotherapy might require premarket approval.*

As a result of the draft guidance, more complex LDTs will be subject to greater scrutiny via either the 510(k) or PMA process. Some in industry speculate that this draft guidance may promote greater drug-diagnostic codevelopment.[365]

2. FDA Guidance for PGx Products

The emergence of PGx focuses attention on the adequacy of regulation of products whose use and effects are influenced by genetic differences. FDA has acknowledged the need to adapt its policies and processes in recognition of this emerging field and is beginning to respond.[366] FDA has issued three guidance documents in an effort to facilitate efficient data submissions and reviews of PGx products. *Guidance for Industry: Pharmacogenomic Data Submissions*, issued in March 2005, pertains primarily to the therapeutic aspect of PGx. By encouraging voluntary submission of genomic data to FDA, this guidance intends to facilitate scientific progress in PGx and use of PGx data in drug development. It provides guidance to sponsors of new drug applications (NDAs) and biologics license applications on (1) when to submit PGx data to FDA, (2) what format to use and content to include when submitting PGx data, and (3) how and when data will be used in regulatory decisionmaking.[367]

In 2007, FDA released *Draft Guidance for Industry; Pharmacogenomic Data Submissions – Companion Guidance*.[368] The information in this draft guidance is based on FDA's experiences since the release of the 2005 guidance and addresses topics such as methodological factors to consider in submitting gene expression data from microarrays, issues related to genotyping, and considerations in proficiency testing, among others.

When voluntary genomic data submissions (VGDSs) are received by FDA, they are routed directly to the Interdisciplinary Pharmacogenomics Review Group, which reviews them and ensures the proper separation of voluntary and nonvoluntary data. To ensure confidentiality, these data are protected in the same ways

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[365] Ray T. Stakeholders consider if FDA's IVDMIA draft guidance can inspire Rx/Dx codevelopment. *Pharmacogenomics Reporter*, May 30, 2007. See http://www.pgxreporter.com/issues/5_22/features/140284-1.html [accessed January 28, 2008].

[366] Phillips KA, Van Bebber SL. Regulatory perspectives on pharmacogenomics: a review of the literature on key issues faced by the United States Food and Drug Administration. *Med Care Res Rev* 2006. 63(3):301-26.

[367] Food and Drug Administration (2005). *Guidance for industry: pharmacogenomic data submissions.* Op. cit.

[368] Food and Drug Administration (2007). *Draft guidance for industry: pharmacogenomic data submissions – companion guidance.* See http://www.fda.gov/cber/gdlns/pharmdtasubcomp.pdf [accessed December 18, 2007].

as other data (e.g., for NDAs) submitted to FDA.[369,370,371] These protections help reassure sponsors that their intellectual property will not be jeopardized as a result of a voluntary submission. However, these protections also limit FDA's ability to share publicly information contained in these submissions.

With the goal of enabling the incorporation of PGx into the drug development process, the VGDS Program provides a more informal opportunity for sponsors and FDA to discuss exploratory scientific issues without concern for regulatory implications. These informal meetings enable sponsors to gather insights about how FDA views the use of genomic information in regulatory decisionmaking, which may be useful later in formal meetings with FDA.[372] FDA also periodically sponsors workshops for the public and relevant stakeholders to communicate lessons learned from the VGDS Program.

Each quarter, FDA receives approximately two or three new data submissions through the VGDS process. As of August 2007, FDA had received approximately 40 VGDSs and had held approximately 25 meetings with sponsors. These submissions have covered a range of therapeutic areas (e.g., cancer, Alzheimer's disease) and diverse scientific areas (e.g., biomarkers, genotyping devices).[373,374]

Many companies had been concerned that FDA might misinterpret their use of exploratory, nonvalidated genomic biomarkers and request more clinical trials or put ongoing clinical trials on hold, causing delays in drug development. The 2005 guidance and 2007 companion draft guidance intended to alleviate concerns about how the agency would handle exploratory genomic data obtained during the drug development process. However, because of the level of interest in PGx, some observers worry that submission of such data could become mandatory for new drug approval in the future.[375] Through its pilot process for qualifying exploratory biomarkers, FDA seeks to help sponsors validate these biomarkers for use in drug development.[376]

Guidance for Industry and Food and Drug Administration Staff: Pharmacogenetic Tests and Genetic Tests for Heritable Markers, issued in June 2007, contains recommendations for sponsors and FDA reviewers as they prepare and review 510(k) and PMA submissions for PGx and other genetic tests. The guidance aims to reduce product development and review times, facilitate the transition of new genetic technologies into clinical laboratories, and encourage informed use of these devices.[377,378] Although FDA has provided assurances that this guidance is not intended to stifle the growth and development of the PGx field, it may

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[369] FDA Web site. Genomics at FDA: Frequently Asked Questions. See http://www.fda.gov/cder/genomics/FAQ.htm [accessed December 18, 2007].
[370] FDA Web site. Genomics at FDA: Genomic Data Submission. See http://www.fda.gov/cder/genomics/GDS.htm [accessed December 18, 2007].
[371] Goodsaid F, Frueh FW. Implementing the U.S. FDA guidance on pharmacogenomic data submissions. *Environ Mol Mutagen* 2007. 48(5):354-8.
[372] Ibid.
[373] Goodsaid F. Pharmacogenomics and EHR. Presentation to the AHIC Personalized Healthcare Workgroup. August 17, 2007. See http://www.hhs.gov/healthit/ahic/materials/08_07/phc/goodsaid_files/800x600/slide8.html [accessed December 18, 2007].
[374] Orr MS, Goodsaid F, Amur S, Rudman A, Frueh FW. The experience with voluntary genomic data submissions at the FDA and a vision for the future of the voluntary data submission program. *Clin Pharmacol Ther* 2007. 81(2):294-7.
[375] Borchardt PE 2006. Op. cit.
[376] Goodsaid F 2007. Op. cit.
[377] Food and Drug Administration (2007). *Guidance for industry and FDA staff: pharmacogenetic tests and genetic tests for heritable markers.* See http://www.fda.gov/cdrh/oivd/guidance/1549.pdf [accessed December 18, 2007].
[378] Food and Drug Administration (2006). *Draft guidance for industry and FDA staff: pharmacogenetic tests and genetic tests for heritable markers.* See http://www.fda.gov/cdrh/oivd/guidance/1549.pdf [accessed December 18, 2007].

have important implications for the types of data that are available on PGx tests, their transition times from FDA approval to adoption, and their accessibility to patients.[379]

PGx is likely to elicit additional FDA guidance and other measures as the field evolves.[380] Currently, the agency is examining a range of regulatory matters pertaining to PGx. These include the extent to which genetic data may be required for drug approval; a determination of whether previously approved drugs should be revisited as relevant genetic data become available; the circumstances under which PGx testing may be required before or after initiation of drug therapy; the codevelopment, comarketing, and labeling of drugs and their companion PGx tests; and an assessment of the relevance of the Orphan Drug Act to PGx products.[381,382,383,384,385]

3. Gap Between PGx Test Approval and Clinical Practice

FDA's requirements and actions—or their absence—influence the ways in which marketed PGx products are used in clinical practice. FDA approval of a PGx test does not necessarily provide guidance on how the test results should inform dosing decisions. For example, neither Roche Diagnostics nor FDA has provided recommendations on how to apply the results of AmpliChip® testing when dosing many commonly prescribed drugs, including antidepressants, antipsychotics, immunosuppressives, and anticancer drugs. Clinical trials could provide the basis for such dosing recommendations. Several trials are under way to provide such information.[386,387,388,389]

Another example is FDA's approval of a change to the label for the anticancer drug irinotecan (Camptosar®). Although the label now includes information about the relationship between *UGT1A1*28* polymorphisms and the risk of ADRs, it does not include a requirement or recommendation for *UGT1A1* testing due to insufficient data to support a dosing recommendation based on genotype.[390] In lieu of a dosing recommendation, the FDA-approved label states that "a reduction in the starting dose by at least one level of CAMPTOSAR should be considered for patients known to be homozygous for the UGT1A1*28 allele … However, the precise dose reduction in this patient population is not known, and subsequent dose modifications should

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[379] Lesko LJ, Woodcock J. Translation of pharmacogenomics and pharmacogenetics: a regulatory perspective. *Nat Rev Drug Discov* 2004. 3(9):763-9.
[380] Melzer D 2003. Op. cit.
[381] Robertson JA 2002. Op. cit.
[382] Lesko LJ 2002. Op. cit.
[383] Salerno RA, Lesko LJ. Pharmacogenomics in drug development and regulatory decision-making: the genomic data submission (GDS) proposal. *Pharmacogenomics* 2004. 5(1):25-30.
[384] Eisenberg RS. Will pharmacogenomics alter the role of patents in drug development? *Pharmacogenomics* 2002. 3(5):571-4.
[385] Issa AM 2003. Op. cit.
[386] National Institutes of Health (2006). *Prospective Evaluation Comparing Initiation of Warfarin Strategies (PRECISE): pharmacogenetic-guided versus usual care.* See http://clinicaltrials.gov/ct/show/NCT00377143?order=1 [accessed December 18, 2007].
[387] National Institutes of Health (2006). *A pharmacogenetic study of warfarin dosing, "The COUMA-GEN Study."* See http://clinicaltrials.gov/ct/show/NCT00334464?order=2 [accessed December 18, 2007].
[388] National Institutes of Health (2007). *Comparison of warfarin dosing using decision model vs. pharmacogenetic algorithm.* See http://clinicaltrials.gov/ct/show/NCT00511173?order=9 [accessed December 18, 2007].
[389] National Institutes of Health (2007). *Study to develop a reliable nomogram that incorporates clinical and genetic information.* See http://clinicaltrials.gov/ct/show/NCT00401414?order=11 [accessed December 18, 2007].
[390] Haga SB, Thummel KE, Burke W. Adding pharmacogenetics information to drug labels: lessons learned. *Pharmacogenet Genomics* 2006. 16(12):847-54.

be considered based on individual patient tolerance to treatment."[391] The subcommittee that reviewed the label further noted that "although there is indication to start with a lower dosage, it is not necessarily an indication that sensitive patients will do well with this dosage."[392] This example illustrates that PGx testing can identify patients who are likely to respond differently to particular drugs but that the results do not necessarily give rise to clear dosing instructions. As such, homozygous patients will have to be monitored and have their dosing adjusted empirically.

It is unclear whether FDA can or should be responsible for including PGx test-informed dosing recommendations in product labels. Such recommendations may need to come from medical professional organizations in the form of practice guidelines, although they too would require adequate evidence on which to base such guidelines.[393,394] Some suggest that FDA seek more input from academic experts, practicing physicians, and pharmaceutical companies to better incorporate large prospective study findings into dosing guidelines.[395,396] The broader gatekeeping role of guidelines developers for PGx is described in section D below.

C. CMS and Other Third-Party Payers

The ability to obtain favorable reimbursement is widely recognized as being essential for the success of innovative health care technologies. Once new PGx products reach the market, they face payer gatekeepers such as Medicare, Medicaid, and commercial payers and other intermediaries such as pharmacy benefit managers. A commercial publication in this market observes:

> *For industry, there's no point in investing in developing personalized drug therapies if payers won't cover them. One thing is sure: manufacturers better not follow FDA too far down the Critical Path to personalized medicine without finding the right formula for payment at the end of the road.*[397]

The following sections describe the importance of reimbursement for the future of PGx and outline reimbursement challenges to PGx in particular.

1. Overview of Reimbursement in the United States

Generally, the term "reimbursement" encompasses three main components: coverage, coding, and payment. *Coverage* refers to whether a payer will pay for a particular item or service as part of the benefits provided to its enrollees. *Coding* refers to the alphanumeric systems used to identify items and services and to which payment levels are assigned. *Payment* refers to the compensation provided by third-party payers to clinicians, health care facilities, or other providers of health care items or services.

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[391] Food and Drug Administration (2005). *NDA 20-571/S-024/S-027/S-028. Camptosar® (irinotecan HCl). Hepatic dysfunction, pancreatitis, UGT1A1. July 21, 2005, Final Label.* See http://www.fda.gov/cder/foi/label/2005/020571s024,027,028lbl.pdf [accessed December 18, 2007].
[392] Food and Drug Administration (2004). Clinical Pharmacology Subcommittee, Advisory Committee for Pharmaceutical Science. Final report of meeting, November 3-4, 2004. See http://www.fda.gov/OHRMS/DOCKETS/ac/04/minutes/2004-4079M1.htm [accessed December 18, 2007].
[393] Jain KK. Applications of AmpliChip CYP450. *Mol Diagn* 2005. 9(3):119-27.
[394] Need AC, Motulsky AG, Goldstein DB. Priorities and standards in pharmacogenetic research. *Nat Genet* 2005. 37(7):671-81.
[395] Secretary's Advisory Committee on Genetics, Health, and Society (2006). Transcript of 9th meeting, March 27, 2006. Op. cit.
[396] Lesko LJ 2004. Op. cit.
[397] Rawson K. Reimbursing designer drugs. *The RPM Report* 2006. 1(10):19-24.

In the United States, the two main categories of payers are public payers, including Medicare and State Medicaid programs, and private payers, such as commercial health plans and employers. Brief descriptions of these payers with regard to their gatekeeping roles for PGx are provided below.

a. Medicare

Medicare provides health care benefits to nearly 43 million individuals in the United States who are either age 65 years or older or who are younger than age 65 with certain disabilities or end-stage renal disease.[398] Administered by CMS, Medicare is the largest single health care payer in the United States and has substantial influence in the health care market.

Medicare's coverage policies and payment levels can affect the willingness of clinicians to provide PGx products, Medicare beneficiaries' access to them, and industry's interest in developing them. Medicare coverage policies and payment levels also greatly influence other public and private payers. For instance, Medicare's payment rates for diagnostic tests have not been adjusted for inflation during most of the past two decades and, therefore, do not necessarily reflect the value of diagnostic tests. Given that many other payers follow Medicare's lead in setting payment levels, these shortcomings often carry over to the reimbursement rates of other payers.[399,400] In recognition of the influence that Medicare has over other payers, the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) suggested in its February 2006 report *Coverage and Reimbursement of Genetic Tests and Services* that it may be inappropriate for private payers to follow Medicare's lead in the area of genetic testing.[401]

Depending on the testing circumstances, Medicare coverage of PGx tests may be limited by a statute that permits coverage only of items or services that are "reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member." Accordingly, Medicare does not cover tests—genetic or other—used for screening purposes (i.e., in patients without signs, symptoms, complaints, or personal history of disease or injury) unless specifically authorized by Congress to do so. For Medicare to cover screening or preventive interventions, Congress must pass new legislation, as it has in several instances (e.g., breast cancer screening, prostate-specific antigen testing for prostate cancer).

Generally, PGx tests (e.g., for *HER2/neu* overexpression) are eligible for Medicare coverage if they identify which patients among those known to have a particular condition are likely to respond to treatment. However, PGx tests also can be performed in the absence of an existing condition for which a drug would need to be prescribed but for which advance knowledge of the test results would be beneficial (e.g., in emergency situations where it could be detrimental to the patient's health to delay administration of the drug but where the risk of an ADR is high and presence of the ADR-associated gene variant could be discerned readily with PGx testing). This example of a screening application of PGx generally would not be covered by Medicare, since the test result would not necessarily be informing a treatment decision at the time of testing. Unless legislation is passed adding preventive services as a Medicare benefit category, it will be difficult for these types of screening or preventive applications of PGx to qualify for Medicare coverage. Clarification

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[398] Kaiser Family Foundation (2007). *Medicare at a glance*. See http://www.kff.org/medicare/upload/1066-10.pdf [accessed March 21, 2008].

[399] American Clinical Laboratory Association Web site. Medicare Reimbursement for Clinical Laboratory Services. See http://www.clinical-labs.org/issues/reimbursement/index.shtml [accessed December 18, 2007].

[400] Goodman C 2005. Op. cit.

[401] Secretary's Advisory Committee on Genetics, Health, and Society (2006). *Coverage and reimbursement of genetic tests and services*. Op. cit.

by CMS regarding the circumstances in which tests are considered screening or diagnostic may reduce uncertainty on the part of providers, manufacturers, and patients.

Adding preventive services as a Medicare benefit category would allow the U.S. Department of Health and Human Services (HHS) to develop coverage and payment policies for these services in a more systematic manner, drawing on the existing processes and expertise at CMS. In its 2006 report *Coverage and Reimbursement of Genetic Tests and Services*, SACGHS recommended that Congress add a preventive services benefit category. Although there is growing awareness of the clinical value of providing a benefit category for screening and preventive services, Congress and CMS would need to consider strategies for financing this expansion of covered services prior to implementation, since establishing a Medicare benefit category for preventive services would have parallel and downstream effects on the use of other preventive, diagnostic, and therapeutic services.

b. Medicaid

Medicaid provides health care and long-term care coverage for more than 55 million low-income individuals in the United States.[402] Each State administers its own Medicaid program, with oversight from CMS. Medicaid is financed jointly by States and the Federal Government. States must offer Medicaid beneficiaries certain mandatory services, including physician services and inpatient and outpatient hospital services, to receive matching Federal funds but have the option of covering additional services such as PGx tests.[403] All 50 States and the District of Columbia have opted to offer a prescription drug benefit.[404] In its 2006 report SACGHS expressed concern that State variations in Medicaid coverage of these optional services could result in disparate access to genetic tests.[405]

c. Private Payers

As noted above, many private payers monitor Medicare's coverage and payment policies and often follow its lead. However, because Medicare must operate within certain statutory parameters that limit its ability to cover screening and preventive services, private payers have had to chart their own course with regard to PGx. To date, private payers have had a significant role in facilitating the integration of PGx technologies into clinical practice and are expected to continue playing an important role in this process.[406]

Little is known about private payers' coverage of PGx products because coverage policies are generally considered proprietary. Some payers, such as Aetna, make their coverage policies publicly available, however. Aetna currently has at least five policies relevant to PGx, including policies pertaining to Herceptin®, tumor markers, inflammatory bowel disease, HIV drug susceptibility and resistance tests, and other PGx testing services. For example, its 2007 clinical policy bulletin regarding Herceptin® states that use of this drug is considered medically necessary for certain breast cancer patients with overexpression

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[402] Kaiser Family Foundation, Kaiser Commission on Medicaid and the Uninsured (2007). *The Medicaid program at a glance.* See http://www.kff.org/medicaid/upload/7235-02.pdf [accessed December 18, 2007].
[403] Kaiser Family Foundation, Kaiser Commission on Medicaid and the Uninsured (2007). *Medicaid: a primer.* See http://www.kff.org/medicaid/upload/Medicaid-A-Primer-pdf.pdf [accessed December 18, 2007].
[404] Kaiser Family Foundation Web site. Medicaid benefits: Online Database. See http://www.kff.org/medicaid/benefits/index.jsp?CFID=18509591&CFTOKEN=44905646 [accessed December 18, 2007].
[405] Secretary's Advisory Committee on Genetics, Health, and Society (2006). *Coverage and reimbursement of genetic tests and services*. Op. cit.
[406] Carlson RJ, Garrison L, Veenstra DL (2007). *Comments on realizing the promise of pharmacogenomics: opportunities and challenges* (public comment draft).

of the HER2 protein or amplification of the *HER2/neu* gene.[407] Aetna's policy bulletin on tumor markers considers Onco*type* DX® to be medically necessary in women whose breast tumor is HER2-receptor negative or HER2-receptor positive and less than 1 cm in diameter, in addition to several other criteria.[408] Findings from various randomized controlled trials (RCTs) and other studies are included in these bulletins to support Aetna's coverage decisions. MammaPrint®, on the other hand, is considered experimental and investigational due to the lack of peer-reviewed medical literature to support its sensitivity and specificity. Similarly, Aetna considers genotyping for CYP450 polymorphisms and the Invader *UGT1A1* molecular assay (for determining optimal dosing of the drug irinotecan for patients with colorectal cancer) to be investigational and experimental because the clinical value of these tests has not yet been demonstrated.[409] To support this conclusion, the bulletin reports conflicting evidence from recent studies and cites the need for additional investigation. Moreover, the bulletin notes that the product label for irinotecan does not specify that *UGT1A1* status should be assessed prior to prescribing the drug, highlighting the importance of product labeling in PGx coverage determinations.

Regarding prescription drug coverage, many health care plans maintain formularies (lists of drugs that are preferred or covered by the payer) to help control costs and utilization.[410] Payers select the prescription drugs they will cover based on the drugs' efficacy, safety, and cost-effectiveness. Drugs selected for inclusion in a plan's formulary often are assigned different tiers, with higher levels of cost sharing assigned to higher tiers. Drugs that are not included in the drug formulary are subject to greater cost sharing or are not covered at all.

PGx may introduce new considerations regarding formulary policies. Patients who receive a PGx test result indicating that a nonformulary or higher tier drug may be more effective or less toxic may be responsible for a greater share of the costs of those drugs that are indicated based on their genetic makeup. Health care plans will need to determine the most effective way of adapting formulary policies in response to the use of PGx. For instance, some plans will make exceptions to their formulary policy if the plan member or health care provider provides information (e.g., PGx test result) indicating that a nonformulary drug is more appropriate.[411] Also, plans commonly provide the means for patients to access medically necessary nonformulary drugs and appeal coverage determinations.[412,413] In the future, health care plans may require members to have a PGx test before it will cover a drug and refuse coverage if the test result indicates that the drug may not be effective or may be harmful. The potential for coverage of clinically beneficial drugs to be conditioned on a PGx test result emphasizes the importance of establishing the clinical validity of PGx tests.

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[407] Aetna Web site. Clinical Policy Bulletin: Herceptin (Trastuzumab). Number 0313. See http://www.aetna.com/cpb/medical/data/300_399/0313.html [accessed December 18, 2007].

[408] Aetna Web site. Clinical Policy Bulletin: Tumor Markers. Number 0352. See http://www.aetna.com/cpb/medical/data/300_399/0352.html [accessed December 18, 2007].

[409] Aetna Web site. Clinical Policy Bulletin: Pharmacogenetic Testing. Number 0715. See http://www.aetna.com/cpb/medical/data/700_799/0715.html [accessed December 18, 2007].

[410] Office of the Assistant Secretary for Planning and Evaluation (2005). *National Opinion Research Center. Final report: issues in the design and implementation of drug formularies and therapeutic classes*. See http://aspe.hhs.gov/health/reports/05/drugformularies/report.pdf [accessed December 18, 2007].

[411] Blue Cross Blue Shield Association (2007). *Comments on realizing the promise of pharmacogenomics: opportunities and challenges* (public comment draft).

[412] The George Washington University, National Health Policy Forum (2004). *The basics: prescription drug formularies.* See http://www.nhpf.org/pdfs_basics/Basics_Formulary.pdf [accessed December 18, 2007].

[413] Burton SL, Randel L, Titlow K, Emanuel EJ. The ethics of pharmaceutical benefit management. *Health Aff (Millwood)* 2001. 20(5):150-63.

Recommendations 9A and 9B

9A. CMS should develop a guidance document detailing current Medicare, Medicaid, and State Children's Health Insurance Program coverage and reimbursement of PGx products. CMS also should survey public and private health plans about their decisionmaking processes and coverage policies to help inform its future PGx coverage and reimbursement decisions.

9B. Because the issues identified in the SACGHS Coverage and Reimbursement report are relevant to issues in this report, SACGHS urges HHS to act on the Coverage and Reimbursement report's recommendations.

d. Health Technology Assessment Groups

Health technology assessments (HTAs) involve conducting systematic reviews and other analyses of clinical and economic data and assessing the strength of evidence for new or existing health care technologies. Although the results of HTAs are not used exclusively to inform coverage decisions, they do provide important information for Medicare and private payers to consider during coverage deliberations. High-profile, breakthrough technologies tend to be subjects of HTAs, particularly if they are expected to have a large impact on health care or related costs. Payers use a variety of strategies for obtaining HTAs. Many larger health care plans have extensive in-house units to perform HTAs. Health care plans that do not have sufficient internal resources or expertise to conduct formal, comprehensive reviews of new technologies can purchase assessments from HTA vendors such as ECRI or HAYES, Inc. CMS has the option to request an evidence review from the Agency for Healthcare Research and Quality (AHRQ) to inform a Medicare coverage decision.

The Technology Evaluation Center (TEC) of the Blue Cross Blue Shield Association (BCBSA) and Kaiser Permanente is a major supplier of HTAs.[414] BCBSA TEC assessments are available to subscribers and often are nationally visible, serving as an important source of information to BCBS plans and other payers. Their HTAs provide health care decisionmakers with "timely, objective and scientifically rigorous assessments that synthesize the available evidence on the diagnosis, treatment, management, and prevention of disease."[415] Although TEC does not generate coverage decisions and the results are not binding on BCBS plans, individual BCBS plans and other private payers frequently use the findings of these reports in making coverage decisions.

2. Importance of Reimbursement for Adoption and Diffusion of PGx

Reimbursement will play a critical role in the future of PGx, affecting product innovation, provider adoption, and patient access, as described in detail below.[416,417]

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[414] The Blue Cross and Blue Shield Association Technology Evaluation Center has been in place since 1985. Its collaborative relationship with Kaiser Permanente began in 1993.
[415] Blue Cross Blue Shield Association Web site. Technology Evaluation Center. See http://www.bcbs.com/tec/ [accessed December 18, 2007].
[416] University of Minnesota, Center for Bioethics, Consortium on Pharmacogenetics (2002). Op. cit.
[417] Phillips KA 2004. Op. cit.

a. Influence on Innovation

As is so for other innovative health care products, the prospect for reimbursement is one of the key considerations for manufacturers when determining whether to invest in PGx product development. Although reimbursement decisions usually are made at the time of or following the appearance of a product on the market, the potential impacts of these decisions cause manufacturers and other sponsors and investors to consider reimbursement earlier in the process. If manufacturers expect that coverage will be difficult to obtain or that payment levels likely are to be inadequate for a new PGx product, they may decide not to invest in its development. If PGx product development lags due to prospects of unfavorable reimbursement, providers and patients ultimately will have access to fewer new PGx products. On the other hand, favorable prospects for reimbursement can help attract investment in PGx product development, speed adoption by providers, and accelerate product demand.

Some recommend reimbursement for health care technologies such as PGx according to the value they provide, taking into account clinical as well as economic benefits. Various arguments have been made to justify a value-based approach to reimbursement, for example:

> *One great hope for pharmacogenetics-based tests is that using genes as predictors will help us find the subset of responders or rule out those patients suffering side effects, for whom the risk-benefit ratio is unfavorable. This ratio can also be interpreted in economic terms: Clearly, those patients experiencing higher levels of benefit in relation to risk are obtaining higher value. Thus, a case can be made that the price—the reward paid to the innovator—should be higher.*[418]

Recent studies have pointed out discrepancies in the extent to which value is considered in current pricing and reimbursement determinations for drugs and diagnostics. Although pricing for new brand-name prescription drugs has been described as "somewhat value-based," reimbursement for new diagnostic tests is not regarded as being value based. Instead, new diagnostic tests are reimbursed at levels commensurate with similar existing tests, without consideration for the added value of the new test.[419] If payment systems for new diagnostic tests were changed to better reflect their value, industry might be more confident in investing in and developing new PGx products. The promise of more favorable reimbursement also might provide an incentive for manufacturers to invest more in translational research on the clinical utility and economic value of new products.[420] However, any shift to a value-based approach for diagnostic tests may require changes to the broader health care reimbursement system.

b. Influence on Provider Adoption

Payment levels also can affect provider adoption of PGx products. Although payers say that billing patterns and provider charges are the main determinants of payment level, health care providers often report that payments are not adequate to cover the cost of genetic testing.[421] If providers performing PGx tests are reimbursed inadequately, the difference between the provider's fee and the insurance payment may be shifted to the patient, or providers may take the loss.

