

Personalized Health Care Expert Panel Meeting

Summary Report

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Submitted to:

Office of the Assistant Secretary
for Planning and Evaluation
US Department of Health and Human Services

Submitted by:

The Lewin Group, Inc.

September 10, 2007

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Prepared for:
**The Office of the Assistant Secretary
for Planning and Evaluation, DHHS**

Prepared by:
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This report was produced under the direction of Sandra Howard and Theresa Lawrence, Task Order Monitors, Office of the Assistant Secretary for Planning and Evaluation (ASPE), Office of Science and Data Policy, Jim Scanlon, Deputy Assistant Secretary for Planning and Evaluation (Science and Data Policy), Jerry Regier, Principal Deputy Assistant Secretary for Planning and Evaluation. The findings and conclusions of this report are those of the author(s) and do not necessarily represent the views of ASPE or HHS.

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Executive Summary

The concept of personalized health care has attracted considerable scientific, medical, commercial and policy interest for its potential to sharpen the focus of health care and improve its effectiveness and efficiency. It is intended to shift diagnostic and therapeutic interventions from more traditional, population-based, empirical approaches to those that are more scientifically-informed and tailored for individual patients. Personalized health care is intended to “deliver the right treatment to the right patient at the right time—every time.”¹

Personalized health care (PHC) draws from information about differences in individual genomes, molecular- and cellular-level disease processes, health states, behavioral and environmental determinants and response to interventions. It applies this to deliver patient-specific health care that reflects individual risks and benefits of particular treatments, to determine risks of particular conditions or diseases and to facilitate the discovery and validation of health care products and other interventions. PHC may involve genetic and molecular testing, functional imaging and other means to determine a patient’s predisposition for particular health care responses and outcomes. Continued advances in health information technology should facilitate PHC research and delivery.

As part of a broader vision of advancing and leveraging medical research to improve and transform health care in the US, the Secretary of the US Department of Health and Human Services (DHHS) has identified PHC as one of the Department’s top 10 priorities in the near- and long-term future.²

In order to advance the Secretary’s vision for PHC, the Office of the Assistant Secretary for Planning and Evaluation (ASPE) commissioned The Lewin Group to convene the PHC Expert Panel for a one-day meeting on March 20, 2007, at the Hubert H. Humphrey building in Washington, DC.

The purpose of the PHC Expert Panel was to provide input to the Office of the Secretary, DHHS, toward realizing the integration of PHC into clinical and public health practice. Panelists’ observations and findings from this facilitated discussion are intended to help inform and enable the Secretary, other policymakers and other stakeholders to chart important steps over the next 5 to 20 years for transforming current medical practice into a system of PHC.

The PHC Expert Panel was comprised to represent various key stakeholder perspectives involved in the integration of new technologies into clinical and public health care. Twenty-two experts representing the private sector (e.g., payers, industry representatives, advocacy representatives) and public sector (e.g., Food and Drug Administration, Centers for Medicare & Medicaid Services, National Institutes of Health) served on the Expert Panel.

¹ HHS Secretary Leavitt Announces Steps Toward A Future of “Personalized Health Care.” Washington, DC: US Department of Health and Human Services. March 23, 2007. Accessed May 1, 2007. <http://www.hhs.gov/news/press/2007pres/20070323a.html>.

² Secretary Mike Leavitt: DHHS priorities. Washington, DC: US Department of Health and Human Services. Accessed April 13, 2007. <http://www.hhs.gov/secretary/priorities/>.

Prior to convening, panel members were provided with background information to help them prepare for the meeting. This included an environmental scan of issues relevant to PHC and a brief discussion guide (both prepared by The Lewin Group) that outlined the main issues, a set of forward-oriented assumptions and a set of questions intended to prompt and focus discussion on each main issue.

During the Expert Panel meeting, panelists considered and discussed the following five main issues pertaining to the integration of PHC into clinical and public health practice:

- Demonstrating clinical validity and utility of PHC
- Demonstrating value/cost-effectiveness of PHC
- Identifying the role of PHC in reducing health disparities
- Educating and engaging providers and patients about PHC
- Using databases to build evidence and inform decisions in PHC

The Expert Panel was not charged with providing recommendations to the Office of the Secretary. However, the Expert Panel was asked to express “what the Office of the Secretary needs to know” toward realizing the DHHS initiative in PHC. In particular, panel members were asked to comment on current and potential enablers and barriers to PHC, incentives and disincentives, the pre- and post-marketing environments, the integration of PHC with health information technology and the potential view of PHC as being “disruptive” to the current health care system. Panel members also were asked to comment on potential stakeholder perspectives (e.g., patients/consumers, providers, payers, policymakers, employers) concerning these issues.

The Expert Panel’s main observations and findings for each of the five main issues are as follows.

A. Demonstrating Clinical Validity and Utility

- The great share of population disease burden arises from complex disease processes involving often inadequately-understood genomic, environmental, behavioral and other factors.
- Although usually preferred where feasible, randomized controlled trials (RCTs) are not the only means of generating needed evidence on the clinical utility (risks and benefits) of tests and other interventions used in PHC.
- Observational studies can augment the evidence base for PHC, including to assess clinical validity of tests. However, they generally are less useful for assessing clinical utility and are not adequate substitutes for RCTs in establishing cause-and-effect relationships between PHC interventions and health outcomes.
- New study designs and methods should facilitate evaluation of PHC technologies.
- Genetic/genomic tests are of little or no clinical value without availability of validated, associated interventions—whether prevention strategies, treatments, behavior changes, life planning alternatives or others—whose use is informed by those test results.

- Clinical utility of genomic testing and other PHC interventions must be supported with data generated in real health care settings.
- Integrated data collection, spanning pre- and post-market phases, is needed to demonstrate clinical validity and utility of PHC.
- Coverage of PHC interventions by public and private sector payers should be subject to data collection throughout their lifecycles.
- Better alignment of requirements and processes of DHHS agencies and other organizations responsible for regulation and reimbursement would improve the generation of evidence for clinical validity and utility.
- Standards are needed to establish robust evidence requirements and methods for assessing the validity and utility of PHC interventions.

B. Demonstrating Value

- While its impact on aggregate health care spending remains to be determined, PHC has considerable potential to improve the return on health care investment.
- Despite its promise, the evidence base for demonstrating the value of PHC on population health outcomes still is sparse.
- The federal government can influence the adoption of PHC by sponsoring comparative effectiveness and cost-effectiveness research.
- To justify payment, a diagnostic test should be demonstrated to alter the prevention or management of a disease or disorder, or inform behavioral or life planning decisions, and to achieve benefits that could not have occurred otherwise as cost-effectively.
- Data sources and methods for determining value and allocating resources for PHC interventions should account for their use, and health and economic impacts, in practice.
- Value assessment of PHC products should be considered within broader economic and social impacts, as with any new genomic application or other health technology.
- Realization of the value of PHC in screening and primary disease prevention in the Medicare population is subject to the limitation of the Medicare statute.

C. Reducing Health Disparities

- More research is needed to understand the causes of health care disparities and means for preventing or reducing them.
- Development and introduction of PHC provide opportunities to learn about factors that may contribute to disparities and ways to prevent or reduce them.
- Reducing disparities will require representing all populations in biomedical research and related data collection.
- The history of health care disparities, and prevailing factors that continue to contribute to them, may raise barriers to adoption of PHC by affected population groups.

- Although PHC has the potential to reduce health care disparities, it also has the potential to create or widen them if its benefits are inequitably directed or accessible.

D. Educating and Engaging Providers and Consumers

- The potential for realizing large-scale benefits of PHC depends on overcoming misconceptions about the role of genetics in disease, e.g., genetic determinism.
- The success of PHC will depend on translating evidence-based research into appropriate use in routine medical practice. This will require modernizing education of health care providers, including physicians, nurses, pharmacists, genetic counselors and others, regarding the benefits, risks and costs associated with PHC.
- The benefits and risks of validated PHC technologies must be communicated to the patient and the consumer. Patients must remain the focus of PHC.
- Patients need to be assured of protections of privacy and against discrimination based on personal genomic data.
- Providers need to be aware of the diverse sources and great volume of health information encountered by patients and other consumers, and to be prepared to share accurate, useful information about PHC and reduce its misuse and potential harm. The federal government can support efforts to create such information sources and make them readily available.

