Comments from Federal Agencies

TABLE OF CONTENTS

DEPARTMENT OF VETERANS AFFAIRS
UNDER SECRETARY FOR HEALTH
WASHINGTON DC 20420

JUN 0 5 2007

Reed V. Tuckson, MD
Chair, Secretary's Advisory Committee on
Genetics, Health and Society
Office of Biotechnology Activities
National Institutes of Health
6705 Rockledge Drive, Suite 750, MSC 7985
Bethesda, MD 20892-7985

Dear Dr. Tuckson:

I commend the Department of Health and Human Services' Secretary's Advisory Committee on Genetics, Health and Society (SACGHS) on the recent draft report, "Realizing the Promise of Pharmacogenomics: Opportunities and Challenges." The report is well written, thorough and thought provoking.

As noted in the report, pharmacogenomics has the potential to revolutionize pharmaceutical treatment decisions to help ensure patients receive drugs tailored to their genomic composition. We are looking forward to a time when we can effectively deploy pharmacogenomics in the Veterans Health Administration (VHA). Improving patient outcomes and delivering high quality, cost-effective care is a hallmark of our system, and pharmacogenomics will enhance our ability to meet these expectations.

Indeed, VHA is uniquely situated to be a leader in the deployment of pharmacogenomic information in the clinic. Our award-winning electronic health record system, together with our research infrastructure and unique relationship with our patient population, means that we can be at the forefront of the systematic use of pharmacogenomic information in the clinic. As indicated in the appendix to the report, VHA is already pursuing research and clinical programs in this area. We continue to be open to other opportunities and ideas to participate in clinical trials or health services research that could include cost effectiveness studies or the testing of clinical decision-making algorithms.

I hope that SACGHS continues to see VHA as a strong potential partner for the Department of Health and Human Services in such efforts and continues to recommend that our two Departments work together in the development and testing of pharmacogenomic applications.

Reed V. Tuckson, MD

Thank you for the opportunity to comment on the Committee's current draft report on pharmacogenomics. Under separate cover letter, VHA staff has forwarded technical comments to the Committee staff. VHA looks forward to receiving the final report. If you would like to discuss VHA's current plans for pharmacogenomics, please contact Joel Kupersmith, Chief, Research and Development Office. Dr. Kupersmith can be reached at (202) 254-0183.

Sincerely yours,

Michael J. Kussman, M.D.

Michael J. Kussman, MD, MS, MACP
Under Secretary for Health

Department of Veterans Affairs

Memorandum

Date: May 8, 2007

From: Sherrie L. Hans, PhD
Deputy Chief Officer, NCEHC

Subj: VHA technical comments on "Realizing the Promise of Pharmacogenomics: Opportunities and Challenges"

To: Sarah Carr, Executive Director, SACGHS

1. Thank you for providing the Veterans Health Administration with the opportunity to comment on the most recent draft report from the Secretary's Advisory Committee on Genetics, Health and Society, "Realizing the Promise of Pharmacogenomics: Opportunities and Challenges." Staff who reviewed the report found it well written, comprehensive, and thoughtful. The following technical comments are offered to help clarify and strengthen the report on a few specific points.

   * SACGHS has been concerned for some time about genetic discrimination in insurance and employment. While this issue is covered in depth by other publications of the Committee, this report does not allude to that work nor note in a sufficiently strong way that information about one's genes can both enhance and impede access to appropriate care.

   * The accuracy of the adverse drug reaction nomenclature and the numbers cited should be reviewed. At one point, the authors quote numbers that appear to refer to adverse events (which may or may not be related to drug reactions) rather than to specific numbers for adverse drug reactions. Standard nomenclature (adverse drug reactions and adverse events) should be defined more clearly in the document and if specific examples refer to adverse events rather than adverse drug reactions, this should be made clear in the report.

   * Are the terms "clinical validity" and "clinical utility" sufficiently well defined (and agreed upon in the community) to be of use in the regulatory arena by FDA? Is it clear that FDA has authority to regulate clinical validity and clinical utility (if the terms are well defined)? FDA staff may want to provide comment on how realistic it may be and what would be required to develop a regulatory scheme for these concepts. (Page 10, D.)

   * Review the details of Exhibit 1, page 29 to ensure the scientific accuracy of what is described and concluded. Evidence with which the commenter is familiar does

not clearly indicate that the FISH test is in fact better than an appropriately labeled immunohistochemistry device.

* OHRP and FDA should review the suggestion on page 45 to align the common rule and 21CFR50 with regard to the rigor of informed consent. Could this be easily accomplished through regulatory action or would statutory change be required?

* On page 53, the description of premarket review of IVD is incomplete. The premarket approval (PMA) and traditional premarket review 510(k) process are described, but the "de-novo" 510 (k) process which was used, for example, for approval of the Factor V Leiden assay, is not described in the paper. This process should probably be noted as an alternative approval process for "moderate risk" IVDs.

2. Thank you again for SACGHS attention to this important issue. Don't hesitate to contact me if you require any follow up information on the technical comments offered here (Sherrie.hans@va.gov; (202) 461-4024.)

-----Original Message-----
From: Long, Rochelle (NIH/NIGMS) [E]
Sent: Thursday, May 10, 2007 4:47 PM
To: Goodwin, Suzanne (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]
Cc: Long, Rochelle (NIH/NIGMS) [E]
Subject: SACGHS report feedback - PGRN

Suzanne, Sarah -

I'd like to make some PGRN-specific comments on the draft SACGHS report, knowing that comments are due. While I think the PGRN is referred to correctly in the final table attached to the report, I don't think that Lewin group got it right in the body of the text, especially on pages 21-24. Here are my specific comments, and recommended replacement text is attached:

- Importantly, PGRN is not mentioned in the "A. Basic..." section at all

- PGRN is not similar to EDRN, in my opinion

- "Translation" is not clearly used in the paragraph on page 23, consistent with the definitions above on the page

- Overlooks the basic discovery component of the PGRN

- Data in PharmGKB also come from beyond the PGRN

- Several NIH insitutes/offices participate (9 total) - it is trans-NIH

I hope you are receiving thoughtful public comments. I am encouraging the PGRN to respond overall.

- Rochelle

PGRN description in SACGHS rep...

Rochelle M. Long, Ph.D.
Chief, Pharmacological & Physiological Sciences Branch
Pharmacology, Physiology, & Biological Chemistry Division
NIGMS, NIH
45 Center Dr., Rm. 2AS-49G
Bethesda, MD 20892-6200

tel: (301) 594-3827
fax: (301) 480-2802
e-mail: rochelle_long@nih.gov
PGRN: www.nigms.nih.gov/pharmacogenetics

ADD TO THE A. BASIC RESEARCH SECTION:

The Pharmacogenetics Research Network (PGRN) is a trans-NIH effort led by the National Institute of General Medical Sciences (NIGMS). This nationwide collaboration of 12 independently funded interactive research groups discovers genetic variation (including, but not limited to SNPs) and studies relationships between genetics and patient drug responses. PGRN investigators perform genotype-to-phenotype studies, which begin by comprehensively cataloging genetic variation in genes of pharmacological interest, and phenotype-to-genotype studies, which are initiated with a collection of carefully-studied patients having characteristic drug responses. Correlations are usually followed by mechanistic biological studies. A major component of the PGRN is the Pharmacogenomics Knowledge Base (PharmGKB), where pharmacogenetics data from within and beyond the PGRN are stored and made freely available for scientists. With data on more than 10,000 human gene variations that affect drug responses, this network enables access of the scientific community to information on genes, drugs and diseases.[123]

REPLACE THE PARAGRAPH IN THE B. TRABNSLATIONAL RESEARCH SECTION:

The Pharmacogenetics Research Network (PGRN) is a multi-disciplinary network intended to interpret and understand, as well as discover, pharmacogenetic information. Ultimately, this information can be clinically tested (T1, above) and, where appropriate, translated (T2, above) into safe and effective drug therapies designed for individual patients. In the past seven years, PGRN scientists have explored the contribution of genetics to the effects of medications for diseases such as asthma, depression, cancer and heart disease. Pathways of drug actions and summaries of very important pharmacogenes (VIPs) are displayed at PharmGKB, along with levels of evidence that variants are significant at the molecular functional level, affect pharmacokinetic properties (drug levels), determine pharmacodynamics properties (drug responses), and whether that impacts clinical outcome. Critical understanding of basic and clinical research results is essential to living up to the promise of pharmacogenomics.[123]

Deleted: The term "translational research" can be used to describe translation at different phases of R&D.¶ Various models depict translational research as a process occurring in two stages.114,115,116 The¶ first, sometimes referred to as type 1 (T1) translation, uses the findings from basic research,¶ including preclinical studies, to inform the development and testing of an intervention in¶ clinical trials, such as phase I-III clinical trials. The second, type 2 (T2) translation, involves the¶ translation of findings from clinical research into clinical and public health practice and¶ policy.117,118¶ ¶ The National Cancer Institute's Early Detection Research Network (EDRN) is *an example of a*¶ program that aims to encourage and accelerate the translation of basic research into clinical¶ research. The program facilitates the development, testing and assessment of promising¶ biomarkers and technologies as well as *assessment of existing, proven ones.*119 Its work¶ products include a list of common data elements; standard operating procedures for assays;¶ methods and protocols for collection and processing of biological samples; other reference¶ materials to assist investigators to conduct experiments in a consister ... [1]

Deleted: The Pharmacogenetics *Research Network (PGRN) is a similar* effort led by the National¶ ... [2]

Formatted: Font: 11 pt, Bold

Formatted: Underline

Formatted: Font: 11 pt, Underline

Formatted: Font: 11 pt, Bold, Underline

Formatted: Font: 11 pt, Bold

Formatted: Font: 11 pt

Formatted: Superscript

Formatted: Font: Bold

Formatted: Underline

Formatted: Font: Bold, Underline

Formatted: Font: Bold

Formatted: Font: 11 pt

Formatted: Font: 11 pt, Not Bold

Formatted: Font: 10 pt, Bold

Formatted: Font: Bold

Page 1: [1] Deleted longr 5/10/2007 4:22:00 PM

The term "translational research" can be used to describe translation at different phases of R&D. Various models depict translational research as a process occurring in two stages.[114,115,116] The first, sometimes referred to as type 1 (T1) translation, uses the findings from basic research, including preclinical studies, to inform the development and testing of an intervention in clinical trials, such as phase I-III clinical trials. The second, type 2 (T2) translation, involves the translation of findings from clinical research into clinical and public health practice and policy.[117,118]

The National Cancer Institute's Early Detection Research Network (EDRN) is an example of a program that aims to encourage and accelerate the translation of basic research into clinical research. The program facilitates the development, testing and assessment of promising biomarkers and technologies as well as assessment of existing, proven ones.[119] Its work products include a list of common data elements; standard operating procedures for assays; methods and protocols for collection and processing of biological samples; other reference materials to assist investigators to conduct experiments in a consistent, reliable manner; and tools for the collection, classification, storage, and analysis of information, enabling access to and sharing of data among multiple organizations.[120] EDRN also fosters collaboration among academic and industry stakeholders in a range of fields and promotes rapid dissemination of information. [121] Researchers outside of EDRN are provided opportunities to collaborate with EDRN investigators to use shared resources through the network, such as new technologies, specimens, high-risk registries, and cohorts, or to seek funding for validation studies.[122]

Page 1: [2] Deleted longr 5/10/2007 4:21:00 PM

The Pharmacogenetics Research Network (PGRN) is a similar effort led by the National Institute of General Medical Sciences (NIGMS). PGRN is a multi-disciplinary network intended to translate pharmacogenetic information into safe and effective drug therapies designed for individual patients. This nationwide collaboration of 12 independently funded interactive research groups studies the relationship between genetics and patient drug response. In the past five years, PGRN scientists have explored the effect of genetics on medications for diseases such as asthma, depression, cancer and heart disease. A major component of PGRN is the Pharmacogenomics Knowledge Base (PharmGKB), where pharmacogenetics data from PGRN are stored and freely available for scientists and researchers. With data on more than 10,000 human gene variations that affect drug response, this network enables access of the scientific community to information on genes, drugs and diseases.[123]

SACGHS Request for NIH Comments
Draft Report: *Realizing the Promise of Pharmacogenomics: Opportunities and Challenges*
June 1, 2007

NIMH

NIMH Feedback on Draft SACGHS Report (Please direct questions to Dr. Marina Volkov)

Realizing the Promise of Pharmacogenomics:
Opportunities and Challenges

This draft report offers a comprehensive view of the complex subject of Pharmacogenomics (PGx), covering topics that range from basic research to ethical and legal issues. This breadth of coverage is both the strength and weakness of the report. For example, the report addresses the "Complexity of the Science" (p 17) of pharmacogenomics with a much needed description and differentiation of the often misunderstood application of PGx in germline and somatic variation, but it does not provide an in depth discussion of the underlying difficulties in applying PGx research to develop clinically relevant applications for the complex phenotypes studied.

The report, while not explicit about needed oversight by the Food and Drug Administration (FDA), makes it clear that the FDA should take a more active role in promoting and integrating PGx research into the drug development and approval process. This also points to a potentially larger role the NIH could assume in this process by working actively with the FDA to stimulate basic, clinical and post-market surveillance PGx studies. The lack of clear recommendations in this regard suggests the need for a federal coordinating entity for PGx research and implementation that bridges these two institutions and coordinates and stimulates activities in the PGx domain.

Overall, this is an excellent summary of the state of PGx research and highlights important areas for future investments in basic research. Most importantly, the report provides recommendations for the implementation of PGx into clinical practice.

NIAAA

May 17, 2007

Dear Dr. Frosst,

We would like to express our appreciation to you and Dr. Collins for the opportunity to review the SACGHS Report: *Realizing the Promise of Pharmacogenomics: Opportunities and Challenges*. Both our Institute's intramural and extramural staff have carefully reviewed the

document and have shared their views on the very comprehensive nature of the overview and recommendations.

Research on alcoholism and the other alcohol use disorders has shown the central importance of genetics and gene by environment interactions in disease expression. Relatedly, there is already evidence that differences in the efficacy of specific pharmacotherapies for alcohol disorders differ as a function of an individual's gene profile. It has also been noted that alcoholism itself is a pharmacogenomic disorder, whereby the nature of an individual's pharmacologic response to the drug alcohol is dependent upon that person's specific gene profile.

We believe the SACGHS Report will foster further research on pharmacogenomics and do not have any suggestions for changes to this excellent Report.

Sincerely,

/s/

Kenneth R. Warren, Ph.D.
Associate Director for Basic Research
National Institute on Alcohol Abuse and Alcoholism
National Institutes of Health
5635 Fishers Lane, #2005
Bethesda, MD 20892

NIA

Dr. Frosst:

Thank you for the opportunity to review the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) draft report titled, Realizing the Promise of Pharmacogenomics: Opportunities and Challenges. We shared the report with NIA staff, who indicated that the report does not appear to consider aging as an issue to be addressed in the field of pharmacogenetics, however, age-related changes are a substantial part of the somatic changes that will need to be considered as the field moves forward.

L. Jeanne Borger
Deputy Director
Office of Planning, Analysis, and Evaluation National Institute on Aging National Institutes of Health
301-451-8395

NHLBI

Dr. Frosst, on behalf of Dr. Nabel, I am pleased to forward the attached comments from the NHLBI on the draft SACGHS report.

With best regards,
Sheila

Sheila Pohl, Chief of Staff
Immediate Office of the Director
National Heart, Lung, and Blood Institute, NIH
Building 31, Room 5A48, MSC 2486
Phone (301)594-5355, Fax (301)402-0818

The NHLBI is privileged to comment on the important and timely SACGHS Report.

The SACGHS report on Pharmacogenomics is very thorough and well written. The Report has comprehensively addressed the opportunities and challenges of this emerging field in biomedical research and its translation into clinical and public health practice. Important issues that the Report clearly highlights include:

- The need for clinical validity and utility
- Clinical trial design and quality of evidence standards
- Protection of personal data & information
- Risk and benefit
- The importance of coordinating efforts amongst stakeholders
- The need for clinical trials of pharmacogenomics diagnostics and drug responses across various patient subgroups
- The range of research from basic research to outcomes research (p. 8), and the inclusion of social, behavioral and environmental factors (p. 9), as all these perspectives are needed.

The Report is extremely optimistic in looking in the future implementation of pharmacogenomics in clinical practice. Issues in the Report that may require additional attention include:

- The need to differentiate between personalized medicine and pharmacogenomics. These two are not synonymous and a brief explanation would be helpful.
- The need for caution when talking about 'extending primary prevention'. As recognized in the report, pharmacogenomics will be most useful when the variation, for an adverse reaction or an effective treatment, is present only at a high frequency in the population
- The need to consider environmental and dietary interaction (bioactive food components and supplements) that may confound pharmacogenomic data based interpretation
- The importance of education and awareness of pharmacogenomics for health care professionals.
- The importance of modeling multi-gene, multi-disease, and multi-drug interactions to provide a proof-of-concept of real-life application of pharmacogenomics.

- The importance of clinical laboratories and health insurers and the role they each will play in pharmacogenomic testing.

Additionally, NHLBI has made specific comments on the Report:

- In the Executive Summary, on page 5, there is a list of Key considerations for realizing the promise of pharmacogenomics. However, the list is missing, or at least should emphasize more, clinical trials that can determine the effectiveness of a screening and identification of genetic-based therapy. The first bullet comes closest, with "Product development and clinical research must be adapted to assess accuracy and predictive value of pharmacogenomics-based diagnostics as well as biological markers, intermediate endpoints, health outcomes and adverse events associated with pharmacogenomics-based therapies in patient subgroups." NHLBI recommend modifying this to create two bullets:
    - Product development and clinical studies to assess accuracy and predictive value of pharmacogenomics-based diagnostics.
    - Clinical trials to determine the clinical efficacy and effectiveness of pharmacogenomics-based therapies, including assessment health outcomes and adverse events, as well as biological markers and intermediate endpoints.

- On page 6, Recommendations (for research) are in the order of 1) Basic Research, 2) Translational Research, and 3) Clinical Trial Design. For 3), NIH should encourage sponsors and researchers to consult with FDA early so that results can be used to support a pre-market review application. The Report does mention that studies should have sufficient statistical power. However, the issues in clinical trial design are much larger than that. Clarification is needed on whether pharmacogenomics-directed treatment needs to show efficacy before it can be marketed. The Report includes language about clinical utility and cost-effectiveness in 5) Analytic Validity and states that cost-effectiveness determine "adoption" of pharmacogenomic technologies. Will FDA approval be based on this same evidence? The Report states that "FDA can promote such studies by encouraging manufacturers to submit the data . . ." - will FDA require such data?

- Page 3, Section A. "Promise of Pharmacogenomics" refers in the first sentence to "public health paradigms", yet nowhere in the document is the potential use of pharmacogenomics in public health approaches mentioned or even inferred, as the Report focuses on delivery of clinical care. This reference is misleading, as it implies a broader-reaching effect than would ever be feasible or politically possible. The Report should indicate situations in which pharmacogenomic can be used in a public-health approach.

- The Report refers to improving "efficiency of clinical trials and lower[ing] their costs" (p. 4) – a statement that seems, at best, wishful thinking. If the trials are going to have "the ability to stratify patient groups using biomarkers and genomic data....[for] discernment of significant treatment effects..." (p. 4) and "sufficient statistical power" (p. 7), then trials will need sufficient power to analyze the intervention vs. control group effects on the outcome in subgroups defined by genetics/genomics. To do this, trials will become more, not less, costly

because they will need to be powered to answer the question within multiple subgroups – a practice almost never used today. Perhaps a long-term perspective could conceivably result in lower trial costs (if one selectively recruits genotype-defined subgroups only and uses surrogate markers as outcomes), but surely trial costs will increase in the short term if they are sufficiently powered to answer pharmacogenomics questions on clinical outcomes.

- The term "Pharmacogenomics products" is used in numerous places. It is not clear what a "Pharmacogenomics product" would be. A designer drug that specifically targets individuals with certain genotypes? The term should be defined or examples given.

- Under "coverage and reimbursement" (p. 6), the Report omits costs of conducting genotyping on patients within clinical care.

- On page 10, item D, in addition to the FDA focusing more attention on ensuring that relevant pharmacogenomics information in included on labels, a mechanism needs to be put in place to ensure that the information is updated as new developments arise and as applications of new technology come to fruition.

- "Decision support systems and tools" (p. 10) will need to be tested to determine their clinical utility – i.e., does use of them improve care and improve patient outcomes? Additionally, these systems should include a means for interpretation of results of pharmacogenomic tests.

- Informed consent from study participants is crucial and should be addressed throughout the document.

- The abbreviation Pharmacogenomics in the table of contents and section headings is distracting, and it would be better if they write out "pharmacogenomics" in those contexts.

- On page 16, the Report indicates that storage of samples and genetic information could help to lower costs. Clarity is needed on how storage of this information will contribute to cost-effectiveness.

- Basic research developments on pages 21-22 describe efforts underway with genome-wide association. It is not clear if these descriptions were meant to be inclusive of all major programs at NIH. If so, the Report should highlight additional efforts, such as those supported by NHLBI [STAMPEED, CARE, and ENDGAME (which is trans-NIH effort)], and dbGAP. The Framingham study is called the Framingham SNP Health Association Resource (SHARE). Nonetheless, more GWAS in pharmacogenomic studies are needed. Most of the efforts underway, as described in this section, are not related to pharmacogenomics.

- On page 23, the PGRN is led by NIGMS, but is a trans-NIH effort with many NIH Institutes supporting studies in this program.

- Various agency efforts that will contribute as an evidence base for pharmacogenomics are mentioned on page 38. However, the Report is not clear as to what specifically about these

efforts are related to pharmacogenomics. If they do not have a specific pharmacogenomics component, they may not be relevant.

- Pages 38-40, and Recommendation 6C describe various databases. How can pharmacogenomics databases be analyzed from these databases? Who will have access to these databases and what policies will be put in place?

- On page 73, nurses should be included in the last paragraph.

- Is the NHII on page 82 the same as the national Health Information Network (NHIN)? If so, the appropriate name should be used.

- Regarding Recommendation 15A on page 95, the NIH and FDA have established and Task Force on the Genetics of Adverse Drug Reactions (the group held a Genetics of Medication Safety Workshop in December 2006). This group could additional assist the SACGHS when needed, and could also be expanded to include other HHS agencies.

- The report should express the importance of enhancing medication safety, and the role it will play common versus rare ADRs, as well as the cost-effectiveness of decreasing these ADRs.

- In March 2007, The Office of the Secretary at DHHS held a Personalized Healthcare Expert Panel. The results of this meeting should be incorporated into the Pharmacogenomics Report, where applicable.

- The Report should indicate the barriers to achieving pharmacogenetics/genomics data on package insert labels for drug prescriptions.

- The FDA has developed guidance and has been receiving pharmacogenomics submissions. The Report should state what FDA is doing with this information, what it plans to do with the information, and how it will help shape pharmacogenomics research and its clinical application.

- In addition to discussing clinical validity and utility, the Report should also describe any issues with proficiency testing for pharmacogenomic tests.

- Standards and coding are needed for phenotyping, medication definitions, and reporting of ADRs.

- NHLBI suggests that the term 'health care providers' be changed to 'health care professionals' throughout the Report.

- In general, the degree of emphasis on data sharing and appropriate attention to ELSI issues is appropriate. The NIH policy for sharing of data for genome-wide association studies is mentioned but it is referred to as a "potential deterrent" to data sharing by companies, because IP claims are discouraged on data in the shared database. However, there are potential inducements for data sharing. For example, companies would gain immediate

access for data mining and other research purposes to large amounts of data that they heretofore would have difficulty accessing. We recommend that some positive elements of data sharing be mentioned.

Comments on the Appendices:

- PROGENI is the acronym for Programs in Gene Environment Interactions.
- NIH also supports a number of SBIR/STTR projects that are developing pahrmacogenomic diagnostics and tests.
- The NIH-FDA Genetics of Medication Safety workshop should be included.

NIAID

Dear Dr. Frosst,

NIAID appreciates the opportunity to comment on the Draft Report entitled: "Realizing the Promise of Pharmacogenomics: Opportunities and Challenges" prepared by the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS). The draft report describes opportunities and challenges in pharmacogenomics in three major areas: 1) research and development; 2) "gatekeepers," i.e., those who are involved in facilitating the progression of pharmacogenomics; and 3) implementation of pharmacogenomics to improve outcomes in clinical and public health practice. With regards to the draft report, we have the following comments:

1) The promise of PGx - Page 3, Line 21-30; Page 4-5:

The report has comprehensively discussed topics and issues of PGx. We agree with the assessment of the report that highlights the earlier successes of PGx, and wish to add the following examples for you to consider.

PGx tests for HIV patients have provided proof of principle that these tests can be used clinically to improve outcomes for patients receiving lifelong combinational antiretroviral regimens. For instance, PGx tests have expanded to those that characterize host mitochondrial and nuclear genomes. Applications of PGx tests are used in HIV patients in quantification of mitochondrial depletion as an early surrogate marker for drug toxicity, to detect host immune haplotypes, and metabolic/transporter genetic polymorphisms for predicting disease progression, such as those for the diagnosis of abacavir hypersensitivity and of efavirenz associated central nervous system (CNS) toxicity.

2) Research and Development – Pages 23-49

There is a need for the development and validation of clinically useful PGx technologies or translational biomarkers. The current PharmGKB of PGRN should expand its utilities to that

direction. Also, the assessment of those PGx data collected from public domain and private sectors, and the identification, development, and validation of clinically useful biomarkers or PGx products should be encouraged and supported by NIH.

Genes that are important genomic targets for HIV drug development include P450, transporters, CCR5, ABC-related hypersensitivity, HLA and hsp70-hom genotype, mitochondrial genomes, and efavirenz's; PNP will be another potential target that needs further validation clinically.

3) Clinical Research – Pages 24-26
The report pointed out the importance of adaptive clinical trial design in the clinical trial design. Such an approach, in fact, is not new statistically, and has not been often adopted and used in Phase III clinical trials in the past. One of the reasons is that the adaptive approach is a "learning" model, but not a "confirmation" model. Therefore, its value in phase III clinical trials is questionable. The other reason is that such an approach may result in a "fractionated" indicated population or market of a drug product. However, this approach may be of value in earlier phases (I and II) of clinical trials to identify margins of drug safety and effectiveness in a stratified patient population, especially when clinically validated biomarkers or PGx tests are available. It may also be of help in decision making to stop a trial at its early phases of drug development. This approach may also be of value in clinical trials that contain substudies of biomarker validation. Another untouched area of this report is the value of therapeutic dose monitoring (TDM) in the development and validation of biomarkers. We suggest that a clarification may be necessary. Finally, we agree that researchers should consult with the FDA early in the study design stage for advice, especially if such approaches are to be adopted in their clinical study designs.

On behalf of the NIAID, we appreciate the opportunity to comment on the Draft Report.

David

David A. Kosub, Ph.D.
Public Health Analyst (Contractor)
Strategic Planning and Evaluation Branch (SPEB)
Office of Strategic Planning and Financial Management (OSPFM)
National Institutes of Allergy and Infectious Disease, NIH, DHHS
Kelly Services
Building 31, Room 7A-46
Bethesda, MD 20892
Phone: 301-443-9424
Fax: 301-402-0492
Email: kosubd@niaid.nih.gov

FIC

Fogarty comments on SACGHS "Request for Public Comment: Realizing the Promise of Pharmacogenomics: Opportunities and Challenges"

Missing from this document is any mention of coordination of international efforts in the proposed pharmacogenomics (PGx) activities.

- While data sharing, even among US entities, is a formidable undertaking, the value of international data-sharing is likely to be significant. This is certainly true, at the least, with respect to immigrant populations in each country and the implications of data on ethnic subpopulations to the countries of origin.
- Even where PGx information is not specifically sought, the results of international clinical trials may point to failures or unusual successes in certain subpopulations that might lead to identification of potential PGx targets or biomarkers.
- This also is relevant to the re-evaluation of disapproved drugs. While the racial testing of Iressa is mentioned, it is not mentioned that this resulted from a clinical trial in Singapore that found higher efficacy in East Asians, warranting FDA approval of the drug after initial rejection. Studies on breast cancer in Nigerian populations may similarly be informative for some African-American populations in the US. The practice of conducting clinical trials in developing countries, even without DNA samples, should have produced rich datasets on variability of response between test sites in different countries, often in the same trial. Since this information is already being collected, some coordination of data sharing and analysis may be of global benefit.
- The caveat of not using racial or ethnic self-identity as a proxy for genomic information is valid, but there are examples where rates of difference (Ethiopian, Saudi, and Nigerian examples in text) may be so high that further investigation is warranted and likely to be fruitful.
- International interoperability of electronic health records, an effort already underway, will facilitate this coordination effort.

Finally, given the ethical issues surrounding collection of DNA samples during clinical trials and in genetics research, training individuals in partnering countries to become full collaborators in these international efforts will both respect international ethics standards and will ultimately benefit the United States and the international community.

Karen J. Hofman M.D.
Director
Division of Advanced Studies and Policy Analysis
Fogarty International Center
National Institutes of Health
Building 16
16 Center Drive, MSC 6705
Bethesda MD 20892-6705
Phone: 301-496-1491
Fax: 301-496-8496
Email: hofmank@mail.nih.gov

DEPARTMENT OF HEALTH & HUMAN SERVICES OFFICE OF THE SECRETARY

Voice - (202) 619-0403 TDD - (202) 619-3257 Fax - (202) 619-3818
http://www.hhs.gov/ocr/

Director
Office for Civil Rights
Washington, DC 20201

May 31, 2007

TO: Sarah Carr, NIH

FROM: Robinsue Frohboese, OCR

RE: Review of SACGHS PGx Draft Report

OCR has reviewed the SACGHS PGx Draft Report and offers the following comments:

- Page 43, last paragraph. We recommend mention of the HIPAA Privacy Rule in this paragraph to indicate that its requirements may apply to protect some patient information in PGx research. In particular, we recommend inserting after the first sentence, which begins "Various technical, social and...", the following sentence: "For example, the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule establishes federal privacy protections for individually identifiable health information held by health care providers that conduct certain transactions electronically, health plans, and health care clearinghouses, many of which may be involved in, or be sources of data for, genomic research. In addition, a 2006 NHGRI..."

- Page 92, 1st paragraph, 1st sentence. For accuracy, replace the existing sentence with the following: "Current federal protection against genetic-based stigma and discrimination and for the privacy of genetic information rests in a number of different laws and authorities, including 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, the Civil Rights Act, the right to privacy established by the Constitution, and related judicial decisions."

- Page A-22. Under "Office for Civil Rights," replace the existing language with the following: "The provisions of the Health Insurance Portability and Accountability Act of 1996 (HIPAA) Privacy Rule apply to individually identifiable health information created or maintained by health care providers who engage in certain electronic transactions, health plans, and health care clearinghouses."

- Page A-20. Under "HRSA" paragraph, insert the following:

  Office for Civil Rights

OCR enforces civil rights laws that prohibit unlawful discrimination against racial and ethnic minority populations and persons with disabilities affected by health disparities. OCR also educates and trains individuals and communities about their rights under the civil rights laws we enforce, which include the Americans with Disabilities Act, Section 504 of the Rehabilitation Act of 1973, and Title VI of the Civil Rights Act of 1964.

Thank you for the opportunity to review the draft report. Please let me know if you have any questions about these comments.

Responses from Members of the Public

TABLE OF CONTENTS

Abbott

Regulatory Intelligence/FDA Liaison Office
1700 Rockville Pike, Suite 310
Rockville, MD 20852

Tel. 301-255-0080
Fax 301-255-0090

June 1, 2007

Reed V. Tuckson, MD
Chair
Secretary's Advisory Committee on Genetics, Health, and Society
NIH Office of Biotechnology Activities
6705 Rockledge Drive, Suite 750
Bethesda, MD 20892

Dear Dr. Tuckson:

Abbott Laboratories is pleased to provide the following comments on the draft report of the Secretary's Advisory Committee on Genetics, Health, and Society entitled, "Realizing the Promise of Pharmacogenomics: Opportunities and Challenges," published March 23, 2007. This paper represents a thorough review of critical issues related to pharmacogenomics and its application in healthcare.

General Comments:

1. The Table of Contents is confusing and inaccurate. For example, it says recommendation 1 can be found on page 22, however, recommendation 1 is only present in the Executive Summary on p. 6. The report should either be revised so the Table of Contents is accurate, or it should provide an explanation of how the Table of Contents is to be used.

2. This document is overly long and contains several sections that could apply to any new medical technology (not just pharmacogenomics [PGx]). We believe these sections are unnecessary and could be deleted. Examples of sections and text that could be deleted are provided in the "Specific Comments" section below. Alternatively, these topics could be placed in a separate section of the report, with an explicit statement that the topics need to be addressed in the context of PGx but are not necessarily unique to PGx.

3. We disagree with several themes that are present throughout the paper:
   a. **An over-emphasis on PGx used to predict adverse drug reactions rather than efficacy or dosing.** While increasing drug safety is a desirable goal, the paper needs to acknowledge that it is less likely that we can discover novel genetic factors for safety than for efficacy.

   b. **Genetic exceptionalism.** One of the barriers to realizing the promise of PGx is the misperception that PGx information is somehow different from most medical data. This report perpetuates that misperception, particularly by raising issues as specific to

PGx when in fact they are general to medical data or new medical technologies. (Examples in this report that perpetuate the idea of genetic exceptionalism are identified and suggested for deletion in the "Specific Comments" section below.) Further, the report does not adequately distinguish between the limited aspects in which genetic information is necessarily different from other medical information, and the many ways in which it is not.

c. **Failure to distinguish between PGx and medical genetics**. The report does not emphasize this distinction as it should. PGx data is no more sensitive than ordinary medical information, and so the data protection issues should be generally the same. Also, unlike medical genetic information, PGx information can be conveyed by an ordinary medical professional, and a genetic counselor or certified geneticist is not required.

4. This report relies too heavily on secondary and tertiary sources such as review, summary, or opinion papers. Many of these sources offer a perspective that is not impartial and accordingly, are inadequate to support the recommendations and other content of this report. We have noted instances in which cited references do not support the statements in the report. (See, for example, our Specific Comments 8, 14, and 17.)

Comments on Selected Specific Recommendations in the Executive Summary:

1. Much of recommendation 1 ("Basic Research") on p. 6 seems to be unnecessary. There is already a well developed body of knowledge on the genetics of drug metabolism, and basic research on the pathways that relate to specific drugs is probably not the best way for the NIH to spend its money. It would be better to conduct NIH sponsored genotype – phenotype clinical studies.

2. Recommendation 3 on p. 7 suggests the NIH could be the intermediary between industry sponsors and the FDA. In fact, there is already open and productive communication between industry scientists and the FDA on these issues, and the need for a facilitating role for the NIH is not apparent.

3. In recommendation 4 ("Development and Co-development of PGx Products") on p. 7, consider citing the draft bill sponsored by Senator Obama entitled, "The Genomics and Personalized Medicine Act of 2007" [referred to Senate committee], as this bill proposes similar incentives.

4. In recommendation 4a on p. 7 rather than focus on the co-development of drugs and diagnostics, it would be better for the SACGHS to recommend that FDA clarify for the pharmaceutical industry the regulatory requirements for a genomic test to be referenced in the drug labeling. Specifically, FDA should clarify the circumstances under which it will require that there be an FDA licensed test (e.g., Analyte Specific Reagents [ASR],

multivariate index analyte in vitro diagnostic [MIAIVD], or in vitro diagnostic [IVD]), or when a test available in a CLIA certified laboratory is considered adequate.

5. In recommendation 7 on p. 9 and its supporting text on pages 42-45 it would be valuable to provide a better understanding of the limits of privacy in research, especially as it compares to the limits of privacy in our daily lives, and to recognize that there is a balance between privacy and individual autonomy, not to mention public good.

Specific Comments:

1. Please revise the second paragraph of subsection a ("Improved Patient Safety") on p. 14 to state that the CYP2D6 genotype, although related to rate of metabolism, has not been shown to be clinically relevant for most of the drugs listed in this subsection of the report.

2. Please revise the last paragraph in subsection B ("Complexity of the Science") on p. 18 to expand on the non-genetic factors and the reasons that PGx testing for warfarin is not widespread.

3. In the last paragraph of subsection C ("Current State of the PGx Field") on p. 19, the report notes that much of the available PGx data in the literature is ignored in prescribing information included in package inserts. However, there is no consensus on the strength of genetic association for most of the drugs or its clinical relevance, and so labeling should not include language to guide therapy via PGx.

4. Care should be taken in the discussion of adaptive trial designs. (See, for example, subsection C ["Clinical Research"] beginning on page 24.) As drafted, this aspect of the paper is misleading since in clinical trials, the term "adaptive" refers specifically to studies in which the design is somehow modified according to the interim results. Selecting participants based on their expected responses is not an example of an adaptive trial.

5. Revise the first paragraph of subsection 3 ("Co-development of Drugs and Diagnostic Tests") on p. 28 to state that a path for co-development of a marker discovered late in drug development is needed. Specifically, this subsection should state that when the need for a marker is not apparent until large clinical trials have been completed, the pathway described in this subsection will not apply.

6. As drafted, subsection 3 ("Co-development of Drugs and Diagnostics Tests") emphasizes industry reluctance to co-develop drugs and diagnostic tests. To provide a counterpoint, consider revising this subsection to describe industry efforts that have supported co-development of drugs and diagnostic tests.