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[418] Garrison LP Jr 2006. Op. cit.

[419] Ibid.

[420] Ramsey SD, Veenstra DL, Garrison LP Jr, et al. Toward evidence-based assessment for coverage and reimbursement of laboratory-based diagnostic and genetic tests. *Am J Manag Care* 2006. 12(4):197-202.

[421] Secretary's Advisory Committee on Genetics, Health, and Society (2004). Coverage and reimbursement of genetic technologies. Issue brief. See http://www4.od.nih.gov/oba/sacghs/reports/SACGHSPriorities.pdf [accessed January 23, 2008].

c. Influence on Patient Access

Aside from matters of innovation or provider adoption, reimbursement decisions influence patient access in other ways. If a PGx product is not covered by a health care plan, patients may not be able to access the product unless they pay for it out of pocket. Similarly, if a PGx product is covered but inadequately reimbursed, patients may have to pay the remainder of the cost. These financial hurdles may result in disparities in patient access to PGx tests and drugs according to the ability to pay.[422]

For PGx technologies with high unit (per patient) costs or high aggregate (population) costs, payers may institute cost sharing. This could discourage patients with insufficient financial resources from undergoing PGx testing. Payers also may take steps to control the use of PGx products by granting coverage for only a tightly defined set of indications or requiring prior authorization for the test to be reimbursed. The use of these cost-control strategies may limit patient access to PGx products, particularly for those with inadequate insurance.[423]

Some PGx tests may be complex and require the services of genetic counseling providers to ensure that patients understand the meaning of their test results. However, genetic counseling providers, particularly nonphysician providers, often report difficulty in obtaining adequate reimbursement for their services.[424] If genetic counseling providers are not reimbursed adequately, their services may not be widely or equitably available.

These access considerations are important to individuals with health insurance coverage, but they are magnified for those who have no health insurance coverage. The number of individuals in the United States who lack health insurance reached 46.5 million in 2006 and continues to rise. Uninsured individuals are more likely to postpone or go without needed medical care and are less likely to follow through with prescribed treatments.[425,426] Also, uninsured individuals do not benefit from discounted rates for tests and services that typically are negotiated between private payers and health care providers. Instead, they often are expected to pay the full cost of a PGx test and any prescribed medications. To the extent that PGx tests are viewed as an optional or discretionary service, those without insurance may opt not to receive these services.

3. Potential Reimbursement Challenges for PGx

The prospects for reimbursement are mediated by various factors, including the need to demonstrate the clinical value of PGx products, satisfy medical necessity requirements, and manage off-label use. These are described below.

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[422] Ibid.
[423] Goodman C, Chen C, Wu L, Villarivera C, Karnes E. *Personalized health care expert panel meeting: summary report.* U.S. Department of Health and Human Services, Office of the Assistant Secretary for Planning and Evaluation (2007). See http://aspe.hhs.gov/health/reports/07/PHC/report.pdf [accessed December 18, 2007].
[424] Secretary's Advisory Committee on Genetics, Health, and Society (2006). *Coverage and reimbursement of genetic tests and services*. Op. cit.
[425] Kaiser Family Foundation, Kaiser Commission on Medicaid and the Uninsured (2007). *The uninsured: a primer.* See http://www.kff.org/uninsured/upload/7451-03.pdf [accessed December 18, 2007].
[426] Kaiser Family Foundation, Kaiser Commission on Medicaid and the Uninsured (2007). *The uninsured and their access to health care.* See http://www.kff.org/uninsured/upload/1420_09.pdf [accessed December 18, 2007].

a. Demonstrating Clinical Utility of PGx

Developing evidence of clinical utility is a critical step in securing reimbursement for PGx technologies, as payers increasingly consider clinical effectiveness when determining whether to cover new technologies. When reviewing a new diagnostic test, payers increasingly are requiring evidence of the test's accuracy as well as its impact on diagnosis, therapeutic selection, health outcomes, and sometimes economic endpoints. More often, payers seek such evidence in the form of controlled clinical trials or other rigorous studies assessing the health outcomes or other impacts of a new test compared with the standard of care. In its 2006 report *Coverage and Reimbursement of Genetic Tests and Services*, SACGHS recommended that the HHS Secretary convene a group of experts to review evidence of a genetic test's analytical validity, clinical validity, and clinical utility to facilitate coverage decisionmaking.[427]

Establishing the impact of diagnostics can be challenging and sometimes impractical, due to the fact that various factors (e.g., use of multiple diagnostics, physicians' desire to rule out conditions, multiple treatment options) can confound these downstream effects. Furthermore, payers increasingly are interested in evidence acquired in routine or community practice, in addition to evidence gathered under more controlled conditions such as in premarket clinical studies performed to gain FDA approval. Such real-world evidence is especially important when skill level, experience, or care setting may affect the accuracy of a test or when the risk profile of the target population differs from that of the more selected or narrowly defined study population.

Current examples of payers' requirements for clinical value evidence include Aetna's nonreimbursement policies for AmpliChip® and *UGT1A1*. The AmpliChip® policy calls for RCTs to determine whether screening of patients' *CYP2D6* and *CYP2D9* genes results in fewer ADRs compared with standard monitoring methods. The policy for the Invader *UGT1A1* test notes that "the clinical value of this testing (i.e., whether testing will lead to better health outcomes) has yet to be established by prospective, randomized, controlled trials."[428]

b. Satisfying Medical Necessity Requirements

Although coverage policies designate the health care products and services for which a payer will reimburse a health care provider, payers reserve the right to determine whether the product or service is medically necessary for a given patient. Whether PGx will challenge currently accepted criteria of medical necessity remains to be seen and depends to a considerable extent on how the tests are used.

Determinations of medical necessity generally are based on a patient's diagnosis or condition and relevant coding. Definitions of medical necessity vary among payers but generally include provisions that the services (1) be appropriate; (2) alleviate a problem involving a patient's health, functioning, or well-being; (3) be in accordance with accepted medical practice; and (4) not be investigational, experimental, or educational.[429]

Medical necessity determinations are controversial, due in part to perceived variations in a health care plan's medical necessity criteria and lack of transparency in its application of the criteria.[430] Some

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[427] Secretary's Advisory Committee on Genetics, Health, and Society (2006). *Coverage and reimbursement of genetic tests and services*. Op. cit.
[428] Aetna Web site. Clinical Policy Bulletin: Pharmacogenetic Testing. Number 0715. Op. cit.
[429] Bare J. Making sense of health plan denials. *Fam Pract Manag* 2001. 8(6):39-44.
[430] Singer SJ, Bergthold LA. Prospects for improved decision making about medical necessity. *Health Aff (Millwood)* 2001. 20(1):200-6.

private payers have taken steps to enhance the transparency of decisionmaking processes. For instance, Aetna makes its coverage policies publicly available. Its clinical policy bulletins "state Aetna's policy regarding the experimental and investigational status and medical necessity of medical technologies and other services for the purposes of making coverage decisions under Aetna administered health benefit plans."[431] A multitude of State and Federal laws pertain to determinations of medical necessity. Some State laws include definitions of medical necessity, and some laws establish a process by which enrollees can appeal a health plan's decision to deny, reduce, or terminate services. At the Federal level, two primary statutes relate to medical necessity: the Employee Retirement Income Security Act of 1974 (ERISA) and the Federal Employees Health Benefit Plan (FEHBP). Under ERISA, health care plans are required to provide enrollees with written notices when a claim is denied.[432] Also, enrollees are entitled to a "full and fair review" of their denied claim.[433] Federal employees and their dependents who receive health coverage through FEHBP are eligible to have their claim reviewed if it has been denied due to failure to demonstrate medical necessity.[434]

Medical necessity determinations often start with a review of codes appearing on billing claims. The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and Current Procedural Terminology® (CPT®) are the two main coding systems used by health care providers when submitting insurance claims to health care plans. CPT® codes describe medical, surgical, and diagnostic services.[435] Currently, generic CPT® codes that describe the laboratory procedures involved in genetic testing are used for billing for PGx testing. In response to concerns that existing CPT® codes were not sufficiently detailed to describe genetic tests, a new set of modifier codes for molecular genetic tests was added for use with the generic CPT® codes. These modifier codes are intended to enable health care providers to submit more complete and specific information in their claim forms about the purpose of the genetic test. However, it is not yet apparent whether these genetic testing modifiers are enabling more accurate billing. Some anecdotal reports suggest low levels of use of these genetic testing modifiers. In addition, concerns have been raised about the specificity of genetic testing modifiers relevant to PGx. For example, one modifier refers to the *CYP2* genes but offers no way of distinguishing among *CYP2C9, CYP2D6,* or other genes within this group. Furthermore, there are concerns that the number of available genetic testing modifiers for PGx tests is not sufficient.[436,437]

ICD-9-CM is the official coding system in the United States for patient diagnoses and conditions and hospital procedures. The Institute of Medicine of the National Academy of Sciences, among other groups, has opined that the ICD-9-CM coding system may no longer be appropriate for determining medical necessity for certain health care services. In particular, some suggest that ICD-9-CM may be outdated for responding adequately to the emerging needs of health care payers and providers in an environment of rapid

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[431] Aetna Web site. Clinical Policy Bulletins (CPBs). See http://www.aetna.com/cpb/cpb_menu.html [accessed December 18, 2007].
[432] Ibid.
[433] 29 CFR 2560.503-1 - Claims Procedure. U.S. Department of Labor (2001). See http://www.dol.gov/dol/allcfr/ebsa/Title_29/Part_2560/29CFR2560.503-1.htm [accessed December 18, 2007].
[434] Substance Abuse and Mental Health Services Administration (2003). *Special report: medical necessity in private health plans*. See http://download.ncadi.samhsa.gov/ken/pdf/SMA03-3790/SMA03-3790.PDF [accessed December 18, 2007].
[435] American Medical Association Web site. CPT Process – How a Code Becomes a Code. See http://www.ama-assn.org/ama/pub/category/3882.html [accessed December 18, 2007].
[436] Ibid.
[437] Miller L. *Chapter and verse on next year's CPT code changes*. CAP Today, December 2004. See http://www.cap.org/apps/cap.portal?_nfpb=true&cntvwrPtlt_actionOverride=%2Fportlets%2FcontentViewer%2Fshow&_windowLabel=cntvwrPtlt&cntvwrPtlt%7BactionForm.contentReference%7D=cap_today%2Ffeature_stories%2F1204cptchanges.html&_state=maximized&_pageLabel=cntvwr [accessed February 3, 2007].

technological evolution.[438] With regard to PGx, some have expressed concern that the ICD-9-CM system does not sufficiently describe the diagnostic indications for use of a PGx product.[439]

c. Potential for Off-Label Use

Generally, payers will reimburse drugs prescribed in accordance with the FDA-approved indications listed in the product label. Payers also reimburse for many off-label uses, particularly for treating certain forms of cancer. Because few PGx products are currently on the market, it is uncertain the extent to which PGx information will be included in product labels for new drugs. If a drug label specifies that PGx testing must be performed prior to administration of a drug, use of the drug without the PGx test would constitute off-label use.

Although payers often cover off-label use, reimbursement is less certain when new products are used off label.[440] Indeed, payers may be justified in not providing reimbursement if peer-reviewed evidence or other data on benefits and harms associated with the intervention are not available to support such off-label use. Until an off-label use moves into the medical mainstream, as many have, providers using PGx products for off-label indications are at risk of receiving no payment or inadequate payment, or patients may have to pay out of pocket. As a result, provider adoption and patient access to the product could be affected.

4. CMS Regulatory Responsibilities: CLIA

In addition to its pivotal role in reimbursement, CMS has regulatory responsibility for laboratory tests performed "for the purpose of providing information for the diagnosis, prevention or treatment of any disease or impairment of, or the assessment of the health of, human beings".[441] CLIA gives CMS the authority to regulate laboratories that perform such tests, including PGx tests.

CLIA established standards for quality assurance, record maintenance, proficiency testing (PT), personnel qualifications/responsibilities, and quality control for all clinical laboratories that return results to patients in the United States.[442,443] CMS's CLIA program requires clinical laboratories to register with CMS and be certified by an approved accreditation body or by CMS. Certification ensures that a clinical laboratory meets certain minimal quality standards related to personnel qualifications, quality control procedures, and PT.[444] CLIA requirements for laboratory certification depend on the complexity of the tests performed; the more complex the test, the more stringent the requirements. There are specific requirements for laboratories that perform tests in certain specialty areas such as microbiology and cytogenetics.

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[438] Wolman DM, Kalfoglou AL, Leroy L. *Medicare laboratory payment policy now and in the future*. Institute of Medicine, Committee on Medicare Payment Methodology for Clinical Laboratory Services (2000). See http://www.iom.edu/report.asp?id=5547 [accessed December 18, 2007].
[439] Williams MS (2007). *Comments on realizing the promise of pharmacogenomics: opportunities and challenges* (public comment draft).
[440] Biotechnology Industry Organization (2005). *Off-label use of anticancer therapies: physician prescribing trends and the impact of payer coverage policy.* See http://www.bio.org/speeches/pubs/CovanceReport.pdf [accessed December 18, 2007].
[441] Centers for Medicare & Medicaid Services Web site. How to Apply for a CLIA Certificate, Including Foreign Laboratories. See http://www.cms.hhs.gov/CLIA/06_How_to_Apply_for_a_CLIA_Certificate,_Including_Foreign_Laboratories.asp [accessed December 18, 2007].
[442] Centers for Medicare & Medicaid Services Web site. CLIA Program. See http://www.cms.hhs.gov/clia/ [accessed December 18, 2007].
[443] Centers for Medicare & Medicaid Services (2007). *Comments on realizing the promise of pharmacogenomics: opportunities and challenges* (public comment draft).
[444] Borchardt PE 2006. Op. cit.

FDA has been involved with CLIA since 2000, when it assumed responsibility for categorizing the complexity level of certain diagnostic tests.[445] LDTs also are subject to relevant FTC regulations for marketing.

CLIA's oversight of genetic tests has been the subject of considerable debate. Over the years, the National Institutes of Health-U.S. Department of Energy Task Force on Genetic Testing, Clinical Laboratory Improvement Advisory Committee, and Secretary's Advisory Committee on Genetic Testing all have called for the establishment of a CLIA specialty area on genetic testing that would create criteria for establishing analytical and clinical validity and require PT.[446,447,448] More recently, SACGHS concluded in its report *U.S. System of Oversight of Genetic Testing: A Response to the Charge of the Secretary of Health and Human Services* that gaps in the oversight of genetic testing laboratories can be addressed without the creation of a genetic testing specialty. Instead, SACGHS recommends that CMS require PT when there is a PT program available for the test; for tests without a PT program, laboratories should use alternative assessment methods. The report also includes a number of recommendations related to the collection, assessment, and dissemination of analytical validity, clinical validity, and clinical utility data.[449]

D. Clinical Practice Guidelines Developers

Once PGx products reach the market, the developers of clinical practice guidelines play an important role in facilitating product adoption and diffusion. These gatekeepers interpret medical evidence, apply clinical judgment, and develop actionable recommendations to help guide patient health care decisions. As described in more detail in Chapter IV. Implementation of PGx To Improve Outcomes in Clinical Practice and Public Health, providers and payers often refer to these guidelines, especially for new technologies.

Evidence-based guidelines will help providers determine when to order PGx tests and which drugs should be prescribed and at what dose and will help payers determine whether PGx use should be reimbursed.[450] They also can serve as an authoritative standard in the context of professional liability, conventional medical practice, and FDA-approved labeling.[451,452]

Medical professional organizations (e.g., American Society of Clinical Oncology [ASCO], College of American Pathologists [CAP], National Comprehensive Cancer Network [NCCN]) and authoritative governmental bodies (e.g., U.S. Preventive Services Task Force, Evaluation of Genomic Applications in Practice and Prevention Initiative) have roles to play in developing practice guidelines for the use of PGx. In addition, initiatives such as the AHRQ National Guideline Clearinghouse® help assemble and qualify

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[445] FDA Web site. CLIA – Clinical Laboratory Improvement Amendments. See http://www.fda.gov/cdrh/clia/index.html [accessed December 18, 2007].
[446] NIH-DOE Task Force on Genetic Testing (1997). *Promoting safe and effective genetic testing in the United States*. See http://www.genome.gov/10001733 [accessed March 31, 2008].
[447] Clinical Laboratory Improvement Advisory Committee (2001). Summary of CLIAC meeting. February 7-8, 2001. See http://wwwn.cdc.gov/cliac/cliac0201.aspx [accessed March 31, 2008].
[448] Secretary's Advisory Committee on Genetic Testing (2000). *Enhancing the oversight of genetic tests: recommendations of the Secretary's Advisory Committee on Genetic Testing*. Draft report. See http://www4.od.nih.gov/oba/sacgt/reports/oversight_report.pdf [accessed on March 31, 2008].
[449] Secretary's Advisory Committee on Genetic Testing (2008). *U.S. system of oversight of genetic testing: SACGHS's response to the charge of the Secretary of HHS*. See http://www4.od.nih.gov/oba/SACGHS/reports/SACGHS_oversight_report.pdf [accessed May 1, 2008].
[450] Phillips KA 2004. Op. cit.
[451] Rothstein MA 2001. Op. cit.
[452] Secretary's Advisory Committee on Genetics, Health, and Society (2006). Transcript of 9th meeting, March 27, 2006. Op. cit.

evidence-based guidelines and related documents and make them accessible through searchable databases.[453] Outside of the United States, agencies such as the National Institute for Health and Clinical Excellence in the United Kingdom provide guidance regarding proper use of prescription medications and PGx tests.[454]

Because PGx is still an emerging field, few evidence-based practice guidelines currently exist for PGx products.[455] ASCO, NCCN, and CAP have published guidelines on *HER2/neu* testing and the use of tumor markers in gastrointestinal and breast cancers.[456,457,458,459] A group of physicians has published guidelines on the use of PGx testing for CYP450 polymorphisms in psychiatry.[460] The National Academy of Clinical Biochemistry drafted guidelines and recommendations on the laboratory analysis and application of PGx in clinical practice.[461]

A report of the Genetics and Public Policy Center addresses the importance of practice guidelines for the successful integration of genetic testing into practice.[462] The report notes the critical role played by health care provider organizations and other stakeholders in developing guidelines. Instead of the prevailing "piecemeal approach" to guidelines development, it proposes a more centralized mechanism, a sustainable source of funding, and support from the Federal Government.

The four types of gatekeepers described in this chapter play complementary roles in enabling the use of new medical technologies in clinical practice. There will be a continued need for guidance from FDA, CMS, and other agencies regarding how PGx products will be regulated, used in practice, and reimbursed and how PGx data may be used in health care decisionmaking, employment, insurance, and other sectors. The degree of openness and transparency displayed by these agencies regarding PGx will influence the willingness of innovators and manufacturers to invest in the development of new PGx products, the public's view of these products, and patients' access to them. The following chapter describes in more detail the factors and challenges associated with implementation of PGx in clinical practice and public health.

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[453] Agency for Healthcare Research and Quality, National Guideline Clearinghouse Web site. About NGC. See http://www.guideline.gov/about/about.aspx [accessed December 18, 2007].
[454] Nuffield Council on Bioethics (2003). Op. cit.
[455] Hampton T. Researchers draft guidelines for clinical use of pharmacogenomics. *JAMA* 2006. 296(12):1453-4.
[456] Wolff AC 2007. Op. cit.
[457] Locker GY, Hamilton S, Harris J, et al. ASCO 2006 update of recommendations for the use of tumor markers in gastrointestinal cancer. *J Clin Oncol* 2006. 24(33):5313-27.
[458] Harris L, Fritsche H, Mennel R, et al. American Society of Clinical Oncology 2007 update of recommendation for the use of tumor markers in breast cancer. *J Clin Oncol* 2007. 25(33):5287-12.
[459] National Comprehensive Cancer Network (2008). *NCCN Clinical Practice Guidelines in Oncology: Breast Cancer*, v.2.2008. See http://www.nccn.org/professionals/physician_gls/PDF/breast.pdf [accessed May 3, 2008].
[460] de Leon J, Armstrong SC, Cozza KL. Clinical guidelines for psychiatrists for the use of pharmacogenetic testing for CYP450 2D6 and CYP450 2C19. *Psychosomatics* 2006. 47(1):75-85.
[461] The National Academy of Clinical Biochemistry (2006). *Guidelines and recommendations for laboratory analysis and application of pharmacogenetics to clinical practice.* See http://www.aacc.org/AACC/members/nacb/LMPG/OnlineGuide/DraftGuidelines/Pharmacogenetics/ [accessed December 18, 2007].
[462] Genetics and Public Policy Center (2006). *Genetic testing practice guidelines: translating genetic discoveries into clinical care*. See http://www.dnapolicy.org/resources/Genetic_Testing_Practice_Guideslines.pdf [accessed December 18, 2007].

IV. Implementation of PGx To Improve Outcomes in Clinical Practice and Public Health

The implementation of PGx in clinical practice and public health should enable the provision of more personalized and effective health care. However, there are many challenges inherent in integrating PGx into the health care and public health systems. Thus, realizing the potential benefits of PGx depends on many factors. The following sections highlight the importance of education and guidance for health care providers, decisionmakers, and patients; information technology (IT); emerging economic implications of PGx technologies; ethical, legal, and social issues (ELSI) specific to the clinical implementation of PGx; and the need for coordination of U.S. Department of Health and Human Services (HHS) activities related to PGx.

A. Education and Guidance

Educational initiatives help patients know when to seek treatment, health care providers know what health care is available and most appropriate for a given patient and how to administer treatment, and other health care stakeholders build the infrastructure and set policies to support the adoption and use of this infrastructure in clinical practice and public health. As PGx tests and associated therapies become more widely available, it will be necessary to educate health care providers, patients, payers, and policymakers to support informed decisionmaking.[463,464]

1. Health Care Providers

Health care providers, including physicians, nurses, pharmacists, and other professionals, will play important roles in implementing PGx in routine clinical practice. Although a range of health care providers likely will be involved in the delivery of PGx tests and services, those with prescribing ability (e.g., physicians, nurse practitioners, physician assistants) will have a particularly important role in introducing PGx into patient care. Education and training in PGx for these and other health care providers will help ensure that PGx technologies are used appropriately and effectively. These health care professionals will need information on PGx to provide accurate information to patients, make health care decisions, interpret PGx test results, and provide or refer patients to counseling.[465] When health care providers recommend PGx testing, they will need to consider PGx test results along with costs, patient preferences, and other patient-related factors (e.g., possible drug interactions) to determine the best course of treatment.[466,467]

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[463] Frueh FW, Gurwitz D. From pharmacogenetics to personalized medicine: a vital need for educating health professionals and the community. *Pharmacogenomics* 2004. 5(5):571-9.
[464] Nuffield Council on Bioethics (2003). Op. cit.
[465] Phillips KA 2004. Op. cit.
[466] Burke W 2002. Op. cit.
[467] Melzer D 2003. Op. cit.

The incorporation of PGx testing and therapies into clinical practice will depend on acceptance by physicians, who are faced with complex concerns regarding the benefits, risks, and costs of PGx.[468] Primary care physicians may be reluctant to incorporate new PGx tests into routine clinical practice, due to their overwhelming clinical responsibilities, unfamiliarity with the tests and the interpretation of their results, and uncertainty regarding payment for the administration of the tests. All health care providers are challenged with maintaining currency about what tests are available, their validity and effectiveness, which patients are good candidates for testing, and how test results should inform therapeutic decisions.

Clinicians also must secure informed consent for genetic testing and, in some cases, arrange counseling. PGx tests may reveal unrelated or unanticipated information in addition to the test result originally sought. For example, some drug-metabolizing enzymes identified by PGx diagnostics also interact with environmental toxins; consequently, test results might reveal susceptibility to certain cancers.[469] The psychological effects of such a revelation can be considerable. As such, health care providers offering diagnostic testing with the potential to reveal damaging secondary information are advised to ensure that the test is performed at a certified laboratory to ensure test accuracy. They also are advised to counsel patients about the possible risks and benefits of PGx testing or refer them to a trained genetic counseling provider.

The complex informational needs of clinicians pose two challenges. First, current understanding of the various factors that may influence clinical outcomes is limited. Second, many clinicians currently do not possess the knowledge to interpret PGx information.[470] Some evidence suggests that drug labels may not contain sufficient information for clinicians to make clinical decisions based on PGx test results. A recent review found available PGx information on drug labels to be inadequate for making treatment decisions. Also, dosing recommendations based on PGx test results are not well established.[471] The ability to overcome these challenges will affect the practical utility of PGx.

Some observers have called for professional organizations to play an active role in encouraging and facilitating education and training in PGx.[472] The National Coalition for Health Professional Education in Genetics (NCHPEG) promotes "health professional education and access to information about advances in human genetics to improve the health care of the nation." Under contract to the Health Resources and Services Administration (HRSA), the National Human Genome Research Institute, and the NIH Office of Rare Diseases, NCHPEG coordinates genetic education programs for health care professionals. In 2005, NCHPEG worked with the American Academy of Family Physicians to develop a series of Web-based continuing medical education (CME) programs on genetically influenced health conditions. NCHPEG also has developed a set of core competencies to help guide the development of educational initiatives in genetics and genetic-based health care.[473,474]

The Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) has recommended that health care providers receive broad training about how to integrate genetics into their practices. Efforts to facilitate this training could include the development of educational models to help health care professionals

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[468] Suther S, Goodson P. Barriers to the provision of genetic services by primary care physicians: a systematic review of the literature. *Genet Med* 2003. 5(2):70-6.
[469] Nuffield Council on Bioethics (2003). Op. cit.
[470] University of Minnesota, Center for Bioethics, Consortium on Pharmacogenetics (2002). Op. cit.
[471] Phillips KA 2005. Op. cit.
[472] Hopkins MM 2006. Op. cit.
[473] National Coalition for Health Professional Education in Genetics Web site. *Core Competencies in Genetics for Health Professionals*, 2007. See http://www.nchpeg.org/core/Core_Comps_English_2007.pdf [accessed May 3, 2008].
[474] American Academy of Family Physicians Web site. Annual Clinical Focus 2005 Genomics. See http://www.aafp.org/online/en/home/clinical/acf/genomics.html [accessed December 18, 2007].

understand the benefits, application, and ELSI components of genetics.[475] The American Medical Association and the Food and Drug Administration (FDA) have developed the online CME course *Pharmacogenomics and Personalized Medicine*, which explains PGx and the influence of patients' genetic backgrounds on drug responses. The program describes how to use PGx information included in drug labels and highlights clinical examples of drug mechanisms that are genetically influenced.[476]

In addition to educating and training practicing clinicians, it is necessary to incorporate PGx education into medical school curricula.[477] Although not specific to PGx, the Association of American Medical Colleges (AAMC) recognizes the increasing importance of clinical training in genetics. As part of its Medical School Objectives Project, AAMC has outlined specific recommendations on the attitudes, knowledge, and core skills that graduating medical students should achieve in genetics as well as future genetics-focused educational needs in residency and practice.[478] The Accreditation Council for Graduate Medical Education, which is responsible for accrediting post-MD medical training programs, outlines common requirements for graduate programs in molecular genetics, including curriculum requirements and core competencies.[479]

Other health care professionals, such as pharmacists, PharmDs, and laboratory personnel, also will need greater understanding of PGx.[480,481] Although pharmacy students receive some instruction in PGx, it is uncertain whether the amount of instruction is adequate.[482] The American Association of Colleges of Pharmacy (AACP) is providing evidence-based materials on PGx to pharmacy students and practicing pharmacists. As part of its Web-based Curricular Resource Center, AACP provides access to materials related to genetics and to PGx in particular.[483] The American College of Clinical Pharmacy provides continuing education credit for pharmacists who complete a course on the applications of PGx to patient health care.[484]

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[475] Secretary's Advisory Committee on Genetics, Health, and Society (2004). *Resolution of the Secretary's Advisory Committee on Genetics, Health, and Society on genetics education and training of health professionals*. See http://www4.od.nih.gov/oba/sacghs/reports/EducationResolutionJune04.pdf [accessed December 18, 2007].