E. Using Databases to Build Evidence, Inform Decisions

- Realizing the potential of PHC, including to accelerate the discovery, development and delivery of diagnostics and therapeutics, will require linking and analyzing large magnitudes of data on genomics, biomarkers, health care interventions, outcomes and costs.
- Before widespread and integrated use of databases in PHC can occur, standards for their design and use are needed.
- Prospectively-generated databases and related studies are needed to further PHC.
- The federal government could facilitate and support efforts to enhance or develop PHC databases in the public and private sectors.
- The federal government could facilitate and support efforts to design and standardize databases and decision-support platforms for incorporation into health care practice.
- Large government and private sector investment in electronic health records, personal health records and other health information technology will be required to validate, implement and track the impact of PHC.
- The protection of privacy and confidentiality will be essential in the development of databases for PHC purposes.

I. Introduction

The concept of personalized health care has attracted considerable scientific, medical, commercial and policy interest for its potential to alter the orientation and delivery of health care. It is intended to shift diagnostic and therapeutic interventions from more traditional, population-based empirical approaches to those that are more scientifically-informed and tailored for individual patients.^{3,4,5,6} In short, personalized health care is intended to “deliver the right treatment to the right patient at the right time—every time.”⁷

Personalized health care (PHC) draws from information about differences in individual genomes, molecular- and cellular-level disease processes, health states, behavioral and environmental determinants and response to interventions. It applies this to deliver patient-specific health care, to determine risks of particular conditions or diseases and to facilitate the discovery and validation of health care products and other interventions. PHC may involve genetic and molecular testing, functional imaging⁸ or other means to determine a patient’s predisposition for particular health care responses and outcomes. Continued advances in health information technology should facilitate PHC research and delivery.

PHC is intended to improve the effectiveness and safety of health care interventions. For example, if successful, it should:

- Enable early and accurate prediction of disease risk
- Help to assess potential impacts of alternative interventions in individuals and specific populations
- Improve prevention and treatment
- Improve drug safety by identifying patients at risk for adverse drug reactions
- Improve quality of life and increase patient satisfaction with care
- Help to reduce health disparities
- Reduce economic burdens of chronic and complex diseases

As part of a broader vision of advancing and leveraging medical research to improve and transform health care in the US, the Secretary of the US Department of Health and Human

³ 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.

⁴ S.3822. Genomics and Personalized Medicine Act of 2006. Washington, DC: 109th 2d Session Congress of the United States, Senate, 2007. Washington, DC: United States Government Printing Office. Accessed April 19, 2007. http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=109_cong_bills&docid=f:s3822is.txt.pdf

⁵ Personalised medicines: hopes and realities. London, England: The Royal Society, 2005. Accessed April 25, 2006. <http://www.royalsoc.ac.uk/displaypagedoc.asp?id=15874>.

⁶ Ginsburg GS, Angrist M. The future may be closer than you think: a response from the Personalized Medicine Coalition to the Royal Society’s report on personalized medicine. *Future Medicine* 2006;3(2):119-23.

⁷ HHS Secretary Leavitt Announces Steps Toward A Future of "Personalized Health Care." Washington, DC: US Department of Health and Human Services. March 23, 2007. Accessed May 1, 2007. <http://www.hhs.gov/news/press/2007pres/20070323a.html>.

⁸ Using positron emission tomography (PET) and nuclear magnetic resonance imaging (MRI).

Services (DHHS) has identified PHC as one of the Department's top 10 priorities in the near- and long-term future.⁹ Four goals of the DHHS Personalized Health Care Initiative are:¹⁰

1. Link clinical and genomic information to support personalized health care
2. Protect individuals from discrimination-based or unauthorized use of genetic information
3. Ensure the accuracy and clinical validity of genetic tests performed for medical application purposes
4. Develop common policies for access to genomic databases for federally sponsored programs

PHC is still in its early stages. Progress at the clinical level has been slower than many early proponents had anticipated. Most of the available literature on PHC focuses on the use of pharmacogenetics or pharmacogenomics (PGx) to inform drug treatment. However, only a small number of PGx-based technologies have reached the market to date and, of those, few have achieved widespread use in practice. Among the challenges to PHC are: 1) modest genotype-specific clinical effects that often are confined to narrowly defined patient groups; 2) narrow applications of interventions to specific therapies; 3) insufficient knowledge regarding multiple gene interactions and modifiers of disease; 4) insufficient education and training of health professionals to deliver PHC where appropriate; and 5) ethical, legal, social and economic challenges to its use in clinical settings.^{11,12,13}

As recognized by the Expert Panel, collective engagement and investment of multiple stakeholders will be required to overcome barriers to successful implementation of PHC. This pertains to discovery and innovation; transparent and efficient (including aligned or integrated) regulatory and payment pathways; capacity for data collection, management and analysis; standards of data collection and sharing; patient and provider education about benefits, risks and value of PHC; protections of privacy and against discrimination based on genomic information; and using PHC to reduce health care disparities.

II. Convening the PHC Expert Panel

In order to further DHHS' understanding of PGx and to help advance the Secretary's vision of PHC, the Office of the Assistant Secretary for Planning and Evaluation (ASPE) commissioned The Lewin Group (Lewin) to convene the PHC Expert Panel for a one-day meeting on March 20, 2007, at the Hubert H. Humphrey building in Washington, DC. The meeting was moderated by Clifford Goodman, PhD, of The Lewin Group.

⁹ Secretary Mike Leavitt: DHHS priorities. Washington, DC: US Department of Health and Human Services. Accessed April 13, 2007. <http://www.hhs.gov/secretary/priorities/>.

¹⁰ Personalized Health Care. Washington, DC: US Department of Health and Human Services. June 25, 2007. Accessed July 1, 2007. <http://www.hhs.gov/myhealthcare/>.

¹¹ Garrison LP Jr., Austin MJ. Linking pharmacogenetics-based diagnostics and drugs for personalized medicine. *Health Aff* 2006;25(5):1281-90.

¹² 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.

¹³ Davies SM. Pharmacogenetics, pharmacogenomics and personalized medicine: are we there yet? *Hematology Am Soc Hematol Educ Program* 2006;111-7.

The purpose of the PHC Expert Panel was to provide input to the Office of the Secretary, DHHS, toward realizing the integration of PHC into clinical and public health practice. Information from this structured discussion is intended to help inform and enable the Secretary, other policymakers and other stakeholders to chart important steps over the next 5 to 20 years for transforming current health care practice into a system of PHC.

A. Selection of Expert Panelists

The PHC Expert Panel was comprised to represent various stakeholder perspectives involved in the integration of new technologies into clinical and public health care. Experts in relevant fields and areas of expertise were approached to participate in the panel, including experts in the following areas:

- Personalized medicine, including pharmacogenomics/genetics
- Technology transfer, diffusion and dissemination
- Drug and device development and approval process
- Publicly-funded health services, including state or locally funded programs, and genetic testing services
- Evidence-based medicine or outcomes research
- Clinical care databases (e.g., claims data, provider surveys)
- Health disparities and medically underserved populations
- Bioethics, particularly the ethical, legal and social implications of genetic research
- Health provider education and training
- Health insurance, particularly coverage decision-making
- Health communication, including with health providers

A total of 22 experts representing the private sector (e.g., payers, industry representatives, advocacy representatives) and public sector (e.g., Food and Drug Administration [FDA], Centers for Medicare & Medicaid Services [CMS], National Institutes of Health [NIH]), researchers and academia agreed to participate in the Expert Panel, listed in Exhibit 1.