7. The first paragraph of subsection 1 ("Clinical Validity and Clinical Utility") on p. 34 says that assessing the actual clinical validity and utility of a test in practice should occur

while researchers are measuring its analytic validity. We disagree with this statement, since typically, analytical performance must be established before clinical validity is tested.

8. In the fourth paragraph of Subsection 1 ("Clinical Validity and Clinical Utility") on p. 35, please verify the link between reference 218 and the statement, "At least twice as many drugs' effects are predicted by these complex, multigene factors than are predicted by a single gene." Since the total number of known (or even suggested) multigene factors in PGx is smaller than the number of established single gene effects, it is doubtful that reference 218 can authoritatively support this statement.

9. According to the first paragraph of Subsection 2 ("Informed Consent") on p. 44, PGx may raise special concerns related to informed consent. However, the issues raised in the report apply equally to non-genetic clinical information, and should be regarded similarly.

10. According to subsection 4 ("Liability Concerns for PGx Drugs and Diagnostic Developers") on p. 49, "Requiring PGx testing as a condition for drug treatment could further reduce pharmaceutical companies' liability risk." We recommend the report be revised to provide a reference or other evidence to support this statement. We also note that liability risk from medical product use does not rest solely with the pharmaceutical industry. It is unclear why this report only addressed this issue in the context of pharmaceutical companies.

11. Revise the second paragraph of subsection 2 ("Co-development of PGx Diagnostics and Drugs") on p. 51 to mention a key co-development barrier, the lack of a clear path for co-development of a marker discovered late in drug development. See comment 5, above.

12. As drafted, the third paragraph of subsection 2 ("Co-development of PGx Diagnostics and Drugs") on p. 51 emphasizes the disincentives to the pharmaceutical industry for the co-development of PGx diagnostics and drugs. We suggest the fact of industry support of PGx be added to this paragraph as a counterpoint.

13. The first paragraph of Subsection B ("FDA") on p. 52 describes the challenge of how to regulate PGx tests that inform the use of FDA-regulated therapies but that may not be subject to FDA regulation themselves. However, the issue of how to regulate tests that inform the use of FDA-regulated therapies is not unique to PGx.

14. See the second paragraph of Subsection 2 ("FDA Guidance for PGx Products") on p. 57. Reference 335 does not provide adequate support for the statement, "However, given the potential impact of PGx and heightened interest in drug safety, it suggests that such data could be mandatory for new drug approval in the future." We recommend deletion of this statement unless there is appropriate evidence to support it.

15. The second paragraph in subsection c ("Influence on Patient Access") on p. 64 describes the influence of reimbursement, particularly the low reimbursement of genetic counseling services, on patient access to care. We believe this issue (low reimbursement) is not exclusive to PGx and should therefore be removed from this report. Furthermore, PGx information should not require genetic counseling services.

16. The last paragraph of subsection c ("Influence on Patient Access") on p. 65 describes several potential adverse consequences of high unit- or aggregate-costs. However, as drafted, this paragraph is unbalanced and speculative. We recommend these statements be supported with more authoritative evidence or removed.

17. As an online news story (see the third paragraph of subsection b ["Product Labeling"] on p. 75), reference 423 is inadequate support for the statement "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 prominent box." Statements of upcoming policy should come directly from official, reliable FDA sources. We recommend that this sentence be referenced appropriately or removed.

18. The second paragraph of subsection 3 ("Patients and the Public") on p. 78 includes the statement, "Most patient preference research to date has generally shown that patient concerns...quality of life." Reference 441, cited to support this statement, pertains to medical genetics, not PGx. Accordingly, we recommend this statement be deleted.

19. In the third paragraph of subsection 1 ("Electronic Health Records") on p. 82, the report expresses a concern that PGx introduces particular considerations for the design of electronic health records. In general, we disagree, as PGx data typically have information content equivalent to most medical information.

20. In the second paragraph of subsection C ("Economic Implications of PGx") on p. 87, costs for genetic counseling should not enter into consideration, since interpretation and communication of PGx results will typically be done by the immediate caregiver.

21. Subsection 1 ("Disparities in Access to Care for Underserved Populations") on p. 90 describes health care access disparities associated with income, race or ethnicity. We believe these disparities are not at all particular to PGx and may be associated with any new advanced medical technologies. Therefore, unless it has been demonstrated that PGx exacerbates or alleviates these disparities, we recommend this topic be excluded from this report.

22. In the second paragraph of Subsection 2 ("Stigma and Discrimination") on p. 91, reference 541 pertains to medical genetics rather than to PGx (see below). The distinction between the two types of tests should be pointed out.

23. Please update the third paragraph of Subsection 2 ("Stigma and Discrimination") on p. 91 to reference Genetic Information Nondiscrimination Act of 2007.

Answers to Selected Questions Posed in the Cover E-Mail Sent With the Report:

1. Are the discussions of topics and issues accurate and complete?
   In general, we found the report accurate and complete. Nevertheless, there is confusion between the informational risks for a medical genetic test and for a pharmacogenomic test. The former provides information on the predisposition for disease or the likely prognosis for disease, whereas the PGx test only provides better information for the choice of treatment for a disease that has already been diagnosed. BRCA1 detection to predict occurrence of breast cancer is an example of medical genetics; blood typing prior to transfusion is an example of pharmacogenomics. This distinction is often lost in the report, but is important for many of the issues the report has highlighted.

2. Have any significant opportunities, challenges, or other issues been missed?
   a. **We suggest the report recommend that the NIH conduct thorough genotype-phenotype PGx clinical studies on off-patent drugs. These drugs (e.g. thioridazine, imiprimine, codeine, warfarin, and mercaptopurine) have well known PGx effects, but studies of adequate size to determine the potential clinical utility of PGx testing have not been done.**

   b. **The report would benefit from a greater emphasis on the use of PGx in prospective PGx studies based on results from previously unblinded studies (prospective-retrospective analysis) to uncover otherwise unknowable PGx effects.**

   c. **The report should discuss the need for access to DNA samples from patients with specific responses to drugs, whether adverse reactions or therapeutic success or failure. Access to well characterized samples continues to be the biggest impediment to scientific advancement.**

3. Does the draft report adequately describe the range of perspectives on the issues?
   As noted, the sources for the report are almost entirely review, summary or opinion papers, rather than the original publications. Many of these have not been peer reviewed for scientific or medical accuracy and can be opinionated, inaccurate or irrelevant to the specific issue. An example is the cited source suggesting that incorporation of PGx will reduce the time needed for new drug development to 3-5 years (see reference 7, cited on p. 4 of the report). To make this report more authoritative, the sources should be checked for factual accuracy.

4. Are the draft recommendations specific enough?
   We found some of the recommendations insufficiently specific. For example, Recommendation 2 states "HHS agencies should facilitate the development of clinically useful PGx technologies… " We recommend that the report be revised to clarify what is meant by "facilitate the development" in this context. The revision should specify how attainment of this recommendation would be measured or assessed. Similar vague recommendations are in Recommendations 5d, 6,7, 10b and c, 11a, and 12b.

We thank the Committee for its consideration of our comments. Should you have any questions, please contact Ms. Melodi McNeil, Director, Regulatory Intelligence, at 301-255-0085, x105 or by FAX at 301-255-0090.

Sincerely,

Melodi McNeil for

Douglas L. Sporn
Divisional Vice President
Regulatory Intelligence
Global Pharmaceutical Regulatory Affairs

AFFYMETRIX®

Reed V. Tuckson, MD
Chair
Secretary's Advisory Committee on Genetics, Health, and Society
NIH Office of Biotechnology Activities
6705 Rockledge Drive, Suite 750
Bethesda, MD 20892

June 1, 2007

Dear Dr. Tuckson,

We commend you and your colleagues on the Advisory Committee for your thorough and carefully considered draft report on *Realizing the Promise of Pharmacogenomics: Opportunities and Challenges.* You have successfully described the complex, intricate landscape and identified the barriers to and enablers of advancing the applications of pharmacogenomic technology.

Affymetrix, Inc. manufactures GeneChip ® Microarrays, and is considered to be a leader in the development of microarray products for the collection and analysis of complex genetic and genomic information. GeneChip® microarrays are used by hundreds of pharmaceutical, biotechnology, agrichemical, diagnostics and consumer products companies as well as academic, government and other non-profit research institutes to study and develop products based on the relationship between genes and human health. Over the years, Affymetrix has actively engaged in dialogues shaping policy surrounding personalized health care through our Government Relations and Public Policy office in Washington and direct participation in the Personalized Medicine Coalition, the AHIC Working Group on Personalized Healthcare, the Coalition for Genetic Fairness, agency hosted roundtable discussions, the OECD, CLSI, international standards development consortia, our own annual Genetic Age Symposium, and more.

We were very pleased to see our contribution to the GAIN initiative included in your report, as well as your consideration of Roche's AmpliChip pharmacogenetic test, which utilizes our GeneChip® microarray technology and is the first microarray test cleared by the FDA. We take pride in our role in advancing pharmacogenomics and wish to continue working with you and other stakeholders to shape policy to usher in this new era of medicine.

The report clearly elucidates the current oversight system for genetic tests, its challenges, and FDA, CMS, AHRQ and CDC efforts to document the validity and improve the quality of genetic tests. In addition to efforts within HHS, advocacy groups, including the Personalized Medicine Coalition and the Genetics and Public Policy Center, are actively engaged in updating and improving the oversight process. Last June, Affymetrix sent a

3380 Central Expressway
Santa Clara, California 95051
Telephone 408 731 5000
Fax 408 481 0422
www.affymetrix.com

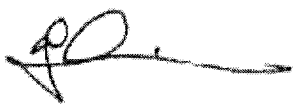
letter to Dr. Mark McClellan, CMS Commissioner, requesting the creation of a genetic testing specialty within CLIA. We also signed onto the Genetic Alliance letter to CMS and voted for the PMC to also formally endorse the creation of this specialty.

Congress is also paying attention to oversight of genetic tests. Senators Obama and Burr have introduced a comprehensive genomics bill that includes a section on oversight, and Senator Obama offered an amendment to the PDUFA calling for an IOM study on the regulation of genetic tests. Additionally, Senators Kennedy and Smith introduced a bill creating a regulatory mechanism for laboratory developed tests. We recommend that your final report also acknowledge the efforts of stakeholders and Congress and their potential impact on the field of pharmacogenomics.

Your report describes the importance of standards for genomic data in its inclusion in electronic health records. We encourage you to also address the need for standards for genomic data in the validation of genetic tests. HHS has partnered with other public and private stakeholders in many international consortia, including the Microarray Quality Control Project, the External RNA Controls Consortium, and the Clinical and Laboratory Genomic and Genetic Standards Group. These groups are working to develop standards for genomic data which will aid in the submission of applications to the FDA and in establishing the validity of pharmacogenetic tests.

Affymetrix greatly appreciates the opportunity to comment on your draft report on *Realizing the Promise of Pharmacogenomics: Opportunities and Challenges.* We look forward to reading the final product and hopefully, the implementation of many of the policy initiatives outlined in the draft report including the creation of an interdepartmental work group to coordinate collaborations within and outside of HHS. Please do not hesitate to contact me or any of my Affymetrix colleagues if we can be of further assistance.

Sincerely,



Thane Kreiner, Ph.D.
Senior Vice President
Corporate Affairs & Advanced Development

From: LAiello@shorememorial.org [mailto:LAiello@shorememorial.org]
Sent: Wed 3/28/2007 3:38 PM
To: Goodwin, Suzanne (NIH/OD) [E]
Subject: Public Comment on Draft SACGHS Report on Pharmacogenomics

Dr. Tuckson,
I was impressed with the draft SACGHS report on pharmacogenomics.

I have one suggestion. Education is recommended for health care professionals. I suggest including information regarding the new nursing competencies. Here is the reference. If I missed it within the document, excuse me.

Consensus Panel on Genetic/Genomic Nursing Competencies (2006). Essential Nursing Competencies and Curricula Guidelines for Genetics and Genomics. Silver Spring, MD: American Nurses Association.

Thank you.

Lisa Aiello-Laws, RN, MSN, APN,C, AOCNS, APNG
Manager, Cancer Program
Shore Memorial Hospital, Cancer Center
1 E. New York Ave
Somers Point, NJ 08244
(W) (609)653-3772
(F) (609)653-3586
Email: laiello@shorememorial.org

STANFORD
SCHOOL OF MEDICINE
Stanford University Medical Center

Stanford University Medical Center
Department of Genetics
300 Pasteur Drive, L301 MC: 5120
Stanford, CA 94305-5120

Russ B. Altman, MD, PhD
Professor of Bioengineering, Genetics & Medicine (& Computer Science, by courtesy)
Chairman, Department of Bioengineering
Director, Biomedical Informatics Training Program

russ.altman@stanford.edu
(650) 725-3394 Fax: (650) 725-3863

March 31, 2007

Reed V. Tuckson, MD
Chair
Secretary's Advisory Committee on Genetics, Health, and Society
NIH Office of Biotechnology Activities
6705 Rockledge Drive, Suite 750
Bethesda , MD , 20892

Dear Dr. Tuckson,

I am writing in response to the request for public comment on the Secretary's Advisory Committee on Genetics, Health and Society (SACGHS) report "Realizing the Promise of Pharmacogenomics: Opportunities and Challenges." I am the Principal Investigator for the PharmGKB (http://www.pharmgkb.org/), an NIH-supported web-resource devoted to disseminating knowledge about pharmacogenomics in order to catalyze research. I have read through the report, and would like to commend the committee on a valuable and thorough treatment of this topic. On balance, the report is quite good. I have a few detailed suggestions.

1. I think that the role of the Pharmacogenomics Research Network (PGRN) funded by the NIH needs to be highlighted more in section II.A "Basic Research." While it is fine to mention important projects such as GAIN and Hapmap, these are really only glancing blows to basic research in pharmacogenomics compared to the efforts of the many investigators involved in this research network solely devoted to the issue of basic research in pharmacogenomics. PharmGKB is part of PGRN and more information about PGRN is at: http://www.nigms.nih.gov/Initiatives/PGRN/

2. It may be useful to highlight the national competitiveness issues associated with pharmacogenomics. In particular, large biobanks created in Iceland, Estonia, United Kingdom, Korea and Japan (with many others considering similar efforts) have a particular interest in pharmacogenomics. Consequently, the U.S. is by no means alone in its interest in this field, and to the extent that there are opportunities for market leadership, it is critical that the US continue its investment in this area.

3. With respect to translational research and clinical research, I think the committee has missed an opportunity: strongly to suggest that all clinical trials supported by federal funds (usually NIH) be required to collect DNA samples in order to investigate potential genetic influences on unexpected outcomes or unexpected variation in outcomes (or explain why not). This should be part of recommendation (3) Clinical Trial Design.

4. We and other members of the PGRN have recently spearheaded an international consortium of pharmacogenomics researchers investigating warfarin dosing. The "Warfarin Consortium" involves about 12 centers worldwide who are pooling their data in order to get more statistical power in predicting safe warfarin doses based on a combination of demographic and genetic parameters. Individual centers rarely have more than 500 subjects, but the pooled resources of the consortium will include more than 4000 subjects. I believe that the future of pharmacogenomics will include more examples like this of international data sharing efforts, and I would recommend that the efforts such as these be included in the recommendations about "Data Sharing and Database Interoperability." I would be happy to discuss with members of the committee how we formed the consortium, and how we plan to replicate this in other areas. Our interest at PharmGKB is to make sure that such consortia are formed, and that they share their data appropriately with the scientific community (for re-analysis and discovery).

5. I think the committee misses an opportunity to stress the importance of supporting basic research on methods for capturing and coding information about environmental exposures. The reality of drug response (like all other phenotypes) is that it is a complex function of both genotype and environment. The human genome project has markedly advanced our ability to assay the genotype space, but we are now lagging far behind with respect to environmental influences. Although environmental factors are mentioned in about a dozen places in the document, there is no focused recommendation that we begin to create methods to assay and encode environmental exposures. On a related point, there is little discussion in the report about the variety of genomes that can be relevant in pharmacogenomics. These other genomes form a very special part of the environment. In addition to the patient's genome (the host), the genome of a pathogen (e.g. HIV, Hepatitis, malaria, or tuberculosis) can also be critical, as well as the genome of a tumor. It may be useful to make a technical note on the difficulty of understanding the full ecology of pharmacogenomics.

Thank you very much for the opportunity to respond to this report, and I would be happy to elaborate further on any of these issues, should the committee find it useful.

Sincerely,

Russ B. Altman

America's Health Insurance Plans

601 Pennsylvania Avenue, NW
South Building
Suite Five Hundred
Washington, DC 20004

202.778.3200
www.ahip.org

June 1, 2007

Reed V. Tuckson, MD
Chair
Secretary's Advisory Committee on Genetics, Health, and Society
Office of Biotechnology Activities
National Institutes of Health
6705 Rockledge Drive, Suite 750
Bethesda, MD 20892

Re: Public Comments in Response to the Draft Pharmacogenomics Report

Dear Dr. Tuckson:

America's Health Insurance Plans (AHIP) is writing to offer comments in response to the draft report, "Realizing the Promise of Pharmacogenomics: Opportunities and Challenges." A Notice requesting public comments was published in the *Federal Register* on March 28, 2007. (72 Fed. Reg. 14577)

AHIP is the national association representing nearly 1,300 health insurance plans providing coverage to more than 200 million Americans. Our members offer a broad range of products in the commercial marketplace including health, long-term care, dental, vision, disability, and supplemental coverage. Our members also have a strong track record of participation in Medicare, Medicaid, and other public programs.

AHIP supports the work of the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) on the topic of pharmacogenomics (PGx). The advances being made in understanding the human genome will likely help advance clinical understanding of the potential causes and effects that genes can have in disease development and treatment responses. We agree with the report's premise that PGx has the potential of making new breakthroughs in personalized medicine by changing the ways that health care providers tailor individual therapies and treatment options based on an individual's unique clinical situation and genetic composition.

Health insurance plans have long supported the use of evidence-based decision-making to improve patient outcomes. In the context of PGx, we hope that the final SACGHS report will prompt health care providers, government agencies and payers, and health insurance plans to review existing processes and ensure that PGx drugs, tests, and services are delivered to individuals in a safe and effective manner.

We recognize that the report is intended to provide timely, policy-relevant information about PGx and we are submitting the attached comments (Attachment A) to help explain and clarify some of the issues and information conveyed in the report. We hope this information and our recommendations help to ensure that the final report accurately and comprehensively represents the issues and information discussed.

We appreciate the opportunity to comment on these important issues. Please contact me by phone at (202) 861-1473 or by email at mzigmundluke@ahip.org with any questions.

Sincerely,

Marilyn Zigmund Luke
Associate Regulatory Counsel

Attachments

Attachment A

America's Health Insurance Plans
Comments in Response to the SACGHS Draft Report:
"Realizing the Promise of Pharmacogenomics: Opportunities and Challenges"

General Comments

Issue: The report contents and recommendations could be more easily identified and understood if the organization and format were changed.

Discussion: Overall, the report attempts to convey a comprehensive evaluation of the issues related to PGx. More than 550 references are cited and 15 specific, detailed recommendations are made in the report. We appreciate the comprehensive effort and attention to detail.

For individuals who may have no clinical background, one of the issues with the report is that it can be difficult for a reader to understand on what information the SACGHS is relying to formulate its specific conclusions and recommendations because the recommendations are not separately listed in the body of the document. As a suggestion, we feel that the report could be better organized by listing more defined, easily discernable topic areas which include the SACGHS recommendations at the end of each of the corresponding segments in the body of the report. This format has been successfully used by the SACGHS in prior reports.

Recommendation: The PGx report could be improved by dividing the contents into specific topical areas followed by the Committee's specific conclusions and recommendations.

Patient Safety and Increased Effectiveness of Care

Issue: When discussing Adverse Drug Reactions (ADRs), the report should expand its discussion to include additional factors that could contribute to ADRs.

Discussion: The report states that ADRs are the leading cause of market withdrawals of drugs. Also, the current "trial and error" process of treating individuals is indicated as a major cause of ADRs because genetic variations of drug-metabolizing enzymes that affect metabolism, transport, distribution, absorption and excretion are highly correlated with such adverse events. As a result, the report concludes that achieving even modest reductions in the rate of ADRs could result in substantial improvements in health care outcomes and costs.

However, this discussion appears to overstate the causes of ADRs by attributing them to a lack of clinical application and use of PGx technologies. In reality, many other factors

have been demonstrated to cause ADRs, including inappropriate prescribing outside the bounds of evidence-based medicine and the inherent toxicity of some Food and Drug Administration (FDA) approved therapies, including antibiotics, pain medications, diuretics and blood-thinners.[1]

In addition, the report could benefit from additional discussion about the use of PGx testing as it relates to the prevention of ADRs for existing drugs.

Recommendation: When discussing Adverse Drug Reactions (ADRs), the report should expand its discussion of additional factors that could contribute to ADRs. Recognizing how other factors (e.g., inappropriate prescribing outside the bounds of evidenced-based medicine) beyond genetic composition can cause ADRs would convey the information more accurately. Also, discussing the effective use of PGx testing as it relates to the prevention of some ADRs for existing drugs would provide a more complete context for this issue.

Development of PGx Products

Issue: Evidence-based medicine should be identified in this section as a primary tool used to guide the clinical decisions of providers and payers.

Discussion: The report recognizes that the influence of PGx on drug development is difficult to predict. For diagnostic test developments, the report discusses on pages 27-28 that a key concern is projecting the utilization of the test, any accompanying return on investment of test development, as well as the added benefits of developing these tests. However, the report should also note that clinicians and payers need to consider whether a PGx test will change the care delivered and/or improve the health outcome for a patient.

Extensive variation in the delivery of health services across the country has been well-documented within the health care industry.[2] To reduce variation, one of the primary tools that providers and payers use to guide their decision-making process is evidence regarding the value of certain therapies for specific populations.

Generally, evidence-based medicine is defined as the integration of best research evidence with clinical expertise and patient values.[3] As PGx tests and drugs are developed, often their clinical effectiveness is unclear or undetermined. When evaluating

---

[1] *Reducing and Preventing Adverse Drug Events To Decrease Hospital Costs.* Research in Action, Issue 1. AHRQ Publication Number 01-0020, March 2001; Agency for Healthcare Research and Quality, Rockville, MD as available at: http://www.ahrq.gov/qual/aderia/aderia.htm.

[2] *See,* EA Kerr, EA. McGlynn, J Adams, J Keesey, SM. Asch. "Profiling the Quality Of Care In Twelve Communities: Results From The CQI Study." *Health Affairs*, 23, No. 3 (2004): 247-256. *See also,* McGlynn, Elizabeth A. The First National Report Card on Quality of Health Care in America. Rand Health Research Highlights. 2006. Retrieved May 22, 2007 from http://www.rand.org/pubs/research_briefs/RB9053-2/ (indicating that only 55% of care delivered is best practice, quality varies across conditions, and quality varies across communities for the same condition).

[3] *Crossing the Quality Chasm*, Institute of Medicine 2001, p. 147.

a particular diagnostic test, clinical evidence and effectiveness should be the determining factors for whether a drug or test is used by practitioners in clinical practice or determined to be medically appropriate for an individual's situation. The development and adoption of PGx products or tests would be inappropriate if there were no demonstrated benefit for the use of these tests. The lack of an evidence-based approach would increase overall health care expenses without improving the quality of care being delivered or improving the health status of individual patients.

Recommendation: In various sections, the SACGHS report provides a complete and accurate explanation of how evidence-based medicine can be used to improve the delivery of health care services. The segment addressing development of PGx products could be enhanced by adding a discussion of how evidence-based medicine can be an effective tool for evaluating the clinical effectiveness and adoption of PGx products and tests.

Co-development of PGx Products

Issue: The SACGHS recommendations addressing co-development of PGx tests and drugs should include a process to evaluate any potential adverse effects or unintended consequences.

Discussion: The report explains that traditionally drugs and diagnostic tests have been developed separately. "Co-development" in the context of PGx refers to the contemporaneous, linked development of drugs and tests, such as when drug makers investigate various biomarker strategies which eventually result in a validated biomarker that is identifiable with a diagnostic test. According to the report, this process makes it possible for the FDA to review drug and diagnostic products simultaneously to potentially accelerate the approval process.

The report also notes that there has been some resistance in the pharmaceutical industry to co-development due to concerns that: (1) the market for a drug may be segmented into parts too small to be profitable; or (2) there is uncertainty about how the FDA can review and regulate diagnostics and drugs developed by different manufacturers.

To address these issues, the SACGHS recommends that: (1) the FDA develop a guidance document which clarifies the review process for co-developed PGx products when a drug is subject to FDA review but the laboratory-developed companion diagnostic test is not; (2) the FDA promote collaboration between drug and diagnostics manufacturers; and (3) the U.S. Department of Health and Human Services (HHS) identify and provide incentives to the private sector to encourage the development of PGx products for smaller markets (e.g., through financial incentives, expedited FDA review, and greater intellectual property protection).

Some of the concerns with this approach include the possibility that co-developed products could adversely affect competition in the marketplace and result in higher prices

for such products (e.g., if unrelated entities join together to create co-developed products or tie tests and products together so that price and competition in the market is adversely affected). In addition, it is possible that modifying or expediting the FDA approval process could prompt some pharmaceutical companies who want to bring a new drug to market to co-develop a test to expedite (and potentially shorten) the FDA approval process.

Recommendation: Overall, we support the SACGHS recommendations for developing additional industry guidance and encouraging collaboration for co-development of PGx products. However, to prevent unintended consequences or potential adverse effects on the market, we encourage the SACGHS to revise it recommendations by: (1) encouraging HHS to grant incentives on a very limited basis and that such incentives include prescriptive criteria; (2) including a phase for "pilot tests" of such projects; and (3) promoting studies of the effects and outcomes, including effects on markets and prices, before HHS grants private sector incentives or officially adopts changes to the FDA review process. The SACGHS should also consider holding future hearings to solicit testimony from industry stakeholders involved in or affected by these HHS projects and processes.

Development and Oversight

Issue: The report should expand its discussion about governmental oversight of PGx tests, drugs, and services.

Discussion: In several sections of the report, the FDA and HHS are discussed as appropriate oversight agencies. However, in some cases PGx tests under development may not be subject to FDA review, and may be offered to individuals or populations without knowledge of whether such tests improve clinical decision-making.

Recommendation: The SACGHS should consider: (1) expanding the report's discussion about oversight for non-FDA approved PGx tests; and (2) proposing definitive recommendations about how effective oversight of non-FDA regulated tests should be accomplished.

Coverage and Reimbursement

Medicare

Issue: It is unclear why the SACGHS makes no recommendation regarding Medicare coverage policies for PGx tests and drugs, but recommends a PGx coverage mandate for private sector health insurance plans.

Discussion: In the discussion about reimbursement, the report provides an overview of the Medicare program as well as private health insurers' coverage policies. The report

states that Congress must pass new legislation for PGx screening or preventive interventions because the Medicare program typically does not cover such services when no treatment is needed (and thus no drug need be prescribed) but an individual or his or her treating provider could benefit from knowing the PGx results for a future clinical application. Without a direct, practical application, however, it seems reasonable to expect that the Medicare program would not cover payment for PGx services. Requiring coverage for PGx testing of asymptomatic individuals would be a drastic change in public policy and health care expenditures.

In addition, the report recognizes that the Medicare program has significant influence over private payers, but because Medicare does not routinely cover PGx testing and drugs, it may be inappropriate for private payers to follow Medicare's lead in this area. To ensure accurate context, the report would benefit from additional discussion about the multitude of private health insurance plans that currently cover PGx tests and drugs, when supported by clinical evidence and when appropriate for an individual's situation, despite Medicare's policy in this area. The report should also be revised so that it does not give a reader an impression that Medicare is somehow blocking PGx testing in either the public or private sectors.

Finally, while the report provides detailed information about the components that determine whether Medicare or private payers cover certain PGx drugs, tests, or services in a plan of benefits, it is unclear why the SACGHS has decided to recommend a coverage mandate for private sector health insurance plans for PGx tests and drugs but not governmental programs.

Recommendation: If the SACGHS chooses to make a recommendation about PGx coverage mandates, it should apply equally to private sector health insurance plans and governmental health benefits programs, including Medicare. We would prefer, however, that the SACGHS not make specific recommendations about private health insurance plans coverage policies and instead encourage the adoption of such policies on a voluntary basis using drug and test results supported by evidence-based medicine, comparative effectiveness, and positive health outcomes.

Evidence-Based Medicine

Issue: It is unclear why the SACGHS is recommending a PGx coverage mandate for private sector health insurance plans.

Discussion: One of the main SACGHS recommendations is that when a validated PGx test is available to guide therapeutic decision-making, private health insurance plans, including Medicare prescription drug plans, should cover the most clinically appropriate drug as indicated by PGx test results. We appreciate that some sections of the report discuss the use of evidence-based medicine to support a link between PGx test results and their impact on diagnosis, therapeutic selection, and health outcomes. Determining

whether a PGx drug and/or test has practical, clinical value is vitally important when a health insurance plan decides to provide coverage for a drug, test, or service under a plan of benefits.

However, it is unclear what the SACGHS means by the term "validated PGx test." In some contexts, a test can be validated, but can have either no clinical utility or be inappropriate for treating an individual's medical situation. Without demonstrated evidence and comparative value, it would be unwise and costly to mandate coverage for PGx tests and drugs, particularly when plan benefits and treatment options may provide for drugs, tests, and services that have been proven as clinically effective and which may be better alternatives for the individual patient. It is also premature to discuss mandated coverage of PGx tests when there is not yet regulation of genetic tests to substantiate the validity and clinical utility of such tests.

Recommendation: We recommend that the SACGHS expand the report's discussion of the importance of evidence-based medicine and the need for clinical outcomes data.

We also recommend that the SACGHS revise its recommendation as follows:

> **"When evaluating coverage policies for PGx tests and drugs, private health insurance plans, including Medicare prescription drug plans, and other governmental programs should consider covering clinically effective drugs in conjunction with PGx test results as supported by evidence-based medicine, positive health outcomes, and individual patient needs."**

Medical Necessity

Issue: The report should clarify how medical necessity determinations can be appropriately made for PGx tests and drugs.

Discussion: The report claims that medical necessity determinations remain controversial, due, in part, to variations in health plan's medical necessity criteria and a perceived lack of transparency in their application. As a result, the report concludes that many emerging PGx technologies can challenge conventional interpretations of medical necessity and individuals can encounter barriers to coverage and payment.

This section of the report does not discuss the existing legal requirements, such as the Employee Retirement Income Security Act and many state laws which require health insurance plans to provide individuals with the specific criteria when a claim for benefits is denied as not being medically necessary. In addition, individuals can often request multiple levels of internal and/or external review if they believe that an incorrect denial of health benefits has occurred. Health care providers can often file such appeals on

behalf of individuals, or can provide evidence to support claims for medical necessity as part of the review processes.

Many state laws fail to require that external reviewers use evidence-based medicine standards, and some of them allow reviewers to base their decisions on prevailing opinion or generally accepted medical practice, which can promote variation in applications of medical necessity guidelines. Ultimately, such factors can lead to confusion about whether a PGx test or drug has been denied by a health insurance plan even if its use is not supported by clinical evidence or is not appropriate for the individual's situation.

Recommendation: The SACGHS report should help promote better understanding of existing legal requirements, the use of clinical evidence, and how an individual's medical necessity affect benefit decisions by health insurance plans.

Issue: When discussing transparency, the report should include current industry efforts and how they can improve understanding of medical necessity criteria used for PGx tests and drugs.

Discussion: On the issue of transparency, HHS, private health insurance plans, and other industry stakeholders have made tremendous strides to make information transparent and available to individuals. For example, private health insurers often make clinical guidelines available online for individual members and their treating providers.

In addition, many industry-wide initiatives have increased the availability of medical literature and medical decision-making tools for practitioners to ensure that services provided are medically necessary based on an individual patient's situation. For example, AHIP assists in such an effort by collaborating with the Agency for Healthcare Research and Quality (AHRQ) and the American Medical Association to establish the National Guideline Clearinghouse (NGC). The NGC is a web-based resource where patients and practitioners can access the latest medical evidence on treatments and technologies for use in evaluating the best course of treatment based on the medical necessity of an individual's situation.

Other examples include the AQA's physician-level performance reporting pilot program and AHIP's development of a Personal Health Record model which can be used by consumers and their treating providers to enable "real-time" access to patient health information and increase the information available at the point of care to help make better health care decisions. While not limited to the area of PGx, these tools can help promote better clinical decision-making and standardization across the industry.

Recommendation: The SACGHS report should help promote better understanding of current transparency initiatives and how these processes and resources can promote the use of consistent medical criteria in clinical decision-making.

Health Technology Assessments

Issue: The federal government should play a major role in advancing health technology assessments.

Discussion: Private payers may have their own processes for evaluating new technologies and establishing reimbursement policies for health technology assessments. While all health insurance plans have processes and procedures in place to evaluate new technologies, some private health insurance plans are able to perform more formal, comprehensive reviews of new technologies. While some large health insurance plans have made progress in this area, we agree that a more consistent approach to making such information available can help advance adoption of PGx technologies in clinical practice.

Recommendation: Overall, we support the intent of the SACGHS recommendations for HHS to provide better resources to identify and address evidentiary gaps in the analytic validity, clinical validity, clinical utility, and cost-effectiveness of PGx, improve evidence-based decision-making, and improve high-quality data resources. We agree that HHS can have a role in initiating and facilitating collaborations between and among public and/or private entities to advance the sharing of knowledge and the analytic validity, clinical validity, clinical utility, and cost-effectiveness of PGx.

Specifically, we recommend that: (1) an independent Comparative Effectiveness Board be established to evaluate methods for appraising new technologies (e.g., drugs, devices, and services/procedures); (2) HHS be directed to take specific steps to promote the coordination of the health services research by constructing a web-based approach for retrieving findings from the latest medical studies and developing fact sheets for patients explaining the results and implications for patient care in easy to understand format; and (3) any HHS-specific efforts be conducted across Agency for Healthcare Research and Quality, National Institutes of Health, Centers for Disease Control and Prevention, and other federal agencies.

Rx

Issue: While some private health insurance plans use formulary and non-formulary mechanisms for covering classes of drugs, these mechanisms are not unique to PGx drugs.

Discussion: For prescription drugs, the report states that plans cover drugs based upon the drugs' efficacy, safety and cost-effectiveness. While some plans use a formulary methodology, the report concludes on page 62 that in certain plan members the preferred formulary drug may be less effective or more toxic than a non-formulary or higher-tiered drug, based on the results of a PGx test. This can leave members with a greater share of the costs to ensure that they are getting the safest and most effective drug based on their

genetic makeup and could raise concerns about appropriate access and genetic discrimination.

This discussion and conclusion is unsubstantiated and appears to be based on anecdotal information. As such, we recommend that this text and conclusion be removed when a final report is issued.

Health insurance plan formulary decisions are based on a number of factors, including scientific evidence, clinical effectiveness, positive outcomes, and the safety and efficacy of a product. While the report attempts to encourage coverage of PGx drugs, it would be misleading to discuss plan formulary decisions and the potential financial effects on individuals without also discussing the increasing price of drugs which prompted the use of formularies as a mechanism to control cost trends and ensure affordability of health insurance products. Because pharmaceutical manufacturers can primarily benefit from rapid adoption of PGx tests and drugs, this section of the report should more accurately discuss the market effects and business outcomes that can result from increased use of PGx tests and drugs. The SACGHS may also consider recommending ways that consumers can benefit from increased utilization of PGx tests and drugs.

Recommendation: The SACGHS report should evaluate additional, practical and affordable ways that patients can gain access to PGx drugs, when appropriate for their individual situations. For example, many pharmaceutical companies have processes and procedures in place to assist individuals who are faced with high pharmaceutical costs, have limited financial resources, and who meet other criteria. The SACGHS should consider advocating for the FDA to evaluate the viability of a common patient pool that would be funded by pharmaceutical companies on a voluntary or required basis to help promote the use of PGx drugs in practical, clinical settings.

We recommend that the report text on page 62 that discusses preferred formulary drugs as less effective or more toxic than a non-formulary or higher-tiered drugs, based on the results of a PGx test is an unsubstantiated conclusion and should be removed from the final report.

Coding and Reimbursement

Issue: Coding requirements for PGx tests and drugs can be improved.

Discussion: With the emerging field of PGx, most electronic claims payment systems and the accompanying coding systems can be inadequate. Often, the current system prevents specific, needed information from being conveyed to justify reimbursement.

Recommendation: As the field of PGx develops, changes in the coding system should be evaluated to accommodate the services provided.

Health Information Technology

Issue: HHS should identify ways to make best clinical practices for PGx more readily available to health providers as they are developed.

Discussion: The report advocates for electronic health record (EHR) systems as a universal feature of the health care system to help promote PGx clinical practices. However, while we fully support the implementation of EHR systems, the report should also note that existing mechanisms can be equally beneficial, as long as the efforts include medical evidence and technology on a broad scale and are not limited solely to PGx drugs, tests, and services.

For example, immediate, practical steps can be taken to make PGx clinical information more readily available. They include:

- investing more in research that compares the clinical effectiveness of PGx treatments and puts clinical research into everyday medical practice through widespread adoption of best practices for PGx drugs, tests, and services.
- promoting uniform adoption of effective health care practices by establishing a national, electronic repository to identify and make publicly available best practices to promote the translation of evidence into practice. This could include, but not be limited to, information about on PGx drugs, tests, and services.
- establishing a national repository and information center to broadly disseminate objective, consumer-friendly information about the latest advances in evidence-based medical practices and practices. Such an effort should include, but not be limited to, information about on PGx drugs, tests, and services.
- evaluating how providers can utilize EHRs to interpret, use, and better identify conditions, genetic factors, and individuals who can most benefit from existing PGx drugs, tests, and services.