[476] American Medical Association Web site. Web-based CME Course Introduces Pharmacogenomics. See http://www.ama-assn.org/ama/pub/category/17787.html#Story3 [accessed December 18, 2007].

[477] PricewaterhouseCoopers (2005). Op. cit.

[478] Association of American of Medical Colleges Web site. Medical School Objectives Project. See http://www.aamc.org/meded/msop/start.htm [accessed December 18, 2007].

[479] Accreditation Council for Graduate Medical Education Web site. Molecular Genetics Program Requirements. See http://www.acgme.org/acWebsite/RRC_130/130_prIndex.asp [accessed December 18, 2007].

[480] Nuffield Council on Bioethics (2003). Op. cit.

[481] University of Minnesota, Center for Bioethics, Consortium on Pharmacogenetics (2002). Op. cit.

[482] Brock TP, Faulkner CM, Williams DM, Smith SR. Continuing-education programs in pharmacogenomics for pharmacists. *Am J Health Sys Pharm* 2002. 59(8):722-5.

[483] American Association of Colleges of Pharmacy Web site. Curricular Resource Center: Pharmacogenomics. See http://www.aacp.org/site/page.asp?TRACKID=&VID=1&CID=1039&DID=6100 [accessed December 18, 2007].

[484] American College of Pharmacy Web site. Pharmacogenomics: Applications to Patient Care. See http://www.accp.com/strphgen.php [accessed December 18, 2007].

Recommendations 10A and 10B

Health providers will need guidance on how to use PGx information when making clinical decisions. The following steps will help ensure that PGx technologies are effectively integrated into clinical practice:

10A. HHS should assist other Federal agencies, State agencies, and private sector organizations in the development, cataloging, and dissemination of case studies and practice models relating to the use of PGx technologies.

10B. HHS should assist professional organizations in their efforts to help their members achieve competencies on the appropriate use of PGx technologies. HHS also should encourage and facilitate collaborations between the organizations and the Federal Government around these activities.

a. Clinical Practice and Dosing Guidelines

The development of clinical practice and dosing guidelines is vital for the successful and effective integration of PGx technologies into clinical practice and public health. Guidelines are an important means of educating clinicians, pharmacists, prescribing nurses, and patients about when PGx testing could be beneficial and how the test results should be used to inform treatment decisions.[485] Guidelines should be based on the current, best available evidence and on expert consensus (although not necessarily unanimity) to be accepted by those involved in health care delivery.[486] Agreement on PGx guidelines will be a challenge for guidelines developers due to the complexity and emerging, evolving nature of the field.

Few PGx guidelines are currently available for a number of reasons, including the relatively few available PGx tests and the limited evidence to support recommendations or guidance on how to use PGx test results to inform treatment decisions. Until evidence to inform the development of clinical practice guidelines becomes more abundant, such guidelines will not be a primary tool for educating health care providers about PGx. The lack of practice guidelines will continue to affect the willingness of providers to offer PGx testing to their patients (see discussion of clinical practice guidelines in Chapter III. Gatekeepers).

[485] The Royal Society (2005). Op. cit.

[486] Grol R, Dalhuijsen J, Thomas S, et al. Attributes of clinical guidelines that influence use of guidelines in general practice: observational study. *BMJ* 1998. 317(7162):858-61.

Recommendations 10C, 10D, 10E, and 10F

10C. As evidence of clinical validity and clinical utility for a PGx technology accrues, HHS should support the conduct of systematic reviews and technology assessments to summarize the evidence base. These systematic reviews and technology assessments should be disseminated to facilitate the development of clinical practice guidelines.

10D. HHS should facilitate the development of evidence-based clinical practice guidelines and dosing guidelines by supporting consensus-building efforts among guidelines developers. These consensus-building efforts should include development of standards that define the minimal levels of evidence required to support guideline decisions. These standards should take into account the clinical contexts (e.g., prevention, diagnosis, treatment) in which the PGx test may be offered.

10E. To inform the development of PGx test and dosing guidelines, HHS should fund clinical studies that provide evidence on whether PGx information is clinically useful.

10F. The HHS Secretary should encourage organizations to submit clinical practice guidelines on PGx testing to AHRQ's National Guideline Clearinghouse to facilitate dissemination and encourage their implementation and use.

b. Product Labeling

As part of its role in approving and clearing new health care products for market, FDA reviews and approves drug and diagnostics labels to guide their use in clinical practice. Drug labels describe the approved indications for use and may specify dosing, contraindications, or other important instructions. Inclusion of genotypic information in drug labels can enhance their value to health care providers.

Two recent FDA guidance documents provide information on the labeling of PGx products. In the 2003 draft guidance on PGx data submissions, FDA describes two main approaches to integrating PGx data into drug labeling: (1) including the data in the drug label on an informational basis and (2) specifying that dose selection or drug safety or effectiveness is contingent on the performance of a PGx test. In the first approach, the label is less restrictive and may be appropriate if the PGx test does not involve a validated biomarker or if an FDA-approved or widely used commercial PGx test is not available. In the second approach, the label is more restrictive and would be based on data from clinical trials in which (1) patients were tested for drug metabolism genotype and dosed according to their test results, (2) patients were enrolled in the trial based on their genotype or gene expression profile, or (3) patients were excluded from the trial based on their genotype or gene expression profile (e.g., because they had markers indicating high risk for an adverse event [AE]).[487] The 2006 draft guidance on PGx and genetic tests specifies that proposed label content should include directions for use; instructions for interpretation of results; information on stability (i.e., shelf life), performance (e.g., sensitivity, specificity), quality control, and precautions; and in the case of PGx tests, testing limitations for drug-metabolizing enzyme alleles.[488]

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[487] Food and Drug Administration (2003). *Draft guidance for industry: pharmacogenomic data submissions*. See http://www.fda.gov/cder/guidance/5900dft.pdf [accessed December 18, 2007].

[488] Food and Drug Administration (2006). *Draft guidance for industry and FDA staff: pharmacogenetic tests and genetic tests for heritable markers*. Op. cit.

In addition to these guidances, FDA is planning to release a new guidance pertaining to genetic information in drug labels. According to an FDA official in February 2007, the agency will introduce a new format for drug labels that will include a PGx section and relevant genetic information in a prominently displayed box.[489] The details of this guidance are uncertain, but its release likely will represent an important development for the labeling of PGx products. FDA also has published a table of valid genomic biomarkers that are mentioned in the labels of FDA-approved drugs and that lists the multiple regulatory contexts in which they were approved.[490]

Currently, there are more than 20 approved drugs for which reference is made to PGx testing in the drug label or package insert; examples include Herceptin® and Gleevec®.[491] A study published in 2006 found that PGx-based prescribing information is available in the published research literature for more than 70 percent of the top 200 most frequently prescribed drugs. However, after examining the package inserts of these drugs, researchers found that only three contained PGx-based prescribing information to help guide treatment decisions.[492] Another study analyzed 3,382 drug package inserts to determine how many contained PGx information and, of those with PGx information, what type of information was included. Only 76 (2 percent) contained PGx information; of these inserts, only 25 contained PGx information sufficient enough to inform treatment decisions.[493] The investigators concluded that PGx-related data are available in package inserts for only a small number of FDA-approved drugs and that the information they contain is insufficient to inform clinical practice.

As more PGx test data are obtained and their predictive power and reliability are established, information about PGx tests may be incorporated into drug labels more frequently.[494] FDA will need to consider the available evidence for diagnostics and drugs and their risk-benefit profile when determining how to present PGx information in labels. For example, a drug-response genotype could be listed as a contraindication, a warning, or a precaution for prescribing a drug. Depending on the drug and available evidence, a drugmaker may seek labeling that expresses the need for a PGx test as a precaution rather than as a more explicit requirement. This inclination may depend on apparent tradeoffs for expanding the use of a drug and concerns about legal liability in the event patients experience adverse drug reactions (ADRs).[495]

In the labeling of PGx products, there are also practical and statutory challenges. First, as the recent FDA guidances indicate, it is critical to have evidence that supports the predictive value of the PGx test and/or the benefit of genetically based dosing. In the cases of *TPMT* testing for 6-mercaptopurine sensitivity and *UGT1A1* testing for hyperbilirubinemia, the absence of substantial prospective data on clinical outcomes was a significant barrier to recommending PGx testing in drug labels.[496] Another challenge is the uncertainty regarding FDA's statutory authority to mandate cross-labeling of PGx tests and drugs. Even if FDA does

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[489] GenomeWeb Web site. GenomeWeb Daily News, February 28, 2007, Ray T. New FDA Guidance Will Make Genetic Data More Prominent in Drug Labels. See http://www.genomeweb.com/issues/news/138673-1.html [accessed December 18, 2007].
[490] FDA Web site. Table of Valid Genomic Biomarkers in the Context of Approved Drug Labels. See http://www.fda.gov/cder/genomics/genomic_biomarkers_table.htm [Accessed January 10, 2008].
[491] The Royal Society (2005). Op. cit.
[492] Zineh I, Pebanco GD, Aquilante CL, et al. Discordance between availability of pharmacogenetics studies and pharmacogenetics-based prescribing information for the top 200 drugs. *Ann Pharmacother* 2006;40(4):639-44.
[493] Zineh I, Gerhard T, Aquilante CL, et al. Availability of pharmacogenomics-based prescribing information in drug package inserts for currently approved drugs. *Pharmacogenomics J* 2004. 4(6):354-8.
[494] Robertson JA 2002. Op. cit.
[495] Ibid.
[496] Haga SB 2006. Op. cit.

have this authority, there is concern that current FDA processes for validating and amending claims in drug labels could be too slow and too costly to keep up with advances in the PGx field.[497]

Physicians can prescribe an FDA-approved product for off-label indications based on their professional medical judgment. Off-label use can include prescribing a drug to patients for indications that were not tested in clinical trials, to patient populations that were not represented in the study sample, or to contraindicated subpopulations. Prescribing a drug without performing a required PGx test also can constitute off-label use. Some regulators are concerned that off-label use may hinder the safe diffusion of PGx products.[498] Although payers cover particular instances of off-label use, such as for certain oncology regimens, reimbursement for off-label use can be unpredictable.[499]

The medical and ELSI consequences of off-label use of PGx products may be more complex than in other cases of off-label drug use.[500] Physicians who prescribe a drug without performing the requisite PGx test may be putting themselves at greater risk for any ADRs or other AEs that occur. Alternatively, patients may ask for and receive a drug without obtaining the required PGx test. If their PGx test results do not indicate use of the drug and they subsequently suffer an ADR, it is uncertain whether the prescribing clinician would be liable.[501] Given that off-label use of PGx products occurs and could become prevalent, exploring its implications may be important for ensuring patient safety.

Readily available information can support prescribing decisions. In an effort to keep label information current and easily accessible, FDA and the National Institutes of Health (NIH) initiated the DailyMed project. Available in Web-based and downloadable formats, DailyMed includes FDA-approved package inserts and medication content information. This open, paperless resource is available to health care providers and the public.[502,503]

Recommendations 10G and 10H

10G. FDA should work with manufacturers to ensure that all relevant PGx information is included in drug labels in a timely manner. When a PGx test is mentioned in a drug label, information should be included about the test's analytical validity, clinical validity, clinical utility, dosing, AEs, and/or drug selection for clinicians to use when making treatment decisions based on PGx test results. FDA should provide guidance on the standards of evidence that must be met for PGx information to be included in the label.

10H. NIH and FDA should continue expanding the Internet-based DailyMed project, which provides up-to-date, real-time prescription drug label/package insert information to individuals who have Internet access. To ensure that all sectors of the public have access to this information, NIH and FDA should develop additional ways to disseminate this information.

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[497] Evans BJ. What will it take to reap the clinical benefits of pharmacogenomics? *Food Drug Law J* 2006. 61(4):753-94.
[498] Melzer D 2003. Op. cit.
[499] Biotechnology Industry Organization (2005). *Off-label use of anticancer therapies: physician prescribing trends and the impact of payer coverage policy.* See http://www.bio.org/speeches/pubs/CovanceReport.pdf [accessed December 19, 2007].
[500] Evans BJ 2006. Op. cit.
[501] The Royal Society (2005). Op. cit.
[502] NIH Web site. About DailyMed. See http://dailymed.nlm.nih.gov/dailymed/about.cfm [accessed December 19, 2007].
[503] FDA Web site. DailyMed Initiative Enhancing Patient Safety Through Accessible Medical Information. See http://www.fda.gov/cder/regulatory/ersr/2003_02_13_dailymed/index.htm [accessed December 19, 2007].

2. Other Health Care Decisionmakers

Efforts to educate other health care decisionmakers, including policymakers, government officials, and others, also are important for realizing the potential of PGx.[504] Among the many challenges for FDA, institutional review boards, and other regulatory bodies is having adequate in-house expertise in PGx to inform the application of PGx to existing regulations and guidance, perceive when new guidance and/or regulations are needed, interact with the pharmaceutical and biotechnology industries, and understand and regulate the use of PGx technologies in clinical trials. Limited awareness and understanding of the health, economic, and social impacts of PGx by these decisionmakers could negatively affect the development and use of these technologies.

For payers, access to PGx expertise will be necessary for making evidence-based coverage decisions and medical necessity determinations. As is the case for other types of health care technologies, payers influence one another within and beyond their respective markets and beneficiary populations. Raising the level of awareness of PGx among key decisionmakers at the Centers for Medicare & Medicaid Services (CMS), large State Medicaid programs, the Veterans Health Administration (VHA), and major national and regional private health care plans will result in broader awareness of PGx among other U.S. payers.

The Personalized Medicine Coalition (PMC) is a nonprofit umbrella organization that comprises pharmaceutical, biotechnology, diagnostic, and IT companies; health care providers and payers; patient advocacy groups; industry policy organizations; major academic institutions; and government agencies. PMC aims to educate "policymakers, government officials and private sector health care leaders about the public and personal health benefits of personalized medicine" and "the interrelated issues that it raises, in a way that avoids duplication of efforts and leverages their activities."[505]

3. Patients and the Public

As PGx products become available, patients will need to be educated about diagnostic and treatment options to help them make informed decisions. Information on PGx from authoritative sources has been tailored to the public and can be found readily on the Internet. For example, NIH provides online materials that help educate the public about personalized medicine.[506] Still, health care providers must be able to explain much of this information to patients. Just as clinicians provide information and consultation to patients regarding genetic tests, they will need to be equipped and ready to convey information about PGx tests, discuss treatment options based on PGx test results, obtain informed consent, and address confidentiality concerns.[507]

Patient perceptions will influence the extent and pace of uptake of PGx. Most patient preference research to date generally has shown that patient concerns about PGx testing focus on their limited predictive value, cost, lack of effective treatment options for those testing positive, privacy and discrimination, and impact on quality of life.[508] There is little evidence regarding the willingness of patients to make higher out-of-

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[504] Lesko LJ 2004. Op. cit.

[505] Personalized Medicine Coalition. Personalized Medicine Coalition Fact Sheet. See http://www.personalizedmedicinecoalition.org/communications/pmc_factsheet.pdf [accessed April 12, 2008].

[506] National Institute of General Medical Sciences (2005). *Medicines for you: studying how your genes can make a difference*. See http://publications.nigms.nih.gov/medsforyou/index.html [accessed December 19, 2007].

[507] Nuffield Council on Bioethics (2003). Op. cit.

[508] Lerman C, Hughes C, Trock BJ, et al. Genetic testing in families with hereditary nonpolyposis colon cancer. *JAMA* 1999. 281(17):1618-22.

pocket payments for genetic testing or for individualized drug therapies. A 1999 poll found that 66 percent of respondents would pay extra for a "genetically customized drug that you knew would work for you."[509] More systematic research with patients involved in health care choices should provide greater insights into patient preferences that are likely to affect demand, particularly in situations where PGx test results reveal only modest increases in risk for ADRs.

Recommendations 11A and 11B

11A. To inform the public about the availability, benefits, risks and limitations of PGx technologies, HHS should ensure that credible educational resources are widely available through Federal Web sites and other media.

11B. HHS should use existing public consultation mechanisms to stimulate dialog on the potential benefits, risks, and limitations of PGx technologies. This dialog should include an assessment of the public's perceptions of and receptiveness to PGx and the public's willingness to use these technologies and participate in PGx studies.

a. Marketing PGx to Consumers

Some PGx tests will evolve into over-the-counter (OTC) products that can be acquired at retail pharmacies and drugstores, via mail, or over the Internet. This raises concerns about whether consumers will know when testing is appropriate, how to acquire the test in a timely and secure manner, how to administer the test, how to interpret the results, and what to do with the results.

When using OTC PGx products, consumers may be put in the position of making personal health decisions without professional guidance. Many consumers may rely on packaging and other materials to inform their health care choices, highlighting the importance of accurate, simply stated marketing materials.[510] Some groups have expressed concern that inaccurate or overstated marketing materials may increase the demand for tests that may have little or no benefit.[511] Others are worried about the potential for misinterpretation of PGx test results and misinformed consumer health care decisionmaking, which could result in patients discontinuing a drug regimen or altering the dosage without consulting a health care professional. These concerns have fueled a debate over whether OTC sales are safe and ethical for PGx products.[512,513,514]

Consumers who are armed with information from OTC PGx tests and consumer-oriented information about prescription drugs may approach clinicians with requests for specific drugs.[515] Such scenarios emphasize the increasing importance of educating and training health care providers and the public about PGx. Consumer demand for OTC PGx products is likely to grow as more of these products reach the market.[516]

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[509] Gorman C. Drugs by design. *Time Magazine*. January 11, 1999. 1-3.
[510] Secretary's Advisory Committee on Genetics, Health, and Society (2004). *A roadmap for the integration of genetics and genomics into health and society.* See http://www4.od.nih.gov/oba/sacghs/reports/SACGHSPriorities.pdf [accessed December 19, 2007].
[511] Gollust SE, Hull SC, Wilfond BS. Limitations of direct-to-customer advertising for clinical genetic testing. *JAMA* 2002. 288(14):1762-7.
[512] Phillips KA, Flatt SJ, Morrison KR, Coates TJ. Potential use of home HIV testing. *N Engl J Med* 1995. 332(19):1308-10.
[513] Gollust SE 2002. Op. cit.
[514] Zitner A. Firms sell gene tests directly to public. *Los Angeles Times*. August 11, 2002. A1.
[515] Rosenthal MB, Berndt ER, Donohue JM, Frank RG, Epstein AM. Promotion of prescription drugs to consumers. *N Engl J Med* 2002. 346(7):498-505.
[516] Gollust SE 2002. Op. cit.

Some evidence suggests that patient demand for genetic tests may be greater for making drug prescribing decisions than for assessing disease risk. Results from the 2000 National Health Interview Survey showed that only 1 percent of respondents reported having had a genetic test for cancer risk.[517] In contrast, there has been strong patient demand and advocacy for access to Herceptin® and for expedited FDA approval of the indications for metastatic and recurrent disease.[518,519]

The increase in OTC use and consumer access to PGx tests without health care provider involvement also highlights concerns about direct-to-consumer (DTC) advertising. Many Web sites already advertise and offer genetic testing to consumers for many applications, from testing for specific drug-metabolizing enzymes to genetic testing for tailored nutritional advice.[520] Projecting from the considerable influence of DTC advertising on the demand for prescription drugs, an increase in DTC advertising for PGx testing could have a substantial effect on patient demand.[521,522,523]

Currently, DTC advertising for health care products is subject to regulation by FDA and the Federal Trade Commission (FTC). However, DTC advertisements for PGx products are not regulated stringently by either of these Federal agencies, and FDA does not appear to have sufficient resources to focus efforts in this area.[524,525,526] To ensure that OTC PGx products are used safely and appropriately, some have called on FDA to examine the regulatory issues associated with DTC marketing of genetic tests and have suggested that new types of regulation may be necessary. In a 2004 letter to the HHS Secretary, SACGHS called for enhanced collaboration between FTC and FDA in addressing the oversight of advertising for genetic tests. It also asked for clarification of FDA's role in monitoring the advertising of laboratory-developed tests and called for an analysis of the public health impact of DTC advertising of and OTC access to genetic tests. As a result of the letter, two interagency work groups were formed. The first, involving FDA, FTC, the Centers for Disease Control and Prevention (CDC), and NIH, provided a forum for these agencies to assess the scientific accuracy of claims made about genetic tests advertised directly to consumers. The second work group, composed of representatives of FDA, CDC, NIH, and HRSA, sought data on the public health impact of DTC marketing of genetic tests. In 2006, CDC included questions about public awareness of DTC genetic tests in its national DocStyles and HealthStyles surveys as well as in three States' Behavioral Risk Factor Surveillance System (BRFSS) surveys. The BRFSS surveys, which are administered to a random sample of State residents, found that 14 percent of respondents were aware of genetic tests being offered directly to consumers but that less than 1 percent had purchased one. Among health care providers responding to the DocStyles survey, about half were aware of genetic tests offered directly to consumers.[527]

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[517] National Center for Health Statistics (2000). 2000 National Health Interview Survey, sample adult person section—public use. See ftp://ftp.cdc.gov/pub/Health_Statistics/NCHS/Dataset_Documentation/NHIS/2000/samaDult.pdf [accessed December 19, 2007].

[518] Friend T. Dying patients plead for unproven cancer drugs. *USA Today*. May 16, 2001. D.09.

[519] Kondro W, Sibbald B. Patient demand and politics push Herceptin forward. *CMAJ* 2005. 173(4):347-8.

[520] Genelex Web site. Health and DNA. See http://www.healthanddna.com [accessed December 19, 2007].

[521] Gollust SE 2002. Op. cit.

[522] Pearson H. At-home DNA tests are here. *The Wall Street Journal*. June 25, 2002. D6.

[523] Rosenthal MB 2002. Op. cit.

[524] Secretary's Advisory Committee on Genetics, Health, and Society (2004). *A roadmap for the integration of genetics and genomics into health and society*. Op. cit.

[525] Gollust SE 2002. Op. cit.

[526] Secretary's Advisory Committee on Genetics, Health, and Society (2006). SACHGS December 8, 2004 letter to The Honorable Tommy G. Thompson. See http://www4.od.nih.gov/oba/sacghs/reports/DTCletter.pdf [accessed December 19, 2007].

[527] Goddard K. Public Awareness and Utilization of Direct-to-Consumer (DTC) Genetic Tests. Presentation at July 10, 2007 SACGHS meeting. See http://www4.od.nih.gov/oba/SACGHS/meetings/July%202007/Goddard.pdf [accessed December 19, 2007].

Other groups, such as the Consortium on Pharmacogenetics, have stressed the importance of strict enforcement of consumer protection laws, calling on vendors to provide clear and accurate information about the predictive value of PGx tests and how they should be interpreted.[528] In a 2006 letter to the HHS Secretary, SACGHS urged FTC and FDA to help raise public awareness about issues related to genetic testing. This letter prompted FTC, FDA, and CDC to issue a warning to consumers about the risks associated with at-home genetic tests.[529] It is likely that the regulatory strategy for DTC PGx products will evolve as the number of approved DTC PGx products increases and as experience is gained with these products.

B. Information Technology and PGx

The widespread adoption of electronic health records (EHRs) has been a key element of ongoing efforts to improve the quality and efficiency of health care delivery. EHRs enable portability, accessibility, and maintenance of personal health information and can facilitate PGx clinical research and therapeutic efficiency and effectiveness. With due regard to necessary provisions for data security and confidentiality, EHR data also can be used for research purposes to enable studies of disease-stage mapping, epidemiological studies, outcomes research, and postmarket surveillance.[530] In addition, as evidenced by ongoing collaborations between industry and academic researchers, EHRs may serve as a source of data for identifying new biomarkers and informing drug development.[531]

1. Electronic Health Records

In addition to making the content of traditional medical records immediately available in multiple health care sites, EHR systems offer higher order capabilities such as clinical reminders, decision support tools, and data collection instruments. Reminder systems provide clinicians with evidence-based clinical reminders of care guidelines specific to a patient's condition.[532] When configured as decision support tools, EHRs capture clinical information that can be used to diagnose conditions and determine the best course of treatment.[533]

After two decades of encouraging but slow diffusion, EHRs are beginning to show signs of improving health care delivery, particularly in certain large systems (e.g., VHA and the U.S. Department of Defense in the Federal Government, Kaiser Permanente in the private sector) and in physician networks.[534,535] After implementing these systems, some health care providers have reported reductions in duplicative processes and improved clinical documentation, decision support, and workflow, allowing for more efficient patient care.[536]

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[528] University of Minnesota, Center for Bioethics, Consortium on Pharmacogenetics (2002). Op. cit.

[529] FTC (2006). *At-home genetic tests: a healthy dose of skepticism may be the best prescription*. See http://www4.od.nih.gov/oba/sacghs/reports/DTC_Consumer_Alert_Jul06.pdf [accessed April 2, 2008].

[530] FasterCures, The Center for Accelerating Medical Solutions (2005). *Think research: using electronic medical records to bridge patient care and research*. See http://www.fastercures.org/pdf/emr_whitepaper.pdf [accessed December 19, 2007].

[531] The American Society for Pharmacology and Experimental Therapeutics (2007). *Comments on realizing the promise of pharmacogenomics: opportunities and challenges* (public comment draft).

[532] Sequist TD, Gandhi TK, Karson AS, et al. A randomized trial of electronic clinical reminders to improve quality of care for diabetes and coronary artery disease. *J Am Med Inform Assoc* 2005. 12(4):431-7.

[533] Ibid.