Exhibit 1: PHC Expert Panel Members

MJ Finley Austin, PhD	Director, Public Policy, F. Hoffman-La Roche, Ltd.
Linda Bradley, PhD	Director, Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Project, National Office of Public Health Genomics, Centers for Disease Control and Prevention
Theresa Ann Cullen, MD, MS	Chief Information Officer, Director of the Office of Information Technology, Indian Health Service
Kevin T. FitzGerald, SJ, PhD, PhD	David P. Lauler Chair in Catholic Health Care Ethics, Research Associate Professor, Department of Oncology, Georgetown University Medical Center Chair, Pharmacogenomics Task Force, Secretary's Advisory Committee on Genetics, Health, and Society

Felix W. Frueh, PhD	Associate Director for Genomics, Office of Clinical Pharmacology, Center for Drug Evaluation and Research, Food and Drug Administration
Alan E. Guttmacher, MD	Deputy Director, National Human Genome Research Institute, National Institutes of Health
Marcia A. Kean, MBA	Chief Executive Officer, Feinstein Kean Healthcare
Allan Korn, MD	Senior Vice President and Chief Medical Officer, Blue Cross and Blue Shield Association
Harlan A. Levine, MD	Chief Clinical Officer, Specialized Care Services, UnitedHealth Group
Patricia Love, MD, MBA	Associate Director, Office of Combination Products, Food and Drug Administration
Peter Neumann, ScD	Director, Center for the Evaluation of Value and Risk in Health, Institute for Clinical Research and Health Policy Studies, Tufts-New England Medical Center
Robert Nussbaum, MD	Holly Smith Distinguished Professor in Medicine, Chief of Division of Medical Genetics, University of California, San Francisco
Christopher O'Donnell, MD, MPH	Medical Officer, National Heart, Lung, and Blood Institute
Kathryn Phillips, PhD	Professor, Health Services and Research and Health Economics, University of California, San Francisco
Steve Phurrough, MD, MPA	Director, Coverage and Analysis Group, Centers for Medicare & Medicaid Services
Tanya Pagan Raggio, MD, MPH, FAAP	Director, Division of Medicine and Dentistry, Bureau of Health Professions, Health Resources and Services Administration
Gurvaneet Randhawa, MD, MPH	Evidence-based Practice Centers Program Task Order Officer, Center for Outcomes and Evidence, Agency for Healthcare Research and Quality
Wayne A. Rosenkrans, Jr., PhD	Business Strategy Director, External Scientific Affairs, AstraZeneca Pharmaceuticals
Michael Schoenbaum, PhD	Senior Advisor for Mental Health, Epidemiology and Economics, Division of Services and Intervention Research, National Institute of Mental Health
Harold C. Sox, Jr., MD, MACP	Editor, Annals of Internal Medicine
Paul Tang, MD	Internist and Vice President, Chief Medical Information Officer, Palo Alto Medical Foundation, a Sutter Health Affiliate
Patrick Terry	Cofounder and Director of Consumer Advocacy, Genomic Health, Inc.; Cofounder Personalized Medicine Coalition; and Cofounder, PXE International

B. Background Materials

Prior to the Expert Panel meeting, panel members were provided with background information to assist them in their preparation for the meeting, including an environmental scan of issues relevant to PHC. The environmental scan highlighted opportunities and barriers related to transferring PGx technologies to clinical and public health practice. Panel members also were provided with a brief discussion guide, which outlined the main issues, a set of forward-oriented assumptions and a set of questions intended to prompt and focus discussion

on each main issue that they were being asked to consider.¹⁴ These materials were prepared by Lewin. The discussion guide can be found in the Appendix.

C. Main Issues and Assumptions for Discussion

During the Expert Panel meeting, panelists considered and discussed the following five main issues pertaining to the integration of PHC into clinical and public health practice:

- Demonstrating clinical validity and utility of PHC
- Demonstrating value/cost-effectiveness of PHC
- Identifying the role of PHC in reducing health disparities
- Educating and engaging providers and patients about PHC
- Using databases to build evidence and inform decisions in PHC

Given that DHHS intends to sustain the effort to implement PHC in the long-term as well as the short-term, panel members were asked to provide input to assist DHHS in charting steps to advance PHC over the next 5 to 20 years. The Expert Panel was provided with a set of forward-oriented assumptions, listed in Exhibit 2, to help guide their comments on the integration of PHC.

Exhibit 2: PHC Expert Panel Assumptions

- Electronic health records (EHRs) will be widely available in 5 to 10 years, and systems will be able to routinely capture data required to support personalized health care principles and practices.
- The terms “molecular tests” and “genetic assay-based tests” also include functional imaging tests that define cellular or molecular interactions and provide mechanistic information supporting clinical decision-making (i.e., PET and MRI, as opposed to radiographic or ultrasound procedures).
- Evidence-based decision-making (e.g., practice guided by clinical protocols) will become widely implemented, particularly through reimbursement strategies for certain diseases.
- DHHS particularly is interested in the possibility of using PHC to address the top chronic diseases that account for the bulk of disease burden that our society encounters, including diseases of the heart, all cancers, stroke and diabetes mellitus.

In particular, panel members were asked to comment on current and potential facilitators and barriers to PHC, incentives and disincentives, the pre- and post-marketing environments, the integration of PHC with health information technology and the potential view of PHC as being “disruptive” to the current health care system.¹⁵ Panel members also were asked to comment on potential stakeholder perspectives (e.g., patients/consumers, providers, payers, policymakers, employers) concerning these issues. In addition to the structured discussion, panelists were asked at the opening and closing of the meeting to provide hand-written comments on particular issues.

¹⁴ The environmental scan and discussion guide were prepared by The Lewin Group.

¹⁵ A disruptive technology or service is a non-incremental innovation that unexpectedly or suddenly replaces an existing dominant technology or service. Initially, it may be unrefined, have performance problems due to its novelty, and may not yet have a proven application. See: Bower JL, Christensen CM. Disruptive technologies: catching the wave. Harvard Bus Rev 1995;Jan-Feb:1-11.

While there was general consensus among the panelists on many of the observations summarized here, some of the views were expressed or agreed upon by smaller subsets of panelists.

A draft version of this summary report was circulated to the Expert Panel members for review and comment. Panelists supplied corrections and suggested clarifications and greater detail to better convey their observations at the meeting. This input from the panelists was integrated, as appropriate, into this final summary report.

III. PHC Expert Panel Observations

This section of the report summarizes key observations that emerged from the Expert Panel's discussion of the five main issues. The following subsections correspond to these main issues and include a brief description of each issue, followed by a summary highlighting relevant key points and observations of the panel.

A. Demonstrating Clinical Validity and Utility

1. *The Issue*

Successfully translating scientific discoveries into PHC will require demonstrating the analytic and clinical validity and the clinical utility of technologies intended for PHC, including genetic and genomic tests. Genetic tests used for detection of variant genes typically are highly accurate, with analytic sensitivities and specificities at or near 99% when conducted using direct sequencing and restriction site assays.¹⁶ However, complicated genetic interactions and gene-environment interactions limit the singular ability of genetic or genomic testing to predict a particular disorder (i.e., phenotype) and health outcomes. While currently identified genes provide some biological clues, they often are poor predictors of disease or drug response.¹⁷ Thus, beyond analytic validity, the clinical validity of a genetic test depends on how well the test identifies phenotype or predicts a particular clinical outcome.^{18,19}

"Health isn't about genes alone; it is about the interaction of genes and environment, about which we need much, much more data."

Panelist

A genetic test with proven analytic validity and clinical validity does not have clinical utility unless it offers a favorable net balance of risks and benefits as used in routine practice. A genetic test with clinical utility has the potential to augment what is known already about an individual's condition—or provide similar information in an alternative, non-redundant, more efficient or cost-effective manner—and inform a decision to undertake a viable and available

¹⁶ Veenstra DL, Higashi MK, Phillips KA. Assessing the cost-effectiveness of pharmacogenomics. *AAPS PharmSci*. 2000;2(3):E29.

¹⁷ Garrison LP Jr. 2006.

¹⁸ Human Genome Epidemiology. Rome, Italy: International Clearinghouse for Birth Defects Surveillance and Research/Centers for Disease Control. Accessed August 4, 2006.

http://www.icbd.org/images/lectures/MKhoury-HumGenomeEpidemiol%20-cambridge_02_lecture1.PPT#396,23,Epidemiologic Approach to Genetic Tests

¹⁹ 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.

intervention, behavior change, life planning or other option that may affect health outcomes, life events or quality of life.^{20,21} (See Exhibit 3 for examples of relevant definitions.)