Recommendation: We agree with the SACGHS recommendation that the Office of the National Coordinator for Health Information Technology, through the activities of the American Health Information Community and in consultation with DVA and DOD, should take steps to ensure the inclusion of clinically validated PGx test results into patient medical records, decision support systems and tools to enhance appropriate test use and interpretation. We encourage the SACGHS to expand this recommendation to incorporate some of the existing options discussed above.

Data Sharing and Database Interoperability

Issue: Interoperability in information technology solutions and standards is a key component for advancing a national health information network.

Discussion: The report recognizes that an infrastructure to promote and support the sharing of PGx databases and repositories is needed. Currently, public and proprietary

databases and data repositories for storing, retrieving and analyzing genetic and genomic data exist and vary in the data sets collected, technologies used, and individual capacities as research tools. However, this reality is not unique to entities and systems that compile and access information on PGx drugs, tests, and services.

As noted in the report, current efforts are underway at the federal and state levels to improve the availability, movement, and access to electronic health information. However, these efforts need additional time to develop the foundations for a national electronic infrastructure. We believe that many policy issues remain unresolved and need to be meticulously evaluated before information can be electronically made available and routinely shared among entities that may have no legal or business relationship.

Recommendation: We agree that the SACGHS should recommend that HHS work with the private sector to identify obstacles to data sharing and identify proposals to overcome them. However, at this point, we believe it is premature for the SACGHS to recommend that HHS encourage private sector entities to voluntarily share proprietary data to advance the development and co-development of PGx products. As an alternative, the SACGHS should consider making a recommendation to HHS that the agency, in conjunction with the AHIC and the Health Information Technology Standards Panel (HITSP) both evaluate potential scenarios (i.e., use cases) for future data sharing and make plans to develop interoperability standards to help facilitate the use of PGx tests and drugs.

Privacy, Data Security and Interoperability

Issue: Interoperability is an ideal goal, but should be practically evaluated to ensure that an individual's right to privacy and security of data is not compromised.

Discussion: While we generally support interoperability of electronic systems and the development and implementation of agreed upon and pilot tested interoperability standards, we hesitate in supporting the SACGHS recommendation that personal medical records and claims databases be interoperable to facilitate research on PGx technologies and build an evidence base at the present time. More discussion and understanding is needed about how such a process could work in a practical business context and not violate existing legal requirements to protect the privacy and security of individually identifiable health information.

In addition, the industry should evaluate whether business practices should enable direct marketing of PGx products to individuals or physicians based on the review and evaluation of commercial pharmaceutical or other data. While PGx drugs, products, and services can facilitate better care, the sharing of private, individual health information between entities should not be routinely used and disclosed for commercial purposes.

Recommendation: We recommend that the SACGHS defer to the AHIC and other federal initiatives to evaluate interoperability and privacy issues before making a

specific recommendation about applications and processes to promote PGx drugs, tests, and services. Specifically, we believe that the SACGHS recommendations can be drafted to: (1) support the necessary privacy and security framework through the work of the AHIC and other federal initiatives; and (2) support pilot testing of necessary interoperability standards, along with a corresponding timeframe for standards development and implementation.

Privacy, Education, and Disease Management

Issue: Individuals consumers could benefit from understanding how existing laws and regulations protect health information, including genetic information, to encourage participation in wellness and disease management programs.

Discussion: As use of PGx drugs, products, and services expands, individual consumers could benefit from understanding how individual health information, including genetic information, is protected from unauthorized uses or disclosures by state and federal legal requirements such as the Health Insurance Portability and Accountability Act. As consumers become informed about the existing legal protections, they may become more willing to participate in disease management and prevention programs that use PGx drugs, products, and services to improve early detection of disease, tailor appropriate treatment and therapies, and increase positive health outcomes.

Recommendation: The SACGHS should consider including a discussion in the report about the role of PGx in wellness and disease management programs.

Population Subgroup Differences in Drug Response

Issue: The health care industry can benefit from educational information about how genetic factors can influence individual responses to specific drugs.

Discussion: As the report recognizes, research has shown that considerable genetic variation exists within specific racial and ethnic groups. Some treatments can be effective for specific racial or ethnic groups.

Recommendation: We do not oppose the SACGHS recommendation that the FDA develop guidance that encourages the collection and analysis of genetic and other biological factors that may better explain differences in drug response.

Analytic Validity, Clinical Validity, Clinical Utility, and Cost-Effectiveness

Issue: Scientific knowledge has yet to be translated into clinical and public health practice.

Discussion: Real challenges currently exist for discerning the links between genes and diseases. Individual factors such as age, sex, weight, health-related behaviors and compliance with treatment plans can affect interpretation of test results, unless they are clearly defined.

In addition, evaluating clinical evidence in the context of PGx can be challenging because what is shown to have clinical validity and utility in some groups may prove to be ineffective for other groups or individuals. In the context of PGx, the existence of some clinical evidence is insufficient unless the evidence is robust enough to empower individuals and their treating physicians by aiding clinical decision-making and improving individual health outcomes.

Recommendation: While we generally support the SACGHS recommendations listed below, we have noted some suggested revisions:

- **We agree that HHS should provide resources to identify and address evidentiary gaps in the analytical validity, clinical validity, clinical utility, and cost effectiveness of PGx. This recommendation should be expanded to include guidelines for appropriate use of these drugs.**

- **To better inform evidence-based decision-making, we support HHS facilitating the development of tools to improve the validity of findings from observational studies, including high-quality data resources; improved methodologies in the design, conduct and analysis of observational studies; and empirical research on the levels of evidence and types of studies required for making decisions for various purposes (e.g., coverage, clinical guidelines, performance metrics) and different clinical contexts. We advocate for expanding this recommendation to also include comparative studies of effectiveness and real-life clinical applications and results.**

- **We agree that it is essential that drug and diagnostics manufacturers conduct studies and disseminate results (both positive and negative) on the clinical validity and clinical utility of PGx in a timely manner through generally accepted published sources. We encourage the SACGHS to revise its recommendation on this issue to make clear and that such results will have the greatest value only when they are released in a timely manner.**

Disparities in Access to Care for Underserved Populations

Issue: The SACGHS should support the decision-making capability of health insurance plans in making benefits decisions related to medical necessity and appropriateness based on an individual situations.

Discussion: We are concerned that the statement contained in the report on page 92 that "insurance companies routinely refuse or modify coverage based on non-genetic factors

that cannot be controlled by patients" and that regulations prohibiting health insurers from using such information in coverage decisions should establish special protections for genetic information.

The report does not cite any resource for concluding that health insurance plans routinely discriminate against individuals based either genetic or non-genetic factors. In fact, there have been very few cases filed to date by individuals alleging genetic discrimination by health insurance plans.

Recommendation: We suggest that the text be revised to more accurately state that some individuals in the public may fear genetic discrimination, although such discrimination does not routinely occur.

Access and Health Education

Issue: The report should emphasize the importance of provider and consumer health literacy, particularly genetics literacy, and the role of genetic counseling in the effective use of genetic technologies.

Discussion: PGx is a highly technical subject for a health care provider to discuss with any individual. In order to make appropriate health care decisions, individuals need to understand the risks and benefits, alternatives, and consequences of refusing drugs, treatments, or therapies. In the context of PGx, much more work needs to be done to ensure that health literacy is improved across all populations and geographic areas.

In conjunction with this consumer health education, providers can benefit from having more information and resources available to explain complex tests or provide valuable decision support. This type of information should explain to the provider appropriate situations when genetic counseling should occur before a genetic test is performed and after the results are received. As discussed earlier, health care practitioners can vary in their understanding of the importance of genetic counseling when using PGx drugs, tests, and services. Such information can help alleviate this variation.

Increasing health literacy and promoting genetic counseling is essential for individuals to understand how the results of PGx drugs, tests, and services can be used in their individual situations.

Recommendation: The SACGHS report should emphasize the importance of improving providers' and individuals' health literacy of PGx tests and drugs. The report should also promote the use of genetic counseling to enable individuals and their treating health care providers better understand their unique clinical situations and make appropriate treatment decisions based on the information presented.

Conclusion

In conclusion, we would like to note that we fully support the following SACGHS recommendations and recommend that they be included in the final report without change:

- **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 professional organizations to facilitate the development of clinical practice guidelines.**

- **FDA and drug and diagnostics manufacturers should focus more attention on ensuring that all relevant PGx information is included in drug and PGx test labels. The information contained in these labels should clearly describe the test's analytical validity and clinical validity and provide adequate and clear information for clinicians to use when making treatment decisions based on PGx test results (e.g., about dosing or drug selection).**

- **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 websites and other appropriate media.**

AMERICAN ASSOCIATION OF OCCUPATIONAL HEALTH NURSES, INC.

Richard J. Kowalski, RN, MSA, COHN-S
PRESIDENT

Ann R. Cox, CAE
EXECUTIVE DIRECTOR

June 1, 2007

Reed V. Tuckson, MD
Chair, Secretary's Advisory Committee on Genetics, Health, and Society
NIH Office of Biotechnology Activities
6705 Rockledge Drive, Suite 750
Bethesda, MD 20892

Via: email

RE: *Department of Health and Human Services: Realizing the Promise of Pharmacogenomics: Opportunities and Challenges*

The American Association of Occupational Health Nurses, Inc. (AAOHN) applauds the committee for under taking the mammoth task of research and development of the draft report of the Secretary's Advisory Committee on Genetics, Health, and Society. AAOHN is pleased to submit the following comments.

General Comments

The basic idea of pharmacogenomics (PGx) to help address and meet unmet health needs, which would enable direct management of individual drug response for such diseases as cancer, cardiovascular disease, asthma and HIV/AIDS, is of particular significance in addressing individual and population health issues and the cost-effective allocation of resources. The challenges will be getting past the possible barriers:

- Myths, untruths associated with genetic testing.
- The inconsistencies in the current information infrastructure of technology and support.
- Stakeholder acceptance.

Understanding "how differences in individual genetics affect different individual responses to drugs" is a new horizon in health care research, which theoretically could improve chronic disease treatments, disparities in health care access and rising health care cost in the U.S. However, in addition to age, sex, diet and underlying medical conditions, there are other variables, which could influence drug responses and should be considered, e.g., activity, weight, exposures (environmental, workplace, etc.), genetic biomarkers, etc. In addition to encouraging research for the discovery of genetic determinants of response to therapeutic agents, it is equally, if not more important to complete comprehensive evaluations of clients to determine the importance of the factors listed above.

Specific Comments

The Association appreciates the committee's efforts to address the multiple issues related to pharmacogenomics, which emphasizes what PGx can do, but we believe that there is much more

that needs to be addressed. The response of the public and the health care community as a whole is currently lagging behind the pace of discovery in genomic research. The specific issues within the document, which the Association recommends addressing in more detail and which are directly related to public and health care response, are as follows:

- Confidentiality
- Discrimination
- Gatekeepers
- Reimbursement

Confidentiality:
Over coming the obstacles to data access and sharing of health information is a mammoth undertaking especially concerning genetic testing. Although genetic testing is not new, the expanding uses of genetics and the need to access medical information is of grave concern to individuals. There is the "trust issue". Will the information be used as intended? Who will have access? And, the use of the electronic record as the primary source for health information documentation and storage, especially at the federal level, i.e., Centers for Medicare & Medicaid Services (CMS), also poses a confidentiality issue on safe guarding access and use or misuse of personal health information.

Although there are a few identified exceptions, the confidentiality of personal health information is held under ethical and legal obligations and should not be disclosed in any form that would identify the individual without individual written consent. It is under these ethical and legal obligations to confidentiality, which is inherent to the practice of health care providers such as occupational and environmental health nurses (OHNs), who strives to safeguard the individual's right to privacy by protecting confidential information and releasing information only upon written consent of the individual or as required by law.

AAOHN agrees with the recommended approaches to protecting individual identity and health information, e.g., limiting the amount of information released, degrading or scrambling data before released, etc. But, the association would also recommend the use of other technology protectors such as firewalls, limiting access per stakeholder, user access codes, etc. Although 45 CFR Part 46 may not apply to "human subject", AAOHN suggest that to get individuals to agree for samples to be used for research informed consent will have to be obtained, whether the specimens are coded or not-coded.

Discrimination:
Discriminatory concerns that include but are not limited to access or availability of services, ability to pay, employment issues such as hiring and firing, etc. will impact the willingness to participate. Because individuals and/or populations may think they are being profiled or biased, the ability to appropriately communicate, educate and counsel them will be important to the success of PGx. Currently, the number of health care providers with the education on the legal, ethical and social implications of genomic advances is insufficient to meet the potential demand. Advances in science must be balanced with programs designed to provide practitioners with the knowledge base needed to counsel and educate individuals and/or populations.

Gatekeepers:
The "trust issue" may be the biggest obstacle with the gatekeepers, not necessarily between gatekeeper and individual, but also between gatekeepers. Who are the gatekeepers and who will

have access and for what purpose? AAOHN agrees that the Department of Health and Human Services (HHS) should initiate and facilitate the collaboration between the public and private entities for sharing of knowledge and information. But, if the Federal Drug Administration (FDA) is the gatekeeper of new health technologies, there needs to be trust and collaboration and coordination between the two agencies. Also, the pharmaceutical industries need to share proprietary data as developer and/or co-developers of drugs with each other as well as HHS and FDA. Is this possible?

AAOHN recommends the involvement of health care providers (physicians, nurses, pharmacists, etc.) as well as all other gatekeeper representatives in the development of clinical practice guidelines. Not having the individual's health care provider involved in the process would be a barrier to facilitation and acceptance of the individual.

Reimbursement:
Will the payers (CMS and private insurance) be willingness to invest in the testing? Will they see the long-term goal as a reimbursement cost savings for the payer? If the individual has to pay out-of-pocket or higher co-payment, the willingness to consent to access and to participate will be slow, at least until the benefits are realized.

The Association appreciates the opportunity to respond to the *Department of Health and Human Services: Realizing the Promise of Pharmacogenomics: Opportunities and Challenges* draft report. As always, we will continue to lend our input and assistance to HHS and other governmental and professional organizations to facilitate safe and healthful workplaces and communities.

Sincerely,

Richard J. Kowalski

Richard J. Kowalski, RN, MSA, COHN-S
President

CC: Ann Cox, Executive Director

ACLA

American
Clinical Laboratory
Association

June 1, 2007

Reed V. Tuckson, MD,
Chair, Secretary's Advisory Committee on Genetics, Health and Society

Via email to Suzanne Goodwin at goodwins@od.nih.gov

Dear Dr. Tuckson:

The American Clinical Laboratory Association (ACLA) appreciates the opportunity to comment on the draft report of the Secretary's Advisory Committee on Genetics, Health and Society titled "Realizing the Promise of Pharmacogenomics: Opportunities and Challenges." ACLA represents local, regional and national hospital and independent clinical laboratories.

In general, the draft report provides a very comprehensive presentation of the policy issues raised by pharmacogenomics and its integration into clinical practice; however, we do have comments on how the report can be strengthened. ACLA fully agrees that the emerging field of pharmacogenomics holds great promise to redirect the health care paradigm to personalized medicine and as such is a powerful tool to improve healthcare. For example, targeted clinical laboratory biomarkers can improve the drug development process and the individual's therapeutic benefit while reducing adverse health events. Clinical laboratories are at the forefront of genomic biomarker innovation and resultant clinical applications, and thus, ACLA members have a significant interest in the field of pharmacogenomics.

SACGHS specifically asked for comment on whether the draft report recommendations are specific enough to prompt needed action. In that regard, more specific recommendations could be made in the section(s) related to the challenges presented by the current coverage and reimbursement of genetic tests. SACGHS released a report in February 2006 on the "Coverage and Reimbursement of Genetic Tests and Services" which found that "significant barriers and unmet data needs are limiting appropriate access and clinical integration" of genetic test services. These barriers continue to impede progress in this area, and therefore, the draft report should address these issues with greater attention and specificity. New approaches to provide economic incentives and eliminate disincentives for the adoption of genetic test services should be a high priority of the Federal government.

ACLA appreciates that the section starting on page 50 titled "Gatekeepers" is intended as an informative road map to the multiple entities that can enable, halt, or redirect the course of pharmacogenomic technology. However, there are incorrect characterizations of regulatory oversight in that section. In writing about the regulatory oversight role of CMS as having responsibility for CLIA, the statement is made on page 68 that "CLIA requires that a laboratory demonstrate the analytical validity and reliability of its in-house tests, but does not require demonstration of the clinical validity or utility of these tests". Likewise, on page 54, the draft report references the argument that "FDA regulation of tests marketed as diagnostic test kits but not tests marketed as in-house services performed by clinical laboratories constitutes an inappropriate

1250 H Street, NW • Suite 880 • Washington, DC 20005 • (202) 637-9466 • (202) 637-2050

double standard." On the contrary, while some further interpretive guidance may be helpful, CLIA regulations implicitly address both clinical validity and clinical utility, and the fact that laboratory developed tests and commercially distributed test kits are overseen under different regulatory frameworks does not mean there is an "inappropriate double standard".

In enacting CLIA, Congress clearly intended CLIA to be the controlling mechanism for regulating laboratory testing services. The laboratory director of a high complexity laboratory – the only type of lab where genetic testing can be performed - is responsible for the overall operation and administration of the laboratory. CLIA regulations under 42 CFR § 493.1445(e) explicitly require the laboratory director to ensure that selected test methodologies are capable of providing the quality of results required for patient care. Implicit in this responsibility is the clear regulatory imperative to choose medically relevant test methodologies that have an effective clinical purpose- otherwise those methodologies could not be said to be "required for patient care." The laboratory director is also responsible for the employment of personnel who are competent to perform test procedures, record and report test results promptly, accurately and proficiently, and for assuring compliance with the applicable regulations. See 42 CFR § 493.1445.

CLIA also requires the laboratory to have a clinical consultant, who "must be qualified to consult with and render opinions to the laboratory's clients concerning the diagnosis, treatment and management of patient care." See 42 CFR § 493.1445. The responsibilities of the clinical consultant are to provide information about the "appropriateness" and "interpretation" of the test results.

Furthermore, CLIA makes the laboratory director responsible for ensuring that the ordering physician can properly interpret results by requiring the laboratory to include pertinent interpretive information in the reports and make consultation available to its clients regarding the quality of the test results and their interpretation. The CLIA regulations thus clearly require that a test have both clinical validity and transparency by requiring the laboratory director to select clinically relevant tests and provide clinical interpretation for those tests.

The determination of whether a test has sufficient clinical utility to be offered is one that should be made by the laboratory director in the exercise of his or her professional judgment, as part of his or her responsibility under CLIA to ensure that selected test methodologies are capable of providing the quality of results required for patient care.

CMS could amend the Interpretive Guidelines for Laboratories to clarify CLIA requirements related to clinical validity and utility. Changes to the Interpretive Guidelines could include some or all of the following clarifications:

- The Laboratory Director of the clinical laboratory is responsible for ensuring that all tests offered by the laboratory are clinically relevant and based upon sound science.
- A test would be deemed to be clinically relevant if its use is well established in clinical practice, described in medical textbooks, or supported by medical guidelines or peer-reviewed literature.

The argument that FDA regulation of tests marketed as diagnostic test kits but not tests marketed as in-house services performed by clinical laboratories constitutes an inappropriate double standard presupposes that test kits and in-house services are similarly situated and should therefore be regulated in the same manner. However, as the draft report itself points out on page 52, "regulatory oversight of PGx testing is subject to a key distinction: whether it is done in the form of a *product* or

a *service*", and an in-house test "generates information – not a product – that is used by the physician for patient care decisions." It would make no more sense to regulate a service as if it were a product than to regulate a product as if it were a service. Rather than creating an "unlevel playing field" for test kits and laboratory developed testing services, Congress and the regulatory agencies have created two separate playing fields – one for products, and one for services - each appropriately designed for their respective subject matters. Any changes in regulatory oversight necessary to meet the challenges of pharmacogenomics should recognize and respect both the fundamental distinctions established in the existing regulatory framework and the rationale for their existence.

A lack of understanding of the distinctions between commercial test kits and laboratory developed tests also appears to contribute to certain deficiencies in the following statement from a section of the Report on page 49 entitled, "Liability Concerns for PGx Drug and Diagnostic Developers":

> "Developers of PGx-based diagnostics also face potential liability risks if PGx test results are incorrect or misinterpreted. Exposure to product liability for PGx testing may depend on whether a test is made available as a product, i.e., as an IVD, or in-house by a clinical laboratory. In the latter case, the clinical laboratory provides a service, i.e., the test results, rather than a product, and is therefore not subject to liability for product defects. As demand for more rapid turnaround of PGx test results increases, and if regulatory oversight of laboratory-developed tests by CLIA and FTC is strengthened, more tests are likely to be offered as kit products. These potential changes could expose companies that manufacture, distribute or interpret genetic tests to product defect liability".

This statement appears to imply that clinical laboratories face no exposure to liability for incorrect laboratory-developed PGx test results, which is not true. While clinical laboratories performing such tests may not be subject to *product* liability, clinical laboratories are subject to liability under traditional tort theories of negligence or malpractice for incorrect PGx test results. Thus, from a civil liability perspective, the legal incentives for clinical laboratories to perform laboratory-developed PGx testing accurately are just as strong as the incentives for IVD manufacturers to produce PGx test kits that perform accurately.

Further, it does not necessarily follow that more tests are likely to be offered as kit products as a result of greater regulatory oversight of laboratory-developed tests by CLIA and FTC. Laboratory-developed tests are developed to meet clinical needs that are not being met by commercial test kits, either because the development of a kit is not economically feasible or because available kits are not sufficiently adaptable to rapidly changing clinical and technological conditions. Deterring the creation of new laboratory-developed tests through greater regulatory oversight will not result in the creation of kit products that would not otherwise have been created, because the existing challenges to commercial kit development would remain; instead, clinical needs would simply go unmet in many cases, because neither a kit nor a laboratory-developed test would be available.

Finally, we urge SACGHS to eliminate the term "home brews" both from this report (where it currently appears on page 54 under the section entitled, "Laboratory-developed PGx Tests") and from the Committee's discourse, and to encourage others to do likewise. This term does not accurately communicate the significant professional expertise and diligence performed by the laboratory in developing these tests and the mere fact of its prevalent use in the past does not warrant continued reference to it. The terms "Laboratory-developed PGx Tests", or "In-House PGx Tests", more accurately and objectively describe the subject matter.

ACLA appreciates the opportunity to submit these comments and the opportunity afforded ACLA for public comment at the SACGHS Committee meetings. We would welcome the opportunity to provide any clarifying information to ensure that clinical pharmacogenomic tests can be effectively used to improve healthcare delivery. Please feel free to contact me or David Mongillo (dmongillo@clinical-labs.org) with any questions.

Sincerely,

Alan Mertz
President

1250 H Street, NW • Suite 880 • Washington, DC 20005 • (202) 637-9466 • (202) 637-2050

AMA
AMERICAN
MEDICAL
ASSOCIATION

Michael D. Maves, MD, MBA, Executive Vice President, CEO

June 1, 2007

Reed V. Tuckson, MD
Chairman
Secretary's Advisory Committee on Genetics,
Health, and Society
Office of Biotechnology Activities
National Institute of Health
U.S. Department of Health & Human Services
6705 Rockledge Drive, Suite 750
Bethesda, MD 20892

Dear Dr. Tuckson:

The American Medical Association (AMA) appreciates the opportunity to review the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) report entitled "Realizing the Promise of Pharmacogenomics: Opportunities and Challenges." The application of genetic technology to the practice of medicine is growing at a rapid pace. We commend SACGHS for its thorough analysis of issues surrounding pharmacogenomics, a subject that has the potential to tremendously benefit patient care. We offer our views on the report, and include AMA policies on some of the related issues.

A large part of the SACGHS report focuses on the importance of educating health care providers on the topic of pharmacogenomics, with medical professional organizations playing a role in this process. The AMA is active in educating physicians on several topics in molecular medicine, including pharmacogenomics. We have recently collaborated with the Food and Drug Administration (FDA) to develop a web-based Continuing Medical Education (CME) program targeting primary care physicians entitled "Pharmacogenomics and Personalized Medicine." We have also developed other CME material, educational forums, and point-of-care tools that focus on the integration of genetic technology into routine clinical practice, and intend to continue these efforts.

However, it is our sense that many primary care physicians may be reluctant to incorporate new tests into routine clinical practice, in part because of their already overwhelming clinical responsibilities, and in part because of the uncertainty surrounding widespread availability, and payment for the administration, of the tests. Furthermore, until their clinical validity has been firmly established, pharmacogenomic tests may be viewed as non-essential, costly, and difficult to integrate into practice. As SACGHS moves forward

American Medical Association 515 North State Street Chicago Illinois 60610
phone: 312 464 5000 fax: 312 464 4184 www.ama-assn.org

in recommending the creation of educational programs, it should keep such concerns in mind. The AMA agrees with Recommendations 10A-C, which urge that educational programs include case studies and highlight the evidence base for using pharmacogenomic tests. It may also be beneficial to seek the guidance and advice of practicing primary care physicians when educational programs are being developed, so that their concerns are appropriately addressed. These approaches may be more effective in persuading physicians that implementation of certain genetic technologies will indeed improve patient outcomes.

The AMA agrees with SACGHS that key pharmacogenomic information is lacking in the product labeling for some marketed drugs, despite strong evidence for a genetic influence on drug metabolism and clinical response Thus, we strongly support Recommendation 10D, in which the FDA and drug/diagnostics manufacturers are urged to focus more attention on ensuring that relevant pharmacogenomic information is included in drug product labeling. However, the lengthy time that is sometimes required to incorporate information on genetic influences into product labeling, even when substantial evidence exists for such influences, needs to be addressed. For example, the FDA Clinical Pharmacology Subcommittee of the Advisory Committee for Pharmaceutical Science recommended in November of 2005 that the product labeling for warfarin be changed to include pharmacogenomic information. To date, these changes have not been made. SACGHS should consider making Recommendation 10D stronger by urging that the FDA place more emphasis on timely implementation of labeling changes. As the SACGHS report notes, drug companies may be resistant to adding language to drug product labeling when that language may reduce the number of patients for whom the drug is appropriate. The FDA could further enhance Recommendation 10D by suggesting that the FDA provide incentives, similar to those mentioned in Recommendation 4B, to those drug companies who incorporate pharmacogenomic information into drug product labeling in a timely manner. The SACGHS report points out that "the agency's (FDA's) requirements and actions – or lack thereof – influence the ways in which marketed PGx technologies are used in clinical practice." While that statement refers to pharmacogenomic tests, which the FDA does not necessarily regulate, it could also apply to drugs whose disposition or actions can be subject to significant pharmacogenomic influences. FDA attention to the appropriate revision of drug product labeling could increase patient safety and the effectiveness of drug therapies by informing physicians that pharmacogenomic testing may be helpful or needed.

As the SACGHS report correctly notes, the regulatory landscape surrounding pharmacogenomic tests is unclear. The number of laboratory-developed genetic tests available to physicians has rapidly increased. Most are not subject to FDA approval, as long as they are considered research tools, and they are not marketed as diagnostic tests. Many laboratory-developed tests are clinically useful, while others have no clinical utility. The AMA urges SACGHS to promote regulations that would establish appropriate oversight of genetic tests, including pharmacogenomic tests. The regulations should ensure that genetic tests offered to physicians and patients are of high quality and clinically useful, but such regulations should not restrict a physician's choice of tools as he or she strives to provide patients with high quality care. The AMA supports "existing federal and

private accreditation and quality assurance programs designed to ensure the accuracy and reliability of tests, but opposes legislation that could establish redundant or duplicative federal programs of quality assurance in genetic testing." (See enclosure.) We also recommend that genetic tests be ordered by and carried out under the supervision of a qualified health care professional, and discourage direct-to-consumer genetic testing. (See enclosure.) In this current environment of rapidly expanding numbers of genetic tests, Recommendation 4, addressing co-development of pharmacogenomic products, is important. Coordination between diagnostics and drug manufacturers could streamline pharmacogenomic product development, and combined with the addition of pharmacogenomic language in drug product labeling, could bring clarity to the question of whether a diagnostic test should be performed before a drug is prescribed.

The expense associated with pharmacogenomic testing may be a significant barrier to its implementation into routine clinical practice. Studies suggest that pharmacogenomic testing is cost-effective in prescribing warfarin (McWilliam et al., 2007, Ref 527 in the SACGHS report). However, without additional data demonstrating that the benefits outweigh the costs for other pharmacogenomic tests, third-party payers may be reluctant to provide reimbursement, and patients will be reluctant to have the tests performed. Thus, the AMA supports Recommendation 13, in which the Department of Health and Human Services (DHHS) is urged to assess the economic value of pharmacogenomic tests.

The AMA appreciates the emphasis SACGHS has placed on consideration of ethical, legal and social issues in Recommendation 14. Similarly, we support Recommendation 8A, which advises that FDA guidance be developed for studies focused on racial differences in drug response. Recommendation 8B, in which it is suggested that the FDA encourage additional post-market studies to identify biological, social, behavioral, and environmental markers that may underlie differential drug response, could be made stronger by also encouraging that the NIH and DHHS provide funding for such studies. Public education regarding pharmacogenomics will be crucial to successful integration. In Recommendation 11, more attention should be paid to ensuring that the public perceives the field appropriately. The notion that race is genetically determined and that genetic technology, including pharmacogenomic testing, is a means to stratify populations based on race is prevalent. Public educational programs should emphasize that pharmacogenomics is a tool that links genetics and health, not race and health.

The AMA is dedicated to the advancement of patient care and public health, and the way in which pharmacogenomics is integrated into clinical practice will have a direct impact. We look forward to the release of the SACGHS' final recommendations made to the Secretary.

Sincerely,

Michael D. Maves, MD, MBA
Enclosure

D-460.976 Genomic and Molecular-based Personalized Health Care
Our AMA will: (1) continue to recognize the need for possible adaptation of the US health care system to prospectively prevent the development of disease by ethically using genomics, proteomics, metabolomics, imaging and other advanced diagnostics, along with standardized informatics tools to develop individual risk assessments and personal health plans; (2) support studies aimed at determining the viability of prospective care models and measures that will assist in creating a stronger focus on prospective care in the US health care system; (3) support research and discussion regarding the multidimensional ethical issues related to prospective care models, such as genetic testing; (4) maintain a visible presence in genetics and molecular medicine, including web-based resources and the development of educational materials, to assist in educating physicians about relevant clinical practice issues related to genomics as they develop; and (5) promote the appropriate use of pharmacogenomics in drug development and clinical trials. (CSAPH Rep. 4, A-06)

H-460.931 Genetics Testing Legislation
The AMA opposes legislative initiatives on genetic testing that would unduly restrict the ability to use stored tissue for medical research; and will continue to support existing federal and private accreditation and quality assurance programs designed to ensure the accuracy and reliability of tests, but oppose legislation that could establish redundant or duplicative federal programs of quality assurance in genetic testing. (Sub. Res. 219, I-96; Reaffirmed: CSAPH Rep. 3, A-06)

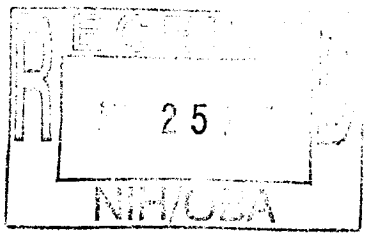
D-480.987 Direct-to-Consumer Genetic Testing
Our AMA: (1) recommends that states restrict the performance of clinical and laboratory genetic testing to individuals under the personal supervision of a qualified health care professional; and (2) will work with all appropriate other organizations to discourage direct-to-consumer genetic testing. (Res. 502, A-04)

AMERICAN NURSES ASSOCIATION

8515 Georgia Avenue, Suite 400
Silver Spring, Maryland 20910-3492
301 628-5000 • Fax 301 628-5001
www.NursingWorld.org

Rebecca M. Patton, MSN, RN, CNOR
President

Linda J. Stierle, MSN, RN, CNAA,BC
Chief Executive Officer



May 15, 2007

Reed V. Tuckson, MD
Chair
Secretary's Advisory Committee on Genetics, Health, and Society
NIH Office of Biotechnology Activities
6705 Rockledge Drive, Suite 750
Bethesda, MD, 20892

Dear Dr. Tuckson:

The American Nurses Association (ANA) is grateful for the opportunity to review the Draft Report, **Realizing the Promise of Pharmacogenomics: Opportunities and Challenges**. We congratulate those who drafted this beautifully written, well organized and articulate document. The recommendations proposed promise to bring Pharmacogenomics (PGx) into all areas of nursing practice. We look forward to participating in the implementation of this important work. The American Nurses Association (ANA) is the only full-service professional organization representing the nation's 2.9 million registered nurses (RNs) through its 54 constituent member associations. The ANA advances the nursing profession by fostering high standards of nursing practice, promoting the economic and general welfare of nurses in the workplace, projecting a positive and realistic view of nursing, and by lobbying the Congress and regulatory agencies on health care issues affecting nurses and the public.

Health care is a top national priority and is likely to remain one for the foreseeable future. RNs provide the 24/7 bedside care that is at the heart of health care in the United States and RNs make up the single, largest professional component of our complex, health care system. For over ten years, ANA has been actively involved in the work of human genetics as it unfolds following the sequencing of the human genome and the development of new technologies used to promote health and manage disease.

We have found the discussion of the topics and issues in the report to be accurate and complete and that significant challenges and opportunities were addressed. Each of the three areas, "research", "gatekeepers" and "implementation in clinical practice" reflects a wide range of perspectives. We would like to comment from a nursing perspective on the third area and the prioritization of the recommendations.

1) Implementation of pharmacogenomics to improve outcomes in clinical and public health practice.

In 2006, the American Nurses Association (ANA) and the National Human Genome Research Institute (NHGRI) of the National Institutes of Health, with a consensus panel of key organizations published the *Essential Nursing Competencies and Curricula Guidelines for Genetics and Genomics* to be used by all registered nurses, regardless of level of academic preparation, practice setting, or specialty. According to ANA President, Rebecca Patton, MSN, RN, CNOR, "Genomic competencies are absolutely crucial for nursing practice because essentially all diseases and conditions have a genetic or genomic component, and ANA .....believes these competencies must be integrated into the Nursing Scope and Standards of Practice, established by ANA in 2004, to promote competent nursing care as genetic and genomic science redefine healthcare." Additionally, Jean Jenkins, PhD, RN, FAAN of the National Human Genome Research Institute, NIH, states, "As the continuum of human health and illness evolves, it is imperative to incorporate the genetic and genomic perspective into nursing education and practice. ANA has been especially instrumental in logistically supporting the development of these guidelines". Efforts are now directed at the dissemination and integration of the competencies into formal and informal education programs throughout the country. The 27 competencies address the use of pharmacogenomics in nursing care, stating that registered nurses:

"examine competency of practice on a regular basis, identifying areas....in which professional development related to genetics and genomics would be beneficial" (p.11)

"incorporate genetic and genomic technologies and information into registered nursing practice" (p.11)

"demonstrate an understanding of the relationship of genetics and genomics to health, prevention, screening, diagnostics, prognostics, selection of treatment and monitoring of treatment effectiveness" (p.11)

" identifies clients who may benefit from specific genetic and genomic information and/or services based on assessment data" (p.12)

"performs interventions/treatments appropriate to clients' genetic and genomic healthcare needs" (p.13).

2) The prioritization of the recommendations.

The ANA suggests the tenth recommendation, **Use of PGx Technologies in Clinical Practice,** receives the highest priority.

- With HHS assistance, case studies and practice models relating to PGx technologies could be developed and disseminated.

- As evidence accumulates from government agencies ANA strongly supports SACGHS intent to disseminate pharmacogenomic guidelines to professional organizations. ANA agrees with SACGHS recommendations that HHS assist professional organizations in their efforts to help their membership achieve competencies on the appropriate use of pharmacogenomic technologies. We recommend that HHS engage with ANA, The International Society of Nurses in Genetics and other nursing organizations that have developed and endorsed *Essential Nursing Competencies and Curricula Guidelines for Genetics and Genomics (2006)* to further these efforts.

The next priority is the eleventh recommendation, **Public Education and Engagement.**

- Registered nurses, who make up the single, largest professional component of our complex health care system, are well positioned to engage the public in dialogue regarding the potential benefits, risks and limitations of PGx technologies.

- When PGx educational resources are being developed for federal websites and other appropriate media, nurses should be involved since they are at the forefront of health education in both inpatient and outpatient settings.

Finally, ANA shares your concern that the integration of PGx not exacerbate health and healthcare disparities, limit access to or decrease the quality of healthcare or result in genetic discrimination. Those and other ethical issues are clearly threaded throughout the document.

Thank you for the opportunity to review this draft. Please do not hesitate to contact me directly at 301-628-5059/ pamela.hagan@ana.org or Martha Turner PhD, RN, BC CNAA, Assistant Director of ANA's Center for Ethics and Human Rights, at (703) 354-8622/ martha.turner@ana.org.