[534] Kemper AR, Uren RL, Clark SJ. Adoption of electronic health records in primary care pediatric practices. *Pediatrics* 2006. 118(1):e20-4.

[535] Garrido T, Jamieson L, Zhou Y, Wiesenthal A, Liang L. Effect of electronic health records in ambulatory care: retrospective, serial, cross sectional study. *BMJ* 2005. 330(7491):581.

[536] Guite J, Lang M, McCartan P, Miller J. Nursing admissions process redesigned to leverage EHR. *J Healthc Inf Manag* 2006. 20(2):55-64.

Although EHR systems can improve care, they are expensive to install and require extensive coordination among health care providers, product developers, and researchers to achieve interoperability.[537,538,539]

Such EHR functions may prove beneficial for PGx technologies, especially given the potential complexity of PGx test results and care that must be exercised when using results to make treatment determinations.[540,541] Efforts are under way in Canada to develop the infrastructure for this type of clinical support. Currently, Genome Québec and the Pharmacogenomics Centre at the Montreal Heart Institute are developing the Pharmacogenomics Health Information Management System, a guidance engine that will deliver health information, such as PGx test results, to health care providers from a data warehouse and receive data back from providers on interventions and outcomes. These data will be used to make improvements in evidence-based clinical practice.[542]

In addition to concerns and safeguards pertaining to other types of medical information, public sensitivity to PGx in particular introduces considerations for EHR design, including which genetic records should be stored in EHRs, who should have access to the stored data, and how the data should be used in clinical decisionmaking. Storing an entire genome in an EHR may not yet be practical or useful, but storing the results of specific genetic tests could help health care providers tailor treatment. These raw data could be accessed and reviewed by a health care provider and analyzed by a decision support tool that provides alerts and reminders.[543] For example, an alert would appear if a physician tried to enter a prescription for a drug or dosage for which a patient was at risk for experiencing an ADR based on her or his PGx test result.

It is difficult to obtain accurate and current information on how many health care providers have adopted EHRs, because system components vary so widely. Under the HHS Health IT Adoption Initiative, The George Washington University and Massachusetts General Hospital/Harvard Institute for Health Policy, in partnership with the HHS Office of the National Coordinator for Health Information Technology (ONC), are assessing the state of EHR adoption and determining the effectiveness of policies designed to accelerate interoperability and increase the adoption rate of EHRs.[544] As noted above, a significant hurdle to the adoption of EHRs has been the lack of standards. Under contract to HHS, the Certification Commission for Healthcare Information Technology (CCHIT) has created a standard for EHR certification. The number of EHR products that have been certified by CCHIT to date is over 100.[545]

To help ensure the reliability and usability of EHR systems in clinical practice, several national initiatives are focusing on the development of and consistency among EHR systems. Several of these initiatives are described below in Exhibit 4. Each of these has implications for PGx.

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[537] Kemper AR 2006. Op. cit.
[538] DHHS Web site. National Health Information Infrastructure. FAQs about NHII. See http://aspe.hhs.gov/sp/NHII/FAQ.html [accessed December 19, 2007].
[539] Shabo Shvo A. How can the emerging patient-centric health records lower costs in pharmacogenomics? *Pharmacogenomics* 2007. 8(5):507-11.
[540] Goldstein MK, Coleman RW, Tu SW, et al. Translating research into practice: organizational issues in implementing automated decision support for hypertension in three medical centers. *J Am Med Inform Assoc* 2004. 11(5):368-76.
[541] Schellhase KG, Koepsell TD, Norris TE. Providers' reactions to an automated health maintenance reminder system incorporated into the patient's electronic medical record. *J Am Board Fam Pract* 2003. 16(4):312-7.
[542] van Rooij T. Behind the PGx challenge: Biofx. *Genome Technology Magazine*. July/August 2007. 19-20.
[543] Mitchell JA. The impact of genomics on E-health. *Stud Health Technol Inform* 2004. 106:63-74.
[544] DHHS Web site. Office of the National Coordinator for Health Information Technology (ONC): Health IT (HIT) Adoption Initiative. See http://www.hhs.gov/healthit/measuring.html [accessed December 19, 2007].
[545] Certification Commission for Healthcare Information Technology Web site. See http://www.cchit.org/ [accessed December 19, 2007].

Exhibit 4. EHR Initiatives

- **National Health Information Network (NHIN).** This HHS initiative focuses on providing a secure, nationwide, interoperable health information infrastructure to connect health care providers, consumers, and others involved in supporting health and health care. NHIN is helping enable the portability of individual health information so that it is available for clinical decisionmaking.[546]
- **Office of the National Coordinator for Health Information Technology.** Within HHS, ONC provides leadership in the development and implementation of a nationwide health IT (HIT) infrastructure intended to enable the secure and seamless exchange of data and records. ONC advises the HHS Secretary on HIT policies and initiatives and coordinates HHS efforts to meet the President's goal of making EHRs available for most individuals in the United States by 2014.[547]
- **American Health Information Community (AHIC).** AHIC is a Federal advisory body that makes recommendations to the HHS Secretary on how to accelerate the development and adoption of HIT. AHIC currently has three workgroups working in areas of relevance to PGx and EHRs: (1) The Personalized Health Care (PHC) Workgroup is charged with facilitating the incorporation of genetic information in to EHRs and the development of analytic tools to support clinicians' and patients' interpretation of genetic information. To date, the PHC Workgroup has developed recommendations on standards for interoperable integration of genetic and genomic test information into EHRs and on clinical decision support tools. In the near future, it plans to address harmonization of PGx data standards for medical applications.[548,549] (2) The Confidentiality, Privacy, and Security Workgroup has developed recommendations on the relevancy of the Health Insurance Portability and Accountability Act of 1996 requirements to electronic health information exchanges. It is in the process of examining whether additional confidentiality, privacy, and security protections are needed.[550] (3) The EHR Workgroup is analyzing barriers to EHR adoption. To date, the workgroup has made recommendations on the adoption and availability of historical laboratory results, the adoption of e-prescribing systems by clinicians, and barriers to and enablers of widespread adoption of EHRs within the physician community. It plans to address barriers to and enablers of widespread adoption of EHRs in hospital and other health care settings as well as health informatics competencies among health care professionals.[551]
- **Certification Commission for Health Information Technology.** CCHIT is an independent organization contracted by HHS to develop certification criteria and a certification process for EHR products developed by the private sector.[552] This certification process ensures that EHR products meet certain functional levels, are interoperable with other systems, and comply with security criteria published by CCHIT.[553]

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[546] DHHS Web site. National Health Information Network (NHIN): Background. See http://www.hhs.gov/healthit/healthnetwork/background/ [accessed December 19, 2007].

[547] DHHS Web site. Data and Technical Standards: Health Information Technology Standards Panel. See http://www.hhs.gov/healthit/standards/activities/ [accessed December 19, 2007].

[548] DHHS Web site. Personalized Health Care Workgroup. See http://www.hhs.gov/healthit/ahic/healthcare/ [accessed December 19, 2007].

[549] Glaser J, Henley DE. Personalized Healthcare Recommendations. Letter to Chairman of American Health Information Community, July 31, 2007. See http://www.hhs.gov/healthit/ahic/materials/08_07/phc/recs.html [accessed December 19, 2007].

[550] DHHS Web site. Confidentiality, Privacy, and Security Workgroup. See http://www.hhs.gov/healthit/ahic/confidentiality/ [accessed December 19, 2007].

[551] DHHS Web site. Electronic Health Records Workgroup. See http://www.hhs.gov/healthit/ahic/healthrecords/ [accessed December 19, 2007].

[552] Commission for Health Information Technology Web site. About CCHIT. See http://www.cchit.org/about/index.asp [accessed May 3, 2008].

[553] DHHS Web site. News release: Announcement to Help Speed Adoption of Electronic Health Records. See http://www.hhs.gov/news/press/2006pres/20060718.html [accessed December 19, 2007].

These efforts, among others, should contribute to more effective integration of PGx into patient health care. Still, there is no guarantee of widespread adoption of EHRs in the short term, because they face initial implementation costs, may appear to be subject to obsolescence, and must first demonstrate interoperability, utility, reliability, and affordability.

In addition to promoting the adoption of EHRs, there are efforts to increase the use of clinical decision support systems. Although widely recognized as important for facilitating the use of PGx and other technologies, implementation of these systems has been limited, or they are still under development or have encountered roadblocks.[554] The American Medical Informatics Association, with sponsorship from ONC, has developed a strategic plan to advance the development and widespread use of clinical decision support tools in health care delivery and to overcome barriers.[555,556]

2. Data Standards

Translation of PGx into clinical practice and public health will rely on the development and use of standards for exchanging, aggregating, and evaluating research and clinical data. Exchange of PGx research and clinical data will require data standards for various areas such as phenotyping, medication definitions, reporting of ADRs, and other PGx-related topics.[557] This infrastructure will need to be flexible to accommodate future innovation and capable of merging personal genomic data with clinical and laboratory data.[558]

Harmonization of data standards to achieve interoperability among PGx research and other health databases is becoming a high priority. The Federal Government is addressing the need for interoperable HIT and data standards through efforts such as the Consolidated Health Informatics initiative under ONC.[559] Also, the American National Standards Institute is under contract to HHS to convene the Healthcare Information Technology Standards Panel, which brings together U.S. standards development organizations and other stakeholders to develop, test, and evaluate a process for harmonizing a set of HIT standards.[560] In September 2006 HHS announced the Personalized Health Care Initiative, which includes the formation of a cross-agency group with representatives from NIH, FDA, CMS, and other agencies and will address the integration of PGx information into clinical information systems.[561]

Several organizations have been established to develop standards for data quality, management, annotation, and exchange. These organizations are described in Exhibit 5 below.

In an ongoing effort to address the need for a national HIT infrastructure, HHS has identified uniform standards to be adopted across Federal agencies. Descriptions of several of these standards appear in Exhibit

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[554] Osheroff JA, Teich JM, Middleton BF, et al. *A roadmap for national action on clinical decision support*. American Medical Informatics Association (2006). See http://www.amia.org/inside/initiatives/cds/cdsroadmap.pdf [Accessed December 19, 2007].
[555] Ibid.
[556] American Medical Informatics Association (2006). Press release: AMIA releases the report A Roadmap for National Action on Clinical Decision Support, supported by the U.S. Department of Health & Human Services. See http://www.amia.org/inside/releases/2006/cdsroadmap_061306.pdf [accessed December 19, 2007].
[557] DHHS Web site. HHS Accelerates Use of E-Prescribing and Electronic Health Records. HHS news release. See http://www.os.dhhs.gov/news/press/2005pres/20051005.html [accessed December 19, 2007].
[558] Shabo Shvo A 2006. Op. cit.
[559] DHHS Web site. Office of the National Coordinator for Health Information Technology (ONC). Consolidated Health Informatics. See http://www.hhs.gov/healthit/chiinitiative.html [accessed December 19, 2007].
[560] DHHS Web site. HHS Awards Contracts to Advance Nationwide Interoperable Health Information Technology. HHS news release. See http://www.hhs.gov/news/press/2005pres/20051006a.html [accessed December 19, 2007].
[561] Government Health IT Web site. Ferris N. HHS Team Tackles Genetics, EHR Integration. See http://www.govhealthit.com/online/news/96044-1.html [accessed January 10, 2008].

6 below. These clinical vocabulary and other data standards are integral to developing an infrastructure for the integration and interoperability of PGx databases and clinical data sources.

There are several challenges that will need to be addressed to implement the various clinical vocabulary and messaging standards for health data. With regard to PGx, these standards will need to support the exchange and use of patient-specific genetic information while maintaining their security. Also, it will be critical for research and clinical databases to use standardized phenotypic descriptions and terminology for classifying and describing drug-response phenotypes. Addressing these challenges will improve data collection and exchange among various clinical trials and facilitate the testing and replication of genetic associations and measurement of clinical outcomes.[562]

Exhibit 5. Data Standards Organizations

- **Microarray and Gene Expression Data Society (MGEDS).** MGEDS facilitates the sharing of data that arise from genomic technologies such as expression profiling and works with other organizations to facilitate the creation of tools to promote these standards.[563]
- **Clinical Data Interchange Standards Consortium (CDISC).** CDISC supports the electronic acquisition, exchange, submission, and archiving of clinical trials and "metadata" through the development and support of "global, platform-independent data standards that enable information system interoperability."[564] CDISC's efforts have included the development of electronic data submission standards specifically for PGx.[565]
- **MicroArray Quality Control (MAQC) Project.** The MAQC Project seeks to establish quality control measures to assess the performance of various microarray platforms and data analysis methods. It involves multiple FDA centers, major providers of microarray platforms and RNA samples, the Environmental Protection Agency, the National Institute of Standards and Technology, academic laboratories, and other stakeholders.[566]
- **Human Genome Nomenclature Committee (HGNC).** Operating under the auspices of The Human Genome Organisation, HGNC is a nonprofit international effort to create standard symbols and names for genes. The standard nomenclature should allow for clearer communication between clinicians and other health care professionals about a patient's genetic markers, consistent entry of this information into EHRs and other databases, and interoperability among EHR systems.[567,568]

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[562] Gurwitz D, Lunshof JE, Altman RB. A call for the creation of personalized medicine databases. *Nat Rev Drug Discov* 2006. 5(1):23-6.
[563] MGED Society Web site. Microarray and Gene Expression Data Society Mission. See http://www.mged.org/Mission [accessed December 19, 2007].
[564] Clinical Data Interchange Standards Consortium Web site. Mission and Strategy. See http://www.cdisc.org/about/index.html [accessed December 19, 2007].
[565] Pochon P, Hernandez J, Reddy U. *CDISC 2005 International Interchange. Pharmogenomics data: source to submission*. Clinical Data Interchange Standards Consortium (2005). See http://www.cdisc.org/publications/interchange2005/session6/PharmacogenomicsDataSourcetoSubmission-JH-1004.pdf [accessed December 19, 2007].
[566] FDA Web site. MicroArray Quality Control (MAQC) Project. See http://www.fda.gov/nctr/science/centers/toxicoinformatics/maqc/index.htm [accessed December 19, 2007].
[567] Rosenbloom ST, Miller RA, Johnson KB, Elkin PL, Brown SH. Interface terminologies: facilitating direct entry of clinical data into electronic health record systems. *J Am Med Inform Assoc* 2006. 13(3):277-88.
[568] Shabo Shvo A 2006. Op. cit.

Exhibit 6. Standardized Clinical Vocabularies

- **Systematized NOmenclature of MEDicine (SNOMED)** is a multiaxial, hierarchical collection of more than 357,000 medical terms developed by the College of American Pathologists and was licensed by HHS in 2003.[569,570] SNOMED will serve as the standard computerized medical vocabulary system for electronically coding terms in the "Highlights" section of prescription drug labels.
- The laboratory portion of **Logical Observation Identifiers Names and Codes (LOINC)** provides a system for the exchange and pooling of laboratory results.[571] HHS adoption of LOINC will enable standardized electronic exchange of clinical laboratory test orders and results.[572]
- **Health Level 7 (HL7)** is a messaging standard system that allows for the communication and exchange of clinical information to help and improve the coordination of health care (e.g., better coordination of admission, discharge, and transfer of patients). HL7 messages also can be used to convey laboratory information to health care providers. HL7's Clinical Genomics Special Interest Group is focused on the development of message standards to communicate genomic data. The group's mission is to bridge personal genomic data and clinical data to facilitate personalized health care.[573,574]
- **Basal Adverse Event Report (BAER)** is a standard set of core medical information for reporting ADRs and other AEs. It is being developed to address the considerable differences among AE reporting requirements promulgated by various Federal agencies. BAER is currently undergoing review and testing by the Federal agencies, with Federal implementation targeted for 2009.

Recommendation 12

ONC, through the activities of AHIC, should study how clinically validated PGx test results are being incorporated into electronic health records. HHS, in consultation with the U.S. Department of Veterans Affairs and U.S. Department of Defense, also should take steps to ensure that the necessary infrastructure is in place to support the representation of PGx data in electronic health records for use in decision support systems and tools. HHS should explore the development of pilot studies that examine the impact of clinical decision support systems for PGx technologies on clinical practice at the point of care to maximize evidence-based best practices.

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[569] DHHS Web site. Office of the National Coordinator for Health Information Technology. Standards. See http://www.hhs.gov/healthit/standards.html [accessed January 31, 2007].
[570] Shabo Shvo A 2006. Op. cit.
[571] Regenstrief Institute, Inc. Web site. Logical Observation Identifiers Names and Codes (LOINC). See http://www.regenstrief.org/medinformatics/loinc/ [accessed January 10, 2008].
[572] DHHS Web site. Standards. Op. cit.
[573] DHHS Web site. Standards. Op. cit.
[574] Shabo Shvo A 2006. Op. cit.

C. Economic Implications of PGx

The rapidly increasing cost of health care is a major concern in the United States. Technological innovation is among the most important drivers of those costs.[575] Although new technologies may improve patient management, health outcomes, and quality of life and be cost-effective, they also have the potential to increase total health care costs. PGx technologies are among those that are expected to contribute to increased health care spending, particularly in the short term.[576,577,578]

With an estimated cost of $40,000 to $60,000 per patient per year, Herceptin®, which is targeted toward the 25 percent to 30 percent of metastatic breast cancer patients whose tumors overexpress the HER2 protein, is an example of a costly PGx product. Because of its steep cost, health care plans may shift some of the cost burden to patients in the form of cost sharing or caps on reimbursement.[579,580,581]

Diffusion of PGx technologies into clinical practice and public health will drive changes in the downstream use of health care services. The nature of and costs associated with these changes will affect whether PGx technologies are cost saving or cost additive. Even if use of a PGx product is cost saving, these savings may not be realized until much later. With individuals changing health care plans every 2 to 3 years on average, payers may be less inclined to cover PGx technologies whose cost savings will likely accrue much later to another payer. As a result, payers likely will scrutinize the cost-benefit tradeoffs of these technologies, especially for tests that target large patient populations or that are used to guide decisions about costly treatments such as Herceptin®.

There is a need to carefully examine the consequences of investments in new technologies, including PGx, from the perspectives of patients, health care providers, payers, employers, and society at large. Clearly, there is economic value to better health outcomes, avoidance of ADRs, improved clinical management, decreased liability and malpractice, and a vibrant public and private research enterprise, among others. On the other hand, investment in technologies with high costs without concomitant benefits may divert limited resources from other more productive investments in health care and other sectors.

1. Cost-Effectiveness

Successful translation of PGx tests and therapies into clinical practice and public health and policy likely will depend on a demonstration of their cost-effectiveness relative to standards of care.

Cost-effectiveness analyses (CEAs) are used to quantify the incremental (difference in) cost per incremental unit of effectiveness achieved with a test vs. the standard of care. Depending on its purpose, a CEA can be conducted from the perspective of clinicians, payers/health care plans, patients, or society at large. CEAs are one type of economic analysis that can be used to evaluate health care technologies and services.

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[575] Chernew ME, Jacobson PD, Hofer TP, Aaronson KD, Fendrick AM. Barriers to constraining health care cost growth. *Health Aff (Millwood)* 2004. 23(6):122-8.
[576] Teutsch SM 2005. Op. cit.
[577] Nuffield Council on Bioethics (2003). Op. cit.
[578] PricewaterhouseCoopers (2005). Op. cit.
[579] Neyt M, Albrecht J, Cocquyt V. An economic evaluation of Herceptin in adjuvant setting: the Breast Cancer International Research Group 006 trial. *Ann Oncol* 2006. 17(3):381-90.
[580] Waltz E. GlaxoSmithKline cancer drug threatens Herceptin market. *Nat Biotechnol* 2005. 23(12):1453-4.
[581] Berenson A. A cancer drug shows promise, at a price that many can't pay. *NY Times* (Print) 2006. Feb 15:A1, C2.

Pharmacoeconomics, which examines the costs and health outcomes associated with pharmaceutical treatments, may be particularly relevant to PGx.

In assessing the effectiveness of a PGx test, the following factors may be taken into consideration:[582,583,584]

- Clinician ability to perform the test and interpret test results
- Timely turnaround of test results
- Test accuracy (sensitivity, specificity, predictive value)
- Impacts on treatment decisions
- Impacts on dosing of therapy
- Impacts on health outcomes and quality of life
- Impacts on AEs
- Impacts on health care utilization

The costs associated with a PGx test can include:

- Equipment costs to collect and analyze biological samples
- Personnel costs (e.g., costs of ordering the test, performing the test, interpreting the results, conveying results to the patient, and using them to manage the patient's care)
- Reimbursement amounts
- Costs to patients (e.g., cost sharing, sick leave, transportation costs)
- Costs/savings associated with actions taken based on test result (e.g., cost of a drug or alternative course of treatment, costs/savings associated with a change in dosage)
- Downstream costs/savings associated with PGx-based treatment decisions (e.g., fewer/increased hospitalizations or health care provider visits)
- Costs of treating AEs or savings associated with their avoidance (e.g., health care costs, legal costs for liability/malpractice lawsuits, costs associated with market withdrawal)

The outcome of CEAs also will be influenced by the probabilities and durations of these potential impacts and costs as well as the size of the target population.

A new PGx product that improves health outcomes but is priced high will raise difficult resource allocation decisions. Major payers and other health care authorities increasingly are interested in economic analyses that can better inform such decisions. Certainly, economic implications vary by product and their intended use and, thus, should be evaluated on a case-by-case basis.

Although moreso in Europe, Canada, and Australia than in the United States, health care authorities are using CEAs to compare health care interventions.[585,586,587] For example, in the United Kingdom, although there is no formal cutoff level, the National Health Service will look more carefully at technologies with

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[582] Veenstra DL 2000. Op. cit.
[583] Wedlund PJ, de Leon J. Pharmacogenomic testing: the cost factor. *Pharmacogenomics J* 2001. 1(3):171-4.
[584] Goodman CS. *HTA 101: introduction to health technology assessment*. The Lewin Group (2004). See http://www.nlm.nih.gov/nichsr/hta101/ta101_c1.html [accessed December 19, 2007].
[585] Luce BR. What will it take to make cost-effectiveness analysis acceptable in the United States? *Med Care* 2005. 43(7 Suppl):44-8.
[586] Siegel JE. Cost-effectiveness analysis in US healthcare decision-making: where is it going? *Med Care* 2005. 43(7):II1-II54.
[587] Maynard A, Bloor K. Dilemmas in regulation of the market for pharmaceuticals. *Health Aff (Millwood)* 2003. 22(3):31-41.

incremental cost-effectiveness ratios exceeding £30,000 per quality-adjusted life year (QALY).[588] In the United States, CEAs are used informally as a means to gauge value-for-money by some commercial health care plans, although not by Medicare.[589] Although no formal threshold is used by U.S. payers, incremental cost-effectiveness ratios of $50,000 to $100,000 or more per QALY are considered high. Nevertheless, many technologies used in mainstream health care exceed that threshold.[590]

To date, some research has been conducted on the cost-effectiveness of PGx interventions, although much more is needed.[591] A recent economic analysis used predictive modeling to estimate the potential value of using genetic information to guide warfarin therapy.[592] This study found that widespread use of genetic testing could result in an annual health care cost savings of $1.1 billion, attributable mainly to the avoidance of serious bleeding events and strokes that can result when warfarin dosage is not properly managed. There also have been studies on the cost-effectiveness of PGx testing prior to treatment with abacavir, a nucleoside analog reverse transcriptase inhibitor used to treat HIV/AIDS. One such study that used data from HIV patients with and without abacavir hypersensitivity found that genotyping could save up to €22,811 for every abacavir hypersensitivity reaction that was avoided.[593]

As PGx products become more readily available, it will be increasingly important to assess society's willingness and ability to pay for them.[594] As more experience is gained with PGx in clinical practice and public health, more data will be available for such analyses.[595, 596]

D. Ethical, Legal, and Social Issues in the Clinical Implementation of PGx

Diffusion of PGx raises important ELSI concerns. These include access to health care, protection of private health-related information, and legal liability for a range of health stakeholders.

1. Disparities in Access to Health Care for Underserved Populations

Disparities in access to health care can be caused by a number of economic and cultural factors. As discussed above, PGx products that reduce ADRs or improve health outcomes for selected population subgroups are likely to be priced at a premium.[597,598,599] If these high-cost PGx products are subject to high copayments, some insured patients may be unable to afford them; low-income insured patients will be disproportionately affected. Moreover, some observers have expressed concern that, even if research draws on data from minority and underprivileged populations, emerging technologies may not be available to or affordable by

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[588] National Institute for Clinical Excellence (2004). *Guide to the methods of technology appraisal (reference NO515)*. See http://www.nice.org.uk/download.aspx?o=201973 [accessed December 19, 2007].
[589] Neumann PJ, Rosen AB, Weinstein MC. Medicare and cost-effectiveness analysis. *N Engl J Med* 2005. 353(14):1516-22.
[590] Veenstra DL 2000. Op. cit.
[591] Phillips KA 2004. Op. cit.
[592] McWilliam A, Lutter R, Nardinelli C. *Health care savings from personalizing medicine using genetic testing: the case of warfarin*. AEI-Brookings Joint Center for Regulatory Affairs (2006). See http://www.aei-brookings.org/admin/authorpdfs/page.php?id=1337&PHPSESSID=5a612bb2e6f9e369bffbdc1f72d8e34c [accessed December 19, 2007].
[593] Hughes DA, Vilar FJ, Ward CC, et al. Cost-effectiveness analysis of HLA B*5701 genotyping in preventing abacavir hypersensitivity. *Pharmacogenetics* 2004. 14(6):335-42.
[594] Teutsch SM 2005. Op. cit.
[595] Dervieux T, Bala MV. Overview of the pharmacoeconomics of pharmacogenetics. *Pharmacogenomics* 2006. 7(8):1175-84.
[596] Phillips KA 2006. Op. cit.
[597] Nuffield Council on Bioethics (2003). Op. cit.
[598] PricewaterhouseCoopers (2005). Op. cit.
[599] Rothstein MA 2001. Op. cit.

them.[600] Uninsured and underinsured individuals face even greater financial hurdles. Some racial and ethnic groups that are more likely to be uninsured or underinsured will be especially affected.[601]

Some evidence indicates that the adoption of and access to new health care technologies among minority populations lag behind the general population, even after adjusting for insurance status.[602,603] Some minority populations reportedly have lower levels of trust for health care institutions.[604] Historical discrimination experienced by these populations may induce fears of genetic discrimination. Although public engagement and education on genetic issues may ameliorate these fears, public health officials will continue to face challenges in reducing health care disparities and ensuring that underserved populations receive necessary and equitable health care.[605]

2. Genetic Discrimination

Knowledge and sharing of one's PGx information raise concerns about the possibility of genetic discrimination. Individuals and families may be concerned that their genetic information could be disclosed to and misused by employers or insurers. Patients may be reluctant to undergo PGx testing if they believe test results could be used as a reason to refuse or modify their insurance coverage or limit employment opportunities, compensation, or benefits.[606]

In a recent study of insurance denial rates, researchers found that individuals with genetic conditions were twice as likely as individuals with other chronic conditions to report having been denied health insurance. The study also reported that nearly 60 percent of participants believed that a health insurance company could obtain their personal medical information without their permission. Individuals with genetic conditions also were more likely to report that their insurance company had limited coverage specifically related to their condition.[607]

Current Federal protections against such discrimination include Title I of the Health Insurance Portability and Accountability Act of 1996 (HIPAA), the HIPAA Privacy Rule, the Social Security Act, the Americans with Disabilities Act, Title VII of the Civil Rights Act of 1964, the right to privacy established by the Constitution, and related judicial decisions. In addition, most States restrict the use of genetic information in insurance and employment settings, although these laws vary greatly.[608]

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[600] Secretary's Advisory Committee on Genetics, Health, and Society (2007). *Policy issues associated with undertaking a new large U.S. population cohort study of genes, environment, and disease. Report of the Secretary's Advisory Committee on Genetics, Health, and Society*. *March 2007*. See http://www4.od.nih.gov/oba/sacghs/reports/SACGHS_LPS_report.pdf [accessed December 19, 2007].