The preferred methods for demonstrating efficacy and safety of PHC interventions, as for most health care interventions, involve controlled clinical trials, particularly randomized controlled trials (RCTs). However, RCTs may have limited external validity, i.e., beyond the conditions of the study, such as generalizability to other populations, care patterns or settings. Further, the pace of technological innovation can exceed the availability of funding to implement the types of large, diverse and long-term RCTs that would be needed to establish clinical utility. Rapid technological change also can outstrip the relevance of findings of long-term trials. As such, observational studies and other relatively timely and lower-cost types of studies may be helpful in providing important information about health status and health care that does not emerge from RCTs and other clinical trials designed for establishing safety, efficacy or effectiveness, e.g., regarding the natural history of disease or clinical practice patterns. On the other hand, the validity of findings from observational studies regarding causal connections between interventions and patient outcomes typically are more subject to selection bias and other methodological flaws than findings from RCTs and other experimental studies. In order to strengthen the evidence base for PHC technologies, the strengths and weaknesses of these study designs for particular technologies and scenarios must be considered.

Exhibit 3: Validity and Utility of Genetic Tests

- **Analytic validity:** A test's ability to accurately and reliably measure the genotype of interest. Analytic validity focuses on the laboratory components of testing, including analytic sensitivity, analytic specificity, laboratory quality control and assay robustness.
- **Clinical validity:** A test's ability to detect or predict the associated disorder (phenotype), including clinical sensitivity (or the clinical detection rate), clinical specificity and positive and negative predictive values. Clinical validity is affected by the prevalence of the disorder, penetrance, analytic sensitivity and genetic and environmental modifiers.
- **Clinical utility:** The net balance of risks and benefits associated with using a test in routine practice. In the ACCE model, other elements or contextual factors to be considered include the natural history of the disorder, availability and effectiveness of interventions, quality assurance, health risks of testing or resulting interventions, financial impacts of testing, adequacy of facilities to provide services, availability of patient and provider education and monitoring and evaluation of test performance in practice.

Adapted from: Evaluation of Genetic Testing. ACCE: A CDC-Sponsored Project Carried Out by the Foundation of Blood Research. Centers for Disease Control and Prevention, National Office of Public Health Genomics. Accessed June 1, 2007. <http://www.cdc.gov/genomics/gtesting/ACCE.htm>.

2. Key Expert Panel Observations

Panel members offered the following views regarding the demonstration of clinical validity and utility of PHC.

- **The great share of population disease burden arises from complex disease processes involving often inadequately-understood genomic, environmental, behavioral and other**

²⁰ Holtzman NA. Bringing genetic tests into the clinic. *Hosp Pract (Off Ed)* 1998;33(1):107-21.

²¹ Grosse SD, Khoury MJ. What is the clinical utility of genetic testing? *Genetics in Medicine* 2006;8(7):448-50.

factors. This complexity poses higher hurdles to establishing clinical validity and utility of PGx testing and other PHC interventions than those that existed for early PGx gains based on the ability to detect and manage conditions or diseases mediated by single genetic traits. Expectations of the public, health care providers and policymakers for PHC may have to be adjusted accordingly. These considerations should be reflected in investment priorities for biomedical and behavioral science and clinically targeted research.

- **Although usually preferred where feasible, RCTs are not the only means of generating needed evidence on the clinical utility (risks and benefits) of tests and other interventions used in PHC.** RCTs are not necessary or usual for establishing clinical validity (ability to detect or predict a disorder) of tests. While RCTs generally are preferred for demonstrating safety and efficacy (or effectiveness) of human health care products and other interventions, they should not be regarded as the only means of generating data to establish clinical utility of PHC interventions. In some circumstances, an RCT may be less desirable and less cost-effective than other study designs for generating such data. For certain rapidly evolving treatment circumstances (e.g., microbial mutations), RCTs may need augmentation from other data sources. In some settings, traditional RCT designs may be underpowered to reveal how various constellations of patient characteristics and environmental factors mediate the health effects of therapies. RCTs used to gain marketing approval for therapeutics may have limited external validity, while practical RCTs can improve understanding of the utility of therapeutics. Population-based research trial designs will be needed to identify and quantify the relationships among genomic traits, biomarkers, therapies and health outcomes to establish the full spectrum of PHC.
- **Observational studies can augment the evidence base for PHC, including to assess clinical validity of tests. However, they generally are less useful for assessing clinical utility and are not adequate substitutes for RCTs in establishing cause-and-effect relationships between PHC interventions and health outcomes.** Observational studies can provide important insights about the effectiveness of PHC technologies. For instance, analyses of retrospective data may suggest the potential utility of genetic testing, as in the case of managing the use of warfarin in patients at high risk for blood clots. Prospective, protocol-based observational studies, such as the Framingham Heart Study, have been very useful in establishing the natural course of disease, identifying factors mediating the risk of disease and identifying rare or long-term adverse effects. Still, observational studies usually are insufficient for confirming cause-and-effect relationships. RCTs generally would establish the specific relationships.
- **New study designs and methods should facilitate evaluation of PHC technologies.** Emerging study designs and methods to examine PHC include adaptive clinical trials, the use of modeling and projections when initial evidence is scarce and prospectively designed post-market studies. Drawing on Bayesian statistical methods, adaptive trial designs can lessen patient exposure to adverse events and increase enrollment of patient types who appear more likely to respond favorably. For example, if interim trial results indicate that patients with particular genetic characteristics respond better to a specific treatment, investigators can recruit more patients of this type to that study arm. This may enable significant reduction in patient enrollment for a trial and associated costs. Such approaches could augment an RCT or observational study design.

- **Genetic/genomic tests are of little or no clinical value without availability of validated, associated interventions—whether prevention strategies, treatments, behavior changes, life planning alternatives or others—whose use is informed by those test results.** In some instances, testing for harmful genetic traits can be useful for life planning (e.g., counseling about conception and prenatal testing for genetic disorders) even when no effective preventive or treatment options exist. In addition, testing for harmful genetic/genomic traits is practical only when gene variants are known to be associated with risk of disease occurrence or progression, when test results are known to contribute to clinical findings (e.g., with new information or more efficiently produced information), when these clinical findings can be used to inform intervention decisions and when interventions tested in patients with and without the gene variants are demonstrated to have important differential effects on outcomes. For some diagnostic tests, co-development with the therapeutic, so that both are available at the time of approval, may be highly desirable. Such co-development may shorten the development time. Also, certain diagnostic tests that are critical in research and development of therapeutics are not necessary for subsequent use in practice.
- “There is no point in developing a genetic test until some treatment or other application is available where use is informed by the results of the test.”*

Panelist
- **Clinical utility of genomic testing and other PHC interventions must be supported with data generated in real health care settings.** While pre-market trials of technologies often are used to assess risks and benefits in controlled settings, these findings are not necessarily generalizable to practice in real health care settings with varying environmental influences. Further data collection in those settings is needed to establish the effectiveness of these interventions in clinical practice.
 - **Integrated data collection, spanning pre- and post-market phases, is needed to demonstrate clinical validity and utility of PHC.** Post-market studies of approved products can be used to demonstrate effectiveness (how well interventions work in community or other routine settings) and detect longer term effects and infrequent, yet serious, adverse effects that could not be identified in smaller controlled trial settings.

 - Although industry takes the lead in developing pre-market evidence for these technologies and conducts considerable post-market data collection, some observers suggest that it may have less incentive to sponsor post-market studies that might reveal adverse effects, lead to narrowed clinical indications or corroborate pre-market findings in different post-market settings.
 - Better integration of pre- and post-market studies may align pre- and post-market regulatory and third-party payment policies, as well as clinical practice guidelines.
 - Study designs and methods of data collection should be commensurate with the type of evidence needed to validate and track the benefits and risks of particular interventions for population groups, health care settings and adaptation to new indications, comparators/standards of care and other evolving factors.
- “DHHS has the opportunity to lead in PHC/genomic medicine by investment over a 5 to 20 year horizon in a balanced portfolio of prospective observational studies, RCTs and careful use of available databases, including EMRs and claims data in adequately sized populations representative of the diversity of our population in the US.”*

Panelist

- Funding of this ongoing data collection should be supported by the public and private sectors.
- **Coverage of PHC interventions by public and private sector payers should be subject to data collection throughout their lifecycles.** This may entail conditional coverage of interventions linked to collection of data on effectiveness in general practice, potential rare and long-term risks, changing indications and other aspects that are not discernable in short-term efficacy studies. Modeling and statistical/epidemiological methods may be appropriate until sufficient primary data can be gathered.
- **Better alignment of requirements and processes of DHHS agencies and other organizations responsible for regulation and reimbursement would improve the generation of evidence for clinical validity and utility.** Such coordination would provide a more clear, efficient pathway to market and patient access and, thereby, would facilitate development of trial designs to provide concurrently the necessary information for product approval and reimbursement. Further, it would support the demonstration of added value in practice.
- **Standards are needed to establish robust evidence requirements and methods for assessing the validity and utility of PHC interventions.** These standards and trial design approaches should be appropriate for the intended purpose of the study and database. The need for standards applies to pre- and post-market phases; nomenclature; testing for prediction, diagnosis and treatment; and adaptation to emerging technologies. The CDC EGAPP is demonstrating a model approach for establishing and applying such evidence requirements.²²

B. Demonstrating Value

1. *The Issue*

The development, adoption and use of PHC will be mediated by its perceived value, including cost-effectiveness or other health-economic tradeoffs, to potential users and purchasers. For example, the use of PGx testing will have economic impacts via unit costs of tests and the volume of the tests, as well as genetic counseling and resulting changes in health events and use of health care services. Given findings about differences in effectiveness and safety of PHC interventions relative to standard care, decision-makers may want objective means of weighing those clinical differences with differences in costs, including short- and long-term costs.