Sincerely,

Pamela C. Hagan

Pamela C. Hagan, MSN, RN
Chief Programs Officer

Council

Elaine Sanders-Bush
President
Vanderbilt University

Kenneth P. Minneman
President-Elect
Emory University

James E. Barrett
Past President
Adolor Corporation

Lynn Wecker
Secretary/Treasurer
University of South Florida

Annette E. Fleckenstein
Secretary/Treasurer-Elect
University of Utah

Patricia K. Sonsalla
Past Secretary/Treasurer
University of Medicine & Dentistry of New Jersey

Bryan F. Cox
Councilor
Abbott Laboratories

Ronald N. Hines
Councilor
Medical College of Wisconsin

Terrence J. Monks
Councilor
University of Arizona

Brian M. Cox
Board of Publications Trustees
Uniformed Services University of the Health Sciences

Jack Bergman
Program Committee
Harvard Medical School - McLean Hospital

Steven G. Holtzman
Long Range Planning Committee
Emory University

Christine K. Carrico
Executive Officer

9650 Rockville Pike
Bethesda, MD 20814-3995

Phone: (301) 634-7060
Fax: (301) 634-7061

info@aspet.org
www.aspet.org

June 1, 2007

Reed V. Tuckson, MD
Chair
Secretary's Advisory Committee on Genetics, Health and Society
NIH Office of Biotechnology Activities
6705 Rockledge Drive
Suite 750
Bethesda, MD 20892

Dear Dr. Tuckson:

The American Society for Pharmacology and Experimental Therapeutics (ASPET) appreciates the opportunity to offer public comment on the draft report to the Secretary of Health and Human Services, *Realizing the Promise of Pharmacogenomics: Opportunities and Challenges*. ASPET is a 4,500 member professional society whose members conduct biomedical research in academia, industry and the government.

ASPET would like to mention four items that the draft report might address with greater specificity to more adequately address the broad range of policy issues raised by the use of genetic tests, including:

A. Use of human specimens for the development of biomarkers

The three entities that have a stake in the use of human specimens for the developments of biomarkers are the Federal government, including NIH, FDA, CDC and NSF; for-profit pharmaceutical, biotechnology and diagnostic laboratories; and non-profit academic research organizations and medical schools.

Federal agencies clearly want to develop biomarkers, are willing to fund research in this area, and are willing to allow the investigators to keep and exploit any resulting intellectual property (IP). Pharmaceutical and related for-profit companies also want to develop biomarkers, but in so doing, they want to own and exploit all IP. Pharmaceutical companies often develop biomarkers in conjunction with their clinical trials conducted at non-profit academic research organizations and medical schools. However, in contracting with non-profit academic research organizations, pharmaceutical companies are often perceived to use over-reaching IP language whereby the pharmaceutical firm keeps all rights to the resulting IP to newly discovered and/or developed biomarkers, regardless of whether the inventors are from pharmaceutical companies, academic research organizations, or joint ventures from both. Academic research organizations increasingly want to keep the IP rights to their own discoveries. Related to this issue is whether academic research organizations should be "selling" the specimens they have collected to pharmaceutical companies for commercial exploitation. These competing economic interests need to be fully discussed and should be made more transparent in the final HHS report [section II-D].

To encourage co-development of both diagnostic biomarkers and pharmacogenomic testing, ASPET recommends the final report include language encouraging equal sharing of IP between the various parties involved. Also, the benefits of placing data immediately into the public sector in advancing the science have clearly been demonstrated. Thus, this practice should be encouraged as much as possible.

B. Use of electronic patient medical records

Increasingly, pharmaceutical and biotech companies have been coming to academic research organizations to contract with them to use the academic research organization's electronic medical records in order for the pharmaceutical company to "mine" these data for developing biomarkers, investigating prescribing profiles for their own and their competitors compounds, and helping to develop either new drugs, or determining new therapeutic areas for development.

In negotiating contracts between pharmaceutical companies and academic research organizations, the pharmaceutical company is often perceived to use over-reaching language whereby they will own all resulting IP developed from this "mining" effort, regardless of who the inventors are. Related to this issue is whether academic research organizations should be "selling" the rights to "mine" their patients' medical records for commercial exploitation. [section II-F, recommendation 6B; section IV-B]

C. Enhanced Guidelines for Health Care Professionals

ASPET feels the educational recommendations in the report need to be enhanced. [section IV-A]. This will be a major obstacle for realizing the promise of pharmacogenomic testing. To address this issue, more emphasis needs to be placed on rejuvenating training programs in clinical pharmacology and rewarding those programs that place a strong emphasis on the application and interpretation of pharmacogenomic information in making diagnostic decisions. The inability of physicians to adequately interpret and apply pharmacogenomic information, particularly in the context of drug-drug interactions, is a major challenge. Merely providing decision-making tools in electronic medical records will not solve this problem. Rather, institutions will need to develop pharmacogenomic consulting teams to facilitate the interpretation and application of pharmacogenomic information, which will require a cadre of individuals trained in this specialty.

D. Encourage Integration

With regards to basic and translational research, the report fails to encourage the integration of pharmacogenomics into the Clinical and Translational Science Centers that are being developed to replace the traditional General Clinical Research Centers. This should be done. Second, although work remains, our knowledge of genetic variation in pharmacokinetic parameters has advanced well beyond our knowledge of genetic variation in pharmacodynamics. Basic research efforts should emphasize a pathway and/or whole genome approach and be weighted toward further elucidating variation in pharmacodynamic parameters. Specifically, it is clear the use of SNP tags as developed through the HapMap project represent a major step forward, but significant limitations remain. Ultimately, the actual clinical implementation of pharmacogenomic results will need to focus on causative variants and as such, more emphasis should be placed on the development and improvement of technologies for economically feasible whole genome sequencing.

On behalf of the ASPET Council I would like to thank you again for soliciting comment on this important issue.

Sincerely,

Elaine Sanders-Bush
President

Heidi Christl Marchand, Pharm.D.
Regulatory Affairs, Executive Director
Global Regulatory Affairs and Safety

AMGEN

Amgen Inc.
One Amgen Center Drive,
Mailstop 17-1-B
Thousand Oaks, CA 91320-1799
Phone - 805.447.4075
marchand@amgen.com

May 18, 2007

Reed V. Tuckson, MD, SACGHS Chair
Office of Biotechnology Activities
National Institutes of Health
6705 Rockledge Drive
Suite 750
Bethesda, MD 20892

Subject: Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) draft report on, *Realizing the Promise of Pharmacogenomics: Opportunities and Challenges*

Dear Dr. Tuckson:

Amgen is a global biotechnology and pharmaceuticals products company based in Thousand Oaks, CA which strives to serve patients by transforming the promise of science and biotechnology into therapies that have the power to dramatically improve people's lives.

We are pleased to provide the attached comments on the recommendations, which the SACGHS has issued in the draft report on, *Realizing the Promise of Pharmacogenomics: Opportunities and Challenges.*

Regards,

Heidi Christl Marchand

Heidi Christl Marchand, Pharm.D.
Regulatory Affairs, Executive Director

Amgen Response
Realizing the Promise of Pharmacogenomics: Opportunities and Challenges
May 18, 2007

Recommendation 1:
Basic Research
We agree that more NIH investment in basic research on biochemical pathways associated with drug metabolism and drug action is beneficial; however, we suggest that the recommendation is restated to "increase funding of basic research determining **which** genes have an impact on safety and efficacy" rather than those known to be related to safety and efficacy of drugs as currently, there are only a few genes (e.g. CYPs) known to impact safety and efficacy.

Recommendation 2:
Translational Research
We agree that HHS agencies should help facilitate the development of clinically useful PGx technologies; however, we believe that the work of technology development and validation is best pursued by those companies developing the diagnostic platforms that PGx test are run on, and that HHS agencies are best positioned to fund clinical trials that encompass the use of these developing technologies.

Recommendation 3:
Clinical Trial Design
We believe that sponsors should consult with FDA early in the study design phase so that meaningful study results can be used to support a pre-market review application. We also believe that clinical trials should be conducted with appropriate scientific methods and rigor to answer the clinical trial's (or experiment's) hypothesis. Specifically stating that "studies should have sufficient statistical power and that quality controls should be in place" implies a level of precision not warranted in a general recommendation.

We agree that NIH should consider including FDA's quality-of-evidence standards in their assessments of the scientific merits of grant submissions that propose to advance scientific evidence around a biomarker's clinical validation.

Recommendation 4:
Development and Co-development of PGx Products
In addition to recommending that FDA build upon its prior efforts to address the co-development of PGx drugs and diagnostics by developing a guidance document, we believe the development of an FDA manual of policies and procedures would also be useful to improve the development and implementation of cross-functional procedures to become systematic for staff involved with ensuring a seamless process to address PGx drugs and diagnostics.

Recommendation 5:
Analytic Validity, Clinical Validity, Clinical Utility, and Cost-Effectiveness

A. We believe that while observational studies may have utility, particularly for serious adverse effects, evidence-based clinical decision-making is better supported by prospectively-designed studies.
B. We agree that facilitating collaborations between public and private entities to advance generation and sharing of knowledge on biomarkers' analytic validity, clinical validity, etc. is important and that it is especially beneficial to focus upon engaging payers to better define test characteristics that will make PGx desirable from a cost-effectiveness perspective. We believe that demand created by payers for cost-effectiveness may result in accelerated adoption and utilization of biomarkers in routine clinical medicine.
C. We believe that it will be beneficial for HHS to encourage collaboration amongst industrial concerns to develop biomarkers in non-competitive spaces, e.g. markers for staging or subtyping disease, or predicting non-specific AEs like QT prolongation.

Recommendation 6:
Data Sharing and Database Interoperability

We agree that interoperability of PGx technologies and databases will facilitate research and support building the necessary evidence base. Uniform genomic data standards, harmonization and development of an infrastructure to enable data exchange are beneficial. We also support current efforts towards standardization (e.g. the work of the MGEDS on gene expression arrays) and encourage that these efforts are effectively leveraged.

Recommendation 7:
Protection of Personal Data
We believe that rather than stronger data security measures, the most pressing need is for practice standards associated with PGx research to become more uniform regarding interpretation of patient consent to the use of the data, especially as regards to genomic/genetic data.

We also believe that HHS should assist in facilitating common technology to allowing patients to retrieve their PGx samples upon request; this should be aligned globally with consideration to the highest privacy standards.

Recommendation 9:
PGx-informed Prescription Drug Coverage
We believe that in those instances where a validated PGx test is available Medicare prescription drug plans should not only cover the cost of the most clinically appropriate drug but also reimburse the cost of the validated PGx test.

Recommendation 10:

Use of PGx Technologies in Clinical Practice

Amgen believes that relevant PGx information may be appropriate to include in drug and PGx test labels, particularly those data relevant to analytical validity and clinical validity. However, there may be instances where **all** PGx data may not necessarily be appropriate for inclusion into product or test kit labels. For example, should all available relevant data for a given analyte, potentially including both commercial and "home-brew" kits, be required for inclusion? Will all published (or potentially even unpublished) validity/utility data be included?

Additionally we question whether a drug manufacturer, tasked with providing the statistics used to represent the PGx test(s) on their own label(s), should be required to assume responsibility for data generated by third parties outside of the manufacturer's oversight.

Recommendation 11:

Public Education and Engagement

Amgen would request clarification of the recommendation. Is the assessment of the public's perceptions of and receptiveness to PGx intended to evaluate the effectiveness of the "public consultation mechanism" or the public willingness to participate in clinical research studies?

Recommendation 13:

Economic Value of PGx

Amgen believes that pharmacoeconomic models for evaluating the outcomes of PGx testing should be designed to carefully explore the impact of differing assumptions regarding hypothetical future policies of private payers towards PGx use and reimbursement.

Recommendation 14:

ELSI Research

Amgen acknowledges that there may be unintended consequences of the advancement of PGx-driven health care. However, a recommendation focusing on "limits access to health care" and "results in genetic discrimination" may be misinterpreted and have a detrimental effect on the advancement and acceptance of PGx testing. We believe NIH should formulate and champion practice guidelines aimed to *prevent* these undesirable (but in many cases unlikely) outcomes of PGx.

Association for Molecular Pathology
Promoting Clinical Practice, Basic Research, and Education in Molecular Pathology
9650 Rockville Pike, Bethesda, Maryland 20814
Tel: 301-634-7939 • Fax: 301-634-7990 • Email: amp@asip.org • *www.amp.org*

AMP Response to SACGHS Draft Report on Realizing the Promise of Pharmacogenomics: Opportunities and Challenges

24 May 2007

Reed V. Tuckson, MD
SACGHS Chair
NIH Office of Biotechnology Activities
6705 Rockledge Drive, Suite 750
Bethesda , MD 20892

Dear Dr. Tuckson and Members of the Secretary's Advisory Committee on Genetics, Health and Society:

AMP is an international not-for-profit educational society representing over 1,400 physicians, doctoral scientists, and medical technologists who perform molecular diagnostic testing based on nucleic acid technology. AMP members practice their specialty in widely diverse settings: academic medical centers, independent medical laboratories, community hospitals, federal and state health laboratories, and the *in vitro* diagnostic industry. In this capacity, AMP members are involved in every aspect of molecular diagnostic testing: administration and interpretation of molecular diagnostic tests, research and development, and education. For the last several years AMP has provided national leadership for the advancement of safe and effective practice and education for molecular diagnostic testing in the health care industry.

AMP's Mission Statement identifies the Society as "dedicated to the advancement, practice, and science of clinical molecular laboratory medicine and translational research based on the applications of genomics and proteomics." Our goal is to represent all members regardless of the setting in which they practice because they are united in the end intent to provide high quality, relevant information for the purpose of directing individual and patient community health management. We acknowledge, however, that different perspectives may emerge from those widely diverse settings. In those instances, our primary responsibility is to comment from the standpoint of molecular testing laboratories and the patients they serve.

Overall AMP applauds the mission and goal of developing guidelines regarding the issues surrounding the implementation of Pharmacogenomics (PGx) into mainstream medicine. This draft report is well-written, with thorough coverage of all aspects of the current state of PGx. Our specific suggestions are as follows:

In several parts of the report, there is reference to development of point-of-care (POC) and direct-to-consumer PGx testing (p7, first paragraph, p53, p58, p64), with traditional POC testing defined as being performed at the bedside or private doctor's office. We feel that supporting POC and direct-to-consumer PGx testing is concerning, as this genetic testing and its interpretation is very complex requiring additional counseling regarding implications and limitations. We recommend wording which would suggest that this testing should be performed and reported only by CLIA certified clinical laboratories for the foreseeable future.

Executive Summary, Section C Recommendations

Recommendation 3: We agree with the notion that the NIH should encourage sponsors and researchers to consult with the FDA early in the study design phase but we would also recommend that NIH explore the possible need for additional education/communication of sponsors and researchers regarding study design, such as sufficient statistical power, quality control, etc.

Recommendation 5 C. We strongly support the notion of wide dissemination of study results regarding the clinical validity and utility of PGx. We also strongly agree with the strategy of publishing negative or non-statistically significant findings. We would encourage the committee to explore mechanisms or provide examples of how to raise awareness of this issue with the scientific and industry communities. One approach could be to provide mechanisms (such as incentives or IP protection) to encourage manufacturers to make this data publicly available.

Recommendation 6 A. We agree with the notion of encouraging the private sector to voluntarily share of proprietary data but would like to expand this consideration to public entities such as public academic institutions. We would like to propose that HHS explore the possibility of developing mechanisms/incentives for those that voluntarily share this information.

Section I Introduction, p16, paragraph 2 – Please clarify what is meant by "Storage of laboratory samples and genetic information for later use could lower some of these costs."

Section II. Research and Development Section D number 5 – We recommend emphasizing that diagnostic testing for PGx does not include all nucleotide changes. There is still a residual risk of unidentified variants that can impact drug metabolism.

Appendix A pA-9 – The Genetic Testing Reference Materials Coordination program recommends that all QC material should be referred to as reference materials.

Typographical errors:
p9, Section 7 – change PGs to PGx
p58, first true paragraph – correct spelling of currently

Thank you for the opportunity to comment on this important document. AMP appreciates being allowed to provide information regarding genetic testing and its implications. Many of our members perform clinical PGx testing in their laboratories, so the topic of this report is very important to our organization. Please do not hesitate to contact V.M. Pratt, PhD, AMP Clinical Practice Committee Chair at victoria.m.pratt@questdiagnostics.com if we can be of further assistance.

Sincerely,

Andrea Ferreira-Gonzalez, PhD
President
(Representing the AMP Council and
Clinical Practice Committee)

AstraZeneca

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

Call for Public Comment 23 Mar - 1 June 2007

1 June 2007

Dear Dr Tucker

Realizing the Promise of Pharmacogenomics: Opportunities and Challenges

AstraZeneca commends the SACGHS on this thorough and extensive report and strongly supports its recommendations. In particular, AstraZeneca perceives the following recommendations as the highest priority:

4(A). FDA should build on its prior efforts to address the co-development of PGx drugs and diagnostics by developing a guidance document on this topic. FDA's guidance should clarify the review process for co-developed PGx products where the drug is subject to FDA review but the laboratory-developed companion diagnostic test may not be.

AstraZeneca would welcome further debate and guidance on this issue. As noted below, requirements to co-develop a PGx-based IVD within the timelines of normal drug development represent a significant challenge that may inhibit innovation and adoption of PGx.

4(B). HHS should identify and provide incentives to the private sector to encourage the development of PGx products for smaller markets. Options to consider might include financial incentives, expedited FDA review, and greater intellectual property protection.

AstraZeneca would welcome further debate on this issue. Co-development of PGx products represents a significant challenge but could potentially address areas of unmet medical need in relatively small patient populations.

9. In instances where a validated PGx test is available to guide therapeutic decision-making, health plans, including Medicare prescription drug plans, should cover the most clinically appropriate drug as indicated by PGx test results.

AstraZeneca strongly supports this recommendation and would welcome further dialogue with appropriate groups and bodies to enable all patients to be able to access the most clinically appropriate drugs.

Detailed comments on the text:

For each change or comment, the page number and paragraph number is given, followed by the comment/ rationale for change, followed by the text with suggested change if appropriate (suggested changes are underlined):

P12, para 2

The definition of pharmacogenomics (PGx) is inconsistent. The definition implies that only DNA sequence leading to differences in gene expression is included. In the report it is clear that the term encompasses a wide range of inter-individual differences, including DNA sequence, gene expression, gene copy number, etc.

In the present document, the term "pharmacogenomics" (PGx) refers to the study of how differences in gene function affect an individual's response to drugs. This encompasses inter-individual genetic differences such as variation in DNA sequence, gene expression, copy number and other factors, related to an individual's metabolism of drugs (pharmacokinetics) or physiological response to drugs (pharmacodynamics).

P14, para 1

The sentence starting "Drug effectiveness can be influenced by genetically-mediated variations ..." is confusing, as the paragraph refers to ADRS (safety).

Drug response can be influenced by genetically-mediated variations that affect the metabolism, transport, distribution, absorption and excretion of the drug"

P18, para 2

The sentence "PGx tests are available to identify women whose tumors have HER2 protein overexpression" is confusing, as the currently available PGx tests measure gene amplification (FISH), rather than protein.

PGx (FISH) tests are available to identify women whose tumors overexpress HER2.

P21, para 3

The description of genome-wide association studies may give the impression that correlations can be determined only with disease status, and that it is only candidate genes arising from the genome wide association studies that can be evaluated against drug response. The suggested changes clarify that the genome wide study may be carried out directly with drug response, but this will still result in candidate genes that should be further evaluated.

Since genome-wide association studies collect large volumes of genotypic and phenotypic information, researchers may be able to determine correlations between a certain genetic makeup and disease status or drug response. These initial correlations may lead investigators to a series of "candidate genes", which can then be further evaluated for their ability to predict drug response (safety or efficacy) in model systems and in clinical trials.

P24, para 3

The quoted figures for reduction of clinical trial design are based on a business report, which refers to an interview with no supporting data. It should be clarified that such figures are highly speculative, to avoid raising false expectations.

Use of PGx in clinical trial design should increase the efficiency and lower the costs of new drug development, although the extent of reductions in clinical drug development time has yet to be demonstrated.

P27, para 4

This is a general comment and does not apply to SNPs in particular

Studies of PGx tests require population sample sizes that are large and diverse enough to assess associations in different sub-strata of the population.

P28, para 2

This comment presumably applies to PGx tests for which patents have been filed, rather than PGx tests in general (compare the table of Valid Genomic Biomarkers at http://www.fda.gov/cder/genomics/genomic_biomarkers_table.htm)

Most PGx tests for which patents have been filed are based on the identification of a small number of SNPs that relate to various patient responses to medication.

P28, para3

AstraZeneca would welcome further debate about this area of ambiguity in the context of parallel drug-development co-development. Requirements to co-develop an IVD in the context of evolving science and within the timelines of normal drug development represent a significant challenge that may inhibit innovation and adoption of PGx. (The word "traditionally" appears twice in the sentence.)

Furthermore, ambiguity remains about FDA regulatory review of "in-house" or laboratory-developed diagnostic tests, which traditionally do not ~~traditionally~~ require the same level of external data-review as tests sold to clinical laboratories.

P23, para1

The statin example used (efficacy) is not relevant to a discussion of PGx testing with ADRs. An alternative example (safety) is suggested (Kindmark et al, TPJ, AOP May 15 2007 http://www.nature.com/tpj/journal/vaop/ncurrent/abs/6500458a.html)

While ADRs can be reduced with PGx testing, PGx testing will not always offer clinical value. A recent study on raised liver enzymes with ximelagatran treatment found that a single PGx biomarker was able to predict only 47% of the patients at risk (Kindmark et al 2007).

P33, para3 - P34, para1

The references given to support the statement that "there is comparatively little information about using these and other tests to monitor response to therapy and predict recurrence of breast cancer" (a) are not recent and (b) refer to response to endocrine treatment only. An updated statement and reference is recommended (Wolff et al, Journal of Clinical Oncology, *25, 2007: 118-145 http://jco.ascopubs.org/cgi/content/full/25/1/118)*

In breast cancer, immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) are the most common assays used for determining HER-2/neu status in tumor tissue. HER2 positivity has now been shown to be associated with worse prognosis (higher rate of recurrence and mortality) and improved response for several systemic therapies, and may be incorporated into clinical decision-making, along with other prognostic factors (Wolff et al 2007).

P47, para3

The comment that the case of BiDil "reflects uses of race and ethnicity as a basis for patenting drugs and securing market share" followed by the statement that "Recent reports have indicated that scientists conducted similar race specific trials" implies that the clinical trials specified were carried out with the intention of developing race-specific indications, which is not the case. The use of clinical trials in self-defined ethnic groups is often recommended by the FDA and other regulatory authorities in the context of global drug development (http://www.fda.gov/cder/guidance/7377fnl.htm) and it is common practice for pharmaceutical companies and academic groups to carry out such trials (see http://clinicaltrials.gov/).

The case of BiDil reflects recent uses of race and ethnicity as a basis for patenting drugs and securing market share. It is becoming increasingly common practice for pharmaceutical companies and academic groups to carry out clinical trials in self-defined ethnic groups (see http://clinicaltrials.gov/).

P96, para 4

AstraZeneca supports this focus on the challenges of developing PGx tests and therapies and would welcome further debate on this matter.

Among the constraints of development and diffusion of PGx into clinical practice is that current third-party payment mechanisms for diagnostic tests can discourage uptake of PGx tests and therapies by providers.

Thank you for the chance to comment on this important document

Ruth March

Senior Principal Scientist
AstraZeneca Pharmacogenomics Partnership

Prepared by:
Issam Zineh, PharmD
University of Florida College of Pharmacy and Center for Pharmacogenomics
Gainesville, FL, USA

Amber L. Beitelshees, PharmD, MPH
Washington University School of Medicine
St. Louis, MO, USA

R.H.N van Schaik, PhD
Erasmus MC
Rotterdam, The Netherlands

To:
Reed V. Tuckson, MD
Chair, Secretary's Advisory Committee on Genetics, Health, and Society
NIH Office of Biotechnology Activities
6705 Rockledge Drive, Suite 750
Bethesda, MD, 20892

We appreciate the opportunity to review and comment on the SACGHS's draft report on pharmacogenomics. As high throughput genomics technologies continue to evolve, so does the sophistication with which genetic and genomic associations with drug response are characterized. We join the committee in recognizing pharmacogenomics as a field with a high potential for impacting health care and public health. We acknowledge the committee's observed need to solidify relationships between researchers, "gate-keepers", health care providers, and patients, and provide the comments below for the Committee's review.

In describing the promise of Pgx, well validated examples of translational Pgx (e.g., HER2/neu and TPMT in cancer) are listed. In addition, non-cancer examples such as that of warfarin are also listed. While we agree that the potential for genotype- or molecularly-guided treatment goes beyond cancer chemotherapy, we urge the committee to carefully select the non-cancer examples it chooses to highlight. For instance, while interesting, the precise algorithms needed to test warfarin pharmacogenetics prospectively are currently highly debated. By highlighting an example with an uncertain future, the public may see any failure in translating warfarin Pgx into practice as a failure of Pgx in general. In another example, while the Committee emphasizes drug metabolizing enzyme Pgx as highly useful, drug metabolism polymorphisms do not reflect significant sources of drug response variability for the majority of drugs to date.

As part of the recommendations, under Translational Research, it is specified that one of the foci of translational research should be the development of more rapid, cost-effective genotyping technologies. We do not share the Committee's enthusiasm for this priority area. Development of high-throughput techniques will allow for generation of large datasets, yet the actual problem in translational research is generating validated and replicated genetic associations with appropriate drug response phenotyping. In other words, the specific emphasis on technology does not address the major issues underlying the lack of translation of Pgx into practice. Moreover, rapid sequencing and genotyping techniques are already available (e.g., 454,

Affymetrix, and Illumina systems), so there is not much value added in making this recommendation such a priority. Rather, a focused recommendation on providing funding for performance of adequate (large) studies to clearly establish the translation of genotype to phenotype for specific treatments, and prove whether it is worthwhile economically and healthwise (prevention ADRs) to perform genotyping for certain therapies would be more useful.

It is stated that "Drug and diagnostics manufacturers should conduct studies and disseminate results on the clinical validity and clinical utility of PGx (e.g., through publication in peer-reviewed journals), including statistically non-significant and negative findings." We strongly support this recommendation. However, implementation requires buy-in from journal editors who typically do not publish neutral findings. Guidelines are needed to encourage journals to publish appropriately powered neutral studies in order to more adequately assess the true magnitude of a genetic effect on drug response. We further urge the Committee to aid in development of novel methods of data dissemination.

Additionally, we urge the Committee to comment on the need for standardizing IRB review of genetic studies, and creating model informed consent language for pharmacogenetic studies that allows for future research. Importantly, we feel that because of the investment and public subsidy of research, all DHHS-sponsored studies should require collection of DNA samples (unless declined at a patient-specific level). We support the recommendation of "adding field to the ClinicalTrials.gov database to identify clinical trials that could incorporate PGx study Components."

In terms of Recommendation 1, we feel this recommendation to not be specific enough. The Committee should devise a specific recommendation regarding a bare minimum of research dollars (or percentage of the NIH budget) that goes specifically to drug studies and Pgx in particular.

The Committee recommends that NIH consider making FDA's quality-of-evidence standards a component of their assessments of the scientific merits of grant submissions. We are not sure what the impetus for this recommendation is since currently conducted Pgx research is generally quite rigorous. Rather, in order to increase the knowledgebase regarding Pgx data, the Committee should encourage pharmaceutical industry to collaborate with academic researchers in order to validate Pgx findings. We find the report to be generally tolerant of industry's lack of participation in Pgx collaborations, especially given the fact that many industry-run trials are substantially financed by the public. More responsibility should be placed on industry to facilitate public-private partnerships in order to maximize use of data (and genetic samples) collected during clinical trials. As suggested in the document (page 40), safeguards are needed to protect industry's patents, while still facilitating these collaborations to gain the most knowledge possible from industry-sponsored studies. Mechanisms for the development of these safeguards which will facilitate industry data sharing should be suggested rather than being complacent with industry's lack of current involvement in Pgx collaborations.

BIO
BIOTECHNOLOGY
INDUSTRY ORGANIZATION

1201 Maryland Avenue SW, Ste. 900
Washington, DC 20024

June 1, 2007

BY ELECTRONIC DELIVERY

Reed V. Tuckson, MD
Chair
Secretary's Advisory Committee on Genetics, Health, and Society
National Institutes of Health, Office of Biotechnology Activities
6705 Rockledge Drive, Suite 750
Bethesda, MD 20892

Re: Draft Report to the Secretary of Health and Human Services (HHS), *Realizing the Promise of Pharmacogenomics: Opportunities and Challenges*

Dear Dr. Tuckson:

The following comments are provided by the Biotechnology Industry Organization (BIO). BIO represents more than 1,100 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and 31 other nations. BIO members are involved in the research and development of health-care, agricultural, industrial and environmental biotechnology products. BIO appreciates the opportunity to comment on the draft report of the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS), *Realizing the Promise of Pharmacogenomics: Opportunities and Challenges.*

General Comments

BIO commends SACGHS for recognizing the significant potential of the emerging science of pharmacogenomics (PGx) and the need to study and address the full spectrum of issues associated with its development and application. We regard the draft report as helpful in

facilitating the efforts of the Department of Health and Human Services (HHS) and stakeholders to construct an informed, coordinated framework for advancing PGx. We would welcome additional focus throughout the draft report on specific areas where policymakers can engage industry on these issues.

BIO believes the draft report presents an accurate and generally balanced discussion of the major opportunities and challenges for PGx. We agree that the prospects for widespread health benefits and economic efficiencies from PGx depend upon a clear, well-integrated policy environment that promotes innovation and the adoption of new technologies.

Our comments below suggest two topics that the draft report should address more completely.

Specific Comments

Section IV.C. Economic Implications of PGx

BIO recommends a more comprehensive discussion of the economic factors surrounding PGx. Specifically, this section should give greater consideration to the role of appropriate reimbursement policies in creating incentives for investment and innovation in the development of PGx technologies, and in ensuring patient access to these innovations.

Resources to Carry Out Initiatives

The draft report should indicate where enhanced congressional appropriations would be required to implement the recommended initiatives. For example, BIO believes the draft report correctly recognizes the importance of investing in basic and translational PGx research programs at the National Institutes of Health (NIH). However, over the past four years, funding for NIH has failed to keep pace with biomedical research inflation. As a result, NIH has lost significant purchasing power needed to harness emerging scientific opportunities like PGx. To restore these resources, BIO and other stakeholders are supporting an increase in NIH funding to $30.8 billion in FY 2008. BIO also suggests that the draft report consider the need for enhanced public funding opportunities for companies to develop innovative diagnostic and research tool technologies to advance PGx.

Additionally, the Food and Drug Administration (FDA) will need resources to facilitate the development/co-development and market entry of PGx products. BIO supports continued implementation of the Critical Path Initiative, and we are requesting that the program be fully funded in FY 2008.

Conclusion

BIO would like to reiterate our appreciation for the opportunity to comment on the draft report, *Realizing the Promise of Pharmacogenomics*. We look forward to working with SACGHS and HHS to ensure that appropriate initiatives are implemented and aligned in order to foster the

development and acceptance of PGx technologies. We would be pleased to provide SACGHS with additional information or clarification of our comments as needed.

Sincerely,

/s/

Sara Radcliffe
Vice President
Science and Regulatory Affairs

-----Original Message-----
From: RickJCarl@aol.com [mailto:RickJCarl@aol.com]
Sent: Friday, June 01, 2007 11:10 AM
To: Goodwin, Suzanne (NIH/OD) [E]
Cc: lgarrisn@u.washington.edu; veenstra@u.washington.edu; sdsull@u.washington.edu; josh@dnable.com; lmeckley@u.washington.edu
Subject: Comments on DRAFT Report/PGx

Suzanne,

We attach our comments on the DRAFT PGx Report. Also attached two research articles supporting our points.

Thank you for the opportunity to comment. Given our experience in this field we would welcome further opportunities to assist.

Rick J. Carlson, JD
Clinical Professor, Policy Programs,
Senior Advisor, Resource Center for Health Policy,
Department of Health Services,
Affiliate Professor,
Department of Pharmacy,
School of Public Health,
University of Washington
Seattle, WA.
206-545-7294
Mailing address:
620 North 34th St. , #620
Seattle, WA. 98103

Lou Garrison, Ph.D.
Professor, Pharmaceutical Outcomes Research & Policy Program
Department of Pharmacy
Health Sciences Building, H375
1959 NE Pacific St., H-375A
Box 357630
University of Washington
Seattle, Washington 98195-7630
Email: lgarrisn@u.washington.edu
Tele: 206-221-5684

David L. Veenstra, PharmD, PhD
Associate Professor
Pharmaceutical Outcomes Research and Policy Program and
Institute for Public Health Genetics
University of Washington
Department of Pharmacy, Box 357630

Health Sciences Bldg, Room H-375J
Seattle, WA 98195-7630
email: veenstra@u.washington.edu
phone (office): 206 221-6936

I. General:

"A mix of scientific, regulatory, social, policy and other issues will shape development of the applications of pharmacogenomics. However, it is fundamental scientific and clinical knowledge that are critical to the long-term success of any health care technology."

"The inherent scientific complexity of the human genome and its interaction with human physiology, the environment, and drugs will continue to present challenges."

These two quotes are taken from the Executive Summary and Introduction to our University of Washington Report on PGx, "Backgrounder on Pharmagogenomics for the Pharmaceutical and Biotechnology Industries, Basic Science, Future Scenarios, Policy Directions." May 2007. (already provided to SACGHS on May 30, 2007, upon request),

Our comments below, reflect our analysis undertaken to prepare this Report, but are independent of that Report and are ours alone. Our purpose in including these quotes from that Report is to note that our focus in developing the Backgrounder differed from the DRAFT SACGHS Report in one fundamental way: the Backgrounder was focused on the state on the underlying genomics science and research, and then secondarily, on the many policy questions also raised in the SACGHS Draft.

This said, the two Reports are consistent in their respective treatment of the policy issues, and, more implicitly, the SACGHS Draft also reflects a consistent perspective on the Science as well. Illustratively, the SACGHS Draft notes on p. 3,

"Realizing the benefits of PGx on a large scale remains a long term goal....."

One other point of differing emphasis, though relative, is that the UW Backgrounder discusses the role of market factors more consistently than does the SACGHS Report, which is more tightly focused on public policy.

II. Specific, Policy:

a. On pp 6, the Report states: "A key reimbursement challenge [to innovation] is.....payer resistance to higher drug prices that may come with PGx-based targeted therapies."

We agree, in general, but the point cuts two ways: it also may be the case, if PGx tests consistently reach threshold levels of incremental clinical utility (not yet achieved, admittedly), that drug therapy tailored by PGx could produce superior therapeutic outcomes and thus support a higher, yet cost-effective price.

b. As to payers, there is a relatively greater emphasis in the SACGHS Draft on the role of public payers. Given, however, the sentinel role that private payers are *relatively* more likely to play with respect to genetic testing technologies, that this emphasis may be misplaced.. (Draft Report, pp 60-62). This is true, from our perspective, for a number of reasons, including the demographics of the relative markets for public and private payers, and because of the statutory constraints facing CMS as to testing and screening. As a result, we believe additional attention should be given to the evolving role of private payers;

c. We wish to underscore the importance of the Section on Translational Research (II E). In the rush to market, many developers (of genetic tests, generally) have failed to appreciate the need for solid research supporting the "clinical utility" of PGx tests, without which payers will be reluctant to provide coverage, and/or provide it at low reimbursement levels;

d. We also commend the Report's authors for including a section on the "underserved". Our work here at UW in all of our many Genomics policy projects, but primarily through a CEER grant from NHGRI, gives due weight to the challenges of disparities in access to testing, a serious problem in health care generally, and one potentially exacerbated by genetic testing;

e. On the bioethical front, we believe it should be noted that ethical issues could arise with PGx testing in cases where the results of the test (at the time of testing or potentially in the future) are also informative for disease risk, generally;

f. In the discussion of policy issues associated with "direct-to-consumer" (DTC) advertising and genetic testing, the Report fails, as does most of the policy literature on testing, to sufficiently distinguish the two. DTC does raise serious policy questions, but those questions are distinguishable from "direct-to-consumer" testing, as such, (which also raises policy issues) which can and often is provided without any DTC; for example one leading "direct-to-consumer" testing company, DNA Direct, does no DTC;

g. Since the focus of our UW Backgrounder was the science and its capacity to drive PGx, there may be merit in incorporating our scenario framework either as quoted text (permission given) or as a citation;

h. Lastly, there is an important discussion about innovation and incentives related to reimbursement. We quote:

> "Some have suggested reimbursing health technologies such as PGx according to the value they provide taking into account clinical as well as economic benefits. If payment systems were changed to reflect value, this might influence the incentive structure for development and use of PGx, as members of industry may be more confident about receiving favorable reimbursement for newly developed products. However, any changes to reflect a value-based approach may require changing the broader system for reimbursing health care." (DRAFT Report, p 64)

We believe this is an important point that deserves further attention and perhaps even a recommendation. Although our work has been cited elsewhere in this report, we think it would be particularly appropriate to cite the attached two papers in this specific context. We are attaching them. [Attached, Ramsey et al, and Garrison and Austin]

A recommendation might be made along the following lines:

Recommendation: HHS should study the implications of current reimbursement systems—for both diagnostics and therapeutics—for encouraging PGx innovation. Options for developing a more flexible, value-based reimbursement system based clinical effectiveness and cost-effectiveness should be explored.

A final more general comment: though PGx is still evolving, and hence the policies associated with it necessarily are as well, the DRAFT Report often proposes more research, more funding, more collaboration, etc. All of these goals are sound, but we would encourage the authors as the final Report is prepared to take a few more risks in the final Recommendations. As an example, consistent reference is made for the need for more HIT, a problem, of course, affecting all of health care. But why not propose a more compelling solution such as federally established requirements for interoperability?