[601] Centers for Disease Control and Prevention, Office of Genomics and Disease Prevention (2005). *Genomics and population health 2005*. See http://www.cdc.gov/genomics/activities/ogdp/2005.htm [accessed December 19, 2007].

[602] Ferris TG, Kuhlthau K, Ausiello J, Perrin J, Kahn R. Are minority children the last to benefit from a new technology? Technology diffusion and inhaled corticosteroids for asthma. *Med Care* 2006. 44(1):81-6.

[603] Ferris TG, Blumenthal D. Investment, innovation, and disparities: a complex relationship. *Health Aff (Millwood)* 2005. Suppl Web Exclusives: W5-580-2.

[604] Smedley BD, Stith AY, Nelson AR, eds. *Unequal treatment: confronting racial and ethnic disparities in health care.* Washington, DC: National Academy Press, 2002.

[605] Centers for Disease Control and Prevention, Office of Genomics and Disease Prevention (2005). *Genomics and population health 2005*. Op. cit.

[606] Nuffield Council on Bioethics (2003). Op. cit.

[607] Bodensiek E. Genetic conditions more likely to lead to denial of insurance. *The JHU Gazette* 2007. 36(23). See http://www.jhu.edu/~gazette/2007/26feb07/26gene.html [accessed December 19, 2007].

[608] Ibid.

There are divergent views on the adequacy of current protections. SACGHS and others contend that current Federal and State laws may not provide adequate protection against the misuse of genomic information and that additional legislation is necessary to prevent discrimination and overcome public fears.[609,610] Other observers assert that current laws protect patients adequately against genetic discrimination. They argue that a perceived need for additional protections is based on a fallacy of "genetic exceptionalism," which holds that genetic innovations pose entirely new challenges to the health care system and require entirely new solutions.[611] In addition, they suggest that, since insurance companies already can refuse or modify coverage based on nongenetic factors that cannot be changed, laws prohibiting health insurers from using similarly unchangeable genetic information is unfairly biased. Some also suggest that laws specifically protecting against the misuse of genetic information may exacerbate rather than allay public fears of misuse.[612,613]

Although there have been some well-publicized cases of misuse of genetic information, the number is small.[614] The sheer cost of collecting, sifting through, and interpreting genomic data may suffice to prevent insurers from misusing them.[615] However, widespread adoption of EHRs and continued efficiencies in HIT may lower such costs and enable such analyses. Furthermore, future research may reveal that seemingly unremarkable personal genetic data actually are informative; anyone in possession of this information could then use it for discriminatory purposes.[616]

Throughout its deliberations, SACGHS has emphasized the importance of Federal nondiscrimination legislation and has gathered evidence documenting fear of genetic discrimination in the United States.[617] Since 2003, SACGHS has submitted several letters to the HHS Secretary calling for the passage of Federal legislation prohibiting genetic discrimination.[618,619,620] In an analysis of Federal and State laws on genetic discrimination, SACGHS concluded that current protections do not comprehensively address concerns about the misuse of genetic information, leaving substantial gaps and uncertain safeguards at best.[621] The Genetic Information Nondiscrimination Act of 2007, which was passed by the U.S. House of Representatives in March 2008 and is pending in the U.S. Senate, is intended to establish nationally consistent legal protections.

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[609] Ibid.
[610] Collins FS, McKusick VA. Implications of the Human Genome Project for medical science. *JAMA* 2001. 285(5):540-4.
[611] University of Minnesota, Center for Bioethics, Consortium on Pharmacogenetics (2002). Op. cit.
[612] Burris S, Gostin LO, Tress D. Public health surveillance of genetic information: ethical and legal responses to social risk. In: Khoury M, Burke W, Thompson E, eds. *Genetics and Public Health in the 21st Century: Using Genetic Information to Improve Health and Prevent Disease.* Oxford, UK: Oxford University Press, 2000. See http://www.cdc.gov/genomics/info/books/21stcentury.htm [accessed December 19, 2007].
[613] University of Minnesota, Center for Bioethics, Consortium on Pharmacogenetics (2002). Op. cit.
[614] Kohane IS, Altman RB. Health-information altruists—a potentially critical resource. *N Engl J Med* 2005. 353(19):2074-7.
[615] Nuffield Council on Bioethics (2003). Op. cit.
[616] Kohane IS 2005. Op. cit.
[617] Notice of meeting: Secretary's Advisory Committee on Genetics, Health, and Society. *Fed Regist* 2001. 69(168):53071.
[618] Secretary's Advisory Committee on Genetics, Health, and Society (2003). SACGHS June 27, 2003 letter to The Honorable Tommy G. Thompson. See http://www4.od.nih.gov/oba/sacghs/reports/letter%20to%20Sec_06-27-2003.pdf [accessed December 19, 2007].
[619] Secretary's Advisory Committee on Genetics, Health, and Society (2004). SACGHS March 29, 2004 letter to The Honorable Tommy G. Thompson. See http://www4.od.nih.gov/oba/sacghs/reports/letter_to_Sec_03_29_2004.pdf [accessed December 19, 2007].
[620] Secretary's Advisory Committee on Genetics, Health, and Society (2005). SACGHS May 3, 2005 letter to The Honorable Tommy G. Thompson. See http://www4.od.nih.gov/oba/sacghs/reports/letter_to_Sec_05_03_2005.pdf [accessed December 19, 2007].
[621] Lanman RB. *An analysis of the adequacy of current law in protecting against genetic discrimination in health insurance and employment*. Secretary's Advisory Committee on Genetics, Health, and Society (2005). See http://www4.od.nih.gov/oba/sacghs/reports/legal_analysis_May2005.pdf [accessed December 19, 2007].

Some have asserted that this type of legislation, which establishes a framework for protecting privacy and ensuring data security, is a necessary precursor for routine sharing of PGx data.[622,623,624,625]

Recommendation 13

HHS should support policies that afford access to PGx technologies in ways that reduce health and health care disparities, improve health care quality, and prevent genetic discrimination. To this end, HHS should continue to encourage and fund research in support of this goal.

3. Liability Considerations for Health Care Providers

The development and marketing of PGx tests and therapies raise new and complex legal issues for health care professionals who use these technologies. Although not unique to PGx, these legal matters will influence the use of PGx by health care providers and their patients. As PGx products are adopted into clinical practice and public health, CEAs, guidelines development, labeling, health care provider education, and decision support tools will all play a role in minimizing potential liability risks.

Exposure of health care providers to liability depends on accepted standards of care. Generally, standards of care for new health care technologies are established in the medical literature, through use in practice, and through the development of clinical practice guidelines. They also are informed by FDA-approved labels for regulated products. There is uncertainty about whether any PGx tests currently available have reached the point of being standard of care. In most cases, the literature on the clinical validity and clinical utility of the test is scant or nonexistent. Also, clinical practice guidelines are rare, and labeling content is limited or nondirective. On the other hand, several PGx tests are being used in clinical practice and paid for by some insurers. This uncertain status raises questions about whether a physician would be liable for not ordering a test prior to prescribing a drug and at what point in the diffusion process liability would accrue.

Health care providers could expose themselves to liability if an ADR occurs that could have been avoided had a PGx test been administered. Physicians and pharmacists also may be accountable for ADRs resulting from off-label use. Current regulatory policy does not address how health care providers should respond to patients who wish to be prescribed a drug that is indicated only for individuals with certain PGx test results but who refuse the associated diagnostic test. This raises questions about the provider's liability if an ADR were to occur.[626]

Clinical application of PGx technologies will require substantial education and training of health care professionals. However, such education and training may increase their malpractice risk. The learned intermediary doctrine requires drug manufacturers to warn prescribing physicians of a drug's potential adverse effects. Doing so may satisfy the manufacturer's duty to warn of a drug's dangers, even though

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[622] Altman RB, Benowitz N, Gurwitz D, et al. Genetic nondiscrimination legislation: a critical prerequisite for pharmacogenomics data sharing. *Pharmacogenomics* 2007. 8(5):519.
[623] U.S. Congress. House of Representatives. 2007. *Genetic Information Nondiscrimination Act of 2007*. 110th Cong., 1st sess., HR 493. See http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_bills&docid=f:h493ih.txt.pdf [accessed December 19, 2007].
[624] Coalition for Genetic Fairness Web site. Current status of GINA. See http://www.geneticfairness.org/act.html [accessed December 19, 2007].
[625] Given SACGHS's active interest in preventing genetic discrimination, the Committee has been in correspondence with HHS to support passage of genetic nondiscrimination legislation since the introduction of GINA in 2003.
[626] Nuffield Council on Bioethics (2003). Op. cit.

the manufacturers may not have warned the end-user patients directly.[627] The doctrine of informed consent provides a basis for legal action where a physician fails to inform a patient of such adverse effects.

Because PGx-based diagnostics and therapies pose so many ELSI challenges, it will be important for public and private entities to work toward resolving these issues. The collective participation of these entities, along with practical experience gained from the use of the first PGx-based products, will help address these challenges.

E. Coordination of PGx Activities

The opportunities and challenges facing PGx call for coordinated attention by Federal and State Governments, drug and diagnostics manufacturers, researchers, health care providers, payers, and professional, patient, and industry organizations, among others. The complex nature of these challenges makes it difficult to advance practical and well-founded solutions. Although many stakeholders already are working collaboratively on issues related to PGx and personalized health care, a single, coordinated framework or action plan could prove beneficial to addressing these challenges.[628] Such a framework could improve information sharing and coordination of ongoing efforts, such as those described in Appendix A.[629]

Recommendation 14

The HHS Secretary should take all necessary steps to review and prioritize these recommendations, assess whether and how to implement them, monitor HHS progress, and report back to SACGHS.

[627] Hall TS. Reimagining the learned intermediary rule for the new pharmaceutical marketplace. *Seton Hall Law Rev* 2004. 35(1):193-261.
[628] University of Minnesota, Center for Bioethics, Consortium on Pharmacogenetics (2002). Op. cit.
[629] Secretary's Advisory Committee on Genetics, Health, and Society (2006). Transcript of 9th meeting, March 27, 2006. Op. cit.

V. Summary

A. The Potential of PGx

PGx has drawn great attention in the United States and abroad for its potential to improve drug research and development, health care delivery, and ultimately, patient health. Using PGx in drug research and development may enhance our understanding of how individuals metabolize and respond to drugs; improve the efficiency of clinical drug trials; increase the safety and effectiveness of new, existing, and failed drugs; and enable more drugs to reach the market by targeting them to genetically defined patient subgroups. Used as a tool for personalizing health care based on individual genetic variations, PGx may decrease the amount of time it takes to identify the most beneficial drug and dosage for a patient, minimize exposure to ineffective treatments, reduce adverse drug reactions (ADRs), and improve the economic efficiency of the health care system.

B. Challenges Facing PGx

As with many other emerging health care technologies, PGx faces considerable hurdles.[630,631,632] Although PGx holds great promise, there have been only a few clinical and public health applications of PGx to date. The biomedical industry perceives several disincentives to investing in PGx research and development, including its potential to reduce market size, difficulty in securing coverage and adequate reimbursement, and uncertainty about the evolving regulation of PGx products. Some health care payers have been reluctant to cover PGx products, and some health care providers are hesitant to use them due to limited evidence of their health and economic impacts, the absence of clinical practice guidelines and dosing recommendations, and a lack of education and training in genetics. Moreover, the current health information infrastructure has not yet been sufficiently developed to enable standardized data collection of PGx and drug response information and interoperability among PGx research databases and clinical information systems. Many electronic health record systems also lack clinical reminder systems and decision support tools that facilitate health care providers' use of PGx products and information in clinical practice. Concerns about privacy and confidentiality of genetic information, genetic discrimination, stigmatization, disparities in access to PGx products for underserved populations, and liability pose additional challenges to PGx research, development of PGx applications, and their integration into clinical practice and public health.

C. Needs and Considerations for the Future of PGx

The following points should be considered and addressed to help PGx overcome its challenges and achieve its potential:

- **Clinical Research and Product Development.** Clinical trial designs and data collection tools may need to be adapted to better assess the analytical validity, clinical validity, and clinical utility of PGx-based diagnostics and therapies. This calls for further guidance from the Food and Drug Administration (FDA), the Centers for Medicare & Medicaid Services, and other major payers and

[630] Tucker G 2004. Op. cit.
[631] Hopkins MM 2006. Op. cit.
[632] Schmedders M 2003. Op. cit.

early communication with these entities on the part of drug and diagnostics developers. Furthermore, given the scarcity of evidence on long-term health outcomes and cost-effectiveness, there is a need for more thorough, sustained postmarket data collection to inform clinical practice, payment, and health care policymaking.

- **Regulation.** Diagnostics, pharmaceutical, and biotechnology companies continue to seek guidance from FDA on data requirements, market clearance, drug-diagnostic codevelopment, postmarket surveillance, and other regulatory matters pertaining to PGx products in their various forms. The degree of transparency and openness of communications with FDA will influence the extent to which industry is willing to invest in the development of new PGx products.
- **Reimbursement.** As more PGx products reach the market, payers will be making more coverage, medical necessity, and reimbursement decisions that take into account the cost and value of these technologies. Current coverage policies for PGx technologies underscore the importance of demonstrating clinical utility and value to payers.
- **Health Information Infrastructure.** Interoperable health information systems are needed that accommodate the level of detail and type of data required for PGx-based treatment decisions, research, and surveillance.
- **Education.** Development, adoption, and use of PGx products will be influenced by health care provider competence in using these technologies. Efforts to educate physicians, pharmacists, other clinicians, patients, and the public about PGx are critical for proper use of these technologies.
- **Ethical, Legal, and Social Issues.** The ethical, legal, and social aspects of PGx may influence the development and diffusion of PGx technologies. To ensure the safe and successful application of PGx, it is necessary to address these issues through well-crafted policies and guidance to providers, payers, industry, patients, and other stakeholders.

Diverse Federal and private stakeholders are beginning to collaborate on approaches to overcoming these challenges and addressing these needs, but there is still much to be done before PGx can reach its full potential. As the field evolves and matures, the legal, educational, regulatory, and health care delivery and financing systems all will need to adapt to ensure that the benefits of PGx are achieved.

Appendix A

Federal Efforts in Pharmacogenomics

This appendix describes some current activities of Federal agencies and other organizations that relate to the pharmacogenomics (PGx) opportunities and challenges raised in this report. This is not intended to be an exhaustive list; there are other ongoing activities that may be specific to PGx or that may have an impact on this field.

1. U.S. Department of Health and Human Services (HHS)

A. HHS Personalized Health Care (PHC) Initiative

The PHC Initiative is a priority of HHS to improve the safety, quality, and effectiveness of health care for every patient in the United States. The goals of the initiative are to link clinical and genomic information to support personalized health care, protect individuals from discrimination based on unauthorized use of genetic information, ensure the accuracy and clinical validity of genetic tests performed for medical purposes, and develop common policies for access to genomic databases for federally sponsored programs. PHC Initiative activities include:

- A broad review of the implications of health information technology (HIT) for confidentiality, privacy, and security of individually identifiable health information, including the identification of specific needs for genetic information.
- A review of existing structures for ensuring that genetic tests are accurate, valid, and useful. The objective is to ensure that responsibilities are clearly and appropriately assigned among HHS agencies to support useful genetic testing for patients.
- Development of consistent HHS agency policies regarding access to and security of federally supported research data. The goal is to provide researchers with open access to information while continuing to encourage discovery and innovation.
- Creation of a new electronic network that brings together the Nation's major health data repositories. This "network of networks" would enable researchers to match treatments and outcomes to learn from clinical practice and improve the safety and effectiveness of medical treatments.
- Identification of HIT standards for genetic test information.

The PHC Initiative released a report in September 2007 that outlines pathways for bringing PHC to fruition and provides an inventory of HHS-supported activities that are important for achieving PHC for all.

http://www.hhs.gov/myhealthcare/

B. American Health Information Community (AHIC)

AHIC advises the HHS Secretary on how to accelerate the development and adoption of HIT. AHIC has seven workgroups to address specific aspects of its overall charge, including one that focuses on PHC. The PHC Workgroup is charged with determining how HIT can be used to help integrate genetic test information

into interoperable electronic health records (EHRs). To date, the PHC Workgroup has developed a PHC use case, a family history core data set, and a vision summary that describes the current status and desired future of PHC from four different perspectives (consumers, clinicians, researchers, health care plans/payers). It also has made recommendations to AHIC related to genetic tests, family health history, and newborn screening.

http://www.hhs.gov/healthit/community/background/

2. Agency for Healthcare Research and Quality (AHRQ)

A. Evidence-based Practice Centers (EPCs)

The EPC Program is an initiative to promote evidence-based practice in everyday health care through the establishment of 14 EPCs. EPCs develop evidence reports and technology assessments based on syntheses and analyses of the scientific literature on topics relevant to clinical, social scientific/behavioral, economic, and other health care organization and delivery issues. The resulting evidence reports and technology assessments are used by Federal and State agencies, private sector professional societies, health care delivery systems, health care providers, payers, and others committed to evidence-based health care.

Through its EPCs, AHRQ has prepared an evidence report on cytochrome P450 (CYP450) polymorphisms in adults with depression. This evidence report was prepared for the Centers for Disease Control and Prevention's (CDC) Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group to inform the development of recommendations on this topic. (For more information about EGAPP, see section 3.A below). AHRQ also has prepared an evidence report on the impact of Onco*type* DX®, MammaPrint®, and the Breast Cancer Profiling test on breast cancer outcomes. EPCs also are in the process of writing evidence reports on *HER2/neu* testing to manage patients with breast or other solid tumors.

http://www.ahrq.gov/clinic/epc/

B. Centers for Education and Research on Therapeutics (CERTs)

The CERTs Program is a national initiative to conduct research and provide education that advances the optimal use of therapeutics. The program consists of 10 research centers and a coordinating center. Research conducted by the CERTs aims to:

- Increase awareness of the uses and risks of new therapeutics as well as of mechanisms to improve their safe and effective use
- Provide clinical information to patients and consumers, health care providers, delivery systems, health insurers and employers, and government agencies
- Improve quality while reducing the cost of health care by increasing appropriate use of therapeutics and preventing adverse outcomes

Several CERTs have conducted or plan to conduct PGx-relevant research. The Vanderbilt University Medical Center CERT studied whether the risk of sudden death from cardiac causes increased use of erythromycin and CYP3A enzyme inhibitors. The Iowa CERT is conducting PGx analyses of doxorubicin toxicity and response. The Arizona CERT at The Critical Path Institute has developed an international registry for drug-induced arrhythmias, which collects information on clinical cases of drug-induced cardiac

arrhythmias. This information will be used to develop detailed profiles of individuals who are most at risk for these arrhythmias and a genetic test that can identify them in advance. The Arizona CERT also is studying relationships among CYP450 genotype, methadone dose, and QT prolongation to determine whether methadone prolongs the QT interval at normal doses and, if so, by how much.

http://www.ahrq.gov/clinic/outcomix.htm#CERTs

3. Centers for Disease Control and Prevention

A. Evaluation of Genomic Applications in Practice and Prevention

The EGAPP Initiative was launched by the CDC National Office of Public Health Genomics to support a coordinated, systematic process for evaluating genetic tests and other genomic applications that are in transition from research to clinical practice and public health in the United States. The primary focus of the EGAPP Initiative is the independent, non-Federal EGAPP Working Group, which:

- Prioritizes and selects topics for review
- Establishes methods and processes for evidence-based reviews and the development of recommendations
- Participates in technical expert panels for commissioned evidence reviews
- Develops recommendations based on the evidence
- Publishes its methods and experiences
- Considers mechanisms to sustain an ongoing systematic process for the evaluation of genomic applications

A key objective of the EGAPP Working Group is to use a transparent process to link scientific evidence with working group conclusions and recommendations and with information that subsequently is disseminated.

To date, the EGAPP Initiative has commissioned four comprehensive evidence reviews through AHRQ's EPCs, including one on testing for CYP450 polymorphisms in adults with depression. The EGAPP Working Group used the findings of this evidence report as the basis for its recommendation, published in 2007, discouraging the use of CYP450 testing in patients beginning selective serotonin reuptake inhibitor treatment until further clinical trials are completed. A review team completed another more targeted evidence report on *UGT1A1* testing in colorectal cancer patients treated with irinotecan. Publication of the *UGT1A1* evidence report is planned for 2008 and will include recommendations of the EGAPP Working Group. Ten other PGx-related tests are currently under consideration for review.

http://www.egappreviews.org/

B. Human Genome Epidemiology Network (HuGENet)

HuGENet is an international collaboration that, among other efforts, synthesizes population-based epidemiological data describing the interactions of genetic variants with modifiable risk factors and their joint contributions to disease risk. HuGENet provides a weekly summary of new scientific articles on human genome epidemiology, a searchable database of HuGENet-related documents, an Internet-based discussion forum, case studies, factsheets, reviews, and information on workshops and publications. HuGENet also

promotes the publication of peer-reviewed, systematic reviews of gene-disease associations that address the following objectives:

- Identify human genetic variations at one or more loci
- Describe what is known about the frequency of these variants in different populations
- Identify diseases associated with these variants
- Summarize the magnitude of risks and associated risk factors
- Evaluate associated genetic tests
- Identify gaps in existing epidemiological and clinical knowledge

PGx has been the focus of several HuGENet reviews, including one on *CYP2C9* gene variants, drug dose, and bleeding risk in warfarin-treated patients.

http://www.cdc.gov/genomics/hugenet/default.htm

4. Food and Drug Administration (FDA)

A. FDA Voluntary Genomic Data Submissions (VGDSs)

To help ensure that regulatory scientists are familiar with and prepared to appropriately evaluate future genomic submissions, FDA encourages sponsors to voluntarily submit genomic data. The VGDS process involves informal meetings with FDA PGx experts. The *Manual of Policies and Procedures: Processing and Reviewing Voluntary Genomic Data Submissions* explains how FDA receives, reviews, and maintains VGDSs. Through this process, sponsors:

- Obtain feedback on PGx issues and/or questions
- Gain insight into FDA's current thinking about PGx that may assist in reaching important strategic decisions or help avoid future delays during review
- Help shape FDA's thinking about future PGx standards, policies, and guidance documents

http://www.fda.gov/cder/genomics/VGDS.htm

FDA has an agency-wide Interdisciplinary Pharmacogenomics Review Group (IPRG) to establish a scientific and regulatory framework for reviewing genomic data. IPRG is the primary review body for VGDSs. IPRG also works on policy development and advises review divisions on the interpretation and evaluation of PGx data submitted as part of required submissions. In addition, IPRG has prepared suggestions for *Best Practices for Effective and Productive VGDS Meetings*.

http://www.fda.gov/cder/genomics/VGDSmeetings.htm

FDA has expanded the VGDS process to provide sponsors with the option of having joint briefing meetings with both FDA and the European Medicines Agency (EMEA). *Guiding Principles: Processing Joint FDA-EMEA VGDSs Within the Framework of the Confidentiality Arrangement* explains how such requests are received, processed, and reviewed by the two agencies.

http://www.fda.gov/cder/genomics/FDAEMEA.pdf

B. FDA PGx Documents

FDA has issued several documents that provide information on its current thinking related to the use of PGx data for regulatory decisionmaking.

- *Guidance for Industry: Pharmacogenomics Data Submissions* facilitates the use of PGx data in drug development. It includes recommendations about when during the product development and review processes sponsors should submit PGx data to FDA, what content to provide and what format to use for submissions, and how and when the data will be used in regulatory decisionmaking. This guidance also includes an attachment that clarifies when it would be appropriate to submit voluntary genomics data and when submission of PGx data is required by regulations.

  http://www.fda.gov/cder/guidance/6400fnl.pdf

- *Guidance for Industry: Pharmacogenomic Data Submissions—Draft Companion Guidance* provides recommendations on technical steps, report contents, and formats to facilitate the submission of genomic data to FDA. Topics covered in the draft guidance include gene expression data from microarrays, genotyping, genomic data in clinical study reports, genomic data from nonclinical toxicology studies, and data submission formats.

  http://www.fda.gov/cber/gdlns/pharmdtasubcomp.pdf

- *Drug-Diagnostic Co-Development: Draft Concept Paper* describes procedural and scientific issues to be considered in drug development in which a new diagnostic test may play a critical role in its clinical use. Topics covered include the processes and procedures for submitting and reviewing codeveloped drug-test products, analytical and clinical test validation, and elements that should be considered when evaluating the clinical utility of test.

  http://www.fda.gov/cder/genomics/pharmacoconceptfn.pdf

- *Guidance for Industry and FDA Staff: Pharmacogenetic Tests and Genetic Tests for Heritable Markers* provides recommendations on the types of data and regulatory issues that should be addressed in a genetic test application. Topics covered by the recommendations include the intended use of a device, device design, analytical studies, software and instrumentation, comparison studies using clinical specimens, clinical evaluation studies comparing device performance with accepted diagnostic procedures, effectiveness of the device, and labeling.

  http://www.fda.gov/cdrh/oivd/guidance/1549.pdf

- *Guiding Principles for Joint FDA EMEA Voluntary Genomic Data Submission Briefing Meetings* explains how FDA and EMEA will process VGDS meetings with the two agencies and sponsors.

  http://www.fda.gov/cder/genomics/fdaemea.pdf

C. FDA Genomics Work Group

The FDA Genomics Work Group addresses issues related to the science, technology, and regulation of new genomic, proteomic, and metabolomic tests, including PGx tests and codeveloped drugs and diagnostics. The group invites outside speakers to update the FDA staff on the latest developments in the areas of genomics and PGx, coordinates educational and regulatory output to FDA stakeholders interested in diagnostic development, and facilitates communication among FDA offices working on PGx.