PGx-based tests and therapies and other PHC technologies may reduce downstream health care costs by preventing or delaying the onset of illness, diminishing its duration and/or severity and avoiding ineffective treatments and adverse drug reactions.²³ PGx tests may help clinicians to identify patients who are more likely to respond to a treatment, potentially eliminating

²² Evaluation of Genomic Applications in Practice and Prevention (EGAPP) is a pilot project initiated by the CDC National Office of Public Health Genomics in 2004. Organized around an independent, non-federal working group, its goal is to establish and evaluate a systematic, evidence-based process for assessing genetic tests and other applications of genomic technology in transition from research to clinical and public health practice.

²³ Bartfai T. Pharmacogenomics in drug development: societal and technical aspects. *Pharmacogenomics J* 2004;4:226-32.

unnecessary treatment for those who have an unfavorable risk-benefit ratio.²⁴ As PGx diagnostics become more readily available, consumers may experience short-term increases in the cost of health care due to adoption and use of tests, drugs and other health care.^{25,26}

Translation of PHC technologies into clinical practice and achieving coverage and adequate payment also will be influenced by demonstrated tradeoffs of the costs and clinical benefits they offer relative to prevailing standards of care. These tradeoffs typically are quantified using cost-effectiveness analysis and related methods. However, little research has been conducted to date on the cost-effectiveness of PGx interventions, and the few available cost-effectiveness analyses of PGx products have yielded largely inconclusive results.^{27,28} As more PHC technologies become available that have high unit costs or that have the potential to be used in high volume, there will be greater demand for information about their cost-effectiveness.

2. Key Expert Panel Observations

Panel members offered the following views regarding the demonstration of value and cost-effectiveness of PHC.

- **While its impact on aggregate health care spending remains to be determined, PHC has considerable potential to improve the return on health care investment.** While some new technologies result in short- and/or long-term net savings, many new technologies increase health care costs by, e.g., substituting for less expensive interventions that provide the same benefit, being adopted and used more widely than anticipated or inducing additional downstream interventions. Even so, some PHC interventions will result in cost-effective improvements (i.e., better returns on investment than existing alternatives) in access, health outcomes and quality of life.
- “Demonstrating the value of personalized care, let alone realizing this value, will require an enormous amount of efficacy and effectiveness research, much of it public. This may be expensive up front, but buying new technologies without adequate evidence, especially given our prevailing quality and organization of care, is almost certainly more expensive.”*

Panelist
- **Despite its promise, the evidence base for demonstrating the value of PHC on health outcomes still is sparse.** Demonstrating the value of new and evolving PHC interventions will require major, long-term investment in data collection and analysis. Though substantial, this investment is warranted relative to the potential risks and costs associated with adoption and use of interventions that otherwise would be inadequately validated and monitored.

²⁴ Garrison LP Jr. 2006.

²⁵ Pharmacogenetics: ethical issues. London, England: Nuffield Council on Bioethics, 2003. Accessed April 25, 2006. http://www.nuffieldbioethics.org/fileLibrary/pdf/pharmacogenetics_report.pdf.

²⁶ Personalized medicine: the emerging pharmacogenomics revolution. New York, NY: PricewaterhouseCoopers, 2005. Accessed April 25, 2006. <http://www.pwc.com/techforecast/pdfs/pharmaco-wb-x.pdf>.

²⁷ Phillips KA. The intersection of biotechnology and pharmacogenomics: health policy implications. *Health Aff* 2006;25(5):1271-80.

²⁸ Phillips KA, Van Bebber SL. A systematic review of cost-effectiveness analyses of pharmacogenomic interventions. *Pharmacogenomics* 2004;5(8):1129-49.

- **The federal government can influence the adoption and reimbursement of PHC, including by sponsoring comparative effectiveness and cost-effectiveness research.** Panel members indicated that comparative effectiveness and cost-effectiveness data would influence adoption and use of PHC interventions, and some panelists indicated that the federal government should lead the effort to support such studies. Collaborations among FDA, CMS and other agencies such as the Agency for Healthcare Research and Quality (AHRQ) and the Centers for Disease Control and Prevention (CDC), can help to identify and address gaps in evidence, toward expediting the advancement of PHC. For example, CMS is attaching more requirements for post-market collection of clinical data to some of its coverage decisions in ways that complement FDA and CDC post-marketing surveillance. Incorporating cost-effectiveness considerations into Medicare coverage decisions, as some observers suggest, could require statutory changes. As instructed by Congress, AHRQ is sponsoring a program of comparative effectiveness research.
- **To justify payment, a diagnostic test should be demonstrated to alter the management of a disease and achieve benefits that could not have occurred otherwise as cost-effectively.** One panel member noted a need to “leverage a payment threshold, in order to yield data that will be helpful in making clinical decisions.” That is, payers should not cover a test whose results do not alter patient or provider behavior in a way that is likely to result in improved outcomes. Similarly, another panel member indicated that “the standards of evidence required for reimbursement of PHC should be set high. Currently, many health care services are paid for based [only] on surrogate outcomes.” Another panelist noted that a broad, high payment threshold approach may discourage needed innovation.
- **Data sources and methods for determining value and allocating resources for PHC interventions should account for their use, and health and economic impacts, in practice.** Data from administrative and other routine databases may help to approximate the costs of PHC in real-world settings more realistically than cost data generated from clinical trials. In addition to the immediate unit cost of an intervention, analyses of claims data can track resulting changes in downstream costs in multiple health care settings, including cost differences that may not have accrued during the follow-up periods of clinical trials.
- **Value assessment of PHC products should consider broader economic and social impacts, as with any genomic application or other health technology.** As is so for other interventions, the value of PHC may depend not only on its cost-effectiveness ratio, but the extent of its impact on population disease burden and aggregate costs. As noted by one expert, “we can have something that affects a large population, but has small individual disease burden. Should we focus where there is a large unmet need or on the issues that represent the largest health care cost centers (e.g., cancer, diabetes)?” Assessment of PHC-based interventions should include consideration of other economic impacts, such as on direct non-health care costs (e.g., of patient time and gaining access to care) and indirect costs (such as worker productivity or family care-giving).
- **Realization of the value of PHC in screening and primary disease prevention in the Medicare population is subject to the limitation of the Medicare statute.** This limitation precludes coverage for such services, except where Congress has intervened for particular services. Removal of this limitation and assigning the responsibility for making coverage decisions for screening and primary prevention services to CMS, using a transparent and

rigorous evidence-based process, would increase the value of certain PHC services to the Medicare population.

C. Reducing Health Disparities

1. *The Issue*

Reducing the considerable disparities in US health care will require lowering broad social, economic, cultural and environmental barriers. There are many opportunities for PHC to lower health care disparities. For example, PGx research has identified genetically-determined differences among individuals in the drug metabolism, clinical effectiveness and adverse effects. To the extent that genetic characteristics linked to drug response are identified disproportionately in particular underserved demographic groups, PGx may assist in improved drug selection and dosing for patients in those groups.