Linking Pharmacogenetics-Based Diagnostics And Drugs For Personalized Medicine

Many scientific and economic challenges remain to be met before personalized medicine takes hold.

by Louis P. Garrison Jr. and M.J. Finley Austin

ABSTRACT: Progress toward personalized medicine in the five years following the sequencing of the human genome has been slower than many expected. We focus on two potential factors that might be important in explaining this disappointing progress: the limitations of genetic prediction and the lack of appropriate economic incentives. Clinical application of DNA-based and other biomarkers is likely to succeed only on a case-by-case basis, depending on such factors as information content of the biomarker, accuracy of current assessment methods, and effectiveness of available interventions. Both strong intellectual property and value-based, flexible pricing systems will be important in making personalized medicine a reality. [*Health Affairs* 25, no. 5 (2006): 1281–1290; 10.1377/hlthaff.25.5.1281]

FIVE YEARS HAVE ELAPSED SINCE THE initial sequencing of the human genome, and the number of new pharmacogenetics applications—that is, those whose drug response varies across individuals because of genetic differences—can be counted on two hands. The recent report from the Royal Society cautions: "Pharmacogenetics is unlikely to revolutionize or personalize medical practice in the immediate future."[1] Progress has been slower than many proponents of "personalized medicine" had hoped or predicted. Robert Califf has argued that achieving this promise will require a major overhaul of the U.S. clinical research enterprise as well as substantial educational efforts.[2] In this paper we explore the potential roles of two factors that could help explain why progress has been slower than expected: (1) the limitations of genetic prediction, and (2) the lack of appropriate economic incentives. We explore both factors individually and also examine their interrelationship in product development and commercialization. We argue that overcoming these challenges could be key to making personalized medicine a reality.

Lou Garrison (lgarrisn@u.washington.edu) is a professor of pharmaceutical outcomes research and policy in the Department of Pharmacy, University of Washington, in Seattle. M.J. Finley Austin is director of U.S. external science policy at F. Hoffmann-La Roche AG in Basel, Switzerland.

DOI 10.1377/hlthaff.25.5.1281

Challenges In The Underlying Genetic Science

■ **Genetics in health care today.** To date, there are very few pharmacogenetics-based targeted therapies. Trasutuzmab (Herceptin, Genentech) is the most prominent example of a linked test and drug for treating breast cancer, although it is not a true genetic test in that "somatic" DNA changes in the tumor are measured (as opposed to "germline" mutations that are present in all cells and are passed to offspring). Although national estimates are not available, it seems clear that most of the volume and recent growth in genetic tests have almost exclusively been for newly identified mutations for rare, "classically" inherited diseases. Examples of these tests include carrier screening for cystic fibrosis mutations (recommended for all pregnant women since 2001), Tay-Sachs screening, and newborn screening for disorders such as phenylketonuria. A few available tests address common diseases, but in limited subsets of patients. This is exemplified by BRCA1 and 2 mutation testing for increased breast and ovarian cancer susceptibility, affecting 5 percent or less of breast cancer cases. These rare, highly penetrant alleles (that is, gene variants associated with a high frequency of disease occurrence, or "phenotypic expression") for common conditions are, in essence, monogenic forms of the disease. They do not, however, account fully for the inherited predisposition for disease; in contrast, most genetic contributions to complex disorders are assumed to be through small, additive effects of multiple gene variants.

Even rare monogenic diseases can show variation in the severity or form of presentation and manifestation, but they are still typically distinct in their "gestalt." By their very nature, they are clearly heritable and causally linked to mutations in DNA. They represent discrete traits that may be multifaceted in presentation but are clearly distinct as a phenotype. Their heritable nature does not abrogate the importance of environment, which can play an equally important role in the determination of a mutation carrier's phenotype and health. For example, biotinidase deficiency is a rare inherited disorder that if left untreated can result in seizures, developmental delay, eczema, and hearing loss. Problems, however, can be prevented with a change in "environment"—that is, a daily supplement of prescription biotin. With highly heritable discrete traits, sufficient variation can be explained by genotype such that testing can be a reliable predictor of phenotype. On the other hand, for common disorders that are multifactorial and continuously distributed, the genotype-phenotype relationship is much more complex and difficult to predict.

■ **Genetics in health care tomorrow.** Because of incomplete penetrance and the complexity of genotype-environment interactions in common traits, disease genes have proved—not surprisingly—to be much more difficult to find and validate than some predicted with the availability of the human genome sequence. While providing biological clues, they are often poor predictors of disease manifestation or response to drug therapies. We read weekly about scientists finding genes for all types of human illnesses and for explaining variations in treatment responses

"Considerable research beyond initial genetic hypotheses is necessary to determine if and when testing is clinically useful."

for those illnesses. Such studies are often small, and substantiating those findings in the broader population often proves difficult. Witness the recent work on COL1A1 Sp1 polymorphisms and risk for osteoporosis and fracture. When this variant was first discovered, it was believed to explain sufficient variation in risk for osteoporosis to be a plausible candidate for risk assessment testing. A large study has now cast doubt that Sp1 contributes enough to the variation to support stand-alone testing.[3] Instead, it appears that genetic testing for the Sp1 variant will need to be part of a test that assesses variants in several genes. Further, to increase the fraction of risk that can be assigned to an individual, this genetic information will need to be used in conjunction with standard indicators of risk before genotype can be a clinically useful addition.

This example illustrates the fact that the level of predictive value of genotype will vary depending on the type of trait—discrete or continuous—and the proportion of the variation observed in the trait contributed by genes. Clearly, considerable research beyond initial genetic hypotheses is necessary to determine if and when testing is clinically useful.

This is of great relevance to therapeutic response prediction. It reminds us that continuously distributed, complex quantitative traits with moderate heri- tability are not simply explained or predicted by genotype. Even if all of the genetic contributions are known and measured, the ability to predict outcome based on genotype is naturally related to the heritability. Typically, heritability estimates for most complex traits that are amenable to study reveal estimates of 0.3 to 0.7 (the ratio of the genetic variance to total phenotypic variance in a population).[4] It is assumed that drug response will often prove to be a continuous, complex trait.

In some cases, drug behavior in the body will be a discrete trait, such as with some instances of metabolism, where, depending on the substance, there can be three distinct phenotypes: ultrarapid metabolizers (UMs), extensive metabolizers (EMs), and poor metabolizers (PMs). Mutations at one locus contribute significantly to the observed phenotype. For example, codeine is metabolized to morphine in part by CYP2D6. Thus, PMs receive little if any pain relief, but as a case example from the *New England Journal of Medicine* illustrates, UMs may experience life-threatening side effects.[5] It should also be noted that in this particular case, numerous factors beyond CYP2D6 status contributed to the adverse event.

What if a continuously distributed complex trait were involved? Consider a hypothetical drug proven to be efficacious but in only 30 percent of patients treated, and this response is continuous: Everyone shows some degree of response, but only those over a certain threshold (for example, the 30 percent) are considered to be truly benefiting from the drug. This is similar to the actual case of lowering

cholesterol and the corresponding reduction in heart attack and stroke risk. The disease risk reduction must be sufficient to outweigh the risk and cost of treatment; thus, some threshold is determined for when patients are receiving medical value and when they are not benefiting. This threshold is not completely arbitrary, because it will relate to some measurable benefit, but it is also not a clear, definitive yes-no relationship. Thus, for a continuously distributed drug response, the heritability of the trait will influence the usefulness of knowing the genotype. If the trait is highly heritable (0.95), genotyping will offer high positive predictive value. But, as is more likely the case, if the response only shows moderate (0.5) heritability, testing will produce higher rates of false positives and false negatives, leading to a corresponding reduction in the predictive power of testing.

In such cases, genotype alone is less likely to be a robust enough predictor to be clinically useful. This will, however, depend on what other predictors are known, how well they inform clinical management, and how well the combined use of these risk factors works in the clinic. Many tests used in risk assessment today are far from perfect yet still prove to be highly beneficial. It should be kept in mind, also, that knowledge of genetic contribution to disease or drug response can have considerable value in drug development—apart from direct clinical application—by informing about molecular events underpinning disease or response. Thus, although there may be disappointment in what the genome project has delivered so far, it has enabled the science considerably. It will, however, take much more research to elucidate specific genotype–phenotype relationships and clinically validate genotyping applications.

■ **Importance of information over analyte.** As the benefits and limitations of genotype have become better recognized, there has already been a gradual and growing appreciation that it is not the biomarker per se—whether the analyte is genetic or not—that is important, but rather the type, amount, and quality of information it provides. Any new biomarkers enter a world in which many health risk determinants are known and applied in practice. To bring value to the health care system, a new test must lead to a change in current clinical behavior. The degree of improvement needed for a new predictive test to provide clinical utility—how it will perform medically in real-world practice—depends on several factors such as disease and therapeutic choice.[6] These relationships—as typified above and in the recent example of epidermal growth factor receptor (EGFR) measurement in non–small cell lung cancer—are proving to be very complex.[7] The initial reports of somatic EGFR mutations predicting tumor response to gefitinib (Iressa, AstraZeneca) led to considerable speculation that a simple test would be a highly accurate predictor of tumor response to EGFR-inhibitory agents. Further studies have not borne this out but instead have revealed a complex biological situation with numerous mutations/markers interacting in tumors.

Although there has been considerable focus on pharmacogenetics, specifically, and genomics, more generally, as the means to reduce uncertainty in medicine, it

"The impact of the patent system will vary depending on type of technology, sector, and business model."

appears that the focus should be on finding and validating predictive biomarkers of high information content, be they genes, proteins, or visible differences.

■ **Other scientific issues.** Recognition of the fact that genes or sets of genes may be weak predictors of drug response raises several related, important scientific questions. First, given the exponential increase in the available data, it seems relatively easy to find gene-variant and disease associations: In one review, more than 600 positive associations between genes and disease were reported; 166 had been studied more than 3 times, but only 6 had been consistently replicated.[8] Weak predictability combined with our lack of understanding of the causal relationship between genes and drug response makes it difficult and costly to conduct appropriate validation studies. These studies are probably going to have to be large-scale, prospective studies that measure genetics and other biomarkers over time and follow up with patients for long-term outcomes. Producing new knowledge this way will be costly and time-consuming in the near future but could enable smarter, faster therapy and diagnostic design in the long term.

Challenges In The Underlying Economics

The translation of the basic science of pharmacogenetics and other "-omics" biomarkers as applied to drug development and clinical care is occurring in a complex legal, regulatory, and reimbursement environment. Just as it may be difficult to predict phenotype from genotype for a complex disease, it is also difficult to predict clinical use and commercial success of a new diagnostic and drug linked via pharmacogenetics. Understanding and appropriately shaping this environment is vital for encouraging biomarker research and personalized health care.

■ **Incentives for innovation: intellectual property and pricing.** The potential to acquire intellectual property (IP) rights for new drugs or new diagnostics, including pharmacogenetics-based tests, can be a powerful incentive for their invention and development. Patents, in effect, grant temporary monopoly rights to inventors, resulting—in theory—in a short-run "welfare loss" (as higher prices reduce use) offset by a higher innovation rate in the long run.

The impact of the patent system will vary depending on type of technology, sector, and business model. The role of patents in pharmaceutical business is well documented. In brief, statutory patent life now lasts twenty years, but because of the eight to twelve years it takes to test and prepare a new drug for market, effective patent life—the actual time of market exclusivity—is typically much shorter.[9] Furthermore, it is common for competitor pharmaceutical companies to be preparing competing "follow-on" compounds—that is, different molecules that rely on the same mechanism of action. This can weaken monopoly power through

competition, potentially benefiting patients who have greater choice and more treatment options.

For the diagnostics business, historically, IP and competition have centered on platform (that is, the instruments used to measure analytes such as blood glucose), not content (or actual analyte measured), but this has been changing. A manufacturer with a widely used, well-established platform benefits when there is free access to validated content (analytes) to run on that platform. Conversely, to have an economic incentive, a discoverer of new biomarkers needs to be able to recoup research costs by profiting either from direct sales of testing services or by licensing to other laboratories or manufacturers, or both, who can put tests in the hands of service providers. In essence, platform providers and laboratories need content, and content discoverers need a distribution route to patients. IP is central to this dynamic tension. Further, depending on the characteristics of the analyte—novel or with well-established relationship to disease—and other factors, test development times can vary widely. Moreover, business development cycles can be shorter than for drugs. Thus, IP is just as important for diagnostics as for drugs, but the best role for patents depends on the view of the stakeholder: The platform manufacturer would prefer broader, low-cost access to a wide range of content (analytes), while those with IP on content want to capture the clinical and economic value of a novel biomarker. Laboratories want broad access to content and freedom to operate using either a platform-based test or in-house testing, whichever they prefer.

How this tension is resolved has major implications for the linked diagnostic-drug paradigm: The monopoly power conferred by a novel and useful patent allows the patent holder to set prices above the level that would normally prevail under open competition. This difference can be thought of as the reward to the innovation. Strong IP protection, however, is not the only factor shaping pricing and reward. Public health insurance systems have adopted various reimbursement policies that affect the size and structure of this reward for both drugs and diagnostics. We distinguish between cost-based and value-based approaches.

In more technical economic terms, a competitive market would tend to yield a price equal to long-term marginal cost, including an appropriate rate of return on investments. Health insurance reimbursement schemes that attempt set reimbursement, or establish or push prices to this level, could be defined as "cost-based" systems. And in the extreme, they may try to set prices closer to short-run marginal cost.

Alternatively, thinking of an implicit societal demand function based on willingness to pay for improvements in mortality, morbidity, or other cost savings, one could define a system that pays closer to what the monopolist would charge to be "value-based." For example, it is generally understood that the U.K. National Health Service (NHS) applies an approximate threshold of £30,000 per quality-adjusted life year (QALY) gained in its coverage decisions. This sends a strong sig-

"Fundamentally, from an economic perspective, pharmacogenetics-based tests do not differ from other tests."

nal to drug and test manufacturers about what willingness to pay and "value" are and what they can charge for them.

■ **Pricing and reimbursement: pharmaceuticals.** Initial pricing for new brand-name prescription drugs in the United States and European Union (EU) can be characterized as somewhat value-based. The manufacturer sets prices to try to capture citizens' willingness to pay in a given country, which is filtered (and possibly heavily distorted) through insurance and payment mechanisms and institutions. Since only about 30 percent of drugs recover more than the average cost of development, many drugs are not profitable in the long run in and of themselves, but they do contribute some amount to recovering pooled fixed costs.[10] But since one cannot know in advance which ones will be these high-return "blockbusters," the mix of high- and low-return investments is necessary to sustain the enterprise as a whole.

Besides follow-on compounds, a number of other factors can make it difficult for pharmaceuticals to achieve the optimal monopoly price. First, economic theory suggests that the optimal price should differ in different countries or local markets, but it is difficult to charge greatly different prices across countries of the EU or U.S. states because of "parallel trade."[11] Second, in some markets, particularly in the EU and Australia, the price negotiation is with a central government that has considerable monopsony power. Third, and most important for this discussion, it is difficult to change a price once a drug is on the market—either for a new indication or for a new targeted subgroup. This is particularly true in the EU, where each country has its own "administered pricing" system but where the initial price is often linked to other countries by "reference" pricing. In the United States, manufacturers are free to raise a price over time, subject to countervailing competitive economic and political pressures.

■ **Pricing and reimbursement: diagnostics.** The pricing and reimbursement model for diagnostics is fundamentally different from that for drugs in both the United States and the EU.[12] Reimbursement systems for diagnostics might best be described as resource- or cost-based, rather than value-based. Furthermore, they are also generally administered pricing systems. In the United States, for example, when new tests enter the market, an effort is made to link them to the existing reimbursement of tests involving similar effort or cost: for example, techniques such as "cross-walking" and "gap filling" are used.[13] Similar systems apply in France and Germany. All of this implies that the reimbursement—the reward for a new test—is not necessarily based on value added.

One can speculate as to why drug and diagnostic pricing and reimbursement systems have evolved differently in developed economies. It could be a matter of economics, politics, historical accident, and other factors. Sorting out these rea-

sons is beyond the scope of this paper, although they could be important for understanding the feasibility and viability of reform. For now, we take the current state as given and discuss its potential impact on incentives to develop pharmacogenetics-based tests.

■ **Pricing and incentives: pharmacogenetics-based tests.** What is unique about using pharmacogenetics-based tests to target subgroups of patients? Fundamentally, from an economic perspective, pharmacogenetics-based tests do not differ from other tests, such as blood tests for high cholesterol or diabetes, that are used to identify which patients are the best candidates for treatment. They are trying to define the set of patients for whom the average risk-benefit ratio is favorable. Within that set, typically, only some patients will respond fully, and only a subset will suffer side effects. For seven of fourteen major drug classes, it has been estimated that 50 percent or less of patients respond.[14]

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. Imagine, for example, a drug for which only 20 percent of patients received benefit, but we could not identify them ahead of time without a pharmacogenetics test. Paying for value would essentially average this benefit over 100 percent of patients. However, if a test were available to identify the 20 percent, we should be willing to pay on the order of five times more, since the total benefit in the population is the same.

But if pricing and reimbursement systems for diagnostics and drugs are not flexible enough to reward this higher ratio of benefit to risk in a subgroup of patients, what is the incentive to find the subgroup and develop a test? In a previous paper we examined the multiple factors that come into play that could affect this incentive in a given situation. These include (1) whether the drug is already on the market (and priced) before the test is developed; (2) the extent to which drug and diagnostic prices are flexible and are value- versus cost-based, (3) the competitiveness of the insurance market, and (4) the strength of the patent protection on the diagnostic versus the therapeutic.[15]

On the face of it, it is obvious that drug manufacturers could be considerably worse off if a pharmacogenetics-based predictive test is discovered after the drug is on the market, and that test developers will have much less of an incentive to develop a pharmacogenetics-based test if they cannot themselves capture a large share of the value created by identifying a responding subgroup. Hence, there will be limited incentives for both drug and diagnostic manufacturers to develop tests for drugs that are already on the market, although the disincentives are greater for drug manufacturers. This would argue for codeveloping test and drugs, coming to the market with the association fully proven.

■ **Other barriers to diagnostic-therapeutic linkage.** In addition to the scientific and economic barriers highlighted above, two other factors deserve mention that might be inhibiting the development of pharmacogenetics-based test-drug combinations. One factor is the high cost of the basic research that is needed to validate genetic markers. Financing this remains a question: What should fall to the public sector, how much should the private sector contribute, and what is best done in partnership are under active debate.

Second, approval and reimbursement for drugs in the United States and EU require greater levels of evidence than is customary for new diagnostic tests. Some would argue that the lower evidentiary requirements for regulatory approval of tests has discouraged the development of better clinical data and that payers practice "cost-based" reimbursement in part because of this lack of evidence on clinical and economic value. In contrast, both the Academy of Managed Care Pharmacy (AMCP) Format for Formulary Submissions guidelines in the United States and the requirements for submissions to the National Center for Clinical and Health Excellence (NICE) in the United Kingdom request economic models that synthesize the clinical and cost evidence to assess value added of new drugs. Similar standards and mechanisms do not exist for diagnostics, although the discussion is beginning.[16] But asking for more evidence means raising the costs of developing—and particularly validating—new diagnostics. What are the incentives for diagnostic manufacturers if no additional rewards are forthcoming through the reimbursement system?

Concluding Comments

In our opinion, pharmacogenetics-based diagnostics and drugs are unlikely to be linked in large numbers unless these scientific and economic challenges can be met. Most importantly, until we have much greater knowledge of the actual predictive power of new molecular markers, useful applications will be much slower in coming than we would hope. This is likely to require a substantial increase in the level of public investment in both basic and translational research.

We also hypothesize that value-based, flexible pricing systems—backed by strong, consistent intellectual property rules—are a necessary, but not sufficient, condition to achieve the promise of personalized medicine. It remains to be determined what the science can deliver with respect to valid clinical applications. Public policy, however, needs to focus on supporting the paradigm of more closely aligned biomarkers, diagnostics, and therapeutics and not focus on a single analyte or technology, such as genetic testing, if the full scientific potential is to be realized. Given the complexities of the biological systems we are attempting to parse and then manipulate, as well as the many years it typically takes to develop and test a new drug or validate a biomarker, this will still most likely take decades. Nonetheless, this new knowledge holds promise in the long run, and major medical progress can be achieved under economic incentives that foster innovation.

The authors have benefited from discussions with Adrian Towse, David Veenstra, Chris Chamberlain, and James Creeden. Lou Garrison worked for Roche Pharmaceuticals from 1995 through May 2004 and has since been a consultant to Roche and other pharmaceutical and diagnostic companies. The views expressed in this paper are those of the authors and should not be attributed to their respective organizations.

NOTES

1. Royal Society, *Personalised Medicine: Hopes and Realities*, September 2005, http://www.royalsoc.ac.uk/displaypagedoc.asp?id=17570 (accessed 31 May 2006).
2. R.M. Califf, "Defining the Balance of Risk and Benefit in the Era of Genomics and Proteomics," *Health Affairs* 23, no. 1 (2004): 77–87.
3. S.H. Ralston et al., "Large-Scale Evidence for the Effect of the COLIA1 Sp1 Polymorphism on Osteoporosis Outcomes: The GENOMOS Study," *PLoS Medicine* 3, no. 4 (2006): e90.
4. D. Boomsma, A. Busjahn, and L. Peltonen, "Classical Twin Studies and Beyond," *Nature Reviews Genetics* 3, no. 11 (2002): 872–882.
5. Y. Gasche et al., "Codeine Intoxication Associated with Ultrarapid CYP2D6 Metabolism," *New England Journal of Medicine* 351, no. 27 (2004): 2827–2831.
6. Centers for Disease Control and Prevention, "ACCE: A CDC-Sponsored Project Carried Out by the Foundation of Blood Research," 1 June 2006, http://www.cdc.gov/genomics/gtesting/ACCE.htm (accessed 12 June 2006).
7. D.W. Bell et al., "Epidermal Growth Factor Receptor Mutations and Gene Amplification in Non-Small-Cell Lung Cancer: Molecular Analysis of the IDEAL/INTACT Gefitinib Trials," *Journal of Clinical Oncology* 23, no. 31 (2005): 8081–8092.
8. J.A. Hirschhorn et al., "A Comprehensive Review of Genetic Association Studies," *Genetics in Medicine* 4, no. 2 (2002): 45–61.
9. J.A. DiMasi and C. Paquette, "The Economics of Follow-On Drug Research and Development: Trends in the Entry Rates and the Timing of Development," *PharmacoEconomics* 22, no. 2 Supp. (2004): 1–14.
10. H. Grabowski, J. Vernon, and J.A. DiMasi, "Returns on Research and Development for 1990s New Drug Introductions," *PharmacoEconomics* 20, no. 3 Supp. (2002): 11–29.
11. P.M. Danzon and A. Towse, "Differential Pricing for Pharmaceuticals: Reconciling Access, R&D, and Patents," *International Journal of Health Care Finance and Economics* 3, no. 3 (2003): 183–205.
12. Lewin Group, *The Value of Diagnostics: Innovation, Adoption and Diffusion into Health Care*, Report prepared for AdvaMed, July 2005, http://www.advamed.org/publicdocs/thevalueofdiagnostics.pdf (accessed 31 May 2006). In France and Germany, price and reimbursement are set by national committees; in the United Kingdom, prices are negotiated between labs and manufacturers.
13. G.G. Raab and L.J. Logue, "Medicare Coverage of New Clinical Diagnostic Laboratory Tests: The Need for Coding and Payment Reforms," *Clinical Leadership and Management Review* 15, no. 6 (2001): 376–387.
14. B.B. Spear, M. Heath-Chiozzi, and J. Huff, "Clinical Application of Pharmacogenetics," *Trends in Molecular Medicine* 7, no. 5 (2001): 201–204.
15. L.P. Garrison and M.J.F. Austin, "The Economics of Personalized Medicine: A Model of Incentives for Value Creation and Capture" (Unpublished paper, March 2006).
16. S.D. Ramsey et al., "Toward Evidence-based Assessment for Coverage and Reimbursement of Laboratory-based Diagnostic and Genetic Tests," *American Journal of Managed Care* 12, no. 4 (2006): 197–202.

COMMENTARY

Toward Evidence-based Assessment for Coverage and Reimbursement of Laboratory-based Diagnostic and Genetic Tests

Scott D. Ramsey, MD, PhD; David L. Veenstra, PharmD, PhD; Louis P. Garrison, Jr, PhD; Rick Carlson, JD; Paul Billings, MD, PhD; Josh Carlson, MS; and Sean D. Sullivan, PhD

Despite the pervasiveness of laboratory tests and their importance to medicine, evidence for their appropriate use often is very limited. In this article, we argue for a fundamental restructuring of the process by which laboratory tests are evaluated and reimbursed. We present an approach that would promote more evidence-based appraisals for laboratory tests. In addition, we urge that coverage and reimbursement for laboratory tests move toward an evidence- and value-based approach, using the tools that largely have been adopted for pharmaceuticals by many US healthcare payers. To address this information gap for laboratory tests, we note several potential strategies to encourage manufacturers, laboratory service providers, and payers to collect outcome and cost data that will better support effective use of new laboratory tests. Integral to increasing appropriate use and reimbursement will be the development of a common language and format for dialogue—facilitating the development, review, and delivery of evidence-based tests by manufacturers, clinical laboratories, and healthcare payers.

(Am J Manag Care. 2006;12:197-202)

Laboratory tests are an important yet often underappreciated component of healthcare and the health economy.[1] It is estimated that as much as $56 billion will have been spent on laboratory diagnostic services in 2005.[2] More important, laboratory tests by their very nature are designed to initiate a cascade of decisions regarding further testing, prevention, or treatment—decisions that ultimately determine the course of illness and cost of healthcare for patients who receive them. A recent report estimated that although diagnostics account for 1.6% of the Medicare total costs, they influence 60% to 70% of downstream treatment decisions.[3]

Despite their pervasiveness and importance to medicine, the evidence for the application and utility of laboratory tests often is limited.[4-6] Tests being brought to market do not require the same data as therapeutics do, and technology assessments of laboratory tests have not undergone the revolutionary changes in evidence review that have occurred for drugs.[7] Instead, payment for tests is linked to an antiquated coding system.[8] Finally, innovative insurance coverage and payment policies that are common for drugs are rare for laboratory tests.[9]

In this article, we argue for a fundamental restructuring of the way laboratory tests are evaluated and reimbursed. We propose that coverage and reimbursement for laboratory tests should move toward an evidence- and value-based approach, using some of the tools that have been adopted for pharmaceutical assessment by many US healthcare payers. Furthermore, reevaluating the methods used to assess and pay for tests is a timely endeavor, as diagnostic tests are on the forefront of the trend toward personalized medicine.[10,11]

CHALLENGES FOR THE CURRENT PROCESS OF ADOPTING LABORATORY TESTS

Public and private health insurers pay for tests performed in laboratories that meet standards certified under the Clinical Laboratory Improvement Amendments (CLIA) of 1988, according to *Current Procedural Terminology (CPT)* codes.[12] In cases where a *CPT* code does not exist, health insurers sometimes reimburse the new test by using a *CPT* code for an existing test, a process known as "mapping."[13,14]

Once a *CPT* code is established, test payments are established by "cross-walking" or "gap-filling." In cross-

From the Fred Hutchinson Cancer Research Center, Seattle, Wash (SDR); the Department of Medicine (SDR), the Department of Pharmacy (DLV, LPG, SDS), and the School of Public Health (RC, JC), University of Washington, Seattle; and the Laboratory Corporation of America, Research Triangle Park, NC (PB).

This research was supported by an unrestricted grant to the University of Washington from Laboratory Corporation of America.

Address correspondence to: Scott D. Ramsey, MD, PhD, Fred Hutchinson Cancer Research Center, 1100 Fairview Ave N, M2-B230, PO Box 19024, Seattle, WA 98109. E-mail: sramsey@fhcrc.org.

walking, a new test is determined to be similar to an existing test, multiple existing test codes, or a portion of an existing test code. Payment is set at an "appropriate" percentage of the payment for the existing test.[15] In gap-filling, insurers are left to determine an appropriate payment amount for the new code. The Centers for Medicare & Medicaid Services uses local carrier decisions as a basis for the next year's clinical laboratory fee schedule.[15]

A recent report by the Institute of Medicine suggested that the process of establishing reimbursement levels for novel laboratory tests is out-of-date and not equipped to handle emerging diagnostic and genomic tests:

> [Medicare] payments for some individual tests likely do not reflect the cost of providing services, and anticipated advances in laboratory technology will exacerbate the flaws in the current system. Problems with the outdated payment system could threaten beneficiary access to care and the use of enhanced testing methodologies in the future.[16]

More broadly, some argue that reimbursement must more accurately reflect clinical and economic value.[3,14]

Public and private payers have not developed uniform methods for requesting information from laboratory test service providers about novel tests. There are several likely reasons. The first reason is historical: most health plans do not have standing test evaluation groups similar to pharmacy and therapeutics (P&T) committees, possibly because laboratory tests have not been viewed as clinically or economically significant enough to justify the expense associated with these groups. Second, in contrast to pharmaceutical manufacturers, neither test manufacturers nor laboratory service providers generally have large, sophisticated marketing teams targeting physicians, health plans, and patients. (A relevant exception may be the marketing of the ThinPrep test.[17]) Third, as noted above, federal regulatory requirements do not compel manufacturers or distributors to provide the type of evidence (eg, randomized clinical trials) that lends itself to systematic review.[18] Finally, the way laboratory tests are used in practice makes it difficult to apply the pharmaceutical evaluation model. Unlike most pharmaceuticals, laboratory tests are used in a wide range of clinical settings. For example, a complete blood count is used in hundreds of clinical situations, while antihypertensive drugs are used in a limited number of conditions.

In lieu of an evidence-driven, value-based approach, the process of adopting new laboratory tests is essentially what economists call an "administering pricing" system. Pricing is set through a negotiation process that may be based on historical comparators in the case of cross-walking or perceived levels of analytic complexity in the case of gap-filling. As a result, there is little reward for creating additional value (either in a clinical or an economic sense) and hence little incentive to create the evidence to support value creation (L. P. Garrison, PhD, and M. J. F. Austin, PhD. The economics of personalized medicine: a model of incentives for value creation and capture. Unpublished observations, January 2006). We describe a process that is designed (1) to improve the quality of the evidence that is available when an insurance coverage decision is being made and (2) to increase the transparency and uniformity of the process by which payers request information from test manufacturers or laboratory service providers.

FRAMEWORK FOR PRESENTING EVIDENCE ON LABORATORY TESTS

Developing a Language for Describing Benefit

Test manufacturers, laboratory service providers, and health insurance plans will benefit from standardizing the way evidence supporting new laboratory tests is presented. Methodological standards for the evaluation of diagnostic tests have been published.[5] In addition, several domains relevant to health insurers, clinicians, and patients are considered in a published framework to evaluate diagnostic technologies (**Table**).[19] Although many agree about the value of using these domains to evaluate tests, there is less agreement on how much evidence is necessary for an insurance coverage decision.

In addition to considering the relevant domains from the Table, it is important to evaluate the incremental impact of a test; that is, the improvement that the new test provides over current diagnostic strategies (L. P. Garrison, PhD, and M. J. F. Austin, PhD. The economics of personalized medicine: a model of incentives for value creation and capture. Unpublished observations, January 2006). Because prospective trials directly comparing new laboratory tests with established diagnostic strategies are uncommon (particularly those evaluating the impact of the tests on patient outcomes), decision-analytic modeling techniques often are necessary to conduct quantitative evaluations.[20] Modeling is an underappreciated approach to evaluating new tests. Models help frame questions, provide transparent mechanisms for stating hypotheses about cause and effect, highlight deficiencies in clinical data, and force decision makers to make explicit judgments about values for data that are used to inform the model. Although some clinicians and health insurance plan executives remain skeptical of decision models, quality standards for models have been published and are readily accessible to

decision makers who wish to assess their quality.[21]

Table. Hierarchy of Diagnostic Evaluation When Determining Test Benefit*

Level	Characteristic	Description
1	Technical feasibility and optimization	Ability to produce consistent results
2	Diagnostic accuracy	Sensitivity, specificity, positive predictive value, negative predictive value
3	Impact on diagnostic thinking	Percentage of time that physicians' estimated probability of a diagnosis changes after the test result
4	Impact on therapeutic choice	Percentage of time that the planned therapeutic strategy changes after the test result
5	Impact on patient outcome	Percentage of patients who improve with the test versus the percentage who improve without the test
6	Impact on society	Cost-effectiveness

*Adapted from reference 19.

Definition of Value for Laboratory Tests

We define value for laboratory tests as it is defined for other health technologies: The intervention provides an overall benefit to the patient at an acceptable cost (ie, it is cost-effective). Petitti notes that there are 4 well-recognized criteria for identifying an intervention as cost-effective[22]:

- Less costly and at least as effective.
- More effective and more costly, with the added benefit worth the added cost.
- Less effective and less costly, with the added benefit of the alternative not worth the added cost.
- Cost saving with an outcome equal to or better than that of the alternative.

Assessing value for tests can be difficult because tests are intermediate steps in the treatment pathway. The advantage of Petitti's framework[22] is that it allows flexibility, because value for tests can be defined narrowly (eg, the least expensive way to make a diagnosis) or broadly (improvement in survival at an acceptable added cost).

Format for Dialogue Among Test Manufacturers, Providers, and Payers

Manufacturers and laboratory service providers cannot expect, and payers cannot promise, coverage of and appropriate reimbursement for every new test that comes to market. Similarly, payers cannot expect, and manufacturers and their delivery partners cannot promise, the same level of evidence for all tests. Nevertheless, the process should be transparent, and adopting a standard format would help clarify expectations and improve the decision-making process. We propose a process for information content and interaction that is intentionally similar to the format developed by the Academy of Managed Care Pharmacy (AMCP) for the evidence-based evaluation of drugs. More than 50 public and private health insurers covering more than 100 million lives have adopted the AMCP format.[7,23] The **Appendix** provides a template for manufacturers' reporting of clinical and economic information regarding laboratory tests. This template takes into account differences in evidence that are typically available for new laboratory tests compared with new pharmaceuticals.

IMPLEMENTATION

Some health plans might have a designated organizational unit that evaluates laboratory tests, providing a structure for soliciting and reviewing manufacturers' products. In the case of pharmaceutical products, that unit is the P&T committee. Health plan staff working with P&T committees usually are receptive to receiving information from manufacturers or service laboratories about new products. Indeed, the "unsolicited request" process pioneered by AMCP was designed to create a structure for dialogue between manufacturers and payers. A similar scheme would improve transparency and the flow of information for new laboratory tests.

P&T committee members often are not health plan employees. Having such a quasi-independent group evaluate novel laboratory tests may improve the credibility of the decision process in the eyes of manufacturers, clinical laboratories, physicians, and patients. Still, maintaining committees is costly, and such maintenance may not be justified given the relatively low volume of tests that are introduced annually. One option is to fold the test evaluation process into the existing P&T structure. Alternatively, payers could hire consultants to evaluate select novel tests and make recommendations regarding coverage and reimbursement.

Payers should be timely both in coverage decisions and in setting reimbursement levels, and when decisions are made, they should be supported with a rationale. In cases where requests for coverage are denied,

such information allows manufacturers to design studies or collect other data that address concerns regarding the quality or content of the information supporting the product.

OPTIONS FOR IMPROVING THE LEVEL OF EVIDENCE SUPPORTING NOVEL LABORATORY TESTS

To address known methodological weaknesses in studies evaluating diagnostic tests,[24-26] we describe in this section options for improving the quality of information. Some focus on market incentives; others are more regulatory in nature. At this early stage, we do not advocate one approach over another. Rather, we hope to foster a dialogue among stakeholders.

Enhancing Regulation in Evaluating Laboratory Tests

Testing services in the United States are regulated by both federal and state laws and agencies, and are further reviewed by accrediting professional entities. All laboratory tests that meet the legal definition of in vitro diagnostic devices (IVDs; generally, diagnostic assays made for distribution outside a single provider laboratory) are evaluated by the US Food and Drug Administration's (FDA's) Center for Devices and Radiological Health. However, most tests offered by laboratory service providers are not IVDs; the manufacture of analytes or other components of such tests (called analyte-specific reagents) may need to meet FDA specifications for legal distribution. IVD approval, which typically is based on analytical performance, does not require other types of evidence that the FDA often mandates for devices that carry significant risk (eg, prospective controlled trials for implantable defibrillators). Although laboratory tests usually pose little direct risk of injury or death, they often lead to a cascade of clinical decisions, sometimes involving procedures that do carry significant risk for patients. For example, a positive prostate-specific antigen test often leads to prostate biopsy, which carries risk of bleeding and infection. As an extreme example, women whose genetic tests show BRCA mutations often choose to have prophylactic mastectomies and oophorectomies.[27] Genomic tests that are used to guide therapy choices also could represent a class of laboratory assays that pose unique patient risks.

To address potential downstream indirect risk, the FDA could require test manufacturers or service providers distributing IVDs to submit clinical algorithms with recommended follow-up plans based on test results. In cases where the downstream consequences are significant, the FDA could require specific postmarketing studies. Another area of concern is laboratory-developed or "home brew" tests—those that are supplied by a single laboratory or laboratory company and therefore are not subject to federal regulatory review beyond CLIA. Many tests, including genetic assays, are brought to market as home brew tests.[28] Strengthening regulatory requirements for some of these tests might enhance the ability of payers and clinicians to gauge their value. With a goal of more uniform quality standards for testing, federal, state, and professional oversight measures should be considered in toto.