D. Initial Investigational Device Exemption (IDE) Review Process

The prereview of IDE applications involves submission and review of sponsors' scientific plans or protocols early in the life cycle of new diagnostic products. This review allows sponsors of new diagnostic devices, including devices used in PGx testing, to educate FDA about the device and learn about FDA's regulatory and scientific expectations for premarket review. The decreased uncertainty resulting from this interchange, along with other regulatory tools (e.g., expedited reviews, *de novo* classifications), can reduce premarket review times.

http://www.fda.gov/cdrh/ode/idepolcy.html

5. National Institutes of Health (NIH)

A. PGx Research Grants

NIH funds over 350 research grants that seek to advance basic, clinical, and translational PGx research. These studies encompass a broad range of disease-related areas, including hypertension, cancers, cardiovascular diseases, arthritis, depression, asthma, alcoholism, and organ transplantation, among others.

http://crisp.cit.nih.gov/crisp/crisp_query.generate_screen

B. NIH Pharmacogenomics Research Network (PGRN)

PGRN is a network of multidisciplinary research groups studying the effects of genes on human responses to a wide variety of medicines. It was formed in 2000 to conduct studies addressing PGx research questions and populate the Pharmacogenomics Knowledge Base (PharmGKB), which serves as a research tool to enable future PGx studies. The goal of this effort is to identify safe and effective drug therapies designed for individual patients. PGRN comprises 12 independently funded interactive research groups, including PharmGKB. Each research group conducts studies of variations in human genes relevant to pharmacokinetics and pharmacodynamics and the relationship of such variations to drug response phenotypes within a specific focus area. The work of the groups ranges from basic research in identifying variations in genes (and functional consequences) relevant to PGx to clinical research aimed at understanding the genetic basis for variable drug responses (both therapeutic and adverse). The resulting data and information accumulated in the field then are made available through PharmGKB.

Scientists involved in PGRN are working on a range of topics, including the PGx of nicotine addiction and treatment, breast cancer, membrane transporters, antihypertensive responses, cardiovascular risk therapy, arrhythmia therapy, antiplatelet intervention, a Phase II drug-metabolizing enzymes trial, and asthma therapy.

PharmGKB has several projects under way, including:

- PharmGKB Community Project: a collection of known PGx-relevant gene-drug relationships from the literature
- Pharmacogenetics Ontology Project: an effort to build an interlinked set of taxonomies to organize, annotate, and index PGx data
- Variant Cross Reference Project: downloadable files of PharmGKB variants matched with variants in other databases
- PharmGKB Web Services Project: provides access to a subset of data from PharmGKB, including gene, disease, drug, and publication information
- Gene-Drug Relationships in the Pharmacogenetics Literature: an automated method for identifying articles in Medline citations that contain PGx data pertaining to gene-drug relationships
- Extracting and Characterizing Gene-Drug Relationships from Literature: a Web site containing data on manually reviewed gene-drug co-occurrences and genes and drugs from PharmGKB

http://www.nigms.nih.gov/Initiatives/PGRN/

C. Genome-Wide Association Studies (GWAS) and the Database of Genotype and Phenotype (dbGaP)

NIH is funding a number of GWAS that are expected to identify, among other possible discoveries, genetic variations that will help clinicians identify which medications are best suited to treat an individual's medical condition or those that confer an increased risk for adverse drug reactions (ADRs). Given the increased interest in GWAS and the value of the data collected, the National Library of Medicine has developed dbGaP as a centralized repository to distribute GWAS datasets. dbGaP will include study documentation and summaries of the measured variables. Also, investigators may be authorized to access individual-level deidentified data, including genotypes, phenotypes, and pedigrees.

NIH issued a data sharing policy that addresses data sharing procedures, data access, intellectual property, and issues relating to the protection of GWAS participants. The policy:

- Defines how investigators are to submit deidentified genotypic and phenotypic data and request access to GWAS data for research purposes
- Encourages investigators to allow submitters of GWAS data a 12-month exclusive publication period before publicly disclosing any analyses that used the contributors' data
- Discourages investigators from obtaining a patent for early, precompetitive information that may impede future research

http://www.ncbi.nlm.nih.gov/sites/entrez?db=gap
http://grants.nih.gov/grants/gwas/index.htm

6. U.S. Department of Veterans Affairs (VA)

A. Genomic Medicine Program (GMP)

VA's GMP was established to conduct research into the role of genetic factors in the prevention and causation of disease, develop clinical programs targeting therapeutic drug response and preventing ADRs, and create information systems to confidentially manage genetic data for patient care and research. The EHRs of military veterans who volunteer to participate in the program will be linked to their genetic information. This information will enable VA health care providers to consider patients' genetic profiles when prescribing treatments or recommending preventive measures.

http://www.research.va.gov/resources/pubs/docs/genomic_fact_sheet.pdf

To help lay the groundwork for the development of GMP, VA established a Genomic Medicine Program Advisory Committee in 2006. The purpose of the committee is to advise VA on the scientific and ethical issues related to the establishment, development, and operation of GMP. This committee is assessing the potential impact of GMP on existing patient health care services. It also is making recommendations regarding policies and procedures for tissue collection, storage, and analysis; development of a research agenda; and approaches by which research results can be incorporated into routine medical care.

http://www1.va.gov/advisory/page.cfm?pg=46

7. Public-Private Partnerships

Several Federal agencies participate in a number of partnerships with non-Federal organizations that are relevant to PGx. A few examples of these partnerships are listed below.

A. The Biomarkers Consortium

The Biomarkers Consortium identifies and qualifies biomarkers to support basic and translational research, guide clinical practice, and ultimately support the development of safe and effective medicines and treatments. It also harmonizes approaches for identifying viable biomarkers, verifies their individual value, and formalizes their use in research and regulatory approval. FDA, NIH, the Foundation for the NIH, and the Pharmaceutical Research and Manufacturers of America were among the founding members. Partners include the Centers for Medicare & Medicaid Services and a number of pharmaceutical and diagnostics companies and nonprofit and trade organizations.

http://www.biomarkersconsortium.org/

B. The Cancer Biomarkers Collaborative

The Cancer Biomarker Collaborative brings together academia, government, industry, and patient advocacy groups to facilitate the use of validated biomarkers in clinical trials. Formed by the American Association for Cancer Research, FDA, and the National Cancer Institute, the collaborative has developed recommendations for effectively integrating predictive biomarkers into clinical trials. Priority areas of

research include biospecimens, bioinformatics, assay validation, and information sharing. This group also is expected to address codevelopment of PGx tests and drugs.

http://www.aacr.org/home/about-us/news.aspx?d=769

C. The Critical Path Institute

The Critical Path Institute is an independent, nonprofit institute that develops innovative collaborative projects to address scientific, safety, and educational aspects of drug development meant to support FDA's Critical Path Initiative. Current research projects include:

- A cancer biomarkers clinical trial that will provide FDA with evidence to guide the selection of biomarkers that predict response to non-small cell lung cancer drug treatments
- A research program that evaluates PGx tests for their ability to predict safer and more effective doses of warfarin to inform the development of PGx testing-based dosage recommendations
- The Predictive Safety Testing Consortium, in which pharmaceutical companies share and validate each other's drug safety testing methods and preclinical safety biomarkers to enable FDA to write new guidance documents that identify more accurate methods to predict drug safety

http://www.c-path.org/

D. The Severe Adverse Events Consortium

The Severe Adverse Events Consortium is a collaboration of several pharmaceutical firms and academic research institutions that aims to identify genetic markers that may help predict who is at risk for serious, drug-related adverse events. The consortium plans to focus its first studies on drug-related liver toxicity and Stevens-Johnson syndrome. All information derived from the consortium's studies will be made publicly available so that identified biomarkers can be validated for the development of PGx tests. FDA provides scientific and strategic input on the design and conduct of the consortium's studies.

http://www.pharmalot.com/2007/09/pharma-and-academia-form-consortium-to-study-side-effects-and-genetics/

Appendix B

Public Commenters

The following individuals, organizations, and Federal agencies responded to a March 2007 request of the Secretary's Advisory Committee on Genetics, Health, and Society for public comment on an earlier version of this report. The comments provided by these entities can be found at http://www4.od/nih.gov/oba/sacghs/reports/pgx_publiccomments.pdf.

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Organizations

Abbott Laboratories
Affymetrix
American Association of Occupational Health Nurses
American Clinical Laboratory Association
American Medical Association
American Nurses Association
American Society for Pharmacology and Experimental Therapeutics
America's Health Insurance Plans
Amgen
Association for Molecular Pathology
AstraZeneca
Biotechnology Industry Organization
Blue Cross and Blue Shield Association
Coalition for 21st Century Medicine
Consumer Action
Eli Lilly and Company
Genetic Alliance
Genetics and Public Policy Center
Genzyme
GlaxoSmithKline
HumGen International
International Society of Nurses in Genetics
Personalized Medicine Coalition
Pfizer Global Research & Development
Pharmaceutical Research and Manufacturers of America
Pharmacogenomic Evaluation of Antihypertensive Responses
Roche Pharmaceuticals and Diagnostics
Schering-Plough
Science and Technology Studies Unit at the University of York
University of North Carolina Center for Education and Research on Therapeutics
University of Utah
World Privacy Forum

Federal Agencies

National Institutes of Health
Office for Civil Rights
U.S. Department of Veterans Affairs

Appendix C

Summary of June 2005 Informational Session on PGx

The purpose of this session was to provide members of the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) (the Committee) with a common understanding of the fundamentals of pharmacogenomics (PGx) and the current state of the field, identify critical policy issues to address as the field moves forward, and determine whether the Committee can play a role in facilitating the translation of this new knowledge into clinical practice.

Fundamentals of Pharmacogenetics: Origins, Definitions, and Concepts

Richard M. Weinshilboum, MD
Professor of Molecular Pharmacology and Experimental Therapeutics and Medicine
Mayo Clinic College of Medicine

Dr. Weinshilboum defined PGx as the study of the role of inheritance in individual variation in response to any xenobiotic, including prescription drugs. His definition represents a convergence between advances in therapeutics that have been made over several decades, which has resulted in a dramatic yet quiet change in the number of therapeutic agents available, and the striking progress made in human genomics, which has been accelerated by technologies that arose from the Human Genome Project.

Dr. Weinshilboum explained that the scientific goal of PGx is to correlate variation in deoxyribonucleic acid (DNA) sequence and/or structure with variation in drug response, the so-called "genotype-phenotype correlation." The clinical goals of PGx include avoiding adverse drug reactions (ADRs), maximizing therapeutic efficacy, and selecting patients who respond best to specific drugs. He noted that all doctors who write prescriptions understand that genetics is only one of many factors affecting individual variation in drug response; the patient's age, gender, underlying disease(s), and drug interactions also have a role. Helping practicing physicians integrate genetic information into the therapeutic encounter will be challenging, however.

Dr. Weinshilboum described thiopurine methyltransferase *(TPMT), CYP2D6, CYP2D9,* and *VKORC1* as examples of biomarkers that have been validated and extensively studied. He also described pharmacokinetic factors that influence the final drug concentration at its target, predominantly drug-metabolizing enzymes and pharmacodynamic factors that influence the response of the target and all the downstream signaling that comes from the target.

Questions and Answers

Dr. Julio Licinio asked why established tests, such as the *CYP2D6* test, are not generally available in mainstream clinical practice. Dr. Weinshilboum replied that practicing physicians may not understand the language of genetic testing. As patients access information on genetic testing via the Internet, they may have the test performed on their own or request it through their doctors.

Dr. Edward McCabe asked whether the Food and Drug Administration (FDA) has discussed including information about *TPMT* testing on drug labels. Dr. Weinshilboum responded that, based on two FDA public hearings he attended, the label has been changed to include information about the existence of the genetic polymorphism and the availability of testing.

Pharmacogenomics: The Public Health Perspective

Robert Davis, MD, PhD
Professor, Department of Epidemiology
University of Washington School of Public Health

Dr. Davis explained that the public health goal for PGx is the same as that of practicing clinicians: to prescribe the right drug for the right person at the right time. However, there is a significant step between understanding how testing works at the clinical level and understanding how this knowledge can be applied at the public health level.

Public health care professionals are trying to determine the real-world effectiveness of PGx and are monitoring its applications. However, the United States needs a system that helps scientists produce the evidence, integrate that evidence, and understand its long-term implications.

To illustrate the differences between approaches to basic science and public health PGx research, Dr. Davis described the increasing evidence on beta-adrenergic agonists, the most commonly used asthma medications. The basic science approach addresses how albuterol and genes work together to affect lung function. The public health approach, on the other hand, asks whether our knowledge of this polymorphism affects measurable clinical outcomes and leads to increased morbidity and mortality among treated asthmatics and whether the polymorphism leads to increased health care costs or decreased quality of life among treated asthmatics. For example, what happens when albuterol's effect is studied with the co-use of prednisone or fluticasone? What happens when it is used by elderly persons who may already suffer from diminished lung function? What happens when it is used by children, for whom asthma is a somewhat different disease from asthma in adults? What happens in various ethnic groups that carry other genes that may modify the effect of the adrenergic receptor?

To obtain the kind of effectiveness evidence that is needed to address PGx issues in the United States, a network of clinical researchers, epidemiologists, biostatisticians, and trialists is necessary. Also, relationships must be developed with large organizations and systems, such as managed care organizations, Veterans Health Administration, Centers for Medicare & Medicaid Services (CMS), and State Medicaid programs, to conduct observational studies, randomized clinical trials (RCTs), and large practical trials that would collect information on measurable clinical outcomes concerning morbidity and mortality in a diverse population set. Data standards also are needed.

Systematic reviews and formal meta-analyses of published randomized clinical trials, large practical trials, and observational studies should be part of a systematic analysis of drug and test effectiveness. Dr. Davis added that such efforts are already under way, noting the Centers for Disease Control and Prevention's (CDC) Evaluation of Genomic Applications in Practice and Prevention (EGAPP) project.

Unlike the United Kingdom, which has The Cochrane Collaboration, the United States is still far behind in systematically integrating evidence into clinical practice. The traditional way to move this evidence into clinical practice in the United States has been to educate doctors. However, doctors who are educated in a specific area do not always apply the evidence. Educating patients yields some results in terms of better knowledge, but unless doctors change their practice, there is little effect.

Dr. Davis described a new movement to perform RCTs or quasi-experimental trials as a means of testing ways to integrate evidence into health care. He stated that these kinds of studies use health services researchers instead of epidemiologists. Ideally, an electronic health record (EHR) system would provide available data to perform these studies. Researchers could collect evidence, conduct trials that integrate evidence into health care, and provide information that guides and monitors clinical care through an electronic system. This EHR system also could provide electronic popup alerts for prescribing medications, collecting family history, or indicating high-risk conditions. Although there is a tremendous need to develop EHRs, none of this technology currently exists. Most existing EHRs are part of homegrown systems, including those developed by large players in the clinical arena. Research is imperative in several areas: collecting and processing information, structuring data in files so they can be extracted for research purposes, and implementing security measures and methods for data transmission.

Surveillance is another area of PGx that needs attention. Surveillance is needed to identify cases of genetic discrimination, decreased access to services, loss of insurance, incorrect use of tests, and adverse events (AEs) and other unintended outcomes. Also, standardized quality control measures are needed to compare data in a national system. Such a surveillance system for PGx will require safety, health services, and ethics researchers who are specially trained to grapple with these issues.

Dr. Davis concluded by stating that a system is needed to create automated files, EHRs, and networks of health care providers and researchers who can develop data standards, collect effectiveness evidence, study the integration of evidence into clinical care, and conduct surveillance. This system will require extensive work and substantial funding, but it is not yet clear who will lead this effort. Funding could come from the Agency for Healthcare Research and Quality (AHRQ), CDC, FDA, National Institutes of Health (NIH), Pharmaceutical Research and Manufacturers of America (PhRMA), and payers.

Questions and Answers

Dr. McCabe noted that the establishment of an electronic infrastructure as well as the development and use of diagnostics might lead to litigation, for which the field may not be prepared. He asked Dr. Davis how he would respond to the medical/legal industry. Dr. Davis acknowledged that although there are no networks in place for PGx, largely due to lack of funding, the capability to set them up has been demonstrated. A substantial allocation of new resources would be needed to do so.

Dr. Emily Winn-Deen asked whether the health care system could handle the costs of large clinical trials needed to develop the evidence base for PGx and what the priority studies should be. Dr. Davis said that genetic testing and PGx have the ability to either bankrupt the system or dramatically reduce health care expenses. Even though a significant amount of money will need to be invested to set up an infrastructure,

the costs of large clinical trials may not be as large as one might think. Most patients in large clinical trials are already being seen by a physician and are receiving medication, and the technology to analyze their DNA and collect information already exists. Rather, it is a matter of putting the pieces together and funding a network.

The next step will be to empower a group of people with the right experience to set the priorities. Priorities are usually driven by morbidity prevalence, mortality rates, and/or cost. The patients considered at greatest need are usually middle-age to elderly individuals who are at risk of death because of congestive heart failure, stroke, or heart attacks. Dr. Davis stated that the priority-setting process also should consider gender-specific effects, pediatrics, and individuals who are quite elderly.

Dr. Winn-Deen asked Dr. Davis whether he had an opinion about which Federal Government agency should take the lead in developing an overarching plan. He responded that there is no single agency that has public health as its mantle. However, Dr. Davis sees roles for AHRQ, CDC, FDA, and NIH.

Since one of the expenses involved is sequencing, Dr. McCabe asked about the anticipated timeframe for achieving the "thousand-dollar genome." Mr. Tim Leshan said that NIH is hoping to reach that goal within the next 10 years, depending on how the technology develops. He noted the need to break down barriers within the academic and physician communities so that the public will want to invest and participate in these advances.

Dr. McCabe asked Dr. Sherrie Hans whether there has been any discussion of starting a pilot study using the military veteran population. Dr. Hans agreed that, at the conceptual level, the U.S. Department of Veterans Affairs (VA) has the necessary patient population, information technology (IT) infrastructure, research infrastructure, and delivery system to undertake such a study. The limiting factor would be the additional costs of running such a large-scale research program under the current budget. Dr. Davis said that although he was encouraged by the interest expressed by the staffs at CMS, VA, America's Health Insurance Plans, and managed care organizations, unfortunately, there are no coordinated discussions taking place among these entities at this time to generate momentum.

Dr. Licinio asked who would fund the large studies needed to validate this effort. He noted that because research studies typically look at the effect of only one drug, natural experiments in settings such as health care organizations would not work because patients often are taking multiple drugs. Ideally, the studies would look at established drugs, not new drugs that are just entering the market. However, drug companies usually are not willing to invest in studies of a drug that is already selling well and possibly is at the end of its patent. Dr. Licinio opined that the NIH Institutes (with the exception of the National Institute of General Medical Sciences [NIGMS]) would be reluctant to conduct this type of large study for PGx because of the high cost and because the effort and cost involved in sample collection may not be considered worth the investment. Dr. Davis agreed and said there are many reasons why people might not want to participate. He said the work would have to done by those who already are paying the costs (e.g., CMS and other payers). Dr. Francis Chesley said that cost would be less of a barrier if a strong business case could be made for conducting such studies. Cost-effectiveness and efficacy research is needed to demonstrate to payers that it makes sound business sense to conduct such effectiveness studies. Dr. Davis predicted that cost-effectiveness studies would show that there is a tremendous amount of waste in the health care system and that such findings would form a basis for the business case.

Pharmacogenomics in the Practice of Medicine

Richard M. Weinshilboum, MD
Professor of Molecular Pharmacology and Experimental Therapeutics and Medicine
Mayo Clinic College of Medicine

Dr. Weinshilboum addressed the challenges and opportunities associated with the translation of PGx information into clinical practice. He began by noting that knowledge of the DNA sequence and structure continually changes, which has practical implications for translation to clinical practice. At Mayo Clinic, Dr. Weinshilboum learned that interaction among basic scientists, molecular epidemiologists, population scientists, clinical investigators, and clinicians is critical to ensuring that the latest developments in health care are incorporated into basic research. Communication and structural barriers must be broken down so that the field can move forward.

He noted that academics tend to think their funding agencies will influence PGx changes. Dr. Weinshilboum described this approach as shortsighted, because drug development in the United States since the Second World War has focused on the pharmaceutical/biotechnology industry. PGx in some form has been used in drug development since the 1930s, despite a lack of incentives for the pharmaceutical industry to develop medications that will work for only a small subset of patients. Although there is some resistance to market segmentation, the pharmaceutical industry's interest in PGx has increased with FDA's growing attention to the field. He predicted that eventually a great deal of PGx would be included in the drug development process, which will create significant regulatory and economic implications. Dr. Weinshilboum emphasized that improvements in information exchange between NIH and FDA will be very important to the advancement of PGx.

Speaking on the challenges and opportunities of PGx, he pointed out that clinical trials should collect DNA as well as blood samples so that researchers can prospectively or retrospectively address the questions raised by Dr. Davis. Dr. Weinshilboum noted the challenges of public/private partnerships, which create significant issues related to intellectual property (IP) and proprietary interests.

He addressed the ethical, legal, and social issues (ELSI) associated with PGx. Dr. Weinshilboum remarked that, as in all other areas of DNA testing, confidentiality is important. He also noted the importance of educating health care professionals. Dr. Weinshilboum shared his experience with gastroenterologists with whom he has worked who have come to see the value of *TPMT* testing. He said the field must recognize that there are sociological differences among the medical subspecialties on how PGx is viewed.

He ended his presentation by reiterating that all doctors want to maximize the efficacy of drugs. Dr. Weinshilboum stated that treatment would be much more cost-effective if doctors could select responsive patients at the front end.

Questions and Answers

Dr. Debra Leonard asked why FDA does not require *TPMT* testing before a mercaptopurine prescription can be filled and whether such a labeling requirement is within the agency's purview. Dr. Felix Frueh responded that an FDA advisory committee decided *not* to require testing, in part because there was no commercial test available. Instead, the advisory committee included the relevant scientific information in the label. Dr. Weinshilboum said he was present at both of the FDA public hearings and believes that the advisory committee approached the issue in a measured and judicious fashion. The concerns expressed were

primarily from the hematology and oncology communities, which expressed belief that the net outcome might be reduced doses of thiopurine and increased mortality. Dr. Leonard countered that, because most physicians do not understand genetics, FDA's approach does not seem to be effective. Dr. Frueh responded that the agency must make sure that information can be applied in the clinical setting, and that at this point in time, the best approach is to provide information and allow physicians and patients to make educated decisions about treatment. He does not think that there is sufficient information to determine what the actual treatment should be.

Dr. Winn-Deen asked Dr. Weinshilboum whether clinical practice guidelines had been developed on the use of *TPMT* testing, including guidelines on how to adjust dosing based on test results. Dr. Weinshilboum responded that such guidelines are being developed or are under consideration. He noted that the FDA advisory committee had expressed concerns about the lack of clearly defined guidelines and systematic clinical trials to guide treatment decisions. The development of practical information for physicians has been a barrier, even for some of the most well-developed examples.

Dr. Leonard asked about Mayo Clinic's *TPMT* testing guidelines. Dr. Weinshilboum responded that the Mayo Clinic uses the test, that homozygous low responders either are not treated with thiopurines or are treated with one-tenth to one-fifteenth of the standard dose, and that patients are monitored over time. The larger, more controversial challenge is the 10 percent of the European population that is heterozygous and has intermediate activity and for whom there is no consensus on what dosage they should receive.

Dr. Licinio asked whether it is realistic to think that clinicians who are "in the trenches" practicing medicine can adjust their therapeutic decisions or whether we will have to wait for the next generation to see changes in clinical practice. Dr. Weinshilboum believes that practicing physicians are educable and that we have no choice but to train the current generation of health care professionals.

Dr. McCabe asked whether any geneticists participate on FDA review panels when PGx is under discussion. Dr. Frueh replied that they do but acknowledged that there is a lack of expertise in this area, which the agency is taking steps to rectify. He heads a group in the FDA Office of Clinical Pharmacology and Biopharmaceutics that is dedicated to genomics.

Dr. James Evans asked whether any lawsuits in this area had been filed by patients and opined that one lawsuit would propel PGx into the mainstream. Dr. Weinshilboum and Dr. Frueh indicated that they had not heard of any lawsuits to date.

Dr. Muin Khoury asked what value PGx adds to clinical practice and whether it would be more effective to monitor drug levels and their toxicities than to use an expensive PGx test to screen the whole population, especially when the prevalence of the genotype is rare. Dr. Weinshilboum said that the costs of not screening must be considered over the long term. It makes more sense to screen first than to administer the drug and see whether the patient develops problems. He advocated that physicians learn to prevent rather than treat ADRs.

Since there already are so many challenges and difficulties demonstrating clinical efficacy for a single gene, Dr. Huntington Willard asked whether PGx testing would be even more difficult for hundreds of variants that are not as well understood. Dr. Weinshilboum agreed that researchers will find many haplotypes scattered across the genome, and eventually they will identify 20 to 30 genes that affect the use and dosing of many drugs. He has great confidence that having this information eventually will be shown to reduce morbidity and mortality and be cost-effective because of ongoing technological advances and that the data

will be validated and become a standard part of clinical practice. Demonstration projects now under way are useful tools for stimulating a discussion of these issues.

Perspectives From Industry

Eric Lai, PhD
Vice President, Discovery and Pipeline Genetics
GlaxoSmithKline (GSK)

Dr. Lai described the current drug development process and how it affects PGx. He emphasized that most drugs are effective for a majority of patients and that all drugs have side effects. Approximately 90 percent to 95 percent of the molecules that GSK researches have no efficacy whatsoever, or they have some efficacy but the major ADRs are so great that Phase IIb and III studies are not performed. PGx studies are not necessary for drugs that are effective in the majority of patients and that have low rates of major ADRs. Many over-the-counter (OTC) drugs fall into this group. On the other hand, PGx research is extremely important in instances where the drug is very effective and the side effects are low enough for the general population. Many cancer drugs, such as Herceptin®, fall into this category. Drugs that are effective in a majority of the population, but have high rates of ADRs, also are good candidates for PGx studies.

PGx studies generally are of two types: those that examine drug efficacy and those that examine ADRs. PGx studies that assess the risk-benefit ratio help doctors target drugs to individuals who are most likely to benefit without risk of an ADR. This type of research can lead to more accurate, clinically relevant information about the safety and efficacy of medicines and result in a more efficient approach to drug development.

Existing barriers to the field affect the application of PGx to clinical practice. Using the example of cytochrome P450 (CYP450), Dr. Lai explained that lack of access to the test, doctors' limited awareness of the test, and the need for careful interpretation when making prescription decisions are among the reasons why this test has not been widely adopted. Also, CYP450 is a complicated gene family, and the assays are difficult.

He concluded that application of genetic information prior to prescribing some medications will increase in the next 10 years. The integration of PGx into clinical practice will help identify patients who respond better to some medications and patients who could have serious ADRs. Dr. Lai emphasized that PGx warrants consideration by policymakers as they attempt to improve health care.

He recommended several areas on which SACGHS should focus. First, public education is needed to change misconceptions. Dr. Lai reiterated that no medication is totally safe and effective, yet drugs have been taken off the market because as few as three or four individuals have experienced ADRs. Next, the public needs protection from and assurance against genetic discrimination. Finally, support from the research and health care environments is necessary for the use of genetic information. Stakeholders involved in the discussion of these issues should include patients, providers, regulators, payers, Government, PhRMA, the diagnostics and biotechnology industries, and bioethics and policy organizations.