Reducing disparities using PHC will involve more than advances in testing and therapies. It also will require changes in how health care is delivered. Health care delivery interventions that have been reported to be effective in reducing disparities include the use of multifaceted approaches, culturally and linguistically appropriate methods, establishment of partnerships with stakeholders and community involvement.²⁹

If not carefully managed, use of PGx-based interventions could create or widen disparities. Subgroups for which viable treatments do not exist may be partitioned out of target populations for drug development. Also, a disproportionate share of PHC data may be generated for those who can afford, whether via out-of-pocket payment or due to their insured status, to be tested more often. For historical, social and other reasons, there may be greater reluctance among some population groups to enroll in clinical trials, including for assessing PHC interventions. To further reduce the risk of exacerbating discrimination and disparities as a result of PHC, various technical, social and legal methods of protecting confidential information from misuse will need to be implemented.

Where targeted therapies are developed, those that are premium priced may be out of reach of underinsured or uninsured patients. Recent experience with BiDil, a combination medication approved by FDA for treating heart failure in self-identified black patients, suggests some support for this concern. Health plans have resisted paying a premium price for this branded drug, which may pose a barrier to its use for many patients who might benefit from it.³⁰ Even so, the two generic drugs that comprise BiDil are readily available at a combined cost that is well below that of the branded drug.³¹

In the absence of accurate tests for determining genetic variants associated with drug response, clinicians and patients seeking to personalize health care decisions may default to making

²⁹ Cooper LA, Hill MN, Powe NR. Designing and evaluating interventions to eliminate racial and ethnic disparities in health care. *J Gen Intern Med* 2002;17(6):477-86.

³⁰ Westphal SP. Heart medication approved for blacks faces uphill battle. *Wall Street Journal*. October 16, 2006:A1.

³¹ BiDil is a combination of hydralazine hydrochloride and isosorbide dinitrate. It is not a PGx product, in that its approved indication is not linked to genomic information and its mechanism of action has not been directly linked to specific genes. See, e.g., Kahn J. Race, pharmacogenomics, and marketing: Putting BiDil in context. *Am J Bioeth* 2006;6(5):W1-5.

suboptimal decisions based on conventional notions of racial and ethnic biology as proxies for more precise selection criteria. Aside from implications for equity, this increasingly appears to be scientifically unjustifiable, as research findings indicate that self-identification of race or ethnicity can be a poor predictor of genetic predisposition for conditions, diseases or health outcomes.^{32,33}

2. Key Expert Panel Observations

Panelists discussed three main aspects regarding health care disparities, including the need for better understanding of the causes of disparities, how PHC could reduce some disparities and the need to ensure that PHC not add to disparities. The Expert Panel provided the following observations regarding the role of PHC and health care disparities.

- **More research is needed to understand the causes of health care disparities and means for preventing or reducing them.** Data mining among existing and linked databases could help to discern disparities and causal factors or proxies such as non-compliance. One opportunity to track new disparities would be to add data fields to existing surveys, such as the AHRQ National Healthcare Disparities Report.
- **Development and introduction of PHC provide opportunities to learn about factors that may contribute to disparities and ways to prevent or reduce them.** The introduction of PHC may result in new health care paradigms that could alter the environment for and causal factors of health care disparities.
 - Prospective and retrospective data collection are needed to identify and track disparities that might emerge from PHC. This data collection should begin during the development of PHC interventions.
 - Among the tools for diminishing disparities are provider feedback and other quality reporting, guidances and regulations, payment policies, professional standards/guidelines and incentives. Incentives through statutory changes, tax incentives or funding support for pre- and post-market research could help to ensure the representation of all populations in the data collection.
- **Reducing disparities will require representing all populations in biomedical research and related data collection.** The findings of large-scale research that involves genomic data can be biased if certain subpopulations are underrepresented due to disparities in access to research or concerns about involvement in research. Given the increasing diversity of the US population, participation in data collection will require culturally competent education and counseling and greater health literacy. Federal non-discrimination laws can diminish concerns about the misuse of genetic data gathered in research or clinical care.

“There are far more disparities arising from economic disadvantages [than from genetics]. Focusing too much on genetics may be a distraction, causing us to ignore harder social questions.”

Panelist

³² Rebbeck TR, Halbert CH, Sankar P. Genetics, epidemiology, and cancer disparities: is it black and white? J Clin Oncol 2006;24(14):2164-9.

³³ Pharmacogenetics: ethical issues, 2003.

- **The history of health care disparities, and prevailing factors that continue to contribute to them, may raise barriers to adoption of PHC by affected population groups.** Therefore, efforts to reduce disparities must also document the benefits, risks and value of PHC and convey these to the affected groups.
- **Although PHC has the potential to reduce health care disparities, it also has the potential to create or widen them, if its benefits are inequitably directed or accessible.** Innovation in PHC could help to decrease disparities by identifying therapies for currently underserved populations. However, panelists noted:
 - PGx can enable drug development efforts to be oriented toward larger groups of patients that are likely responders, which may exclude less likely responders from clinical trials and the ultimate benefits of pharmaceutical R&D.
 - Identification of new patient subgroups through testing could lead to disparities in access and treatment. Even within therapeutic categories for subpopulations, there could be varying degrees of benefit. Although socioeconomic factors are at the root of many health disparities, advancements in PHC could redefine disparity based on differential drug response in different population groups.
 - Developing drugs for small subpopulations generally is not in the business interest of industry, unless these products can be expected to demand price premiums. Even if industry has the capacity to find solutions for affordability problems, developing highly effective drugs for the largest populations is usually the priority.

D. Educating and Engaging Providers and Patients

1. *The Issue*

As PGx testing and related approaches to PHC progress from development to practice, it will be necessary to develop and implement educational tools and programs for providers, patients and others. These sources will help stakeholders to make informed health care decisions in light of medical advances and policies related to PHC. Health care providers, including physicians, nurses, pharmacists, genetic counselors and others, will play important roles in implementing PHC in practice. Adoption and routine use of PHC will depend on their acceptance of PGx tests and other technologies, given complex concerns regarding the benefits, risks and costs associated with these tests.³⁴ Providers will be challenged to remain informed about test availability, indications, accuracy, clinical utility and costs.

As PHC becomes widely adopted, patients will need to be aware of and understand their diagnostic and treatment options. Some information on PGx has been tailored to consumers and can be found on the Internet, such as online PHC education resources provided by NIH.³⁵ Still, much of this information must be incorporated into provider-patient communications. Patients will seek information from their providers about risks and benefits of testing and their treatment options based on test results. Providers will need to be prepared to provide accurate

³⁴ 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.

³⁵ Medicines for you: studying how your genes can make a difference. Bethesda, MD: National Institute of General Medical Sciences, 2005. Accessed May 7, 2006. <http://publications.nigms.nih.gov/medsforyou/index.html>.

and comprehensible information to patients and the means to provide or refer them to counseling, as appropriate.³⁶

Also, providers will need to be able to address the consent and confidentiality concerns of their patients.³⁷ Among these concerns is protection specific to genetic information. For example, the Genetic Information Nondiscrimination Act of 2007 (GINA) is intended to prohibit the use of genetic information (e.g., results of genetic tests and family history of disease) by employers in employment decisions and by health insurers and health plans in making enrollment determinations and setting premiums.³⁸ A national survey performed in early 2007 found that, while Americans generally were supportive of the use of genetic information to improve health care, 92% were concerned that this information could be used in ways that harm them. Further, 76% supported legislation that would prevent health insurers or employers from accessing their genetic information or using it to make decisions about their employment or insurability.³⁹

2. Key Expert Panel Observations

The Expert Panel identified the following points regarding educating providers and patients about PHC.

- **The potential for realizing large-scale benefits of PHC depends on overcoming misconceptions about the role of genetics in disease, e.g., genetic determinism.**⁴⁰ This understanding pertains to the relative contribution of genotype to disease risk, the ability of tests to assess these traits and the ability of targeted or personalized therapies to prevent or cure genetically-mediated diseases. Beyond the basic model of a single genetic test for a single disease, PHC will involve using and linking complex genomic, biomarker, imaging and other datasets to predict and manage many disease states. Also pertinent are different implications of testing for and managing conditions derived from inherited, as opposed to somatic, genetic variations. Conveying the multifactorial basis of most genomic-influenced diseases will require extensive education and continuing education that is tailored for clinicians, public health workers, patients, providers, payers and policymakers.
- **The success of PHC will depend on translating evidence-based research into appropriate use in routine medical practice.** Beyond the need to generate rigorous research findings on PHC interventions, much greater emphasis is needed on interpretation and practical application of research findings in clinical care. This would benefit from incorporating aspects of PHC into medical school and other health professional curricula. Clinical practice and payment are unlikely to change unless the utility of PHC is demonstrated persuasively. Possible steps toward modernizing the education of health professionals include:

³⁶ Phillips KA 2004.