Levies to Support Clinical Research

To increase funding of high-quality clinical studies focused on patient outcomes,[29-32] some advocate levies on medical services to fund prospective and retrospective clinical and economic studies for new and existing technologies.[33] Such research could be directed through existing agencies within the National Institutes of Health, the Agency for Healthcare Research and Quality, or freestanding private clinical research facilities. Such a system would be expensive and difficult to administer and manage only for laboratory tests, however, given the inconsistencies in reimbursement for tests across the settings where they are ordered. Levies also may create a significant disincentive for test development. In this context, levies could not be directed solely at laboratory testing; rather, they should include all reimbursable health services.

Improved *CPT* Coding and Risk Pooling

Under current *CPT*-based reimbursement, if novel tests are not promptly and specifically assigned codes, reimbursement and hence use are hindered. And because *CPT* codes are updated only annually, opportunities for gathering clinical information are lost. To avoid these problems, novel tests could be assigned unique temporary *CPT* codes that would allow billing and tracking of the test's use in delivery systems, and its effect on clinical decision making and patient outcomes.

These unique codes would allow manufacturers or service laboratories to obtain reimbursement for novel tests, but such a strategy would shift a large part of the cost of test development and evaluation to payers. To address this problem, a risk-sharing approach could be implemented: payers could agree to preliminarily cover new tests on the contingency that manufacturers and service laboratory providers have a certain amount of time to establish clinical utility and value. Although these types of agreements are just beginning to be used for pharmaceuticals, they may offer promise for laboratory tests, given the fact that the evidence available at

the time of market launch is different from the evidence that will be available after clinical use.[34]

Value-based Reimbursement

Finally, and perhaps most important, consideration should be given to rewarding innovative and novel tests with greater reimbursement based on an explicit measure of the additional value they create. Health economists have developed techniques for measuring the incremental value of new technologies in terms of cost savings, morbidity reduction, and life extension, and for integrating these impacts into models that provide a measure of overall incremental value. Furthermore, higher expected levels of reimbursement can be used to justify greater investments in measuring and demonstrating ultimate clinical utility and economic value.

CONCLUSION

Laboratory tests are developed under a different regulatory structure than pharmaceuticals and have a unique and complex function in medical care. Novel tests may come to market with little information supporting their role in clinical decision making or evidence regarding their impact on patient outcomes. To address these issues and to improve patient care and outcomes, we have outlined a structure and process for information sharing among laboratory test manufacturers, clinical laboratories that provide tests, and payers that make coverage and reimbursement decisions about these tests. Although it is unlikely and perhaps unnecessary that the evaluation process for laboratory tests will equal that required for drugs, we can move much further toward a system that supports better gathering and sharing of high-quality evidence. Test manufacturers, clinical laboratories, payers, and clinicians all must play a role in this process.

REFERENCES

1. **Food and Drug Administration, Department of Health and Human Services.** CFR Title 21 809.3. Title 21: Food and Drugs. Subchapter H: Medical Devices. Part 809: In vitro diagnostic products for human use. Subpart A: General provisions. Section 809.3 definitions. Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm. Accessed August 2005.

2. **BlueCross BlueShield Association.** *Medical Technology as a Driver of Healthcare Costs: Diagnostic Imaging.* Available at: http://www.bcbs.com/coststudies/reports/Medical_Tech_Drivr_Rept_10.pdf. Accessed August 2005.

3. **The Lewin Group.** *The Value of Diagnostics Innovation, Adoption and Diffusion into Health Care.* Report prepared for The Advanced Medical Technology Association (AdvaMed). July 2005. Available at: http://www.advamed.org/publicdocs/thevalueofdiagnostics.pdf. Accessed August 2005.

4. **Feinstein AR.** Misguided efforts and future challenges for research on "diagnostic tests." *J Epidemiol Community Health.* 2002;56:330-332.

5. **Reid MC, Lachs MS, Feinstein AR.** Use of methodological standards in diagnostic test research. Getting better but still not good. *JAMA.* 1995;274:645-651.

6. **Weinstein S, Obuchowski NA, Lieber ML.** Clinical evaluation of diagnostic tests. *Am J Roentgenol.* 2005;184:14-19.

7. **Neumann PJ.** Evidence-based and value-based formulary guidelines. *Health Aff (Millwood).* 2004;23:124-134.

8. **Raab GG, Logue LJ.** Medicare coverage of new clinical diagnostic laboratory tests: the need for coding and payment reforms. *Clin Leadersh Manag Rev.* 2001;15:376-387.

9. **Fendrick AM, Smith DG, Chernew ME, Shah SN.** A benefit-based copay for prescription drugs: patient contribution based on total benefits, not drug acquisition cost. *Am J Manag Care.* 2001;7:861-867.

10. **Collins FS.** Shattuck lecture—medical and societal consequences of the Human Genome Project. *N Engl J Med.* 1999;341:28-37.

11. **Langheier JM, Snyderman R.** Prospective medicine: the role for genomics in personalized health planning. *Pharmacogenomics.* 2004;5:1-8.

12. **Centers for Medicare & Medicaid Services.** Clinical Laboratory Improvement Amendments (CLIA). Available at: http://www.cms.hhs.gov/clia/. Accessed November 2005.

13. **Young DS.** Earning your keep: succeeding in laboratory reimbursement. *Clin Chem.* 1998;44:1701-1712.

14. **Young DS.** Reforming laboratory reimbursement: issues, impact and innovations. A summary of the clinical chemistry forum held on November 15, 2001. *Clin Chem.* 2002;48:792-795.

15. **Centers for Medicare & Medicaid Services.** Glossary. Available at http://www.cms.hhs.gov/glossary/. Accessed August 2005.

16. **Wolman DM, Kalfoglou AL, LeRoy L, eds.** *Medicare Laboratory Payment Policy: Now and in the Future.* Washington, DC: The National Academies Press; 2000:17.

17. **Rappaport KM, Forrest CB, Holtzman NA.** Adoption of liquid-based cervical cancer screening tests by family physicians and gynecologists. *Health Serv Res.* 2004;39(4 pt 1):927-947.

18. **Tatsioni A, Zarin DA, Aronson N, et al.** Challenges in systematic reviews of diagnostic technologies. *Ann Intern Med.* 2005;142:1048-1055.

19. **Fryback DG, Thornbury JR.** The efficacy of diagnostic imaging. *Med Decis Making.* 1991;11:88-94.

20. **Buxton MJ, Drummond MF, Van Hout BA, et al.** Modelling in economic evaluation: an unavoidable fact of life. *Health Econ.* 1997;6:217-227.

21. **Weinstein MC, O'Brien B, Hornberger J, et al.** Principles of good practice for decision analytic modeling in health-care evaluation: report of the ISPOR Task Force on Good Research Practices—Modeling Studies. *Value Health.* 2003;6:9-17.

22. **Petitti DB.** *Meta-Analysis, Decision Analysis, and Cost-Effectiveness Analysis: Methods for Quantitative Synthesis in Medicine.* New York, NY: Oxford University Press; 2000.

23. **Fry R, Avey S, Sullivan S.** The Academy of Managed Care Pharmacy Format for Formulary Submissions: an evolving standard. A Foundation for Managed Care Pharmacy Task Force report. *Value Health.* 2003;6:505-521.

24. **Nierenberg AA, Feinstein AR.** How to evaluate a diagnostic marker test. Lessons from the rise and fall of dexamethasone suppression test. *JAMA.* 1988; 259:1699-1702.

25. **Banta HD, Thacker SB.** Electronic fetal monitoring. Lessons from a formative case of health technology assessment. *Int J Technol Assess Health Care.* 2002; 18:762-770.

26. **Blackmore CC, Black WC, Jarvik JG, Langlotz CP.** A critical synopsis of the diagnostic and screening radiology outcomes literature. *Acad Radiol.* 1999;6(suppl 1):S8-S18.

27. **Wainberg S, Husted J.** Utilization of screening and preventive surgery among unaffected carriers of a BRCA1 or BRCA2 gene mutation. *Cancer Epidemiol Biomarkers Prev.* 2004;13:1989-1995.

28. **Food and Drug Administration, Department of Health and Human Services.** Notice. Agency information collection activities; submission for OMB review; comment request; medical devices; classification/reclassification; restricted devices: analyte specific reagents. *Fed Regist.* January 5, 2001;66:1140-1141. Available at: http://www.fda.gov/OHRMS/DOCKETS/98fr/010501c.htm. Accessed August 2005.

29. **Goldman DP, Schoenbaum ML, Potosky AL, et al.** Measuring the incremental cost of clinical cancer research. *J Clin Oncol.* 2001;19:105-110.

30. **Rockey D.** The crisis in clinical research [letter]. *JAMA.* 1999;282:1914; author reply 1915-1916.

31. **Nathan DG.** Clinical research: perceptions, reality, and proposed solutions. National Institutes of Health Director's Panel on Clinical Research. *JAMA.* 1998;280:1427-1431.

32. **Antman K, Schnipper LE, Frei E 3rd.** The crisis in clinical cancer research. Third-party insurance and investigational therapy. *N Engl J Med.* 1988;319:46-48.

33. **Reinhardt UE.** An information infrastructure for the pharmaceutical market. *Health Aff (Millwood).* 2004;23:107-112.

34. **Chapman S, Reeve E, Rajaratnam G, Neary R.** Setting up an outcomes guarantee for pharmaceuticals: new approach to risk sharing in primary care. *BMJ.* 2003;326:707-709.

See Appendix on following page.

Appendix. Evidence and Transparency Standard to Support Coverage and Reimbursement for Diagnostic, Therapeutic, and Genetic Testing

1. **Product Information**
   - 1.1. Product description.
   - 1.1.1. Place of the product in therapy.
   - 1.1.2. Disease description. The disease description should include the disease and characteristics of the patients in the target population.
2. **Supporting Clinical and Economic Information**
   - 2.1. Evidence-table spreadsheets of all published and unpublished clinical trials.
   - 2.2. Outcome studies and supporting data for economic evaluation (3-4 pages maximum per study).
   - 2.2.1. Evidence-table spreadsheets (noted above) of all published and unpublished outcomes studies.
3. **Cost-effectiveness Modeling Report**
   - 3.1. Model overview. We recommend that producers and users of modeling studies subscribe to the sound guidance provided by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Good Practice Modeling Principle.
4. **Product Value and Overall Cost**
5. **Supporting Information**
   - 5.1. References contained in dossiers.
   - 5.2. References for economic models.

21st centurymedicine

VIA ELECTRONIC TRANSMISSION

Email: goodwins@od.nih.gov

June 1, 2007

Chairman Reed Tuckson, M.D.
Secretary's Advisory Committee on Genetics, Health, and Society
National Institutes of Health, Office of Biotechnology Activities
6705 Rockledge Drive, Suite 750
Bethesda, MD 20892

Re: Draft Report to the Secretary of Health and Human Services:
Realizing the Promise of Pharmacogenomics: Opportunities and Challenges.

Dear Dr. Tuckson:

The following comments are provided by the Coalition for 21st Century Medicine (the Coalition) (www.twentyfirstcenturymedicine.org). The organization represents molecular diagnostic and technology companies developing innovative translational medicine solutions dedicated to enabling the promise of personalized medicine. The Coalition represents some of the world's most innovative diagnostic technology companies, clinical laboratories, venture capitalists, and patient advocacy organizations – all linked by a common mission to develop advanced diagnostics that improve the quality of healthcare for patients.

We appreciate the opportunity to comment on the draft report of the Secretary's Advisory Committee on Genetics, Health, and Society (the SACGHS), *Realizing the Promise of Pharmacogenomics: Opportunities and Challenges.*

The Coalition believes that the report provides a very comprehensive overview of most of the challenges presented by the use of genomic technologies and their integration into routine clinical practice. The Coalition also believes that the report appropriately presents the real opportunities pharmacogenomics (PGx) holds to individualize medicine in our healthcare delivery system. We would like to highlight some of our specific concerns as they relate to portions of the report. We look forward to continuing our dialogue with the SACGHS and participating in the public engagement process on this very important topic. Thank you for reviewing and considering our input on this draft report. We will make ourselves available to the SACGHS and your consultants if additional clarification is required.

P. O. Box 15519 ▪ Arlington, VA 22215-0519
1-800-226-9494
www.twentyfirstcenturymedicine.org

21st centurymedicine

General Comments:

Topic - BioMarkers:

We think that the report should make a more intentional delineation between the concepts of PGx as outlined in this report and Biomarkers generally. The report should consider contextualizing additional science and technologies (e.g., *phenotyping, invasive or virus typing, methylation, phosphorylation, intermediate or surrogate markers, gene-protein-antigen profiling, metabolomics, functional imaging, in vivo tagging, nanotechnologies, and applications of biostatistical data for personalization*) that could have implications for PGx, therapeutic guidance, and personalized medicine. There seems to be a diverse set of public and private activities and expertise that is artificially segmented by these definitional distinctions or emerging disciplines (PGx vs. Biomarkers). There should be a more sharply defined and elucidated narrative for the variety of Biomarker activities that could impact the direction and/or recommendations covered in this narrowly focused PGx report.

Topic - Value-Based Reimbursement:

The report includes statements in support of differential reimbursement for PGx-guided therapeutics but not specifically for the value creation produced by the diagnostic. We believe that the unique attributes of the diagnostic innovation in and of itself should be acknowledged in the report.

Page 64, Par. 2: The report only touches on the concept of value-based reimbursement for diagnostics. We believe that the report should include a much more comprehensive review of both the incentives and disincentives as they currently exist for PGx diagnostics.

We believe that the report should include a specific recommendation for HHS to explore new financial and process incentive models, premium pricing evaluation methods, public/private partnerships, specific workshops, and/or demonstration projects for designated PGx products.

Topic - Theranostics / Diagnostics Business Models:

The report presumes that there are no clear examples of successful business models for PGx testing and linked products. We suggest that there are currently a number of emerging business models within the Coalition's membership that represent successful PGx businesses today.

P. O. Box 15519 ▪ Arlington, VA 22215-0519
1-800-226-9494
www.twentyfirstcenturymedicine.org

Topic - Institute of Medicine / National Academy of Science (IOM / NAS):

We are struck by the fact that the report does not include any mention of the potential role and/or responsibility of the IOM to convene a topic roundtable to review and propose solutions for any of the identified challenges. We suggest that the SACGHS consider recommending to HHS a specific set of priorities for IOM to consider.

Topic - Regulatory Science:

The report does not include any mention of the opportunities to apply the new science and technology of PGx to improve current regulatory practices. There should be some inclusion in the report of the need for HHS, NIH, or the various regulatory agencies to review, benchmark, and attempt to define current best practices in a transparent manner and to institute process efficiency improvements as a matter of modern regulatory science.

Topic - Adaptive Clinical Trials:

The concept of Biological Correlative Trials – prospectively defined protocols using archival patient samples from existing clinical trials, observational, and/or epidemiological studies – should be considered as an important approach to develop evidence-based PGx associations.

Topic - FDA and CLIA Oversight and Regulation:

The report fails to acknowledge the historic trajectory of molecular diagnostics and laboratory medicine that is delivering PGx diagnostics from discovery research, verification, validation, clinical delivery, and reduction to practice. The evolution of the new PGx science and technology may warrant a re-evaluation of a traditional regulatory scheme. HHS should be asked to engage stakeholders to attempt to harmonize medical device regulation with quality systems regulations under the Clinical Laboratory Improvement Amendments (CLIA). It can be argued that these two existing regulatory systems are inadequate at the task of appropriate oversight.

Page 28, Sec. 3, Par. 3: The Coalition believes that this section of the report mischaracterizes the FDA and CLIA regulatory situation and the extent of data submission and review for laboratory developed tests.

P. O. Box 15519 ▪ Arlington, VA 22215-0519
1-800-226-9494
www.twentyfirstcenturymedicine.org

Page 35, Sec. 1, Par. 1: Again, the Coalition believes that this section of the report mischaracterizes the FDA and CLIA regulatory situation and the extent of data submission and review for laboratory developed tests.

Page 54, Sec. B, Par. 4: The Coalition believes that this section of the report recognizes the current debate over appropriate regulation of PGx tests but should also include the recognition that FDA's jurisdictional authority over laboratory developed tests has not been substantiated by a legal determination, court decision, or new legislative clarification.

Page 55, Sec. B, Par. 3: The Coalition believes that FDA's draft guidance on the rule governing Analyte Specific Reagents (ASRs) should be considered very controversial and that the concept of "Single Moieties" may have significant unintended consequences to the practice of manufacturing and supplying high quality assay components. We believe that the SACGHS should be very careful about characterizing the recent FDA guidances as being helpful for industry and for providing regulatory certainty. The SACGHS should review the public comments submitted to the docket for the draft guidance as well as the numerous articles published on this topic within legal and trade journals to completely understand the controversies for PGx testing.

Page 68 ,Sec. 4: We believe that the CLIA oversight section is grossly mischaracterized and needs to be revised to more accurately reflect the oversight and regulatory functions of CLIA, third party accreditation organizations, and various state agencies. The report should revise the sections on CLIA review of analytical validity and reliability, clinical validity, or utility for in-house developed laboratory tests. We recommend that the SACGHS review the explicit and implicit requirements of CLIA regulations (42 C.F.R. § 493.1445) to accurately characterize the responsibilities for laboratories, laboratory directors, and clinical consultants for clinical validity, clinical utility, and professional laboratory medical standards for offering a clinical test.

Directed Comments:

Page 3, Sec. A, Par. 1:

The report should include an additional reference (Reference #3) that provides the counter argument to the Royal Society's position in the British Medical Journal.

P. O. Box 15519 ▪ Arlington, VA 22215-0519
1-800-226-9494
www.twentyfirstcenturymedicine.org

GS *Ginsburg, et al.*, The Future May be Closer Than You Think: A Response from the Personalized Medicine Coalition to the Royal Society's Report on Personalized Medicine. Journal of Personalized Medicine 2006 3(2).

Page 4, Sec. A, Par. 2:

The report should include an additional reference (Reference #8) that provides an excellent example of a current and novel NIH trial design that employs a Biomarker / genomics to stratify a heterogeneous patient population for breast cancer treatment selection.

The National Cancer Institute's PACCT 1 Program Trial: TAILORx Breast Cancer Trial. (URL: http://www.cancer.gov/clinicaltrials/ECOG-PACCT-1).

Page 5, Sec. A, Par. 3:

The last sentence of that paragraph describes a very large and important question about translation PGx evidence to clinical implications and to practice: *"Much of the valuable information about PGx that is available remains to be put to work."*

We think that the report should address this specific issue with a much more thorough investigation than is presently outlined in the draft report or in the specific recommendations. Uncovering the current and specific hindrances associated with this statement (which we believe to be true) will be important for the SACGHS to identify and make recommendations to resolve.

Page 5, Sec. B, Par. 1:

The statement regarding the challenges presented by PGx to regulators and the regulatory framework identifies an issue that is of great concern to the Coalition. The practical issues related to the acceleration of complex scientific knowledge and technological advancements will only continue to exacerbate the divide between innovators and the regulatory establishment.

While we agree with the recommendations in the report calling for continued and enhanced interaction between regulators and industry, we feel that the current forums for exchange are not sufficient. The issues related to capacity building, personnel training, current knowledge sharing, and technology demonstration are not adequately addressed by the regulatory agencies to permit full engagement which would enhance and most certainly expedite the advancement of innovative solutions.

Page 6, Sec. Regulation:

We recommend that "other agencies and regulatory bodies" be added to this sentence.

We believe that transparency and clear communications from regulatory groups such as CMS, CLIA, CDC, FTC, and NIH should be highlighted in this section.

Page 6, Sec. Coverage & Reimbursement:

P. O. Box 15519 ▪ Arlington, VA 22215-0519
1-800-226-9494
www.twentyfirstcenturymedicine.org

We recommend that "and diagnostics" be added to the end of the last sentence.

Page 6, Sec. C, Par. 1 & 2:

We recommend that the SACGHS consider calling for a gap analysis of what is currently taking place in the public sector for both basic and translational PGx research.

Page 8, Sec. C, Par. 2:

We recommend that the SACGHS consider providing more detailed report language around the concepts of "uniformed genomic data standards" and "standardized phenotypic data." We suggest that the report make a recommendation concerning a review of the infrastructure needs and similar considerations necessary to facilitate a standards platform for PGx data and reporting.

Page 11, Sec. 15, Part A:

The Coalition fully endorses the recommendation of instituting an "Interdepartmental Work Group" for PGx and for that group to be accountable to review and present periodic progress reports.

Page 16, Sec. B, Par. 2:

We recommend that the SACGHS consider expanding the report section concerning the collection and storage of biological specimens to facilitate biological correlative PGx studies using linked archival patient samples. These concepts should be linked with the sections for biobanking, adaptive clinical trials designs, PGx test validation, evidence-based PGx data creation, and post launch PGx monitoring.

Page 18, Sec. B, Par. 2:

The Herceptin example should be revised to reflect the recently extended clinical indication for use beyond metastatic breast cancer.

Page 18, Sec. B, Par. 4:

We recommend that the SACGHS consider providing more detailed report language around the concepts of "tracking the impact of PGx" and "providing dosing recommendations." The report should request that HHS delineate who and how these two specific activities should be conducted.

Page 19, Sec. C, Par. 2:

We recommend that the SACGHS consider providing more detailed report language around the concepts of "new methods of conducting clinical research" and link that to adaptive trials and biological correlative trial designs using archival samples.

Page 19, Sec. C, Par. 1:

P. O. Box 15519 ▪ Arlington, VA 22215-0519
1-800-226-9494
www.twentyfirstcenturymedicine.org

We recommend that the SACGHS consider expanding the report section concerning the statement suggesting the lack of application of available PGx information in prescribing. The SACGHS should explore this important issue and include some analysis and explanations for this circumstance.

Page 27, Sec. 1, Par. 2:

The Coalition endorses the concept framing in this final paragraph and we recommend that the SACGHS consider expanding the report section. We also suggest that HHS monitor these dynamics and respond accordingly over time.

Page 30, Recommendation 4A:

We recommend that the SACGHS request that HHS organize a formal FDA and stakeholder engagement program to create alternative regulatory pathways for just-in-time PGx tests introduction or retrospective review and clearance of laboratory developed tests to be linked to a previously approved therapeutic. This should include an analysis of the unique circumstances in phase III, phase IV, or post marketing situations, or in a drug rescue process.

Page 37, Recommendation 5D:

We recommend that "molecular diagnostic and diagnostic tools companies" be added to this recommendation as preferred partners for this effort to facilitate rapid PGx translation.

Page 51, Sec. 2, Par. 3:

We recommend that the SACGHS consider making the explicit request that FDA engage the stakeholders on clarifying a least burdensome approach to a co-development pathway and agency interactions. One of the challenges, for example, isthe logistical and communication challenge of interacting with multiple divisions involved in data review and clearance.

Page 55, Sec. B, Par. 4:

The report language should be corrected. The MammaPrint® assay was "cleared" not "approved" by FDA.

Page 56, Exhibit 3:

The report language should clarify that the Oncotype DX® assay is currently a CLIA-approved and CAP-accredited laboratory service, and has been since 2004.

The report language should clarify that the assay is currently covered and reimbursed by Medicare and is available for 140 million Americans under third party private insurance.

The report language should clarify that the purpose of the NCI's TAILORx Trial is to determine if patients with middle range recurrence scores on the Oncotype DX test (11-25) benefit from adjuvant chemotherapy added to hormonal therapy.

P. O. Box 15519 ▪ Arlington, VA 22215-0519
1-800-226-9494
www.twentyfirstcenturymedicine.org

21st centurymedicine

Page 61, Sec. A, Part 2:

The Coalition fully endorses the SACGHS recommendation that there should be a preventive services benefit category for Medicare beneficiaries to include PGx testing and diagnostic procedures.

Page 64, Sec. A, Part 2, Par. 1:

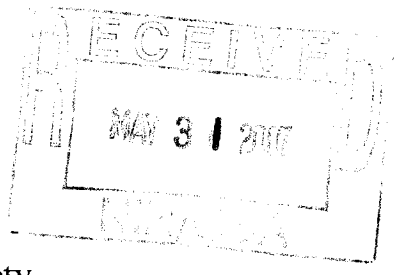
The Coalition agrees with the report's assessment concerning reimbursement challenges and uncertainty and its direct impact on investment, innovation, and PGx product development.

The Coalition believes that the unique attributes and value proposition of PGx diagnostic should be acknowledged in the report.

We recommend that the SACGHS consider providing more detailed report language around the concepts of "creating a special PGx" or "personalized medicine" product designation and making specific recommendations for a value-based reimbursement approach. The report should request that HHS pursue an incentive program for a value-based reimbursement approach for PGx products.

Sincerely,

Joseph Eyer
Administrator
Coalition for 21st Century Medicine
P. O. Box 15519
Arlington, VA 22215-0519
www.twentyfirstcenturymedicine.org



CONSUMER ACTION
www.consumer-action.org

Reed Tuckson M.D.
Chair, Secretary's Advisory Cmte. Genetics, Health & Society
NIH Office of Biotechnology Activities

Dr. Tuckson:

Consumer Action appreciates the opportunity to add its comments to the Secretary's Advisory Committee draft report, "Realizing the Promise of Pharmecogenomics: Opportunities and Challenges".

Consumer Action (www.consumer-action.org) is a national non-profit education and advocacy organization that has served consumers since 1971. Consumer Action (CA) serves consumers nationwide by advancing consumer rights in the fields of credit, banking, housing, privacy, insurance and utilities. CA offers many free services to consumers and communities. Consumer Action develops consumer education modules and multi-lingual materials for its network of more than 9,000 community based organizations. The modules include brochures in Chinese, English, Korean, Spanish and Vietnamese.

Consumer Action believes that all research activity that uses any identifiable health information should be required to have a *certificate of confidentiality*. Additionally, if research has any type of patient specific genetic information a certificate of confidentiality ought to be required. Even if the information is not identifiable today, as technology progresses, it may be in the future. When genetic information becomes part of a typical health record it could end up in many others' hands such as insurers, marketers, data brokers etc.

We would request that NIH reinstate a full time, independent privacy advocate to provide oversight. S/he would be responsible for creating a privacy impact assessment for each major project.

Lastly, we would support controlled data release arrangements with commitments to privacy and confidentiality *before* gaining access to any information.

Thank you for considering our recommendations.

Ruth Susswein
Deputy Director, National Priorities Consumer Action

ruth.susswein@consumer-action.org

www.consumer-action.org

www.lilly.com

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285
U.S.A.

Phone 317 276 2000

May 31st 2007

Comments to Draft Report

BY ELECTRONIC DELIVERY

Ms. Suzanne Goodwin
Secretary's Advisory Committee on Genetics, Health, and Society
National Institutes of Health, Office of Biotechnology Activities
Department of Health and Human Services
6705 Rockledge Drive, Room 750
Bethesda, MD 20892

RE: **Draft Report to the Secretary of Health and Human Services (HHS),** ***Realizing the Promise of Pharmacogenomics: Opportunities and Challenges***

The following attachment is a submission of comments to the above reference from Eli Lilly and Company (Lilly).

Lilly appreciates the opportunity to comment on the draft report, *Realizing the Promise of Pharmacogenomics.* We would be pleased to provide SACGHS any additional information or clarification of the comments and recommendations outlined in the attachment.

Sincerely,
ELI LILLY AND COMPANY

Jennifer L. Stotka, MD
Vice President
U.S. Regulatory Affairs
Eli Lilly and Company

Phone: (317) 276-1249
jlstotka@lilly.com

ELI LILLY AND COMPANY

Usha Srinivasan

Usha Srinivasan
Regulatory Scientist
U.S. Regulatory Affairs
Eli Lilly and Company

Phone: (317)433-0542
us@lilly.com

Attachment – Eli Lilly and Company

RE: Draft Report to the Secretary of Health and Human Services (HHS), *Realizing the Promise of Pharmacogenomics: Opportunities and Challenges*

Eli Lilly and Company (Lilly) appreciates the opportunity to provide comments to this draft report, which represents the challenges and promise of the emergent field of pharmacogenomics (PGx).

General Comments:
The report is comprehensive and well written providing a fairly accurate (the gaps are highlighted as comments and recommendations below) and objective summary of the challenges and promise of pharmacogenomics (PGx). It serves to both educate and evoke ideas from all players in drug development that may be using pharmacogenomics (PGx) to tailor or target indications. We feel the value of this type of report is in its timeliness and would like to see the next iteration published sooner than the projected timeframe. Policy (including standards, guidelines, and guidances) needs in this area are great and it is essential to build these in a timely manner to enable the utility of the innovation.

More basic research needs to be conducted and enabling tools developed to move to the next level in PGx. We have a long way to go in understanding the role of genomics in drug disposition beyond (the coding region polymorphisms in) cytochrome P450's, to other metabolizing enzymes, transporters and structural variations that play uncertain roles in drug responses.

Our comments below suggest six topics that the draft report should address more completely.

Section: Executive Summary B and C.
Lilly agrees with the recommendations made, pursuant to the challenges and key considerations (page 5, section B and page 6 section C). Lilly would like to highlight a few key points in the spirit of providing momentum for the changes to come. While data standards for PGx are being defined by consortia, data sharing and database interoperability should become an area of focus with efforts building on what is already available. This is an opportunity for HHS and FDA to create avenues to communicate information already available and lead by example on a couple of specific areas {in addition to everything listed on page 8, section 6 (A-D)}. There is already much information available on genomic factors that may be more meaningful predictors of drug response or risk than race and ethnicity. This needs to be communicated and be made accessible beyond changes to individual product labels.

Section II. D. Development of PGx Products.
The comments in this section implicitly provide justification for sponsors to collect PGx data on as many patients as possible in Phase III or even sooner in development. It might be possible that an analysis of efficacy measures in an entire patient population in the

Phase III trials does not yield statistical significance, but close evaluation of the PGx data along with the clinical data might identify a key biomarker that defines safety or efficacy for a targeted subset of the larger patient population that is exhibiting significant efficacy. What is necessary in this scenario is an FDA guidance document on retrospective validation of genomic biomarkers, including the questions, challenges and strategies for developing useful relationships to clinical outcomes. (S-J Wang, N Cohen, DA Katz, G.Ruano, PM Shaw and B.Spear. The Pharmacogenomics Journal (2006) 6, 82-88). NIH collaborations must be leveraged.

Along the same theme in Section III, there is a need to define clinical utility and clinical validity and what is considered by the FDA to be acceptable clinical utility.

Section II. G. Ethical, Legal and Social Issues in Research and Development
Lilly would like to emphasize that coded samples are critical in PGx research to correlate the genetic information with the clinical outcome to gain any value with respect to identifying the right patient for the drug. As long as strict control procedures are used with coded samples (as outlined in the draft consensus guideline ICH E15 Terminology in Pharmacogenomics), patient privacy is at minimal risk, and patients can eventually benefit from pharmacogenomic discoveries made through the use of coded samples. Privacy is important and patient privacy even more so, but some HIPAA restrictions may create a hurdle that could hinder innovation.

Section III. A. Gatekeepers – Industry
The release of FDA guidelines and concept papers is helpful to address the technical challenges in PGx, but does not directly address the broader policy issue of rewarding the risks that go along with PGx product development. While the report states that pharmaceutical companies may employ new financial strategies in order to adapt to smaller target markets, there is no mention of incentives for development. There are several approaches for adapting the pharmaceutical industry model to maintain revenue for R&D and innovation outside of the blockbuster business model. These include incentives such as expedited review, extended marketing exclusivity or other approaches that allow the pharmaceutical industry to recover development costs. Incentives have been highly successful in generating data for areas such as pediatric use. We recommend SACGHS engage stakeholders in exploring ideas for improving incentives and report their suggestions for broader input in the next release.

Section IV. B. Information Technology and PGx
Amongst other topics, the section discusses incorporation of clinical genomics data into patient Electronic Health Records (EHR). Most discussion, rightly so, focuses on integrating only the portions of raw genomic output that are relevant to clinical practice, since the physician at the point of patient care is considered to be the primary 'consumer' of the EHRs. However, increasingly, bioinformatics and clinical researchers from universities and pharmaceutical companies also utilize EHRs for their own research. This raises some special needs. For example, as the methods for analyzing and interpreting

genomic data become more sophisticated, there would be an increasing need to expose increasing amounts of 'raw' genomic data into EHRs and other clinical records. This would allow for better evidence tracing and secondary or future re-processing, as new analysis methodologies develop. This requires increased utilization of bioinformatics mark-ups (such as MAGE and BSML) by individual EHRs. Furthermore, from a researcher's perspective, the ability to combine EHR data from many patients (and merge associated raw clinical genomics data) would be of considerable benefit in developing genotype-phenotype relationships. In concert with this, we agree it would be important to develop clear policies restricting the use of genomic data from EHRs to scientific inquiry, and not allow this information to be used for other purposes (see Section II).

Section IV. C. Economic Implications of PGx

More discussion on the economics of PGx development would be helpful to provide a realistic assessment of the potential impact of PGx on healthcare. The hope of PGx is that it will lead to the development of drugs of greater value for patients. Although PGx will likely produce drugs with improved patient targeting, the cost to society may be higher to either cover the cost of investment in PGx, or because pricing will be higher (as has been the case with a number of recently developed cancer therapies).

It is difficult to create a compelling business case for technological innovation because the benefits are divided among fragmented players in the healthcare delivery system. While new technologies may improve the length and quality of life and be recognized as cost effective, they will increase cost of development in the short term and theoretically, total cost will increase if the healthcare delivery process is not modified to leverage the value from the innovation. The use of PGx technology investments by all stakeholders (industry, NIH, academia and FDA) needs to be aligned with the healthcare decision process and not be seen as a panacea to improve healthcare.

Conclusion:

Eli Lilly and Company appreciates the opportunity to comment on the draft report, *Realizing the Promise of Pharmacogenomics.* We would be pleased to provide SACGHS any additional information or clarification of the comments and recommendations outlined above.

UNIVERSITY OF MINNESOTA

Twin Cities Campus

Division of Environmental Health Sciences
School of Public Health

1260 Mayo Memorial Building
Mayo Mail Code (MMC) 807
420 Delaware St. SE
Minneapolis, MN 55455-0381
Phone: 612-624-2967
Fax: 612-626-4837
Electronic: tosca001@umn.edu
http://enhs.umn.edu

June 4, 2007

To: Reed V. Tuckson, MD
SACGHS Chair
c/o Suzanne Goodwin
goodwins@od.nih.gov
Re: Public comment on draft report, *Realizing the Promise of Pharmacogenomics: Opportunities and Challenges*

Dear SACGHS Members:

American scientists and science policy makers must recognize that the public is a key stakeholder of the thinking society, with particular interests, concerns and questions about science and technology innovations. Increasingly, science and technology intersect with people's ethical beliefs and values.

In order to address the new public of science, one-directional flow of information needs to be replaced by dialogue, engagement and participation. That means questioning some of the bland and often pejorative stereotypes of the public often held by some experts, discovering and respecting public values, and developing ways of communicating with the public more effectively.

There is often a condescending notion that public discussion is fine inasmuch as it is about understanding policy but when it comes to *formulating* policy, it is only expert opinion that should matter. We propose public involvement to be instrumental in the *formulation* of policy.

Within this context, and as members of "the public" and students currently enrolled in a three-week course in public health genomics as part of a Public Health Summer Institute at the University of Minnesota, we are responding to the SACGHS request for public comment on a draft report to

the Secretary of Health and Human Services, *Realizing the Promise of Pharmacogenomics: Opportunities and Challenge.*

In one of our recent class sessions, we enjoyed a thought-provoking two-hour presentation on pharmacogenomics. The comments below are drawn largely from that presentation together with a review of the key findings of a 2005 survey of 1,018 Americans, "Public Perception of Genomics/Genetic Testing," conducted by Cogent Research, and those sections of the SACGHS draft report relevant to Recommendations 11A. and 11B. on public education.

In light of these two SACGHS recommendations, we considered three additional questions:

- Do patients have the information they need to make educated treatment decisions based on PGx testing?
- In your view, is the above information (the two HHS brochures) sufficient to meet the goal of generating informed public education?

Are there strategies other than brochures—or more printed information that needs to be included in the SACGHS-recommended brochures (p. A13)—designed to (better) educate patients about PGx and the spectrum of ethical, legal and policy issues likely to be generated by PGx research?

Throughout our class discussions of pharmacogenomics and the dream of future pharmacogenomic research: personalized medicine, we were impressed by the complexity of the science which makes pharmacogenomics possible. At the same time, we were challenged to imagine how the scientifically-naïve layperson would react to being asked to contribute their tissue (blood, skin) to clinical research studies in an environment of scientific illiteracy, in general, in the U.S.

Even more importantly, we wondered how likely is it that patients suffering from adverse drug reactions (ADR) in this country (the fourth leading cause of death in the U.S.) would ever be able to comprehend the information they need to make educated treatment decisions based on pharmacogenomic testing?

Not very likely, we concluded.

This is especially true when one considers our already overburdened primary care physicians, those to whom patients turn for information. How are these health care professionals expected to comply with, for example, the issue of obtaining true informed consent from a patient when neither the caregiver nor the patient understand the social and ethical issues associated with—much less the science which lay behind—PGx technologies? What if, because of lack of information, a physician misses a test that "could" have changed things for the patient? Is (s) he vulnerable to the possibility of litigation? Is a "genetic educator" going to have be part of the new medical office staff of the future?