Walter Koch, PhD
Vice President and Head of Research
Roche Molecular Systems

Dr. Koch discussed the policy challenges associated with PGx, including those pertaining to the development of PGx tests for drugs that are already on the market. Once drugs are on the market, manufacturers typically do not sponsor PGx studies. Therefore, the burden of establishing the clinical validity and utility of on-the-market drugs falls on the diagnostics developer.

Multiple duplications, deletions, and other genetic variations also pose challenges to the development of PGx tests. Analytical validation is difficult for uncommon allelic variants. For instance, although Roche researchers work with many investigators around the world, in some cases they could not find a sufficient number of DNA samples to validate performance. Instead, they made the variants by site-directed mutagenesis and pooled them back into real genomic DNA to prove they could be detected. Also, because humans are so genetically rich, biomarkers discovered and validated in one population may not be predictive in a population with different ancestry. He said that tests need to be broad so that they are useful in a country as diverse as the United States. Roche's AmpliChip® was made with these considerations in mind.

Novel microarray-based technologies also are opening doors for multiplex assays that had not previously been contemplated. As more variants are discovered, updates will be made to these tests.

FDA has expended considerable effort to provide guidance on the codevelopment of drugs and diagnostics, covering topics such as the analytical properties of multiplex tests and PGx data submission by pharmaceutical companies. An important point in the guidance documents is that an analytically validated test could be conducted in the preclinical phase. However, researchers frequently do not know which marker predicts efficacy or ADRs until Phase II studies. Therefore, it is unlikely that a fully validated *in vitro* diagnostic (IVD) device that demonstrates clinical utility in the pivotal Phase III trial would be available. Investigators are asking whether a well-validated prototype test that demonstrates clinical utility in Phase III can be used to cross-validate the IVD so that the drug and diagnostic efforts can merge and launch at the same time. Absent such an approach, it would be very difficult for the drug and diagnostic to be developed in parallel without one substantially delaying the other. In addition, there are risks on the diagnostic side because many drugs do not survive Phase III, and tests developed for these drugs would never be used. Dr. Koch said that the alternative—two independent Phase III trials—would be very expensive for routine clinical practice and would hamper PGx efforts.

Clinical drugs ultimately will require prospective clinical trials sponsored through public/private/academic partnerships. The results of these trials will be used to make differential drug or dose decisions and demonstrate outcome differences. He highlighted several CDC statements that endorsed large clinical and epidemiological studies to assess PGx issues. The NIH Pharmacogenetics Research Network (PGRN) provides some support for translational clinical research to determine the utility of PGx tests. Dr. Koch recommended that more partnerships among academia, Government, and the private sector be created so that PGx can reach clinical practice and provide patients with better health care.

Another challenge relates to IP. As an example, he stated that his company could not test for a specific allelic variant because it was not able obtain a license to do so.

Concerning PGx education needs, Dr. Koch pointed out that package inserts contain extensive information for physicians, but often they are not read. He suggested that this information be made more user-friendly.

Dr. Koch also addressed the antiquated reimbursement system for PGx diagnostics. Reimbursement models for preventive actions do not exist. Also, the Medicare system is fraught with inconsistencies, is not value based, is in need of a new coding structure, and is subject to continual budget cuts.

Questions and Answers

Dr. Kevin FitzGerald asked what size subgroup is needed to determine whether the market is sufficient to pursue product development. Dr. Koch said that when there is a real medical need and benefit for both therapy and diagnostics, the science will drive it. In fact, many of the early examples of marketed products were pursued based on the science, not on the market size. For example, Gleevec® is doing well, and a companion diagnostic test is available, despite the small number of patients who use the drug.

Dr. Leonard asked whether FDA expects diagnostic-therapeutic combinations to be submitted jointly. Dr. Joseph Hackett replied that they are assuming some applications will come in together, but FDA is uncertain how many to expect. Dr. Koch added that although it would be ideal, there often is no way to have an IVD final product ready for the pivotal Phase III trial, and it is difficult to align the two processes so that they come together at the end.

Dr. Leonard asked whether FDA takes laboratory-developed tests (LDTs) and analyte-specific reagents into account when determining whether to approve drugs. Dr. Hackett said the agency is looking at this issue, with a focus on early communication with industry so that problems can be resolved as they arise.

Mr. Leshan asked about reimbursement for AmpliChip®. Dr. Koch responded that the Current Procedural Terminology® codes used for billing AmpliChip® are procedure based. He thinks it is a mistake to use technical steps to assess the value of a test; rather, the relevance of the clinical information provided should drive reimbursement. Although two tests might follow the same procedures, the values of their predictive information may be very different.

Ms. Barbara Harrison asked whether diverse populations should be studied before guidelines are developed. Dr. Weinshilboum said he agreed, noting that PGRN uses samples from African Americans, Caucasian Americans, Hmong Chinese Americans, and Mexican Americans in its resequencing studies, finding striking differences in allelic frequencies and types among these different populations.

In response to a question from Dr. Khoury, Dr. Lai said SACGHS and FDA should consider developing an evidence-based decision analysis model to determine which drugs should be integrated into clinical practice, especially those for which there is no clear-cut decision. The model would need to consider the size of the target audience, the target audience's responsiveness to the drug, the severity and frequency of side effects, and the long-term medical costs associated with the inability to predict an ADR. Pharmacoeconomic models for ADRs that have been developed in Europe could serve as a model.

Noting the high percentage of failed drugs (90 percent to 95 percent), Dr. Khoury asked whether there is a way to save some of them. Dr. Lai responded that many drugs fail because they are directed at the wrong target or have high toxicity. PGx studies allow researchers to determine why the drugs failed.

Dr. Leonard asked for more information on PGRN. Dr. Weinshilboum explained that PGRN is a network supported by multiple NIH Institutes, with NIGMS taking the lead. PGRN has approximately a dozen research centers and one knowledge base/database at Stanford University. The research centers perform both

basic and translational studies, including laboratory-based studies, discovery of new polymorphisms and haplotypes, functional characterizations, and testing for enhanced efficacy and decreased toxicity. Funded studies focus on a range of conditions, including cancer, cardiovascular disease, asthma, and psychiatric illness. Research teams include molecular epidemiologists, statistical geneticists, and laboratory-based investigators. The goal of the PGRN core facilities is to provide broad analysis across many research programs and interface with various ongoing clinical trials. Dr. Weinshilboum noted that PGRN has proposed a regional translational research center to raise the profile of PGx throughout the biomedical science community.

NIH Efforts and Future Directions in Pharmacogenomics

Rochelle Long, PhD
Chief, Pharmacological and Physiological Sciences Branch
NIGMS, NIH

Dr. Long reviewed the portfolio of PGx work supported by the NIH Institutes, specifically the extramural grants, and described PGRN. Through a search of the Computer Retrieval of Information on Scientific Projects, she found over 400 NIH awards that have PGx as their key phrases. Approximately 70 awards are for training programs, and 70 are cooperative agreements. The latter includes some large, multimillion dollar awards through PGRN as well as clinical trials that have a PGx component. There is support for 40 large centers and programs concentrated at a single institution, as well as awards to 2 facilities and centers. Dr. Long found that nearly 200 individual research grants, 15 small business awards, and 8 conference grants are supported by NIH.

Many of the NIH Institutes are conducting large-scale clinical trials to identify genetic contributions to complex diseases and are banking DNA samples for subsequent analysis. She provided examples of the ongoing work at NIH with a PGx component. At the National Institute of Mental Health, the Sequenced Treatment Alternatives to Relieve Depression trial is analyzing biological samples for genetic predictors to determine which individuals might respond to specific drugs used to treat depression. The National Institute of Child Health and Human Development supports the Pediatric Pharmacology Research Unit Network, which includes a limited number of PGx studies. The National Heart, Lung, and Blood Institute sponsors Programs for Genomic Applications, which support tools for researchers' use, both nationally and internationally. The National Institute of Diabetes and Digestive and Kidney Diseases sponsors the Drug-Induced Liver Injury Network, which comprises researchers who set protocols to collect materials from individuals with severe drug-induced liver injuries. The National Human Genome Research Institute supports the HapMap Project, which uses single nucleotide polymorphism blocks to look at how genetic variation influences drug responses. The National Institute on Drug Abuse has studied drug-metabolizing enzyme systems that are common to many different classes of drugs. The National Institute on Aging supports clinical trials for apolipoprotein E alleles and Alzheimer's disease correlations.

PGRN was started by NIGMS in 2001, with nine NIH Institutes and Offices now contributing funds to the network. Each of the groups involved was charged with putting together an interdisciplinary team with pharmacological, genetics/genomics, and statistics backgrounds, along with clinical researchers. Dr. Long said that the groups are studying areas such as metabolism and transporters, breast and colorectal cancers, leukemia in children, cardiovascular and pulmonary diseases, and research on the implications of PGx studies for minority populations.

PGRN is united by the Pharmacogenomics Knowledge Base (PharmGKB), which determines the functional and clinical implications and medical decisionmaking points for predicting responses to drugs. It allows researchers to browse through genes, look at primary data, enter simple queries, and pull up data. At present, PGRN is primarily focused on cutting-edge research. Researchers are establishing the knowledge base and actively depositing genotype, phenotype, and genotype-phenotype correlation data in PharmGKB. Dr. Long emphasized that PharmGKB was conceived as, and still is, a research tool. A great deal of research must be done before genetic contributions to drug responses can be accurately predicted. At this time, practicing physicians cannot access the system to determine which drug to prescribe for a patient.

Policies have been developed to address informed consent and IP concerns. The strategy encourages provisional patent applications so that important and meaningful results can be commercialized while also being shared with others. PGRN is developing principles for clinical study designs, statistical analyses, and methods for more efficient experiments. Dr. Long said that PGRN participants are encouraged to share their work with the research community. The network has generated sample sets from individuals in Hmong Chinese communities and others from Mexican Americans in Greater Los Angeles. Extensive community consultation was conducted prior to these efforts, and a concerted effort was made to inform individuals that their samples were to be used for research purposes.

PGRN is developing a series of four white papers. The first will provide an overview of cutting-edge issues, barriers, and recommendations for PGx studies. The second paper examines PGx testing for research purposes, including processes, considerations, and ethical and regulatory frameworks. The third will deal with guidelines for educating health care professionals in this area. The fourth white paper plans to address PGx association studies. Each paper will ultimately be targeted to a journal that will reach and stimulate discussion among the appropriate audiences.

FDA Efforts and Future Directions in Pharmacogenomics

Felix Freuh, PhD
Associate Director for Genomics
Office of Clinical Pharmacology and Biopharmaceutics
Center for Drug Evaluation and Research (CDER), FDA

PGx was identified by the FDA Critical Path Initiative as one of the key opportunities that could lead to new medical products. To be successful, regulatory efforts must address the combination of drugs and diagnostics. FDA has developed a series of guidance documents that illustrate FDA's current thinking on this issue.

The guidance document for PGx data submissions was published in March 2005. It explains how FDA will review genomic data submissions. It also is a guide to drug development, empowering FDA to make the review process more efficient and describing several new ways for industry to interact with the agency. The guidance introduces a classification of genomic biomarkers and clarifies the type of genomic data that must be submitted to FDA. It also describes a new voluntary submission pathway that encourages industry to submit exploratory genomic data and a new agency-wide review body, the Interdisciplinary PGx Review Group. Dr. Freuh said the most important point for industry to understand is that the guidance does *not* create new processes for the review of data submissions; it places genomic data within the existing framework.

The Voluntary Genomic Data Submission (VGDS) Program was developed for exploratory data, whether as part of an active investigational new drug application or a new drug application. The VGDS process is intended to build expertise and a foundation for developing scientifically sound regulatory policies. The VGDS Program provides a forum for scientific discussions with FDA outside the regular review process. The data discussed in the voluntary forum are not used for regulatory decisions, which allows for more interaction between FDA scientists and industry scientists. The first voluntary submission was received in March 2004, with another dozen submissions since then. FDA is evaluating the complex raw data received and is having ongoing dialogs with investigators.

Another FDA guidance document addresses the instrumentation of clinical multiplex test systems. These devices are intended to measure and sort multiple signals generated by an assay from a clinical sample. They are used with a specific assay to measure multiple, similar analytes that establish a single indicator to aid in diagnosis. These devices are intended for testing DNA to identify the presence or absence of human genotypic markers encoding a drug-metabolizing enzyme and aid in determining treatment choices and in individualizing dosages. Because these devices are highly complex, FDA must look at them in combination.

Dr. Freuh acknowledged the difficulties that companies have in developing tests and drugs simultaneously. Labeling is a critical component and can be crucial in determining whether the product reaches market. In April 2005, FDA published a drug-test codevelopment concept paper outlining a strategy for combining the device and drug development processes. The concept paper describes key steps during concurrent drug and device development. Interaction among CDER, the Center for Devices and Radiological Health, and the Center for Biologics Evaluation and Research is critical during this process.

Dr. Freuh described several benefits of drug-diagnostic codevelopment, including the potential to prevent drugs from being withdrawn from the market and to rescue candidate drugs that otherwise would be stopped in the drug development process. It also can be used for patient stratification and to enrich clinical trials, which affects both safety and efficacy.

CDC Efforts and Future Directions in Pharmacogenomics

Muin J. Khoury, MD, PhD
Director
Office of Genomics and Disease Prevention, CDC

Dr. Khoury described key CDC efforts in genetic testing over the past 10 years. In response to an NIH/U.S. Department of Energy task force report, several U.S. Department of Health and Human Services interagency working groups were formed in 1999 to analyze the data needed to transition genetic tests from research to clinical practice and consider ways to monitor the impact of genetic tests. After the Secretary's Advisory Committee on Genetic Testing issued its oversight report in 2000, CDC started the **A**nalytical validity, **C**linical validity, **C**linical utility and associated **E**thical, legal, and social implications (ACCE) project, which laid the foundation for the kinds of questions that could be asked about all genetic tests, from analytical performance in the laboratory to ethical issues.

The EGAPP Initiative began in 2004 as a 3-year model project to establish and evaluate a sustainable, systematic, evidence-based process for assessing genetic tests and other applications of genomic technologies in transition from research to clinical practice. Its goal is to move genomic applications into clinical practice

at a faster pace. The planning objective is to integrate previous recommendations for action with knowledge gained from the ACCE project, existing processes for evaluation and appraisal, and international experience from the United Kingdom, Canada, and other international groups.

The basic infrastructure is the EGAPP Working Group, a multidisciplinary, independent working group that interacts with various stakeholders, including health care providers, consumers, professional organizations, policymakers, public health officials, regulatory groups, industry, laboratories, payers, and purchasers. The EGAPP Working Group will request AHRQ's Evidence-based Practice Centers (EPCs) to conduct evidence-based reviews to identify gaps in knowledge about genetic tests. On the basis of the information received from EPCs, the EGAPP Working Group will develop and disseminate information to health care providers, consumers, policymakers, payers, and purchasers. EGAPP may refer a small number of tests to AHRQ's U.S. Preventive Services Task Force and CDC's Task Force on Community Preventive Services for more direct appraisal.

In January 2005, CDC held a meeting on evidence-based reviews of genomic applications that included 21 experts in evidence-based medicine, health care, genomics, epidemiology, ethics, and health economics. It considered existing and potential methods for systematic evaluation of genetic tests and other genomic applications. The EGAPP Working Group was formed in March 2005, and its first meeting was held in May 2005, during which three subcommittees were formed. The Topics Subcommittee is deciding on potential topics for evidence-based reviews, focusing first on applications recognized as common and important, such as screening tests and tests used in clinical situations to guide interventions. The Methods Subcommittee is finalizing the analytical framework that was formulated at the January 2005 meeting. The Outcomes Subcommittee is looking at health outcomes and patient- and family-related outcomes.

Dr. Khoury said that forthcoming EGAPP Working Group products include a description of its methods, criteria and prioritized list of topics, approved evidence-based reviews, conclusions and recommendations, and lessons learned.

Questions and Answers

Dr. FitzGerald asked whether there is a specific definition or threshold of clinical benefit that will help avoid controversy as PGx moves forward. Dr. Frueh replied that there is no generally applicable definition; it is considered on a case-by-case basis.

Dr. Licinio asked whether PGRN efforts would be coordinated with NIH's General Clinical Research Centers that are addressing PGx. Dr. Long noted that PGRN is trying to identify the groups working in this area so that it may coordinate with them.

Ethical, Legal, and Social Issues of Pharmacogenomics

Patricia Deverka, MD, MS, MBE
Fellow, Duke Institute for Genome Sciences & Policy
Duke University

With the emergence of PGx, a novel framework is needed to deal with the ELSI aspects of the field. The United States' history of eugenics and belief in genetic determinism have contributed to sensitivity surrounding genetic testing. In addition, PGx challenges the traditional approach to genetic testing for disease susceptibility, which has predominantly focused on rare disorders. Since genetic testing has been misused in the past when only a handful of experts were using it, society is concerned that widespread use of PGx testing in primary care settings may result in more widespread mishandling.

Informed consent for DNA banking is a particular concern for clinical PGx research. Because informed consent is the primary mechanism by which human subjects are protected in the research setting, some have argued that the framework for informed consent needs to take into account the large biorepositories that may be created. Because privacy and confidentiality concerns vary depending on whether the data are identifiable or coded, procedures are needed to limit unauthorized disclosures. Breaches in confidentiality could result in genetic discrimination. In addition, a failure to guard privacy could harm individuals, families, and groups if test results reveal susceptibility to certain diseases. Furthermore, stratifying individuals on the basis of PGx test results has caused concerns that new orphan drugs will be created.

Ethical issues arise because researchers other than those who collected samples may be the ones conducting research on the samples. Informed consent is complicated in these situations because future studies will likely be conducted by unspecified investigators. There is concern that various groups may want to access these biorepositories. The traditional emphasis on protecting subjects from physical harm through the informed consent process is moving to the need for protection from informational harm. Although these studies would be facilitated by blanket consent, which would allow any future use of the specimens, blanket consent might be too broad to meet the ethical standards of informed consent. Informed consent processes are needed that both protect subjects and minimize the need to recontact them to obtain consent for future studies.

Dr. Deverka suggested that informed consent's traditional exclusive focus on the individual research subject is arbitrary from an ethical point of view. She suggested that researchers should be addressing risks to groups. Dr. Deverka used the example of specific population groups that could be stigmatized if genetic findings were made available on their group's responses to drugs.

Turning to the topic of PGx and race, she stated that there is no precise biological or genetic definition of race. The prevailing thinking is that race is a social construct. However, researchers have found that certain PGx variants are more common in some ethnic and racial groups than in others. Published studies demonstrate differences in response to conventional treatments across various racial groups. However, some people debate the scientific validity of these studies because they claim that self-identification of one's race is imprecise. Dr. Deverka pointed out that this type of research can be harmful if it reinforces the notion that racial differences have a genetic basis. Drugs marketed to particular racial groups in a misleading manner could leave the impression that all members of a group would benefit. For instance, a drug such as BiDil® could be incorrectly claimed to be more effective than other nonracially defined medicines. If certain genotypes are linked to poor medication response in specific racial minorities, those groups could be stigmatized by the implication that they are more difficult or more expensive to treat.

Ultimately, the primary concern is that physicians will "take shortcuts" and use race, rather than genotype, as the basis for drug selection.

She talked next about the pharmaceutical industry. Many members of the public mistrust pharmaceutical companies because they have not always been transparent about the safety of some drugs. In addition, drug companies have not fully published all of their clinical trial results and charge high prices for their products. Thus, there is concern that they cannot be trusted to use PGx appropriately; that is, they might "cherry pick" drugs to address pipeline and profitability problems.

The pharmaceutical industry focuses predominantly on the development of new drugs, not on researching drugs already on the market. Many pharmaceutical companies have few resources to conduct PGx studies on marketed drugs, and there is no financial incentive for them to do so. Dr. Deverka encouraged SACGHS to think about how PGx research on marketed drugs could be encouraged.

She explained that there are two kinds of orphan genotypes. First, through PGx data, it can be shown that a particular drug is unlikely to be safe or effective for a particular genotypic subgroup within a general population or disease group. The second type of orphan genotype occurs when a disease has no genotypic subgroups large enough to attract commercial investment. These scenarios raise concerns that drugs will not be developed for these genetically defined subgroups. Although large pharmaceutical companies may not be interested in these diseases, Dr. Deverka believes that these diseases will interest smaller startup companies. Although ethical concerns may arise if there is no other safe and effective treatment available for a disease, she believes it is unlikely that a subgroup would be so small as to never attract investors.

A benefit of PGx is that drugs can be marketed more rapidly if subjects are selected for trials on the basis of their PGx profiles. However, some argue that this might result in fewer data supporting the drug's safety and efficacy at the time the product goes to market. Clinicians who do not follow label instructions when prescribing can exacerbate safety problems.

With regard to the introduction of PGx tests into clinical practice, Dr. Deverka expressed concern that due to the lack of a regulatory framework or an evidence base, PGx is entering the marketplace and clinical practice without adequate validation. She noted that problems could arise from rapid, unmanaged introduction of genetic tests into the marketplace. The predictive value of many PGx tests is likely to be too low to be clinically useful. Excitement about PGx could cause resources to be diverted away from more effective ways of improving public health.

Suboptimal access to and use of PGx testing result from professionals' and payers' significant lack of knowledge about genetics as well as difficulty in interpreting probabilistic information. In addition, it is not clear when physicians are obligated to offer PGx tests. Physicians and pharmacists could be considered negligent if they do not offer "a reasonable standard of care," and pharmaceutical companies could be liable if they do not disclose a knowable safety problem with a drug.

Another clinical practice issue relates to the need to determine when informed consent is needed for PGx testing. PGx testing will not be very controversial because it will be viewed as therapeutic drug monitoring to inform dosing decisions. Dr. Deverka noted that many believe Federal nondiscrimination legislation will be necessary to help people feel comfortable with genetic testing. She also expressed concern that higher drug costs could lead to access barriers. Pharmaceutical companies may not pass the savings gained in the drug development process on to the consumer.

PGx discoveries will only become an important element of clinical practice if they are reimbursed. Therefore, PGx must be evaluated in the context of current cost-containment practices. From an ethical standpoint, PGx is clearly on a par with, if not superior to, current practices and has the added benefit of being tailored to an individual. At the individual and group levels, there is a stewardship obligation to manage resources by not paying for drugs that are unsafe or ineffective. However, this will be difficult to operationalize in clinical practice because of the probabilistic nature of the results.

Managed care is a significant actor in this area. With the new Medicare prescription drug benefit, managed care organizations are expected to play a larger role in personalized prescribing. Because these companies are perceived to be primarily focused on cost containment, individuals and agencies (such as CMS) are reluctant to trust them. Furthermore, their approaches to cost containment as well as their use of restrictive formularies and therapeutic substitution run counter to the concept of personalized prescribing. Some are concerned that these practices may hinder market entry of PGx products.

Dr. Deverka described payers' hopes concerning the use of PGx in the real world, including decreased health care costs, improved compliance, better health outcomes, and a reduction in AEs. However, payers are also concerned that PGx will increase costs, as is usually the case with new technologies. Although ultimately PGx tests will be more cost-effective and provide more information, advances in this field may not initially result in cost savings.

With regard to direct-to-consumer access to PGx testing, she noted that it may be permissible in some situations. However, there must be appropriate standards for analytical and clinical validity, and the results must be conveyed in an accurate and understandable manner. It could be unethical to restrict access to PGx tests for OTC drugs or dietary regimens. Dr. Deverka also expressed her belief that individuals should have direct access to testing when they have insurance coverage for the drug but not for the test. In other cases, individuals may not want to go through their employers' health plans to obtain testing due to concerns about discrimination or stigmatization.

She discussed reasons for and against the idea that PGx is unique relative to other medical technologies. Dr. Deverka opined that ELSI concerns are the same as in other areas of medicine. Some argue that the issues are different because DNA is uniquely identifying and predictive, the sample can be kept indefinitely, and there is a tremendous amount of information involved. She acknowledged the concerns about stigmatization by race or ethnicity because of the likelihood of genetic variability in those groups. Dr. Deverka said it is important to see genetic variation as only one of many factors that affect drug response. Otherwise, the negative ideas of genetic determinism and exceptionalism will be reinforced and will make patients less willing to be tested.

In conclusion, she noted that PGx emphasizes the need to resolve longstanding problems on how to integrate new technologies into clinical practice. It should be seen as a tool to help physicians decide which is the best intervention for a specific patient. Dr. Deverka suggested areas in which more information is needed, including an extensive IT infrastructure, regulatory requirements, and cost-effectiveness data.

Questions and Answers

Dr. Licinio asked what ethical standards should be used if it becomes known that a study participant has a gene variant that can cause ADRs or that can result in no response to treatment for a life-threatening disease. Should the subject be recontacted even if she or he specified no further contact? Dr. Deverka responded that it is important to allow people the option of not being recontacted but agreed that PGx is different.

This question could arise if a researcher has information that would affect a patient's outcome and no other treatment option exists. However, in most cases, researchers do not have a means of recontacting subjects. From an ethical standpoint, she said that she would follow the express wishes of the subject.

Mr. Leshan asked whether studies had been conducted that showed higher costs as a result of the implementation of privacy standards. Dr. Deverka pointed to the cost of implementing the Health Insurance Portability and Accountability Act but acknowledged that there have not been any specific studies. It seems logical, however, that if genetic information is being treated differently from other health information, there will be costs associated with doing so.

Dr. FitzGerald asked how PGx technologies could be supported without concomitantly raising fears of genetic reductionism and genetic determinism. Dr. Deverka agreed that how the vocabulary is used is critically important. Some suggest not using the word "genetics" when talking about drug response profiles. For example, in the clinical setting, a patient could be told that a test will help the physician decide which drug is best.

Dr. Winn-Deen stated that it seemed, from the comments on *TPMT* testing and in the white paper on companion diagnostics, that FDA has not formally recognized LDTs as a way of providing PGx services. She asked whether there is a requirement that an IVD assay be developed before an FDA drug label would recognize a PGx test. Dr. Hackett responded that anything other than a biomarker must go through the regular approval process, because it is considered similar to a research product. Dr. Frueh stated that two separate issues were being raised. One concerned a combination (codeveloped) product that requires a test for the drug to be used. Such companion PGx tests must be approved by FDA. In more than 100 other cases, PGx information is provided in the drug labels, even in the absence of an FDA-approved test.

Appendix D

Summary of October 2005 Informational Session on Pharmacogenomics

The purpose of this session was to continue factfinding on some of the issues identified at the June 2005 meeting so that the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) (the Committee) could proceed with the development of recommendations.

Update From the Food and Drug Administration (FDA)

Steven I. Gutman, MD, MBA
Director
Office of In Vitro Diagnostics
Center for Devices and Radiological Health
FDA

Allen Rudman, PhD
Associate Director
Office of Clinical Pharmacology and Biopharmaceutics
Center for Drug Evaluation and Research
FDA

Dr. Gutman began his part of the presentation on the diagnostic aspects of the PGx pipeline by describing two PGx tests approved by FDA in the past year: Roche Diagnostic Corporation's AmpliChip® and a PGx test for *UGT1A1*. The products were considered class II medical devices and reviewed under the *de novo* process, which is intended for new tests that lack a clear predicate and are low risk or have some ability to mitigate risk.