³⁷ Pharmacogenetics: ethical issues, 2003.

³⁸ GINA was passed by the US House of Representatives in April 2007, but the Senate had not voted on it at this writing.

³⁹ US Public Opinion on Uses of Genetic Information and Genetic Discrimination. Washington, DC: Genetics and Public Policy Center, April 24, 2007. Accessed July 1, 2007.

http://www.dnapolicy.org/resources/GINAPublic_Opinion_Genetic_Information_Discrimination.pdf.

⁴⁰ Genetic determinism refers to the belief that genotype completely determines phenotype.

- Training health care providers in principles of evidence-based medicine and providing decision-support tools and evidence-based guidelines pertaining to PHC interventions.
 - Strengthening training and support for genetic counseling and coping with emotional and social impact on patients and families of unfavorable test results.
 - Accelerating initiatives on information access and education in genomic medicine by professional groups such as the American Medical Association, American Nurses Association and the American Academy of Family Physicians, as well as the National Coalition for Health Professional Education in Genetics (NCHPEG).^{41,42}
- “[Providers] don’t care about the black box [workings] of the genetic test, but what to do with the output.”*

Panelist
- **The benefits and risks of validated PHC technologies must be communicated to the patient and the consumer. Patients must remain the focus of PHC.** Ongoing, appropriately tailored PHC education will be needed for patients and consumers. Conveying the benefits and risks of using personal genetic and genomic data should include information about protections against its misuse. The following general steps could be taken to engage and educate patients about PHC:
 - Convey to patients and other consumers readily comprehensible evidence for the value to personal health of testing and awareness of personal genetic information.
 - Improve health care professionals’ ability to interpret and convey to patients the additional information about probabilities of adverse events and treatment effectiveness that arises from PHC test results.
 - Convey to patients that they, like their clinicians and other stakeholders, have responsibilities (e.g., behavior and lifestyle changes, compliance with therapies), as well as opportunities for realizing the benefits of PHC.
 - Support institutions such as NCHPEG that are involved in education and incorporation of the patient’s perspective.
 - Evaluate the effectiveness of pay-for-performance programs aimed at patients (i.e., financial incentives for seeking and complying with PHC).
 - Adjust procedure coding and payment levels to include incentives for physicians and other providers to educate patients about PHC.
 - **Patients need to be assured of protections of privacy and against discrimination based on personal genomic data.** The large, aggregated datasets of population-based genomic data that will be used in PHC research and clinical practice raise consumer concerns about misuse of such data in, e.g., employment or insurance discrimination. Patients, providers, the public and other stakeholders must be engaged at every stage of PHC development and delivery in establishing and updating protections against such misuse, educated about

⁴¹ Annual clinical focus 2005 genomics. Leawood, KS, American Academy of Family Physicians, 2006. Accessed May 5, 2006. <http://www.aafp.org/online/en/home/clinical/acf/genomics.html>.

⁴² National Coalition for Health Professional Education in Genetics, 2006. Accessed April 12, 2006. <http://www.nchpeg.org/index.asp>.

them and assured of their implementation. It is not apparent that the body of existing protections, including the Health Information Portability and Accountability Act (HIPAA), are adequate. Further protections, such as the Genetic Information Non-Discrimination Act of 2007 or related legislation, are needed.

- **Providers need to be aware of the diverse sources and great volume of health information encountered by patients and other consumers, and to be prepared to share accurate, useful information about PHC and reduce its misuse and potential harm. Government can support efforts to create such information sources and make them readily available.** Consumer uptake of health care information from sources beyond the traditional provider-patient interface is increasing rapidly. Consumers independently acquire information through the Internet, direct-to-consumer (DTC) advertising and other sources outside of clinical settings. Providers should be aware of these trends and be prepared to educate patients, answer their questions and counteract incorrect information and patient misunderstanding.

E. Using Databases to Build Evidence and Inform Decisions

1. *The Issue*

As described in Section A above, clinical trials, and RCTs in particular, are the preferred methods for assessing cause-and-effect relationships of interventions on designated outcomes. These methods are subject to certain weaknesses (e.g., may lack external validity for different populations and clinical settings) and disadvantages (e.g., high cost, design not applicable to different uses, insufficient duration to discern long-term effects) and are not the best approaches for answering certain questions pertaining to PHC in clinical practice. Various forms of observational studies can complement clinical trials in many respects.

Among observational data sources, routine or administrative databases (e.g., medical records systems, insurance claims, registries, etc.) can be used to provide timely and relatively low-cost information about PHC's influence on health status and health care, including data on health outcomes, patterns of use and costs. For instance, data from insurance claims, other administrative sources or medical records can help to determine how often the use of a therapy is accompanied by a record of the appropriate test and of a test result that indicated use of the therapy. Claims data also can yield information on use of health services that can serve as proxies of health outcomes, e.g., health events, hospitalizations, medical and surgical procedures and readmissions.⁴³

These and other observational sources are limited by their original purpose and how the data were collected and validated. They often provide insufficient data on health status to enable assessing effectiveness of interventions and insufficient detail for making risk adjustments needed to standardize and compare patient groups. Many routine data sources are proprietary and may be inaccessible or costly to outside users. Continued concerns and restrictions for protecting patient confidentiality and consent may reduce access to clinical databases and their utility for research. Even where data are available from EHRs, pharmaceutical records,

⁴³ Raftery J, Roderick P, Stevens A. Potential use of routine databases in health technology assessment. *Health Technol Assess* 2005;9(20):1-106.

laboratory reports and other sources, they may be difficult to assemble into datasets suitable for research.⁴⁴ Efforts to use data from administrative databases to evaluate the effect of PHC on health status, health outcomes and health services use must account for these limitations.

1. Key Expert Panel Observations

Panel members provided the following observations on the use of databases for PHC.

- **Realizing the potential of PHC, including to accelerate the discovery, development and delivery of diagnostics and therapeutics, will require linking and analysis of large magnitudes of data on genomics, biomarkers, health care interventions, outcomes and costs.** This will require drawing from a diverse portfolio of sources, including RCTs, other clinical trials, prospective observational studies and other population-based data, claims and other administrative/routine data and EHRs. The selection and linking of these sources and the magnitude of data collection will depend on many factors, including type of intervention, application, patient population, health care setting and impacts or outcomes of interest.
- **Before widespread and integrated use of databases in PHC can occur, standards for their design and use are needed.** Data for supporting PHC will be drawn from diverse sources. It is important to determine the original purpose and characteristics of each database, to understand the limits of the data and to determine how data collection can be improved and standardized. The Expert Panel emphasized that researchers and policymakers must remain cognizant of database limitations for inferring causal relationships between interventions and outcomes. Design and implementation of databases, including their respective data fields, should anticipate clinical, administrative and research needs. In order to further enable their integration in PHC, development of these databases should be informed by the desired applications and standards of large integrated health systems.

“There is a need for a database that is almost prescient, telling us that [data] we need to collect and how to use it.”

Panelist
- **Prospectively-generated databases and related studies are needed to further PHC.** As noted above, the evidence base for PHC remains sparse. Data on dosing, monitoring, long-term health outcomes, other clinically-relevant aspects and cost-effectiveness are sparse. Data fields should be prospectively defined in order for future research to provide the evidence to support clinical decisions related to PHC.
- **The federal government could facilitate and support efforts to enhance or develop PHC databases and decision-support platforms for incorporation into health care practice in the public and private sectors.** DHHS could sponsor an effort to establish a vision for data collection, management and use that could fill gaps in and connect existing sources. This vision should entail how to meet the potentially substantial costs of large-scale, diverse database development. Federal support could advance understanding of applications of databases. Also, support is needed to enable incorporating genetic information into observational and experimental data sources and personal health records (PHRs). This

⁴⁴ Ibid.

capacity would help to identify and track health disparities that may emerge or be affected by PHC.