In our opinion, what is critically needed in this country is a constellation of "rational" public consultation processes which, themselves, are designed to educate and engage a broad spectrum of prospective patients, along with our health care providers, researchers and policy makers, in a constructive dialogue about the potential benefits, risks and limitations of, in this case, pharmacogenomic technologies. Ordinary citizens do not need to be scientists to understand the importance of pharmacogenomics to be part of the conversation about how society want to use these technologies for the common good.

How this public opinion is being solicited in the case of PGx is, in itself somewhat problematic because the pool of respondents will not be diverse. This makes the design of how public consultation is carried out even more important.

In that regard, we feel that there is a need to build a new platform for linking the public voice with the policy process, one that is rooted in the values of the public and contains the accepted measurements of good public policy (fairness, justice, equality, freedom, opportunity). This would require that the public, as stakeholders, evaluate the risks and opportunities of the application of a given technology (like PGx), and experts evaluate the relative likelihood that a given technology will deliver on its promises.

For example, in our opinion, a systematic methodology for any application of genomics technologies would have to include the following elements:

- An understanding of the science;

- An understanding of what the current policy governing the use of that technology means; or
- The direction(s) which future policy could (or needs to) take in the context of new applications—and social and ethical implications—of the technology (e.g. personalized medicine and genetic privacy).

Using this strategy, the quality of public input to public policy decision-making could become an effective partner to citizen-relevant policy making. Public consultation strategies that include public values in the policy making process occur in Europe. One of the most enduring is used by the Danish Board of Technology, an arm of the Ministry of Science, Technology and Development for more than two decades http://www.pantaneto.co.uk/issue6/andersenjaeger.htm. In spite of good intentions, however, benchmarks and best practices for similar public consultations in the United States are lacking.

Of course, there are many reasons for this.

The broad spectrum of the U.S. public, including the under-served and under-represented populations, low English language proficiency, low health literacy, seniors and varying education levels, together pose huge challenges to obtain "public comment" in a representative way. For example, how will we include a discussion of personalized medicine with the public when most American citizens have no real access to genomics-educated health care professionals?

While "education" alone is clearly an important part of any mechanism for informed citizenship, enacting social responsibility in a democracy requires more than education alone. It calls for clear articulation of community values that are likely to have an impact on policy options. It demands finding a way for ordinary citizens to work in partnership with technical and scientific experts to produce policy that expresses community values and use the best facts available.

In the U.S., "public consultation" is thought of primarily as "public education." Public consultation, as such, is rarely considered, and in the process, the policy process remains largely impervious to public values.

For genome science to move in socially responsible directions, ahead-of-the-curve practices different from those generally practiced in the U.S. are needed.

In the above context, we, the undersigned students enrolled in the three Public Health classes (PubH 7200 “Genomics in Public Health” and “Application of Genomics in Public Health, Parts I and II”) currently being taught in the School of Public Health at the University of Minnesota, respectfully offer the following with regard to draft recommendations 11A. and 11B. for SACGHS consideration:

Recommended Action Items

From the outset of any consultative process, public values **must** be sought from diverse groups using diverse means.

The outcomes of such a study would not only reflect the diverse makeup of the United States, but its very design will need to be informed by the active input of a broad array of American society. Studies should be designed to address two overarching issues: 1) to assess the feasibility and effectiveness of different approaches to public consultation in the U.S.; and 2) to generate a preliminary inventory of public understanding, attitudes and concerns across diverse communities.

This could be accomplished by establishing centers for that purpose at specific locations throughout the U.S. These centers could:

- Design multiple modes of public consultation as well as a way of bringing the data together;

- Design modes of public education that incorporate *different* kinds of strategies – visual arts, storytelling, performances, leaflets, Internet, public advertisements – to ensure that genomics becomes part of the public vocabulary;

- Educate teachers, physicians and community leaders about genomics and pharmacogenomics as these individuals can be conduits to large sectors of people;

- Make conscious efforts to reach diverse communities, under-served

- and under-represented populations with lower income, education and access to health care;

- Establish clear guidelines about how these communities can benefit from these studies from the outset and not as an afterthought;

- Incorporate the *unsolved* issues of genomics, such as in what way is the repository of genomic information going to be maintained? Who will have access? If there is private funding involved and any of it is for-profit, what happens to the people who participate in the trials? How will true-informed consent be gathered?

Using these approaches, the educational goals of "…engaging the public in a constructive dialogue" (Rec. 11A.) and "inform(ing) the public about the availability, benefits, risk and limitations of pharmacogenomic technologies" (Rec.11B.) will be met.

Instead of limiting HHS to use "…existing public consultation mechanisms to engage the public in a constructive dialogue (Rec. 11A)", a better approach might be to identify funding and issue a national call for proposals to explore a spectrum of public consultation practices to inform the design of a longitudinal cohort study of the potential benefits, risks and limitations of pharmacogenomic technologies.

How the public perspectives will be ultimately sought, collected and coded is, in itself, a study design challenge that needs to be addressed. Various Internet repositories and various real-time public meetings and forums all collectively have the potential to include groups whose voices might not be otherwise heard.

In her new book, "Designs on Nature: Science and Democracy in Europe and the United States," Sheila Jasanoff writes:

"Given the profundity of the challenges thus brought into public and policy debates, democratic theory in the era of the knowledge society must take on board the involvement of citizens in the production, use and interpretation of knowledge for public purposes.

There is a need to generate new approaches to the governance of science that can learn from past mistakes, cope with social complexity, and harness technological change for the common good."

In the above spirit, we respectfully submit this document for your consideration.

This letter was read and approved by the undersigned professors and students in the Public Health Genomics Course:

Greg Fowler, Ph.D.,
Course Instructor

Kristin Peterson Oehlke, MS,
Course Instructor

William A. Toscano, Ph.D.
Course Instructor

Students:

Bobbi Kostinec, M.D.
Davavani Chatterjea, Ph.D.
David McNamara,
Petrona Lee,
Rajan Shukla, MBBS
Colleen M. Kingsbury,
Tyler Johnson,
Gillian Gurley
Sue Clemmings

VIA ELECTRONIC TRANSMISSION

Email: goodwins@od.nih.gov

June 1, 2007

Chairman, Reed Tuckson, MD
Secretary's Advisory Committee on Genetics, Health, and Society
National Institutes of Health, Office of Biotechnology Activities
6705 Rockledge Drive, Suite 750
Bethesda, MD 20892

Dear Dr. Tuckson,

Thank you for the opportunity to comment on the draft report entitled *Realizing the Promise of Pharmacogenomics: Opportunities and Challenges*. Genetic Alliance commends the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) on your efforts in regard to this policy issue. Pharmacogenomics is a growing field that has the potential to improve patient outcomes while decreasing costs. Investment in this area will yield opportunities for Americans and those across the globe to proactively manage their health while providing a savings to healthcare systems as the cost of medical care rises.

Genetic Alliance includes more than 600 advocacy, research, and healthcare organizations that represent the interests of millions of individuals living with genetic conditions. We have a clear understanding of how pharmacogenomics affects healthcare consumers, especially those with chronic or rare disease. Consumer access to pharmacogenomics is vital so that immediate medical needs can be managed and future concerns can be addressed through research and the development of new treatments.

As the representative of many hundreds of organizations focused on rare conditions, we are especially supportive of pharmacogenomic products for smaller markets. Rare disease communities may have the most to benefit from pharmacogenomic technology and such incentives should be fully encouraged.

We strongly support efforts to engage the public on pharmacogenomics and its potential benefits for public health and individual disease management. As such, we are happy to submit the below comments and engage in further dialogue with the Committee on this matter.

General Comments:

Topic - BioMarkers:

We think that the report should make a more intentional delineation between the concepts of PGx as outlined in this report and Biomarkers generally. The report should consider contextualizing additional science and technologies (e.g,

phenotyping, invasive or virus typing, methylation, phosphorylation, intermediate or surrogate markers, gene – protein - antigen profiling, metabolomics, functional imaging , in vivo tagging, nanotechnologies, and applications of biostatistical data for personalization) that could have implications for PGx, therapeutic guidance, and personalized medicine. There seems to be a diverse set of public and private activities and expertise that is artificially segmented by these definitional distinctions or emerging disciplines (PGx vs. Biomarkers). Perhaps there should be more sharply defined and elucidated narrative for the variety of biomarker activities that could impact the direction and/or recommendations covered in this narrowly focused PGx report.

Topic - Value-based Reimbursement:

The report includes statements in support of differential reimbursement for PGx guided therapeutics but not specifically for the value creation produced by the diagnostic. We believe that the unique attributes of the diagnostic innovation in and of itself should be acknowledged in the report.

Page 64 Par 2: The report only touches on the concept of value-based reimbursement for diagnostics. We believe the report should include a much more comprehensive review of both the incentives and disincentives as they currently exist for PGx diagnostics.

We believe the report should include a specific recommendation for HHS to exploring new financial and process incentive models, premium pricing evaluation methods, public/private partnerships, specific workshops, and/or demonstration projects for designated PGx products.

Topic - Theranostics / Diagnostics Business Models:

The report presumes that there are no clear examples of successful business models for PGx testing and linked products. We suggest that there are currently a number of emerging business models that represent successful PGx businesses today.

Topic - Institute of Medicine / National Academy of Science (IOM / NAS):

We are struck by the fact that the report does not include any mention of the potential role and/or responsibility of the IOM to convene a topic roundtable to review and proposed solutions for any of the identified challenges. We suggest that the SACGHS consider recommending to HHS a specific set of priorities for IOM to consider.

Topic - Regulatory Science:

The report does not include any mention of the opportunities to apply the new science and technology of PGx to improve current regulatory practices. There should be some inclusion in the report of the need for HHS, NIH, or the various regulatory agencies to review, benchmark, and attempt to define current best practices in a transparent manner and to institute process efficiency improvements as a matter of modern regulatory science.

Topic - Adaptive Clinical Trials:

The concept of Biological Correlative Trials – prospectively defined protocols using archival patient samples from existing clinical trials, observational, and/or epidemiological studies should be considered as an important approach to develop evidence-based PGx associations.

Topic - FDA and CLIA Oversight and Regulation:

The report fails to acknowledge the historic trajectory of molecular diagnostics and laboratory medicine that is delivering PGx diagnostics from discovery research, verification, validation, clinical delivery, and reduction to practice. The evolution of the new PGx science and technology may warrant a reevaluation of a traditional regulatory schema. HHS should be asked to engage stakeholders to attempt to harmonize medical device regulation with CLIA quality systems regulations. It can be argued that these two existing regulatory systems are inadequate at the task of appropriate oversight

Page 28 Sec. 3 Par 3: Genetic Alliance believes that this section of the report mischaracterizes the FDA and CLIA regulatory situation and extent of data submission and review for laboratory developed tests.

Page 35 Sec. 1 Par 1: Genetic Alliance believes that this section of the report mischaracterizes the FDA and CLIA regulatory situation and extent of data submission and review for laboratory developed tests.

Page 54 Sec. B Par 4: Genetic Alliance believes that this section of the report while recognizes the current debate over appropriate regulation of PGx tests the report should also include the recognition that FDA's jurisdictional authority over laboratory developed tests has not been substantiated by a legal determination, court decision, or new legislative clarification.

Page 55 Sec. B Par 3: Genetic Alliance believes that the FDA's guidance on the ASR rule can be considered as very controversial and that the concept of "Single Moieties" may have significant unintended consequences to the practice of manufacturing and supplying high quality assay components. We believe that SACGHS be very careful about characterizing the recent FDA guidances as being helpful for industry and for providing regulatory certainty. SACGHS should review the public comments submitted to the open docket as well as the numerous articles published on this topic within legal and trade journals to completely understand the controversies for PGx testing.

Page 68 Sec 4: We believe that the CLIA oversight section is grossly mischaracterized and needs to be revised to more accurately reflect the oversight and regulatory functions of CLIA, third party accreditation organizations, and various state agencies. The report should revise the sections on CLIA review of analytical validity and reliability, clinical validity or utility for in-house developed laboratory tests. We recommend that SACGHS review the explicit and implicit requirements of CLIA Regulations 42 CFR § 493.1445 to accurately characterize the responsibilities for laboratories, laboratory directors, and clinical consultant for clinical validity, clinical utility, and professional laboratory medical standards for offering a clinical test.

Directed Comments:

Page 3. Sec A. Par 1:

Include an additional reference (reference#3) that provides the counter argument to the Royal Society's position in the British Medical Journal.

GS *Ginsburg, et al.*, The Future May be Closer Than You Think: A Response from the Personalized Medicine Coalition to the Royal Society's Report on Personalized Medicine. Journal of Personalized Medicine 2006 3(2)

Page 4. Sec A. Par 2:

Include an additional reference (reference#8) that provides an excellent example of a current and novel NIH trial design that employs a biomarker/genomics to stratify a heterogeneous patient population for breast cancer treatment selection. The National Cancer Institute's PACCT 1 Program Trial: TAILORx Breast Cancer Trial. (URL: http://www.cancer.gov/clinicaltrials/ECOG-PACCT-1)

Page 5. Sec A. Par 3:

The last sentence of that paragraph describes a very large and important question about translation PGx evidence to clinical implications and to practice.

Much of the valuable information about PGx that is available remains to be put to work.

We think that the report should address this specific issue with a much more thorough investigation than is presently outlined in the draft report or the specific recommendations. Uncovering the current and specific hindrances associated with this statement (which we believe to be true) will be important for the SACGHS to identify and make recommendations to resolve

Page 5. Sec B. Par 1:

The statement regarding the challenges presented by PGx to regulators and the regulatory framework is very real and is of great concern to Genetic Alliance. The practical issues related to the acceleration of complex scientific knowledge and technological advancements will only continue to exacerbate the divide between innovators and the regulatory establishment.

While we agree with the recommendations in the report calling for continued and enhanced interaction between regulators and industry we feel that the current forums for authentic exchange are not sufficient. The issues related to capacity building, personnel training, current knowledge sharing, and technology demonstration are not adequately incentives or rewarded by the regulatory agencies to permit full engagement which would enhance and most certainly expedite the advancement of innovative solutions.

Page 6. Sec. Regulation:

We recommend that "other agencies and regulatory bodies" be added to this sentence. We believe that transparency and clear communications from regulatory groups such as CMS, CLIA, CDC, FTC, and NIH should be highlighted in this section.

Page 6. Sec. Coverage & Reimbursement:

We recommend that "and diagnostics" be added to the end of the last sentence.

Page 6. Sec. C Par. 1 & 2:

We recommend that the SACHGS consider calling for a gap analysis of what is currently taking place in the public sector for both basic and translational PGx research.

Page 8. Sec. C Par. 2:

We recommend that the SACHGS consider providing more detailed report language around the concepts of "uniformed genomic data standards" and "standardized phenotypic data". We suggest that the report make a recommendation concerning a review of the infrastructure needs and similar considerations necessary to facilitate a standards platform for PGx data and reporting.

Page 11 Sec. 15 Part A:

Genetic Alliance fully endorses the recommendation of instituting an "Interdepartmental Work Group" for PGx and for that group to be accountable to review and present periodic progress reports.

Page 16 Sec. B Par 2:

We recommend that the SACHGS consider expanding the report section concerning the collection and storage of biological specimens to facilitate biological correlative PGx studies using linked archival patient samples. These concepts should be linked with the sections for biobanking, adaptive clinical trials designs, PGx test validation, evidence-based PGx data creation, and post launch PGx monitoring.

Page 18 Sec. B Par 2:

The Herceptin example should be revised to reflect the recently extended clinical indication for use beyond metastatic breast cancer.

Page 18 Sec. B Par 4:

We recommend that the SACHGS consider providing more detailed report language around the concepts of "tracking the impact of PGx" and "providing dosing recommendations". The report should request HHS to delineate who and how these two specific activities should be conducted.

Page 19 Sec. C Par 2:

We recommend that the SACHGS consider providing more detailed report language around the concepts of "new methods of conducting clinical research" and link that to adaptive trials and biological correlative trial designs using archival samples.

Page 19 Sec. C Par 1:

We recommend that the SACHGS consider expanding the report section concerning the statement suggesting the lack of application of available PGx information in prescribing. SACGHS should explore this important issue and include some analysis and explanations for this circumstance.

Page 27 Sec. 1 Par 2:

Genetic Alliance endorses the concept framing in this final paragraph and we recommend that the SACHGS consider expanding the report section and suggest that HHS monitor these dynamics and respond accordingly over time.

Page 30 Recommendation 4A:

We recommend that the SACHGS request that HHS organize a formal FDA and stakeholder engagement program to create alternative regulatory pathways for just-in-time PGx tests introduction or retrospective review and clearance of laboratory developed tests to be linked to a previously approved therapeutic; to include analysis of the unique circumstances in phase III, phase IV or post marketing situations, or in a drug rescue process.

Page 37 Recommendation 5D:

We recommend that "molecular diagnostic and diagnostic tools companies" be added to this recommendation as preferred partners for this effort to facilitate rapid PGx translation.

Page 51 Sec. 2 Par 3:

We recommend that the SACHGS consider making the explicit request that FDA engage the stakeholders on clarifying a least burdensome approach to a co-development pathway and agency interactions which currently includes the logistical and communication challenges of interacting with multiple divisions involved in data review and clearance.

Page 55 Sec. B Par 4:

The report language should be corrected. The MammaPrint® assay was "cleared" not "approved" by the FDA.

Page 56 Exhibit 3:

The report language should clarify that the Oncotype DX® assay is currently an approved CLIA and CAP accredited laboratory service since 2004.
The report language should clarify that the assay is currently covered and reimbursed by Medicare and is available for 140 million Americans under third party private insurance.

The report language should clarify that the purpose of the NCI's TAILORx Trial is to refine and improve the clinical utility of the Oncotype DX test and determine if patients with middle range recurrence scores on the Oncotype DX test (11-25) benefit from adjuvant chemotherapy added to hormonal therapy.

Page 61 Sec. A Part 2:

Genetic Alliance fully endorses the SACGHS recommendation that there should be a preventive services benefit category for Medicare beneficiaries to include PGx testing and diagnostic procedures.

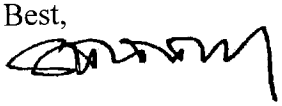
Page 64 Sec. A Part 2 Par 1:

Genetic Alliance agrees with the reports assessment concerning reimbursement challenges and uncertainty and its direct impact on investment, innovation, and PGx product development.

Genetic Alliance believes that the unique attributes and value proposition of PGx diagnostic should be acknowledged in the report.

We recommend that the SACHGS consider providing more detailed report language around the concepts of "creating a special PGx" or "personalized medicine" product designation and perhaps making specific recommendations for a value-based reimbursement approach. The report should request HHS to pursue an incentive program for value-based reimbursement approach for PGx products.

Best,



Sharon F. Terry, MA
President and CEO
Genetic Alliance
4301 Connecticut Avenue, NW
Suite 404
Washington, DC 20008
202.966.5557
sterry@geneticalliance.org

JOHNS HOPKINS
UNIVERSITY

Genetics and Public Policy Center

Berman Bioethics Institute
1717 Massachusetts Ave., N.W., Suite 530
Washington D.C. 20036
202-663-5971 / Fax 202-663-5992
www.DNApolicy.org

June 1, 2007

Reed V. Tuckson, MD
Chair
Secretary's Advisory Committee on Genetics, Health, and Society
NIH Office of Biotechnology Activities
6705 Rockledge Drive, Suite 750
Bethesda, MD 20892

Dear Dr. Tuckson:

On behalf of the Genetics and Public Policy Center, we are submitting comments in response to the Committee's Draft Report, *Realizing the Promise of Pharmacogenomics: Opportunities and Challenges.* As requested, these comments respond to the specific questions posed by the Committee concerning the accuracy and completeness of the report as well as whether a sufficient range of perspectives was addressed.

With respect to accuracy, the report incorrectly states that a "physician prescription is required for a clinical laboratory to perform an in house test" (p. 52). In fact, whether a laboratory can test a patient sample or return a test result to a patient without a physician (or other provider) prescription is a question of state law. Currently about half the states permit direct ordering of genetic tests by consumers. According to FDA's regulations for analyte specific reagents (ASRs), laboratory developed tests that use ASRs may be ordered only by "physicians and other persons authorized by applicable State law to order such tests." Thus, if state law permits direct ordering, FDA law does not prohibit it. Additionally, as a practical matter, this provision has not been the subject of active FDA enforcement, and the number of genetic tests offered directly to consumers, including PGx tests for which clinical validity or utility have not been established, continues to expand.

With respect to completeness, the report is quite comprehensive in many respects. It is, however, glaringly incomplete in its discussion of the current inadequacies of the Centers for Medicare and Medicaid Services (CMS) in administering the Clinical Laboratory Improvement Amendments of 1988 (CLIA), and the impact of those inadequacies on the success of PGx.

The report correctly notes that the adoption of PGx technologies will hinge on the availability of evidence of their analytic validity (p. 37). CMS, through CLIA, is the agency designated by HHS to ensure the analytic validity of tests. The report incorrectly states that CLIA applies only to in house developed tests (p. 68). In fact, CLIA's scope extends to *all* clinical laboratories, including those using FDA-approved test kits.[1]

---

[1] 42 U.S.C. 263a.

The purpose of CLIA is to ensure the quality of laboratory performance regardless of the testing methodology used.

While the report correctly notes that genetics is not recognized as a CLIA specialty area (p. 68), it fails to discuss the significant detrimental impact of this omission on PGx. Lack of a specialty area means that there are no specific quality control, personnel, or proficiency testing regulations for genetic testing laboratories, including those performing PGx testing.[2] A survey of genetic testing laboratory directors conducted by the Genetics and Public Policy Center in 2006 reveals the negative consequences of not requiring proficiency testing on genetic testing laboratory performance.[3]

While the report makes specific recommendations for increased oversight by FDA and other agencies, it makes no recommendations for CMS with respect to CLIA. Nor does it mention that two previous government advisory committees, including this Committee's predecessor, have recommended that CMS strengthen its oversight of genetic testing laboratories under CLIA.[4] Nor does it acknowledge the overwhelming support for the creation of a genetic testing specialty that has been expressed by a variety of stakeholders, including clinical laboratories, the medical device industry, professional organizations, and patient advocates.[5]

We therefore strongly recommend that the report explore more fully the consequences of the lack of a genetic testing specialty under CLIA,[6] and that it make specific recommendations for strengthened genetic testing oversight by CMS.

Thank you for the opportunity to provide these comments.

Sincerely,

Kathy Hudson

Kathy Hudson, PhD
Director

Gail Javitt

Gail Javitt, JD, MPH
Law and Policy Director

---

[2] Javitt, G., Hudson, K. 2007. The right prescription for personalized genetic medicine. Personalized Medicine 4(2): 115-118.
[3] Hudson K., Murphy, J., Kaufman, D., Javitt, G., Katsanis, S., Scott, J. 2006. Oversight of US genetic testing laboratories. Nature Biotechnology 24 (9): 1083-1090.
[4] Secretary's Advisory Committee on Genetic Testing 2000. Enhancing the Oversight of Genetic Tests: Recommendations of the SACGT; Holtzman, N., Watson, M. eds. 1997. Promoting Safe and Effective Genetic Testing in the United States: Final Report of the Task Force on Genetic Testing.
[5] Terry, Sharon et al. pers. comm. to Mark McClellan, June 6, 2006; Reproductive Health Technologies Project et al. pers. comm. to Mark McClellan, July 13, 2006.
[6] Javitt, G., Hudson, K. 2006. Public Health at Risk: Failures in Oversight of Genetic Testing Laboratories, Genetics and Public Policy Center, Washington, DC.

genzyme

Genzyme Corporation
[illegible] Kendall Street
Cambridge MA 02142
T 617-252-7500

June 1, 2007

Reed V. Tuckson, MD,
Chair, Secretary's Advisory Committee on Genetics, Health and Society
Via email to Suzanne Goodwin at goodwins@od.nih.gov

RE: Realizing the Promise of Pharmacogenomics-*Draft Report, March 23, 2007*

Dear Dr. Tuckson:

As a leader in understanding genetic-based disorders and in developing both tests and therapeutics for such disorders, Genzyme Corporation is in a unique position to comment on this Report. Genzyme's corporate infrastructure includes a Diagnostics business unit and the Genzyme Genetics laboratory services business, allowing the corporation a comprehensive and unique view of the personalized medicine approach to therapy. Genzyme has differentiated its product offerings based on our understanding of particular diseases and the relationship of diagnostic test results to patient response. We also have considerable experience in studying rare genetic disorders and small patient populations. We successfully have launched therapies for four rare genetic disorders and provide diagnostics testing to identify those patients. Recently, Genzyme has expanded its research and development efforts in oncology and pathology. It also has a smaller business unit, Analytical Services within Genzyme Genetics, which provides contract research and development for pharmacogenomic and other testing services for the pharmaceutical, biotech and medical devices industry.

According to page 20:
"The purpose of this report is to explore the opportunities for PGx to advance the development of diagnostic, therapeutic, and preventive strategies to improve health and to identify challenges to the integration and application of PGx to clinical practice and public health. The report addresses the current and evolving environment for PGx and its potential to inform the decisions of clinicians, policymakers and other stakeholders. It is intended to provide policy focused background information on PGx to help frame recommendations to the Secretary and other policy-makers and stakeholders."

In general, Genzyme believes the draft report provides a very comprehensive presentation of the policy issues raised by the use of genetic technologies and their integration into clinical practice. We fully agree that the emerging field of pharmacogenomics holds great promise to redirect the healthcare paradigm to personalized medicine and, as such, is a powerful tool to improve healthcare. SACGHS specifically asked for comment on whether the draft report recommendations are specific enough to prompt needed action. One area where there could be more specific recommendations is the section(s) related to the challenges presented by the current coverage and reimbursement of genetic tests. SACGHS released a report in February 2006 on the "Coverage and Reimbursement of Genetic Tests and Services," which found that "significant barriers and unmet data needs are limiting appropriate access and clinical integration" of genetic test (including Pharmacogenomic) services. We believe these barriers continue to impede progress, and that more attention and specificity should be included in the draft report. New approaches to provide economic incentives and eliminate disincentives for the adoption of approaches to genetic test services should be a high priority of the Federal government. Reimbursement and projected utilization of the tests and accompanying return on investment are a key concern for test developers. The life cycle of tests and drugs are disparate and further complicate the co-development of PGX tests.

Another area we believe the report can be more specific is the significant challenge of defining clinical validity and utility of a PGx test. The complexities of the biological processes and confounding factors make it difficult to accept the definitions proposed in this report. Directly relating the clinical validity and utility of the test to improved patient outcomes is implied throughout despite the discussions of the challenges involved. We include specific suggestions later in this comment to improve the report.

Further, the recommendations around the facilitation of gathering of the evidence base to assess utility are contingent on ideal, large population-, observational trials and/or the classic randomized controlled trials which may not be suitable for the personalized medicine approach that pharmacogenomic tests offer.

The following are specific comments (both substantive and editorial):

P. 3 Executive Summary, A. Promise of PGx, first paragraph. We recommend adding a reference for the "use of warfarin for those at risk of harmful blood clots" sentence.

P. 7, top of page, last sentence before section 3. We recommend that the following edits be made: End the last sentence as "..efforts at CDC to develop point-of-care diagnostic tests." Then add "An example of this is the development effort to rapidly detect human cases of H5N1 avian influenza." The existing sentence implies that the only point-of-care opportunity currently in development is in Avian flu.

P. 9, section 7, Protection of Personal Data, last sentence. We recommend the following edits: Delete "may be" and replace with "will be." There may be good examples of specific groups having better IT protections of sensitive genetic/genomic/clinical information, but we believe the general consensus is that this is still an area where more work needs to be applied in establishing a uniform code of conduct/protection.

P. 17, Section B, Complexity of the Science. We recommend that the section focus on the complex science behind PGx, rather than including application and utility examples with comments. We believe complexity relates to the vast numbers of SNPs, the HAPs, relating these to an outcome (ADR or beneficial response), cataloging and retrieving the relevant information from the potential mountains of data (from Whole Genome Data). Additionally, **third paragraph**, this general statement is repeated from page 14 and is repeated again in subsequent sections, generally conveying the same information. **Fourth Paragraph and similar illustrations**: These would be better as Exhibit boxes as examples of how these tests are being used. The document inconsistently provides examples as Exhibits or leaves them in the text as separate vignettes. We recommend that one or the other should be chosen and used throughout.

P. 18 Section C This section is better described as the "Challenges to PGx as a tool in aiding Clinical decision making".

P. 21, A. Basic Research, Sentence beginning "SNPs are inherited..." We recommend inserting "generally", to read "SNPs are ***generally*** inherited in blocks", as those blocks can vary between individuals and groups and the clinical utility of a "block" will need to be established in each case.

P. 24, top of the page, Paragraph "As described in Section..." the Section should be "F" not "C" as noted.

P. 27. On this page, the intended use or utility of PGx tests is explained: This explanation should be used consistently throughout the report. It states: "Genetic testing originated, and continues to

be used primarily, to determine the risk of developing a genetic-based condition or disease. PGx testing is a particular form of genetic testing that is used to inform therapeutic decisions, including whether to use particular drugs and in what doses."

In several locations in the document, the challenge of identifying an appropriate dose for an individual patient based on a PGx result is discussed. It should be clarified that the PGx test can identify that modification to a standard dose is required/needed, but the test result does not include the drug dose. This is closely related to attempting to define clinical utility of the PGx test, in the context of broadly varying patient demographics (weight, overall health and other drugs patient is taking).

P, 32 Subsection 6. This paragraph begins by implying that the Orphan Drug legislation may be a potential incentive/route to the development of PGx tests if the end result is a small target population, but then points out that it could end in eroding the goal of the OD Act and may result in more scrutiny by the FDA. The document may be strengthened by pointing out that separate legislative incentives may be needed to address the use of PGx instead of risking the erosion or further regulation of Orphan Drug beyond its intended purpose.

P. 33 There is background information given in relation to PGx and small target populations. However the pros and cons of the "orphan" approach provided by law to devices require further development. Clearly, the advantages, protections and incentives afforded to devices are considerably inferior to the provision the law affords to drugs. The statement: "Policy options such as expanding the criteria for the Orphan Drug Act to include PGx tests, or raising the population threshold for an orphan device, have been suggested to assure available treatment options for all genomic-based populations" is misleading as to the complexity of implementation as significant new legislation would be required. Humanitarian Use Designation and Exemption provided by current law to devices is not a clear incentive and, some would say, an actual disincentive.

P, 34, Subsection 1. Add "Analytic Validity" to the Heading and then break each of the heading topics out into their own discussion as each poses a challenge.

P. 34–37 The full paragraph at the top of the page describes the challenges facing stakeholders in discerning the clinical utility of a PGx test. However, the section immediately following is inconsistent with this paragraph. In the Section titled "Clinical Validity and Clinical Utility," it uses definitions of these terms not generally accepted by industry, academia or professional societies. Clinical utility should not be defined as to the accuracy of which a test predicts clinical outcomes. As stated in the paragraph at the top of the page, too many factors post test results can confound the relationship to outcome. Also the statement: "Assessing the actual clinical validity and utility of a test in practice should occur while researchers are measuring its analytic validity" is not in keeping with internationally recognized good clinical practice regulations. The analytical validation should always be completed before entering into clinical trials. Further discussion on pages 35 and 36 illustrate the challenges of providing criteria to be used in assessing clinical validity and utility. Different stakeholders have different expectations as to the demonstration of utility.

A number of professional societies, (CLSI, OECD, NACB, ICH and others) have discussed defining clinical validity and clinical utility, but no consensus has been reached.

P. 35. Footnote, #214 and 215 refer to the same study. 215 should be "ibid".

P. 37 Section 2. A reference is needed for AHRQ, as the data from that group is said to be released and therefore should be cited.

P. 38. We recommend the following edit: begin the first paragraph as " Another example is the evidence report published in November..."

P. 37. Recommendation 5A should have increased emphasis on the need for new tools, including study designs and levels of evidence in the different clinical contexts.

P. 37. Recommendation 5C Making data publicly available is problematic for test developers as there is no exclusivity or typically little or no patent protections. In fact, the public display of data will nullify any IP that may be patented. This is further discussed on p. 40 but seems to be ignored in this recommendation.

P. 46-47 Exhibit 2. The case of BiDil. We do not believe that the final comments of this Exhibit about stock price are relevant to the discussion of population stratification and race, unless it is included as an example of the negative repercussions that can be associated with targeting a therapeutic to one racial group as opposed to individuals who have a particular genetic signature relevant to the therapeutic.

P. 55, Fifth paragraph, Sentence beginning "MammaPrint, developed by company in the Netherlands..." We recommend that the omitted name of the company be restored, or the sentence be changed accordingly.

P. 59. The quote from Rawson is critical to understand why PGx test developers are slow to jump on the bandwagon and it should be emphasized (or at least given more prominence.

P. 66 Second paragraph, We recommend the following edit: Change to read "current examples of payer" as more than one example is given CYP2D6 and UGT1A1 by two different technology platforms.

P. 77. Recommendation 10 D is problematic in that the information on analytical and clinical validity already appears on IVD labeling per regulation.(21 CFR 809.10). For lab developed tests, the laboratory director of a high complexity laboratory – the only type of lab where genetic testing can be performed - is responsible for the overall operation and administration of the laboratory. CLIA regulations under 42 CFR § 493.1445(e) explicitly require the laboratory director to ensure that selected test methodologies are capable of providing the quality of results required for patient care. Implicit in this responsibility is the clear regulatory imperative to choose medically relevant test methodologies that have an effective clinical purpose—otherwise those methodologies could not be said to be "required for patient care." The laboratory director also is responsible for the employment of personnel who are competent to perform test procedures, record and report test results promptly, accurately and proficiently, and for assuring compliance with the applicable regulations. See 42 CFR § 493.1445.

CLIA also requires the laboratory to have a clinical consultant, who "must be qualified to consult with and render opinions to the laboratory's clients concerning the diagnosis, treatment and management of patient care." See 42 CFR § 493.1445. The responsibilities of the clinical consultant are to provide information about the "appropriateness" and "interpretation" of the test results.

Furthermore, CLIA makes the laboratory director responsible for ensuring that the ordering physician can properly interpret results by requiring the laboratory to include pertinent interpretive information in the reports and make consultation available to its clients regarding the quality of the test results and their interpretation. The CLIA regulations thus clearly require that a test have both clinical validity and transparency by requiring the laboratory director to select clinically relevant tests and provide clinical interpretation for those tests.

The determination of whether a test has sufficient clinical utility to be offered is one that should be made by the laboratory director in the exercise of his or her professional judgment, as part of his or her responsibility under CLIA to ensure that selected test methodologies are capable of providing the quality of results required for patient care.

We believe that CMS could amend the Interpretive Guidelines for Laboratories, which provide insight to laboratories and inspectors regarding CMS' responsibility for clinical validity and utility. Changes to the Interpretive Guidelines could include some or all of the following clarifications:

- The Laboratory Director of the clinical laboratory is responsible for ensuring that all tests offered by the laboratory are clinically relevant and based upon sound science.
- A test would be deemed to be clinically relevant if its use is well established in clinical practice, described in medical textbooks, or supported by medical guidelines or peer-reviewed literature.

Genzyme believes the discussion above also negates the draft report finding, starting on the bottom of page 54, that there is a double standard between FDA-approved tests and laboratory-developed tests in terms of the requirement to demonstrate clinical validity.

As stated before, labeling of dosing information cannot and should not be the responsibility of the test developer or laboratory director.. The patient's physician is the only one with sufficient knowledge of the patient, the disease/or condition under consideration and the environmental influences to make recommendation on dose or drug selection.

P. 97. Reimbursement We believe that this section does not provide the most adequate summarization of the consideration for advancing PGx as a tool and would be strengthened by replacing the current text with the 2006 *Coverage and Reimbursement of Genetic Tests and Services* report. In this report, SACGHS recommended that the Secretary of HHS convene a group of experts to review the evidence on a genetic test's analytical and clinical validity and clinical utility in order to identify areas of adequacy and inadequacy. Establishing causal effects of diagnostics, particularly on health outcomes, can be challenging and sometimes impractical, as various factors (e.g., use of multiple diagnostics, physicians' desire to rule out conditions and multiple treatment options) can confound these downstream effects.

Genzyme appreciates the opportunity to submit these comments and the opportunity afforded Genzyme for public comment at the SACGHS Committee meetings. We would welcome the opportunity to provide any clarifying information to ensure that pharmacogenomic tests can be effectively used to improve healthcare delivery.

Sincerely,

Robert E. Yocher, RAC
Vice President, Regulatory Affairs and
Corporate Quality Compliance
Genzyme Corporation

Response from:	**GlaxoSmithKline Draft 2 May 11 2007**
To:	**Reed V. Tuckson MD, SACGHS Chair**
Topic:	**Secretary's Advisory Committee on Genetics, Health and Society: Realizing the Promise of Pharmacogenomics: Opportunities and Challenges**

GlaxoSmithKline (GSK) is a research-based pharmaceutical company with the mission to improve the quality of human life by enabling people to do more, feel better and live longer. This mission gives us the purpose to develop innovative medicines and products that help millions of people around the world. Pharmacogenomic/pharmacogenetic (PGx) research is an integral component of the company research and development strategy, and the potential of genetic data to help develop safer and more effective medicines is explored across R&D. GSK welcomes the opportunity to comment on the SACGHS report.

GSK is of the opinion that PGx research holds significant potential for improving the productivity of the drug development pipeline and increasing the safety and effectiveness of drugs in patients for a wide range of diseases. GSK therefore encourages SACGHS to support the scientific research and clinical development that is critical to securing the evidence base upon which this field can progress.