Dr. Gutman also described an FDA concept paper on the codevelopment of drugs and diagnostics that lays out the scientific issues associated with establishing the analytical validity, clinical validity, and clinical utility of these types of tests. The paper states that when a diagnostic is used to select a drug, the two become inextricably intertwined (i.e., the diagnostic might drive the performance of the drug, or the drug might drive the performance of the diagnostic). After comments on the concept paper are reviewed, it will be converted into draft guidance. Additional comments will be sought on this guidance before it is finalized.

Dr. Gutman also stated that a separate guidance on PGx tests is in the final stages of review and is expected to be completed in 2005.

There has been interest in revisiting FDA's regulation of the analyte-specific reagents (ASRs) and laboratory-developed tests (LDTs). Dr. Gutman noted that the Advanced Medical Technology Association, with input

from the laboratory community, had submitted a frequently asked questions document to FDA that attempts to clarify ASR regulations, which FDA may use as the basis for a draft guidance.

Dr. Gutman described an *ad hoc* group working to identify misuses of direct-to-consumer testing. Because FDA regulations for LDTs and FDA-cleared and -approved devices are not strong enough, the group used Federal Trade Commission's (FTC) criteria to evaluate genetic testing Web sites and planned to use FTC's enforcement mechanisms. The task was more challenging than expected, because over time, the Web sites under review changed the tone of their advertisements in ways that made them more elusive.

In closing, Dr. Gutman said that efforts are under way to establish a working group that brings together the pharmaceutical and diagnostics communities to explore ways to address the unique challenges they are facing.

Dr. Rudman spoke about the drug aspects of the PGx pipeline. He began by explaining that FDA's mission is to protect and advance public health by helping speed innovations that make medicines and food more effective, safer, and more affordable. This mission is reflected in FDA's Critical Path Initiative. The white paper *Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products* describes how emerging PGx and proteomic techniques show great promise for increasing drug effectiveness. In addition, the National Cancer Institute and FDA have a joint program to streamline cancer drug development, one of its goals being the development of biomarkers for evaluating new cancer medicines.

In March 2005, FDA finalized guidance on Voluntary Genomic Data Submissions (VGDSs). The goal of the guidance is to encourage companies to voluntarily submit genomic data. The VGDS process also includes convening conferences, workshops, and meetings with industry, the public, and NIH. To date, 24 VGDSs have been received, and 12 submitters either have scheduled or have held meetings with FDA. Companies are now providing followup information and submitting with formal applications. Genomic information has been received in the therapeutic areas of cancer, Alzheimer's disease, hypertension, hyperglycemia, depression, obesity, and rheumatoid arthritis. Scientific information has been received on biomarker development, genotyping devices, microarray analysis, analysis software, databases, metabolic pathways, biostatistics, and enrichment design.

Dr. Rudman explained how biomarkers are used in drug development, from basic research to FDA approval. The key questions that arise during this process are: What does the test's analytical validation process consist of? How should validation be done? What criteria should be used to assess its validity? What are the test's preclinical feasibility, clinical validity, and clinical utility? Dr. Rudman noted that just because a test exists does not necessarily mean that it will be useful for public health purposes.

Internal (within FDA) and external education on PGx is also an important goal. An Interdisciplinary Pharmacogenomics Research Group (IPRG), which has representatives from numerous FDA centers and offices, has been established to help achieve this goal. Located in the Office of Clinical Pharmacology and Biopharmaceutics, IPRG performs numerous functions, including reviewing VGDSs. Research efforts include a cooperative research and development agreement on biomarker validation, guidance on the design of clinical trial protocols, and analysis of label information relating to PGx. Information technology efforts include the development of new software and databases.

Dr. Rudman described the steps being taken toward international harmonization of regulatory review processes. Because most large pharmaceutical companies are global, he stated that it is increasingly

important to have consistency across Europe and the United States. On May 17, 2005, the first joint meeting of FDA and the European Medicines Agency (EMEA) was held via videoconference. Interactions before the meeting included indepth scientific evaluation of sponsors' questions and premeeting dialog between FDA and EMEA, since they operate under different regulatory environments. FDA and EMEA issued joint minutes of the VGDS meeting and shared them with the sponsor. The evaluations by the two agencies had only minor differences. Three more joint meetings are scheduled. The information resulting from this process is informing the development of guidance documents, concept papers, and several workshops.

In his concluding remarks, Dr. Rudman stated that FDA's VGDS and PGx programs have been very successful. The VGDSs have provided FDA with a wealth of genomic data and therapeutic, scientific, and technical information that would otherwise be unavailable to the agency. To expedite the approval of new drugs and indications and get them to the public, PGx research must be seen in the context of biomarker development and validation as well as disease management. SACGHS could help by recommending the formation of a task force to develop national standards for PGx assays.

Questions and Answers

Dr. Julio Licinio asked for advice on how to start developing national standards for PGx testing and where the authority for such an effort lies (e.g., FDA? CDC?). Dr. Rudman responded that numerous questions must be addressed first; responsibilities could be assigned accordingly. Dr. Gutman added that for the diagnostics industry, the Clinical Laboratory Standards Institute (CLSI) is the premier group for crafting standards and is also the Executive Secretariat for the international standards group for laboratories. Although CLSI focuses largely on diagnostics issues, its scope could be broadened.

Dr. James Evans asked about FDA's purview related to how test results are reported to clinicians. Dr. Gutman said that FDA does not regulate the reporting system itself. Dr. Muin Khoury noted that the Secretary's Advisory Committee on Genetic Testing developed recommendations related to the oversight of genetic testing and their transition from research to clinical practice; however, there are many gaps in the process that are being uncovered by PGx. He recommended that SACGHS consider taking on these issues.

Ms. Agnes Masny asked Dr. Rudman to elaborate on the educational initiatives he mentioned. Dr. Rudman described the numerous internal Web sites, seminars, and training sessions in genomics available at FDA. Externally, workshops and a Web site are among the mechanisms being used to educate the public. Also, there have been preliminary discussions with universities and the American Association for Clinical Laboratory Science about developing additional educational programs.

Feasibility of Integrating Pharmacogenomics Into Drug Development From an Economic Perspective

Thomas A. Metcalfe
Head of Biomarker Program
F. Hoffman-Roche Ltd.

Mr. Metcalfe defined biomarkers as an objective measure or evaluation of normal biological or pathogenic processes or pharmacologic responses to therapeutic, preventive, or other health care interventions. They can increase understanding of drug metabolism, action, efficacy, and safety; facilitate prediction of therapy response; expand the molecular definition of disease; and provide information about the course of disease

progression. This broad definition includes all diagnostic tests, imaging technologies, and other subjective measures of a person's health status.

He described new developments in genetics, genomics, proteomics, and modern imaging techniques that allow scientists to measure many more markers than they could previously. Mr. Metcalfe also explained how an improved understanding of the targets of pharmaceutical interventions, signaling pathways, metabolism, and mechanisms of toxicity has helped researchers better understand biomarker data. These new biomarker data help researchers make decisions during late research and early development phases about which projects should move forward. However, few validated surrogate markers currently exist that can decrease the duration of trials, and there are few highly informative response biomarkers available that can be used to select study participants and thereby decrease the sample size needed.

Drug development includes pharmacodynamic markers that confirm biological activity and optimize dosing and scheduling, prognostic markers that correlate with disease outcome, disease-specific markers that correlate well with the presence or absence of a disease, and predictive markers that correlate strongly with the activity of drugs. In many cases, disease biomarkers lack the specificity to be used as predictive pharmacodiagnostics. Pharmacodynamic and prognostic tests tend to be valuable because of their ability to improve dosing, decisionmaking, and trial design and reduce attrition, which offsets the cost of biomarker research and development. The impact of predictive markers on value, on the other hand, is less clear. They may reduce the size of the market, but this reduction may be offset by improvements in market penetration, increased average duration of therapy, and pricing.

To include response markers in a drug development program, it is important to have a reliable understanding of the biology of the marker and the test for that marker. Considerable time is spent early in the process on drug development and biomarker discovery, then on biomarker test development and validation, and as the drug is introduced, on the collection and storage of samples. The most informative time in early development is Phase II. After a test has been developed, it is possible to conduct a retrospective analysis of the biomarkers on samples collected during Phase II and correlate these with response and possibly safety. One could prospectively recruit patients for Phase III trials using biomarkers found to be useful at the end of Phase II but only if they are very informative and reliable biomarkers. Alternatively, one could make sure that the various arms of a trial are equally populated with patients who have a good chance of response using the marker. This would require more tracking of information, but it would not change the drug trial's protocols.

Next, Mr. Metcalfe talked about the issues related to the definition of "response." At the end of Phase II, researchers try to correlate biomarkers with responders. If it is not clear who is a responder and what the response phenotype is, problems can arise. He spoke about the acceptable response rate for a novel drug and when it would be appropriate to use stratification with a response biomarker. When the response rate is very low, the drug might not be viable. A response marker might make sense, however, when the response rate is above 10 percent. A response rate above 50 percent is excellent for a novel drug.

Another set of questions relates to the response rate and safety markers. The balance between increasing efficacy and increasing safety should tilt toward increasing safety. Researchers also must take into account the balance between efficacy and risk as they relate to the specific indication under study. If there is a great medical need, greater risk might be justified in light of the potential benefits.

From a practical standpoint, the test should not be particularly invasive and the results should be returned within a short time. The availability and reliability of the test, its predictive value, and ease of administration also are important.

Some of the challenges in coordinating drug and diagnostic development include identifying the right biomarker early enough, coordinating the drug and diagnostic development timelines, and collecting enough samples and storing them effectively. Pharmaceutical companies must have incentives for codeveloping drugs and diagnostics because the work is expensive.

When discussing the economic rationale for personalized medicine, Mr. Metcalfe explained that capturing the value of an innovative medicine depends on pricing and reimbursement conditions, intellectual property protection, competition, and timing, as well as scientific and clinical considerations. In his opinion, value-based, flexible pricing and reimbursement systems should be encouraged to reward both diagnostic and therapeutic innovations. Current reimbursement schemes for diagnostics do not reward value creation, which discourages diagnostic companies from investing in such research.

Value also is measured by the amount informed patients are willing to pay for life-years gained, improvements in quality of life, reduction of morbidity, and reduction in uncertainty. Targeting use to good responders leads to strong net benefits. Good responders also may have improved compliance, which especially benefits companies who offer long-term therapies for chronic conditions.

Inability to set price is a disincentive for manufacturers to conduct PGx research. The price for novel drugs is nearly always set early in the drug's life, immediately after registration. Manufacturers want to reduce the uncertainty concerning the number of responders, since this affects the setting of price.

Economic Challenges of Integrating Pharmacogenomics Into Clinical Practice

Kathryn Phillips, PhD
Professor of Health Economics and Health Services Research
University of California, San Francisco

Dr. Phillips explained some of the economic challenges associated with integrating PGx into clinical care. She explained that the first step in maximizing the value of PGx is understanding the importance of economic and noneconomic incentives. Adoption of PGx will occur only if there are properly structured, aligned, built-in incentives. These incentives vary based on the characteristics of the intervention, including:

- Whether the condition that the intervention targets is life threatening or chronic
- Whether there is strong interest by advocacy groups or industry
- Whether it is covered by health insurance and is well reimbursed
- Whether PGx is used early in the pipeline
- Whether it is used for immediate treatment decisions
- Whether it is used for focused treatment decisions
- Whether it can be used off label
- Whether it is used for ongoing monitoring rather than a one-time use
- Whether it targets an acquired mutation rather than an inherited mutation
- When it dictates the type of treatment that will be used as opposed to suggesting the treatment or dosage

- When it is not considered PGx, but rather personalized medicine, targeted therapy, or smart drugs, knowing that people find it easier to understand and support the concept of personalized medicine than genetic testing

Dr. Phillips next talked about the economics of several PGx products. Herceptin®, for example, had a very fast and successful adoption, which proved that targeting small populations is feasible and profitable for industry. One economic analysis concluded that Herceptin® cost $125,000 per quality-adjusted life-year gained (usually, any cost over $50,000 raises questions about the overall benefits of a drug). Iressa®, on the other hand, is an example of a fast but unsuccessful adoption. FDA accelerated approval of the drug, but it essentially has been withdrawn from the market because postapproval clinical trials showed no significant survival benefit. Cytochrome P450 (CYP450 testing is an example of slow adoption. There have been many implementation challenges, including the multifactorial nature of drug response, lack of data linking mutations and clinical outcomes, and variability across and within drug classes.

For Herceptin® and Iressa®, it will be challenging to develop and determine the most appropriate diagnostic. Several tests were approved for Herceptin®, but there is still debate over which test is best. The CYP450 testing example illustrates that it will be challenging to adopt PGx when the product is relevant to multiple diseases, because CYP450 testing takes place only once in a lifetime, but the results are relevant to multiple diseases, drugs, and clinical specialties. Also, Medicare coverage of the test is uncertain because it is unclear whether the Centers for Medicare & Medicaid Services (CMS) considers it to be a diagnostic or a screening test (Medicare covers diagnostic but not screening tests).

There is little documentation of the value of PGx. There have been only 11 cost-effectiveness analyses of PGx interventions under a limited range of conditions, and the results have been mixed. In addition to cost-effectiveness analyses, data linking PGx to outcomes and data on comparative effectiveness would help determine value.

There are few incentives to assess economic value from a societal perspective. Advocates, industry, FDA, CMS, and insurers usually do not evaluate PGx from the societal perspective. Another challenge is that PGx often prevents harms (e.g., the prevention of adverse drug reactions), which are hard to measure.

Dr. Phillips suggested that innovative approaches be used to evaluate diagnostics, codeveloped diagnostics, and drugs. These approaches may require cooperation between historically divided industries and regulatory mechanisms. Three key barriers to early consideration of diagnostics are money for initial investment, reimbursement, and availability of data and samples. Also, the clinical utility of tests is often not evaluated, making it difficult to demonstrate the value of diagnostics.

She closed by emphasizing the importance of developing an evidence base, citing the databases being developed by the Pharmacogenetics Research Network and the Evaluation of Genomic Applications in Practice and Prevention Initiative as examples of the Federal Government's involvement in facilitating appropriate use of PGx. Dr. Phillips expressed belief that there would be an inevitable push toward PGx because it is part of a larger trend toward personalized medicine.

Questions and Answers

Dr. Khoury commented that there are a number of drugs that are effective for many people but have side effects for a small percentage and, therefore, are withdrawn from the market. He asked why such drugs are withdrawn instead of studying why a small number of people have side effects. Mr. Metcalfe responded

that large studies would be required to reliably predict who is likely to suffer an adverse event when the percentage of cases is small. If an alternative drug is available, there is less incentive to invest in the drug with side effects.

Dr. Kevin FitzGerald asked whether drug products that failed could be rehabilitated if the groups who could benefit from them were identified. Mr. Metcalfe stated that as long as there is sufficient patent protection, there are many incentives to use such drugs for new indications. Because reimbursement is not based on the value of the test, there are no incentives for the diagnostic industry to invest speculatively.

Noting that liability can serve as an incentive, Dr. Evans wondered about the lack of lawsuits against physicians who do not test for thiopurine methyltransferase. Mr. Metcalfe responded that when there is a clear standard of care that is not adhered to, there is a much higher risk of litigation. Dr. Evans also asked whether insurers would try to deny coverage for individuals if there is evidence that they may not respond well to a drug. Mr. Metcalfe answered that this would definitely happen if there is clear evidence that a patient is highly unlikely to derive benefit. The less clear-cut cases have not been sufficiently debated. Dr. Phillips added that patient advocates have a role in determining which PGx interventions move forward. In the case of Herceptin®, the manufacturer was reluctant to move forward, but patients demanded the drug.

Dr. Emily Winn-Deen asked the panelists whether there were specific steps that should be taken by the U.S. Department of Health and Human Services (HHS) that could benefit PGx. Dr. Phillips suggested more funding of economics research. Mr. Metcalfe recommended development of a clear regulatory framework and set of standards, more funding for translational research, and incentives for profit-oriented companies.

Ethical and Social Issues Associated With Using Race and Genetics in the Study of Differential Drug Response

Wylie Burke, MD, PhD
Professor and Chair
Department of Medical History and Ethics
University of Washington

Dr. Burke began by explaining that the term "race" is generally used to identify groups with shared ancestry. In the United States, it is assumed that race is closely related to genetics; however, the definition of racial groups has changed over time, and the term can take on a variety of meanings.

There is an indirect relationship between race and PGx. Self-reported race is correlated only in a rough way with genetic measures of geographic ancestry. Researchers have developed marker panels for the five major racial groups: African, European, Asian, Native American, and Oceanic. Categorizing people by race in this way indicates the prevalence of many gene variants, some associated with drug response. For example, the presence of *CYP2C9* variants has been associated with a need for reduced warfarin dosage, for Asians in particular. However, most warfarin studies have been conducted in North America with people of European descent. The evidence base for Asian patients is not strong, yet this is widely believed based on clinical observation.

A study of *VKORC1* provides evidence that the gene may be contributing to slower metabolism of warfarin among Asians. This study looked at the association between warfarin dosage and two *VKORC1* variant

haplotypes (Group A and Group B). Group A was associated with low-dose requirements; Group B was associated with high-dose requirements. There was a difference in prevalence among racial groups related to these two haplotypes. The Asian sample had a high proportion of the *VKORC1* haplotype associated with low dose, indicating a genetic explanation for the clinical observation. There likely are many other genes involved in the metabolic processes by which the body responds to ingested warfarin, most of which have not been studied. In addition, nongenetic factors such as diet, age, multiple interacting drugs, and presence of other health conditions may be involved.

Another study of the prevalence of the apolipoprotein E4 allele in populations around the world demonstrates that racial groups are highly heterogeneous, another reason to be cautious about generalizations. The only populations for which a broad distribution was not seen were three populations of Oceanic origin, which suggests that sampling individuals of *similar* geographic ancestry does not necessarily mean that the *same* geographic ancestries are sampled. Broad sampling is important because race and geographic ancestry are related but not congruent. Estimates from genetic testing indicate that the West African contribution to individual African American ancestry averages 80 percent but ranges from 20 percent to 100 percent. Approximately 30 percent of self-identified European Americans have less than 90 percent European ancestry. The mixture is even higher and more variable among people who self-identify as Hispanic.

Dr. Burke addressed whether race is clinically important in drug treatment. Although race captures many potential group differences, it is uncertain whether it has sufficient predictive value to assist in drug treatment. To identify all the variants relevant to a particular drug response, diverse populations must be studied in large numbers. Therefore, any one observation must be examined for its place within that mix. Gene-gene and gene-environment interactions also are likely.

Switching to the topic of orphan genotypes, she explained that rare genotypes that predict drug response are less likely to be studied and could be neglected in drug development. In the United States, genotypes common in minority populations but not in the population overall could become orphan genotypes. For instance, a group of researchers wrote an article in 1999 in the *Journal of the National Medical Association* claiming racial bias in Federal nutrition policy, which recommends milk products as an important source of calcium, because lactose intolerance is high in virtually all racial groups except Europeans. One could argue that the policy was based on a group that is in the majority in the U.S. population but not in other parts of the world.

Turning to ethical issues, Dr. Burke noted that data suggest that there is more mistrust about the misuse of genetic information among minority populations. For example, in a survey of minority premedical students, 74 percent agreed strongly that genetic testing might lead to discrimination. Thus, it is critical to develop partnerships that incorporate minority communities in research.

She described the significant risks that derive from the use of race and genetics and the study of differential drug response. There is too much research in the United States and Europe and not enough in other parts of the world, where the populations that are a minority in this country are the majority. Attention also must be paid to sample sizes and sampling methods used in research. More attention needs to be given to multiracial groups since we live in an increasingly multiracial society. There is a need to recognize that, even when a genetic predictor is found that helps identify those with a higher or lower likelihood of adverse effects or effective responses to a drug, it is only one of many contributors, and its importance should not be inflated beyond what the findings indicate. As PGx moves forward, the field must not misrepresent race as having a genetic basis. Researchers must recognize that there are many social causes of racial group differences and much genetic variation within racial groups.

Dr. Burke emphasized the need to move beyond hypotheses about benefit to actual proof that drug outcomes are improved by genetic testing. Her final point highlighted the fundamental concern about equal access to quality health care.

Questions and Answers

Dr. Licinio said that in some countries in which many residents are of mixed ancestry, the concept of race is almost nonexistent. Dr. Burke stated that this point speaks to the importance of making sure research occurs in populations other than those in the United States, where there is less clarity about racial categories and their use will have less utility. Good population sampling should look for relevant variants and other nongenetic factors.

In response to a request for suggestions on possible recommendations for HHS, Dr. Burke said the Department should make sure that research study samples represent a broad cross-section of the population. She encouraged studies to include individuals from countries other than the United States and advocated for approaching communities that do not have experience participating in research studies and that may have some mistrust about doing so. The public needs assurances that research will be conducted in respectful and appropriate ways. Regarding clinical integration, Dr. Burke raised the following questions: How can outcome studies be funded, and how can postmarket studies be conducted? She also said that it is imperative for HHS to consider access issues. In addition, genetics should be integrated into public school curricula, and models should be developed for educating health care providers.

Appendix E

List of Abbreviations and Acronyms

AACP	American Association of Colleges of Pharmacy
AAFP	American Academy of Family Physicians
AAMC	Association of American Medical Colleges
ACCE	Analytical validity, Clinical validity, Clinical utility and associated Ethical, legal, and social implications
ADR	adverse drug reaction
AE	adverse event
A-HeFT	African American Heart Failure Trial
AHIC	American Health Information Community
AHRQ	Agency for Healthcare Research and Quality
AIDS	acquired immune deficiency syndrome
ALL	acute lymphoblastic leukemia
AMIA	American Medical Informatics Association
ASCO	American Society of Clinical Oncology
ASPE	Assistant Secretary for Planning and Evaluation
ASR	analyte-specific reagent
BAER	Basal Adverse Event Report
BCBS	BlueCross BlueShield
BCBSA	BlueCross BlueShield Association
BRFSS	Behavioral Risk Factor Surveillance System
caBIG	cancer Biomedical Informatics Grid
CAP	College of American Pathologists
CARe	Candidate gene Association Resource
CBER	Center for Biologics Evaluation and Research
CCHIT	Certification Commission for Healthcare Information Technology
CDC	Centers for Disease Control and Prevention
CDER	Center for Drug Evaluation and Research
CDISC	Clinical Data Interchange Standards Consortium
CDRH	Center for Devices and Radiological Health
CEA	cost-effectiveness analysis
CERTs	Centers for Education and Research Therapeutics
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments of 1988
CLSI	Clinical Laboratory Standards Institute
CME	continuing medical education
CMS	Centers for Medicare & Medicaid Services
C-Path	Critical Path Institute
CPB	Clinical Policy Bulletin

CPT®	Current Procedural Terminology®
CRpac	Clinical Research Policy Analysis and Coordination Program
CYP450	cytochrome P450
dbGaP	Database of Genotype and Phenotype
DEcIDE	Developing Evidence to Inform Decisions about Effectiveness
DNA	deoxyribonucleic acid
DOD	U.S. Department of Defense
DTC	direct-to-consumer
EGAPP	Evaluation of Genomic Applications in Practice and Prevention
EHR	electronic health record
ELSI	ethical, legal, and social issues
EMEA	European Medicines Agency
ENDGAME	Enhancing Development of Genome-Wide Association Methods
EPC	Evidence-based Practice Centers
ERISA	Employee Retirement Income Security Act of 1974
FDA	Food and Drug Administration
FEHBP	Federal Employees Health Benefit Plan
FISH	fluorescence *in situ* hybridization
510(k)	premarket notification pathway
FNIH	Foundation for the NIH
FTC	Federal Trade Commission
GAIN	Genetic Association Information Network
GEI	Genes, Environment and Health Initiative
GMP	good manufacturing practices; Genomic Medicine Program
GSK	GlaxoSmithKline
GWAS	genome-wide association study
HapMap	human haplotype map
HDE	humanitarian device exemption
HGNC	Human Genome Nomenclature Committee
HHS	U.S. Department of Health and Human Services
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIT	health information technology
HIV	human immunodeficiency virus
HIV/AIDS	human immunodeficiency virus/acquired immune deficiency syndrome
HL7	Health Level 7
HRSA	Health Resources and Services Administration
HTA	health technology assessment
HUD	humanitarian use device
HuGENet	Human Genome Epidemiology Network

ICD	International Statistical Classification of Diseases and Related Health Problems
ICD-9-CM	International Statistical Classification of Diseases and Related Health Problems, Ninth Edition, Clinical Modification
IDE	investigational device exemption
IHC	immunohistochemistry
IP	intellectual property
IPRG	Interdisciplinary Pharmacogenomics Review Group
IT	information technology
IVD	*in vitro* diagnostic
IVDMIA	*in vitro* diagnostic multivariate index assay
LDT	laboratory-developed test
Lewin	The Lewin Group
LOINC	Logical Observation Identifiers Names and Codes
MAQC	MicroArray Quality Control
MGEDS	Microarray and Gene Expression Data Society
NCBI	National Center for Biotechnology Information
NCCN	National Comprehensive Cancer Network
NCHPEG	National Coalition for Health Professional Education in Genetics
NCI	National Cancer Institute
NDA	new drug application
NHGRI	National Human Genome Research Institute
NHIN	National Health Information Network
NHLBI	National Heart, Lung, and Blood Institute
NIGMS	National Institute of General Medical Sciences
NIH	National Institutes of Health
OBA	Office of Biotechnology Activities
OCP	Office of Combination Products
OHRP	Office for Human Research Protections
OIVD	Office of In Vitro Diagnostic Device Evaluation and Safety
ONC	Office of the National Coordinator for Health Information Technology
OTC	over the counter
PDUFA	Prescription Drug User Fee Act
PGRN	Pharmacogenetics Research Network
PGx	pharmacogenomics
PharmGKB	Pharmacogenomics Knowledge Base
PHC	personalized health care; Personalized Health Care Initiative, Workgroup
PhRMA	Pharmaceutical Research and Manufacturers of America
PMA	premarket approval application
PMC	Personalized Medicine Coalition
P^3G	Public Population Project in Genomics
PT	proficiency testing
QALY	quality-adjusted life year

R&D	research and development
RCT	randomized controlled trial
SACGHS	Secretary's Advisory Committee on Genetics, Health, and Society
SHARe	SNP Health Association Resource
SNOMED	Systematized Nomenclature of Medicine
SNP	single nucleotide polymorphism
SSRI	selective serotonin reuptake inhibitor
STAMPEED	SNP Typing for Association with Multiple Phenotypes from Existing Epidemiologic Data
T1	type 1 translation
T2	type 2 translation
TAILORx	Trial Assigning IndividuaLized Options for Treatment (Rx)
TEC	Technology Evaluation Center
TPMT	thiopurine methyltransferase
UCSF	University of California, San Francisco
UW	University of Washington
VA	U.S. Department of Veterans Affairs
VGDS	voluntary genomic data submission; VGDS Program
VHA	Veterans Health Administration
VKORC1	vitamin K oxidoreductase