- **The federal government could facilitate and support efforts to design and standardize databases for incorporation into health care practice.** Developing uniform software standards and requirements for knowledge management will enable providers to use information from databases more readily. PHC may offer an opportunity to highlight the potential benefits of these databases, such as linking databases, electronic health records (EHRs) and decision support systems.
- **Large government and private sector investment in EHRs, PHRs and other health information technology will be required to validate, implement and track the impact of PHC.** PHRs can capture not just clinical data but data on personal history, environment, diet and lifestyle, thereby providing a richer basis for understanding associations between genotype and phenotype. Aside from “data mining” applications, PHRs can serve as data collection tools for clinical trials. The success of PHR-based databases will depend on reliable patient de-identification procedures and related protections of personal data. To the extent feasible, inclusion of genomic mapping into large numbers of PHRs will greatly increase the utility of PHRs as research tools. Some major US payers are developing systems for analyzing observational data from EHRs and PHRs of millions of patients. Effective delivery of PHC will depend on decision support systems that can access and draw upon multiple data sources.
- **The protection of privacy and confidentiality will be essential in the development of databases for PHC purposes.** Data firewalls and other means are necessary to ensure that sensitive health information is not readily disseminated to third parties. An ongoing challenge will be to achieve a practical balance between privacy protection and ability to collect and analyze data of sufficient volume and quality to generate meaningful research findings. Currently, the DHHS-appointed American Health Information Community (AHIC) is making efforts to ensure the privacy of health data as part of the National Health Information Infrastructure. Also, continued work is underway to improve coding or encryption of genomic information, particularly as more sophisticated means arise to breach these protections. Along these lines, CMS has proposed to link Medicare prescription drug claims data to other Medicare data on hospitalizations, physician visits and other types of patient care in order to gather evidence on the impact of therapies on health care use and costs. CMS recognizes the need to ensure appropriate privacy protections as required by the Privacy Act and HIPAA.⁴⁵

⁴⁵ CMS Office of Public Affairs. Medicare proposed to improve care through learning from prescription drug data. Press release. October 13, 2006. Accessed April 12, 2007.
<http://www.cms.hhs.gov/apps/media/press/release.asp?Counter=2036>

IV. Conclusion

The PHC Expert Panel provided input to the Office of the Secretary, DHHS, toward realizing the integration of PHC into clinical and public health practice. This information is intended to help chart important steps for the federal role in this field over the next 5 to 20 years.

Although the Expert Panel was not charged with providing formal recommendations to the Office of the Secretary, it was asked to express “what the Office of the Secretary needs to know” toward realizing the DHHS initiative in PHC. Panel input was organized into a total of 34 findings and observations across the five main designated issues.

As reflected in its findings and observations, the Expert Panel applied objective scrutiny to the field of PHC and what is needed to realize its potential. It emphasized the need for high standards, based on rigorously derived evidence from practice as well as research settings, for demonstrating clinical validity and utility to consumers, providers and payers. The Expert Panel stressed that much work is needed to demonstrate economic value, as well as clinical and public health value, for PHC interventions. Panelists emphasized that the potential of PHC can be realized only through linking and analysis of large magnitudes of data on genomics, biomarkers, health care interventions, outcomes and costs with commensurate protection of privacy and confidentiality. Also emphasized was careful consideration of translating research into practice, involving attention to premature and late adoption, potential misuse, unintended consequences and cost implications of PHC interventions. Panelists encouraged enhancing provider capacity for interpreting and conveying test results and related PHC information to patients and families, supported by practice tools and consumer education. Panelists noted that, while PHC has the potential to help reduce health disparities, it also could exacerbate them, and much greater understanding is needed of the causes of disparities and practical means of reducing them. Given the evolving and often complex scientific, technological, social, legal and ethical aspects of PHC, as well as the potential for misconceptions about it, panelists recognized the importance of targeted education and information sharing with providers and consumers. These efforts to advance PHC will be resource-intensive and require widespread, concerted involvement of scientists, clinicians, consumers, provider institutions, payers and other stakeholders.

“Successful implementation of PHC will necessitate collective engagement of all persons involved with or affected by PHC. [This includes] determining the pathways for assessing the value added or lost, addressing scientific modes for continuous development of targeted therapeutics and diagnostics, resolving DHHS (FDA, CMS, etc.) discontinuities in decisions, and establishing standards for information sharing and databases and methods for monitoring and minimizing disparities, and resource commitment.”

Panelist

Appendix A: Personalized Health Care Expert Panel Meeting Discussion Guide

Main Objective

- Provide input to the Office of the Secretary, DHHS, toward realizing integration of personalized health care (PHC) into clinical and public health practice. Examine the following areas:
 - Demonstrating clinical validity and utility of PHC
 - Demonstrating value/cost-effectiveness of PHC
 - Role of PHC in reducing health disparities
 - Educating and engaging providers and patients about PHC
 - Using databases to build evidence, inform decisions in PHC
- Consider:
 - Facilitators and barriers
 - Incentives and disincentives
 - Pre- and post-marketing environments
 - Integration with health IT
 - Stakeholder perspectives (patients/consumers, providers, payers, policymakers, employers, et al.)
 - What may be ‘disruptive’
- Take the longer-term view: next 5-20 years

Assumptions

Our discussion will be guided by the following assumptions and will address the following key questions:

- Electronic health records will be widely available in 5-10 years, and systems will be able to routinely capture data required to support personalized health care principles and practices.
- The terms “molecular tests” and “genetic assay-based tests” also include functional imaging tests that define cellular or molecular interactions and provide mechanistic information supporting clinical decision-making (i.e., PET and MRI as opposed to radiographic or ultrasound procedures).
- Evidence-based decision-making (e.g., practice guided by clinical protocols) will become widely implemented, particularly through reimbursement strategies for certain diseases.

- DHHS particularly is interested in the possibility of using PHC to address the top chronic diseases that account for the bulk of disease burden that our society encounters, including diseases of the heart, all cancers, stroke and diabetes mellitus.

Questions

- 1) PGx-based molecular assays are widely used in preclinical and clinical drug development. However, these assays are not as widely used for improving safety and effectiveness in clinical medicine. PGx offers significant future opportunities to reduce adverse events and improve effectiveness of clinical response.
 - a) Can clinical practice models or best practices be identified or envisioned that would facilitate integration of these testing protocols into clinical medical management?
 - b) Can we describe or identify more cost-effective clinical care pathways resulting from adoption of these PGx-based molecular assays?
- 2) If personalized medicine indeed can provide additional information for tailoring individual patient care that yields greater value (particularly in the form of improved safety and health outcomes and greater efficiency), what approaches can be used to demonstrate the cost savings or other economic impact of appropriate of molecular tests?
 - a) Is it feasible to develop economic models that examine the effect of including genomic and molecular analyses in clinical practice?
 - b) What types of evidence (including in the context of clinical pathways ranging from tests to impact on long-term health outcomes) must be developed to demonstrate the value of these tests for informing third-party payer coverage decisions?
 - c) What are the considerations for developing reimbursement policies for predictive and preventive genomic tests, especially in the Medicare setting?
- 3) What are some potential applications of genetic tests and molecular assays for strategies to overcome patterns of disparities in health care and health outcomes?
 - a) Among those conditions or disease areas that currently are subject to significant disparities, which have the greatest potential to be positively influenced by adoption of genetic tests and molecular assays?
 - b) What factors or inquiries are needed to address unmet health needs of those population subgroups that are unlikely to benefit from currently available or emerging forms of diagnostic or therapeutic personalized medicine?
- 4) In terms of PHC, evidence suggests that health practitioners are insufficiently prepared for the integration of molecular analysis and genetic assay-based tests on a large scale in medical practice.
 - a) What initiatives should be undertaken in education, training and knowledge development, to enhance adoption of PHC practices?
 - b) Given widely recognized examples of patient adoption of clinical tests (e.g., cholesterol

testing, PSA testing), what patient communication approaches or strategies should be considered for enhancing appropriate adoption of genetic and molecular tests into routine health care practice?

- 5) Experiential and observational clinical data (e.g., claims data, large health plan databases, population surveys) may be used in support of clinical protocol development, coverage decisions and marketing approval.
 - a) How can databases of these clinical data be used to evaluate the use and effectiveness of genetic and molecular test in disease monitoring?