The GSK response to the SACHGS consultation is structured as follows :

- The questions specifically raised by SACGHS on issues of accuracy, completeness, range of perspectives, level of detail, strategies, Federal priorities and related initiatives.
- The 15 SACGHS Recommendations.

GSK would be pleased to provide further input as required and to participate in key activities resulting from the SACGHS report.

Allen D. Roses MD
Senior Vice President Pharmacogenetics
GlaxoSmithKline
Five Moore Drive, 5-5616
Research Triangle Park, NC 27709, USA

GSK FEEDBACK ON SPECIFIC QUESTIONS RAISED BY SACGHS

Are the discussions of topics and issues accurate and complete?

The report is a comprehensive compilation of issues and perspectives fairly well covered in the published literature and in a variety of public fora. In this regard, the report is a useful, consolidated reference on PGx. It also methodically chronicles the checkpoints for new therapies from research laboratory to regulatory review to clinical medicine to reimbursement. What is missing from the report is the Committee's insight and expert guidance on how (or perhaps whether) to steer nascent PGx science and technologies to benefit health care. The SACGHS is a blue ribbon committee of experts, supported by a wide range of government resources, yet the draft report is largely a map of the potential hurdles with no informative or suggested path over them.

A broader input from the pharmaceutical / biotech industry, which has pioneered many of the advances in PGx to date, also appears to be missing.

Have any significant opportunities, challenges, or other issues been missed?

The report should be expanded regarding the Committee's expert views on the justification for PGx. Does the Committee believe there is sufficiently compelling justification for PGx in health care so that the litany of items identified (e.g., health professional education, potential disparities in care, legal liability) are perceived as issues to be managed rather than barriers to progressing PGx? Virtually all significant therapeutic advancements (e.g., imaging technologies, implants, and micro-surgical techniques) faced similar unknowns but the positives were deemed to outweigh the negatives so that the health care "system" adapted to incorporate them. The report is neutral on whether PGx should be a health care investment priority for HHS. GSK encourages SACGHS to support the scientific research and clinical development that is critical to securing the evidence base upon which this field can progress and healthcare decisions made.

One point that is mentioned in the report, but not given adequate consideration, is the anticipated role for PGx in reducing pharmaceutical R&D attrition. Most reasonable persons do not believe that all needed medicines have been discovered. Accordingly, attention must be paid to the functionality and productivity of processes for discovering and developing new therapies. Currently the R&D costs for a new chemical entity are nearing $1 Billion. Roughly fifty-percent of new drugs fail during the lengthy, costly Phase 3 of development. Approximately 3 out of 10 marketed drugs recoup their R&D costs. The current R&D model is therefore facing a number

of critical hurdles that negatively impact business economics. Organisations with drug discovery expertise, e.g., NIH, FDA and the pharmaceutical industry, contend that PGx will improve our ability to identify better molecules and how best to progress them through development. The report doesn't adequately address the Committee's views on whether this PGx rationale is persuasive.

A significant missed opportunity is the Committee's ability to provide the Secretary of HHS with direction and prioritization of government- conducted and/or sponsored PGx research. Currently, over 50% of prescriptions in the US are filled with generic products. This percentage is expected to exceed 65% within the next few years as a significant number of widely-used innovator products go off patent. ["Obstacles to Generic Drugs Criticized," Washington Post, Apr. 19, 2006, Page A06.]. There will be no meaningful private sector R&D for these products. Rather than the somewhat nebulous research recommendations (1-3) for NIH, the Committee should consider whether NIH might commit its research acumen and collaboration skills to progress PGx for generic products (as per The Department of Health in the United Kingdom). If NIH were able to improve the benefit: risk profiles for some of these medicines, the health care impact (improved patient outcomes and cost-savings) could be appreciable.

It is recognized that the focus of the Committee is on provision of healthcare in the US. However, the majority of the issues discussed are pertinent to the potential of utilising PGx knowledge in global pharmaceutical development, and healthcare provision in many countries. The SACGHS report makes no reference to key activities outside the US. The report should include a section discussing international PGx research and applications, and seek to promote a framework conducive to global collaboration in research, development and utilisation. A practical example of this would be SACHGS endorsement of the proposed ICH definitions for genomic biomarkers, pharmacogenomics, pharmacogenetics, genomic data and sample coding practices (http://www.ich.org/LOB/media/MEDIA3383.pdf).

Does the draft report adequately describe the range of perspectives on the issues?

The report is thorough and reasonably balanced on most issues. A few issues, Economic Implications of PGx (page 86) and Liability Considerations for Health Care Providers (page 93) lack objectivity. On page 87, the estimated annual cost of therapy with Herceptin® is cited to support that assertion that PGx, like other new technologies, is likely to increase health care costs. Herceptin® is a complex monoclonal antibody indicated for HER2 positive breast cancer in both metastatic

and adjuvant settings. As a rule, monoclonal antibodies are exceptionally expensive (resources, time and money) to discover, develop and manufacture on a commercial scale. These factors, not necessarily the fact it is a targeted therapy for certain breast cancer patients, affect treatment costs. Oncology therapies tend to be among the most costly, and citing an oncology example as a cost benchmark for PGx is misleading.

The report's discussion on Liability Considerations for Health Care Providers (pp 93-94) is overly pessimistic. Clinical medicine would never advance if health care providers are paralyzed by the fear of liability. To the extent that PGx can assist prescribers and their patients in making more informed risk-benefit decisions, bad outcomes (in the health care and legal contexts) can potentially be avoided. Health care professionals will need to understand and use PGx information appropriately and consistent with applicable standards of care that will evolve - as they have with other advances in medicine. This liability section and the discussion on the economic implications of PGx appear to implicate PGx for pre-existing challenges to provision of healthcare in the US.

Are the draft recommendations specific enough?

The fact that one of the Committee's recommendations is to form a work group to review the recommendations and determine whether and how to implement them is suggestive that more focus and direction are warranted. Each recommendation should be reviewed with an eye to guiding HHS on which issues, with actionable steps, need attention in the near-term versus issues that need to be addressed once there is a sufficient number of PGx examples upon which to make informed public/health policy decisions. For example, recommendation 5 states: "HHS should provide resources to identify and address evidentiary gaps in the analytic validity, clinical validity, clinical utility and cost-effectiveness of PGx." These parameters will vary among PGx tests and will be influenced by what marker(s) are being measured and what purpose the test result will serve. If the test is to predict the likelihood of a serious adverse event, the test specifications will be very different than a test used to select patients likely to respond efficaciously to a medicine. Because PGx is still very much in the formative stages, a useful recommendation would be to advise HHS to grant sponsors of PGx drugs and tests early and often access to PGx experts in regulatory authorities so that agreement can be reached on data requirement, labelling and clinical use.

Which draft recommendations should be of highest priority for the Federal government to address?

PGx data should be construed as a component of a patient's medical information. The Committee's recommendations for modernizing and optimizing the management and utilization of all medical information should be priorities for HHS (recommendations 6, 7, 12). These measures are actionable now and will benefit health care in the US independent of how quickly PGx transitions into mainstream clinical practice.

GSK FEEDBACK ON 15 SACGHS RECOMMENDATIONS

1) Basic Research

The potential application of PGx to healthcare improvement will only be realised if pertinent research data is first generated and accepted in both the private and public sectors.

As with all fields of innovation, accumulation of knowledge will be constrained if exploration is focussed purely on areas with existing data and *a priori* assumptions. Basic PGx research should therefore not focus on a specific technology, nor merely on known '*biochemical pathways associate with drug metabolism and drug action*' but in some instances involve genome-wide exploration to identify novel PGx markers associated with drug response. Furthermore, the application of markers e.g. SNP profiles, to drug development and ultimately prescribing, should not be contingent upon a complete understanding of the biological pathways involved. Any requirement of this nature would be in excess of that required for other therapeutic interventions and would therefore pose an unwarranted hurdle to the implementation of PGx.

As drug safety is a core component in the assessment of a drug's risk benefit: ratio, the NIH should sponsor/support research into adverse events which are common to a number of drug classes e.g. hepatotoxicity, arrhythmias, or hypersensitivity. Identifying biomarkers that predict susceptibility to adverse events could have a substantial positive impact on health care costs. In addition, research into the frequency of specific medical conditions within a disease population would be helpful in identifying if an adverse event is a real drug-related safety signal. Possible examples include arrhythmias in COPD and ischemic colitis in IBD. More consistent standards for defining/diagnosing adverse events may also prove useful.

2) Translational Research

Translational research is integral to the conversion of PGx scientific knowledge into patient healthcare benefits. HHS agencies are in key positions to identify and address potential hurdles to the acceptance of PGx into clinical practice.

The Committee should consider whether NIH might commit its research acumen and collaboration skills to progress PGx for generic products (as per The Department of Health in the United Kingdom). If NIH were able to improve the benefit: risk profiles for some of these medicines, the health care impact (improved patient outcomes and cost-savings) could be appreciable.

Organisations in both the public (e.g. CDC) and private sector (pharmaceutical, diagnostic companies and service providers) have for several years worked successfully on the issue of increasing the capacity and reducing the cost of genotyping. Any isolated activity by NIH to address these issues is likely to result in unnecessary expenditure and duplication and should therefore be conducted in partnership with other technology stakeholders. HHS agencies however are in a key position to facilitate the translation of PGx information into healthcare provision via activities such as laboratory standards.

3) Clinical Trial Design

Establishment of the Voluntary Genomic Data Submission (VGDS) framework by the FDA has facilitated the discussion with pharmaceutical sponsors on the application of PGx information to drug development, including the design of clinical trial programmes, labelling and clinical use. It is recommended that NIH sponsored studies also take advantage of this engagement opportunity to ensure consistency of standards in data that may impact drug prescribing.

GSK supports the proposal that NIH sponsored studies directed towards elucidating a PGx component of drug action with the intent of affecting the use of drugs in a clinical setting adhere to the FDA's quality-of-evidence standards.

4) Development and Co-development of PGx Products

A. A regulatory framework that is conducive to the development and authorisation of a medicine, and where appropriate co-development and co-authorisation of a PGx test, must be established if the potential benefits of PGx are to be realised.

In some instances PGx data will be used to augment decision making in the drug R&D process i.e. 'in-house' to select compounds for progression, without the necessity to have a PGx test for clinical use. However, in situations where prescribing is contingent upon test availability, development and availability of the test must be on the same timescale as that of drug development in order to avoid delays in regulatory approval of either, or ultimately in access to the medicine. In instances where test development only becomes evident in the later phases of clinical development, facilitating strategies should be in place. This may include creative approaches to accelerate and coordinate timelines for review and approvals of tests (e.g., PMA, 510(k)) and improved interactions between drug/device reviewing divisions of the FDA.

B. In some situations it may be critical for national health authorities to play a more active part in encouraging development of the field of PGx by providing incentives to enable the development of medicines (and any associated PGx tests) which are clinically desirable but which may not be economically viable, and by enhancing cooperation between public bodies, industry, patients, and academia.
However, before any legislative or regulatory changes (e.g., orphan drug provisions) are contemplated due to PGx, it will be prudent to consider the wider perspective of how biomarkers (of which PGx are a subset) impact research agendas within large pharmaceutical companies and also in smaller biotechnology enterprises (what is financially attractive may vary with the scale of the company). The practice of larger companies out-licensing niche compounds with lower market potentials to smaller companies should be a component of this evaluation.

The position of the SACGHS that '*Companies can readily obtain new patents for existing products by making small changes that do not introduce significant therapeutic benefits .....*' (page 32), does not accurately reflect the dynamics between research, intellectual property and the return on investment. The availability of funding for PGx research on existing drugs may depend not only on the potential for a PGx test to be feasible, convenient and to offer clinical value, but also on the potential for a return on research investment. Although not as high-risk as development of a new drug, PGx research is time-consuming and costly, and return on research investment can only be achieved through sales of a test or of the drug. The likelihood of such research costs being recouped is increased if there is the possibility of a limited period of market exclusivity associated (with either the new test or with the drug). PGx research could lead to the identification of new indications for existing drugs, may assist in defining subpopulations in whom the drug is more beneficial (or has a better side-effect profile), may result in differentiated presentations (e.g. different doses or drug release profiles for poor and good responders) or may lead to the development of a new predictive test – which may result in patentable inventions and/or a further period of market exclusivity for the drug. However, such further patent protection or market exclusivity is commensurate with the scope of the new development. Once the original patent and market exclusivity on the drug has expired, competitors will be able to launch generic versions of the drug for the original indication, and those generic products will compete in the market place with the originator's product. It will be the medical community that will decide whether any price premium for a patent-protected new presentation, new test etc. is worth paying. Without the availability of this limited

protection any generic product would be able to compete in the new indication and/or presentation, or a competitor test could be produced, undermining sales and reducing the likelihood of the PGx research investment being recouped.

5) Analytic Validity, Clinical Validity, Clinical Utility, and Cost-Effectiveness

A. HHS should grant sponsors of drugs and tests employing PGx information early and frequent access to regulatory authorities so that agreement can be reached on data requirements, labelling and clinical use.

B. Electronic medical records are integral to research, prescribing practice, pharmacovigilance and public health. Strategies to optimise electronic data usage should be debated with all key stakeholders including the pharmaceutical industry, and appropriate steps taken now to implement.

C/D. GSK has a transparent approach to the public disclosure of summary clinical trial information relating to GSK prescription products i.e. pharmaceutical and vaccines.

GSK publicly discloses the results of GSK-sponsored clinical trials that are relevant for patient care, irrespective of whether the results are positive or negative for GSK prescription medicines and vaccines. Whenever possible, public disclosure is via publication in scientific peer-reviewed publications. In addition GSK provides clinical trial results via the GSK Clinical Trial Register [http://ctr.gsk.co.uk/welcome.asp]. Here, GSK provides the results of all trials (phase I-IV) of marketed prescription medicines and vaccines. GSK will also post trial results of investigational medicines and vaccines that do not make it to market when relevant to patient care (e.g. when related to an important safety issue).

GSK also posts protocol summaries of all ongoing GSK-sponsored clinical trials (phase I-IV) of prescription medicines and vaccines to clinicaltrials.gov. [http://www.clinicaltrials.gov/]. The trials posted here by GSK exceed the requirements of the International Committee of Medical Journal Editors which recommends the posting of Phase III trials.

It is unclear what purpose would be served by requiring sponsors to identify on ClinicalTrials.gov which studies specifically included PGx, or any other given technology.

6) Data Sharing and Database Interoperability

A/B. Pharmaceutical companies routinely share information related to clinical research (see response to Recommendation 5 C/D)).

However a balance must be struck between the release of proprietary information for research by other entities and the conduct of R&D in the private sector. Requirements for further release of proprietary information could negatively impact biomedical innovation as third parties could "copy" innovative clinical development strategies and more readily embark on "fast follower" strategies. There would therefore be little or no incentive to develop innovative approaches in the first place. Reducing these incentives not only negatively impacts the research-based pharmaceutical industry by reducing potential returns on investments; it also compromises the ability of the research-based pharmaceutical industry to meet patients' needs.

With regard to data sharing, an important patient/research subject interest to be respected is the individual's consent covering their medical information or research data. Legitimate limitations on who can access data and for what purposes may exist.

C. The need for community-wide standards or best practice that will facilitate large-scale data integration and exchange to benefit PGx utilisation in healthcare were recently highlighted by GSK in the company response to the US Department of Health and Human Services (DHHS) - Request for Information (RFI) concerning Health Information Technology (HIT). (See: Appendix 1 - Comments from GlaxoSmithKline December 2006)

7) Protection of Personal Data

Achieving a pragmatic balance between protecting the confidentiality of medical data and facilitating vital research and healthcare provision must be sought.
Assumptions that PGx data are more sensitive and thus require a higher level of protection that other medical data should be challenged. Additional data security specifically for PGx data is unwarranted and will likely result in the restriction of access to key clinical and phenotypic data that will stifle healthcare innovation and provision.
Conceptually, all genetic data are part of the overall spectrum of confidential medical information and cannot be categorised separately. The information content of any medical data are highly contextual and genetic exceptionalism should be avoided. The management of all medical data, including genetic data, must satisfy equally high standards of quality and confidentiality and data systems, coding categories, regulation and legislation on data privacy protection are already established for the global management of research (Good Clinical Practice) and medical data. Categories and definitions of data coding strategies for use during development of

medicinal products are currently being defined by the International Conference on Harmonisation (ICH) and should be endorsed by SACGHS.

8) Population Subgroup Differences in Drug Responses

The utilisation of specific covariates during clinical trials, such as gender and race is a requirement of various drug regulatory authorities and has application for understanding the relevance of covariates such as allelic frequencies. Patient characteristics such as race or ethnicity can provide general information on the likely efficacy or tolerability of some medicines. However, race and ethnicity are at best crude, approximate markers for distinct genotypes that vary among individuals. Patients should be assessed individually, on the basis of genotype rather than phenotype. Excluding patients from clinical treatment based solely on race and ethnicity may unfairly disadvantage some individuals who would have been good responders.

A PGx test will provide information relating to the likelihood of a response (beneficial or adverse) in a given patient. The healthcare professional, in consultation with the patient, will then use that information, together with the drug label information, other medical information such as severity and course of the disease, availability of alternate treatment strategies to decide on an appropriate course of action. It is inaccurate to portray any pharmacogenetic test as being completely predictive and thus debates concerning population access in clinical practice must be carefully explored on a case by case basis.

9) PGx-informed Prescription Drug Coverage

A co-ordinated system of healthcare provision must be established to ensure that access to, and reimbursement of, any PGx test or patient/physician consultation, is not rate limiting to the access of beneficial medicines.

Because it is generally not possible to predict patients' responses to medicines, some patients will be effectively treated while others will not. PGx offers the possibility of effectively treating more patients and reducing these inequalities in the provision of effective healthcare. In addition, PGx can improve the basis for decision-making regarding allocation of resources for medicines based on clinically relevant data, further reducing inequities. On the other hand, lack of access to tests through the healthcare system could create disparities in the quality of medical care. A co-ordinated system of healthcare provision must be established that seeks to address current inadequacies in the evaluation of costing, reimbursement, treatment guidelines and coding. These include:

- Lack of incentive for stand alone drug plans to look at the overall cost impact of therapeutic intervention and the need for CMS or HHS to take account of overarching costs when devising cost-effectiveness evaluations.
- Lack of consideration of PGx by treatment guidelines committees.
- Delays in process for acquiring a new Current Procedural Terminology code for a test and the current necessity to have multiple codes (for different steps in the molecular testing process) designated when ordering a test.

Any consultation on these topics, including benefit categories for preventative services should involve all stakeholders, including the pharmaceutical industry.

Evidence based assessments of clinical utility and economic value to the health care system are now being undertaken including curtailing duration and burden of illness and costs related to avoidable adverse events (Hughes et al. 2004).

10) Use of PGx Technologies in Clinical Practice

B. Education on PGx will need to become an integral part of the standard curriculum in medical, nursing and pharmacy training programmes if healthcare professionals are to make the potential of PGx fully available to their patients. HHS should encourage collaboration with educational groups in other countries who are similarly focussed on educational, for example the National Genetics Education and Development Centre in the United Kingdom.

D. All drug labels, whether they contain PGx information or not, should be in a format that provides clear and relevant information to the prescriber. Definitions as to what constitutes validation of a PGx marker and is 'relevant 'for labelling will be critical.

PGx may help physicians prescribe the most appropriate medicine, or dose, for an individual patient and thereby help to maximise therapeutic outcome. Currently PGx testing is recommended for a small number of oncology medicines (e.g., purine analogues, imatinib, Herceptin ® (trastuzamab). Generally therefore, physicians are unprepared to cope with the likely increase in the use of such testing across the health care system. Liaison with other groups educating HCPs should be undertaken. Education should accurately position PGx alongside the other clinical procedures that the professional may undertake. The use of PGx information in prescribing for common diseases is expected to fall within the normal interactions between physicians, clinical analysis and patients, and not within the framework currently used for genetic service provision i.e. genetic specialists and counsellors.
It is recognised that knowledge to relay PGx information to a patient needs to be

acquired by a great many practicing physicians, however any assumption that such information will be overly complex, is not supported by examples such as Herceptin®. Moreover, physicians routinely interpret other risk factor data e.g. blood pressure, cholesterol levels and family history during prescribing selection.

Although PGx tests will not be primarily used for the diagnosis or prediction of disease, it is possible that sometimes a test may reveal additional information relating to health status or risks. There are two ways in which this may occur. Firstly, in some case, disease-associated genotypes might be among the genetic variable influencing drug response. Where this is related to the disease being treated, this situation is unlikely to raise ethical issues since the patient is presumably already aware of the disease diagnosis. The second scenario is that a test may provide information revealing the presence of, or risk a different disease. If a test is known to have the potential of revealing such information, this should be discussed with the patient, and will then be part of their consultation and decision regarding the test. There may also be measures that could help preserve confidentiality with regard to the possibility of testing providing collateral or unsolicited health-related information. For example, based on consent, the result of the test may not reveal the genotype at each individual marker to the prescribing healthcare professional or patient. It would merely report the likelihood of effectiveness or of a side effect. In addition, PGx tests would likely be comprised of patterns of markers. If specific markers within these patterns provided collateral or unsolicited information it may be possible to delete or replace them with other markers and retain their value as medicine response predictors.

11) Public Education and Engagement

A/B. Patients must be appropriately informed about the information any PGx test will provide to them and their physician e.g. what are the consequences of taking or not taking the test with regard to treatment options, and the likely clinical outcomes entailed in each scenario.

The objective of PGx testing is neither diagnosis nor prediction of disease, but determination of an individual's likely response to therapy. As a first step, it is important that patients are made aware of the variation that occurs in the response to all medicines and the potential role that PGx may play in treatment selection. While medicines do provide significant benefit to individuals and society, there are challenges associated with taking a medicine. These include the risk of side effects and the impact (therapeutic and financial) of prescribing a medicine that does not reduce the burden of illness. Such factors are often not fully appreciated, yet they are

the reference points for the positive impact of PGx.
Patients must also be provided with information to allow them to differentiate between the various clinical applications that utilise genetic information e.g. PGx vs. disease diagnosis vs. genetic screening vs. prenatal diagnosis and to have a clearer notion of 'susceptibility' or likelihood of an outcome.
In the longer term, it is likely that with the increasing knowledge of PGx amongst healthcare providers and patients, facilitated by the gradual introduction of medicines using PGx information, will come a level of patient awareness that is associated with current medical practice. Steps to achieve this should include:

- 'Patient-friendly' materials and resources should be developed and made available at the national level to provide information about PGx (and the differentiation from genetic disease testing and genetic screening etc) through a variety of media.
- Science curricula at all levels should include reference to progress and potential of medical genetics
- Efforts to promote dialogue, education, information and debate be encouraged

12) Health Information Technology

Clinical research and post marketing safety surveillance stand to gain a great deal from advances in HIT through implementation of electronic health records (EHRs).
The advantages of EHRs include:

- More rapid understanding of community health whether from naturally occurring events (epidemiological, observational, public health).

- The ability to better understand the population targeted for a clinical trial. Access to comprehensive EHRs will make protocol development and recruitment much more effective. This benefits all segments of the healthcare community involved in clinical research.

- Enhancing systems of post marketing surveillance with innovative frameworks such as PGx and EHRs could provide key biological information, collected in a consistent and timely fashion, so enabling improved detection of safety signals and additional research. Uncommon and serous drug reactions are often difficult to detect during clinical development, but their occurrence post-marketing can trigger the withdrawal of a new medicine. Such action eliminates the return on substantial investment made by a company and more importantly denies access to the medicine by the vast majority of patients who could have used the medicine safely and gained therapeutic benefit.

The necessity for improved HIT and EHRs were recently highlighted by GSK in the company response to the US Department of Health and Human Services (DHHS) Request for Information (RFI) concerning Health Information Technology (HIT)December 2006 (See Appendix 1).

Governance, standards and interoperability are the core requirements for a system to provide reliable and re-usable healthcare data. Organizational cultural resistance, limited training and education in the application and analysis of e-healthcare data, and the lack of a unique individual identifier (e.g. a reference number to collate data sets) are the major barriers.
The Committee's recommendations for modernizing and optimizing the management and utilization of all medical information should be priorities for HHS (recommendations 6, 7, 12). These measures are actionable now and will benefit health care in the US independent of how quickly PGx transitions into mainstream clinical practice.

13) Economic Value of PGx

The scope of the application of PGx will necessitate case-by-case economic evaluation as there will be no single model for PGx integration. Using Herceptin®, a complex monoclonal antibody, as a reference point for economic modelling is misleading.
Any evaluation of the long term impact of PGx investments on specific sectors and '*society as a whole'* should be approached with caution. PGx is a developing concept in medicine and it is vital to recognise that the application of PGx will evolve over time rather than there being a rapid evolution in medicinal parties. Some aspects of PGx may cause us to assess our current predictions and models for research and clinical practice, whilst many others will align with the current framework for healthcare delivery. Given the limited examples of PGx in clinical practice, any long term predictions could easily produce results which are not evidence based and have little relevance to the future of PGx. Economic modelling of variables at a societal level is not appropriate and should be given a low priority.

PGx may enable more medicines to be developed. Currently, the economics of drug development are such that if an investigational medicine has limited efficacy in a broad population it is unlikely to be developed - even though some patients benefit - because the sub-population of responders (or non-responders) cannot be identified. In this situation, there is no return on R&D investment. PGx may change that. The ability to identify prospectively those patients who will benefit may enable these

medicines to be developed. This provides benefits to patients, a return on R&D investment, and improved cost-effectiveness.

A recent example of drug efficacy in a genetically defined population is rosiglitazone (RSG; a PPARγ agonist) for mild-to-moderate Alzheimer's disease (AD). In a Phase IIb study, no statistically significant differences in primary endpoints were detected between placebo and any dose of RSG in the intention-to-treat population. However, exploratory analyses suggested that *APOE ε4*-noncarriers exhibited cognitive and functional improvement in response to RSG, whereas *APOE ε4* allele carriers showed no improvement and some decline was noted. These preliminary, hypothesis-generating findings are currently being confirmed in Phase III trials (Risner et al 2006).

The assumption that smaller market share means higher prices, is over-simplistic. The ability to identify those patients who are likely to benefit from a medicine may result in more patients being treated with that medicine than if a more general population were targeted. In addition, the ability to predict which patients are likely to respond well (or poorly) to a medicine will provide important clinical information to entities (e.g. formulary committees in the US) that make coverage and access decisions. Coverage for medicines may expand if the responder population of patients can be identified prospectively.

When PGx is used in the clinical setting to provide predictive information relating to the response of patients to marketed medicines, the costs could be met by healthcare payers/insurance companies as there will be considerable cost savings by getting the right medicine, to the right patient, at the right dose, the first time.

14) ELSI Research

Any research should focus on working examples, not speculation, and not on the assumption that PGx information is automatically more predictive or health critical than other information. Many of the ELSI challenges identified to date are comparable to those in other fields of medicine.

Considerable work has been conducted to date on the potential ELSI aspects of PGx. This includes comprehensive work by national, regional and international policy makers and advisors including:

- The (US) Consortium on Pharmacogenetics (2002)
- The Nuffield Council on Bioethics (2003)
- The Council for International Organisation of Medical sciences (CIOMS)

(2005)

- European Commission on the Ethics of Genetic Testing (2004)

Such reports have taken the opportunity to carefully consider the nature of pharmacogenetic information alongside the spectrum of healthcare information and to articulate the importance of considering test results on the basis of the informational content rather that the genetic nature of the test.

Informed consent is an integral component of patient protection for both research participation and clinical practice. The SACGHS report's statement that PGx consent however *'may be coercive'* should be strongly cautioned against.
PGx will provide important benefits to patients, as they are more likely to be prescribed an effective and well-tolerated medicine. However, patients may choose to refuse a PGx test, just as they might other tests. In this circumstance, the treatment decision will have to be made in the absence of this information and will turn on a risk: benefit assessment for that particular patient. The healthcare professional, in consultation with the patient, will use the available information to decide on an appropriate course of action. Whether the patient should nevertheless receive the medicine may be related to guidelines issued by insurance companies or other payers and is a matter of clinical judgement and patient input. Where a PGx test is mandated in the product labelling and has high predictive value, healthcare professionals may be reluctant to prescribe the medicine in the absence of the test, based on the prevailing standard of care. This is analogous to patients who refuse a diagnostic test, with the consequence of limiting their healthcare professional's ability to suggest appropriate treatment options.
Any ELSI work advocated by SACGHS should focus on any evidence for the extent or opportunity for unfair discrimination regarding healthcare and not implicate PGx for pre-existing challenges to provision of healthcare in the US.

SACGHS should seek to address the current hurdles to research. For example:

- The return of individual research results has already been identified as a common issue by stakeholders as rate limiting to the exploration of implementation of PGx (Renegar et al 2006). The authors identified the lack of differentiation being made in some quarters between PGx research data generated during exploratory research phases, and information that would need to be generated for clinical care (i.e. CLIA standards). Points to consider during any return of individual research data, including scientific validity, clinical relevance, quality assurance, and clarity of information provision - all

taken from the plethora of bioethical guidelines on the issue of returning results were explored. The authors have called for a pragmatic debate and guidance on the topic (Renegar et al 2006).

- Inconsistency in pharmacogenetic knowledge of IRBs

15) Co-ordination of PGx Activities

B. Co-ordination of activities resulting from the SACGHS recommendations will be important if activities are to be prioritised and focussed.

The SACGHS should liaise with key stakeholders in other countries who are also seeking to maximise the potential of PGx so that a framework conducive to global drug development and is achieved.

Please refer to international initiatives provided in Appendix A.

REFERENCES

Consortium on Pharmacogenetics (2002): Pharmacogenetics - Ethical and regulatory issues in research and clinical practice. Report of the Consortium on Pharmacogenetics - Findings and Recommendations.

Council for International Organizations of Medical Sciences. (CIOMS) 2005 Pharmacogenetics: Towards Improving Treatment with Medicines. . ISBN 92 9036 078X.

Department of Health (United Kingdom) White Paper. (2003) Our inheritance, our future: realising the potential of genetics in the NHS. http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4006538

European Commission (2004).Ethical legal and social aspects of genetic testing: research, development and clinical applications.. http://europa.eu.int/comm/research/conferences/2004/genetic/pdf/report_en.pdf

Hughes et al. (2004) "Cost effectiveness analysis of HLA B*5701 genotyping in preventing abacavir hypersensitivity" Pharmacogenetics 2004; 14: 335-42.)

International Conference on Harmonisation (ICH) of Technical requirements for Registration of Pharmaceuticals for Human Use. Draft Consensus Guideline. Terminology in Pharmacogenomics E15. step 2 version. 25 October 2006: http://www.ich.org/LOB/media/MEDIA3383.pdf

National Health Service (United Kingdom) National Genetic Education and Development Centre. http://www.geneticseducation.nhs.uk.

Nuffield Council on Bioethics. (2003) Pharmacogenetics: Ethical Issues. http://www.nuffieldbioethics.org/go/browseablepublications/pharmacogenetics/report_224.html

Renegar G. et al. (2006) Returning Genetic Research Results to Individuals: Points-to-Consider. Bioethics 20, 24-36.

Risner M.E. et al. (2006) Efficacy of rosiglitazone in a genetically defined population with mild-to-moderate Alzheimer's disease. The Pharmacogenomics Journal. 6(4):246-54.

Appendix A. Other Relevant Initiatives

International Conference on Harmonisation (ICH) of Technical requirements for Registration of Pharmaceuticals for Human Use. Draft Consensus Guideline. Terminology in Pharmacogenomics E15. Step 2 version. 25 October 2006: http://www.ich.org/LOB/media/MEDIA3383.pdf

Department of Health (United Kingdom) White Paper. (2003) Our inheritance, our future: realising the potential of genetics in the NHS. http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4006538

National Health Service (United Kingdom) National Genetic Education and Development Centre. http://www.geneticseducation.nhs.uk.

Appendix 1

C:\Documents and Settings\CB30662\My

US Department of Health and Human Services (DHHS)

Request for Information (RFI) concerning Health Information Technology (HIT)

Comments from GlaxoSmithKline

December 2006

Last Page

From: Greenway, Kirk (IHS)
Sent: Fri 5/25/2007 4:51 PM
To: Goodwin, Suzanne (NIH/OD) [E]
Subject: response to Realizing the Promise

TO: Reed V. Tuckson, MD, SACGHS Chair

FROM: Kirk Greenway, MA, MPH, Senior Statistician, Patient Care Statistics, Indian Health Service, Rockville, MD

RE: Realizing the Promise of Pharmacogenomics: Opportunities and Challenges

First, please allow me to state that my observations are my own, and they do not represent those of the agency I work for, the Tribes it serves, or any aspect of the department or the US government.

Given this, I thought it necessary to address specific issues mentioned either peripherally or not at all in this document as they relate specifically to marginalized or small population groups which may fail to be favorably impacted by the proposed document.

Diabetes mellitus is an example of a disease for which an assay may be developed which would allow one to determine predisposition to develop the disease either type 1 or 2 rather early in one's life. The current versions of the test ask if one will test not only oneself, if one is tested positive, to test one's relative(s) who tested positive for the disease. As the test is being conducted in an open access environment, such information would be used by the company to develop further refinements of the test.

The possibility then exists in the foreseeable future that developments in the pharmacogenomics of such tests will not hinge on what is most intellectually fascinating at this moment, the possibility of mapping diseases to loci on the genomic map, but on the testing technologies themselves. Eventually, economies of scale will force ever more efficient and cheaper technologies for determining matches. Alternatively, tests will be developed which would look for several things at once in a panel.

For the economically disadvantaged, this is a problem. Many in this group need basic education to understand what these tests are saying, and how to respond to their results. We should make the understanding of such information accessible to all. This is a test whose results are indeterminate and based on behaviors: health care seeking, nutritional, psychological, and even economic.

Yet, also for small population groups, there is the possibility that the genomic techniques can be used to identify a genetic pattern which if replicated in other individuals or used as a template in rational drug development could develop a very profitable treatment. Interestingly enough, the same set of decisions and risks that a corporation would make to deploy such a treatment on a large scale are analogous to the long term legacy of genealogy and intermarriage which preserved this genetic heritage that was so indicative or so valuable. In some cases, a genetic pattern is a legacy of constant suffering which might be changed by delivery technologies to introduce somatic cell mutation. The most obvious possibility here, though, is that since genomic alteration may not be possible, alternative techniques to use genetic identification and consequent delivered vehicles to manipulate the organelles of a cell

to stimulate apoptosis or other cellular processes might occur. These might be ethically patentable.

If they were, to what degree is it proper that companies exploit their mining of the genome and use of more sophisticated education and cultural capital which is the privilege of the few to deploy technologies to further economically advantage them and not include those groups whose suffering or serendipitous possession of an evolutionarily advantageous genetic pattern in the wealth? Alternatively, is it right that genetic inheritance empower individuals with wealth? One can think of numerous examples in history where cultural perceptions of inherited bodily superiority (the polygamous kulins of nineteenth century Bengal, for example) where such matters greatly distorted patterns of the society in which they lived.

Technologies which manipulate the processes of organelles within the cell, if developed to work through the use of genetic markers to identify and manipulate cells, such as those now being developed by start up firms such as Telomolecular Corporation of Delaware should have economic pay outs to the public to ensure that groups are empowered who have provided their genetic information.

It will, in my opinion, be especially important to share the wealth which comes from these technologies in the future. If a Tribe possesses individuals who never have multiple sclerosis or another such dread disease, why should they share this with the public unless they stand to benefit in return? It is better to live one's life in peace and die a good death than to realize one has taken the most significant part of who one is from a person and sold it for the gain of another group. There are numerous such individuals in the world, and we can benefit from their serendipity in having such a genetic legacy to give us. Yet, we must be prepared to provide for everyone that legacy, sharing it fairly, and not allow ourselves to naively believe that the ultimate promise of pharmacogenomics is the rational drug development of very successful and profitable treatments and drugs.

Kirk Greenway
117 Pontiac Way
Gaithersburg, MD 20878

Invited consultation response to 'Realising the promise of Pharmacogenomics: opportunities and challenges'

By Dr. Michael M Hopkins, University of Sussex, UK.[1]

June 2006

Background

I am grateful for the invitation and opportunity to comment on the above report. The perspective I offer is that of an independent social scientist researching the *evolution* of genetic testing services, primarily in the UK but also in the USA and EU member states.

I have carefully read the draft report of the Secretary's Advisory Committee on Genetics, Health and Society (SACGHS) which I feel provides a comprehensive overview of the issues arising from the introduction of pharmacogenomics in the clinic. In particular the report emphasises the need for a cohesive framework to support PGx, which colleagues and I have often agreed is essential given the systemic nature of medical innovation and the desire to avoid unnecessary bottlenecks in the translation of socially desirable medical advances into clinical tools.

In recent years a number of UK authors have contributed to a body of literature for policy makers on pharmacogenomics. Much of this work is represented in the current draft SACGHS report[2] although certain more recent reports are not cited explicitly and so may provide further insights.[3] In particular work by independent social science researchers provides a useful comparative (EU/US) regulatory perspective (IPTS 2006), as well as detailed examinations of PGx and its role in research and

---

[1] Dr. Michael M. Hopkins is a Research Fellow of the UK's Economic & Social Research Council and Medical Research Council, based at SPRU: Science and Technology Policy Research, The Freeman Centre, University of Sussex, Falmer, Brighton, BN1 9QE, UK. Contact: m.m.hopkins@sussex.ac.uk

[2] For example, Nuffield Council on Bioethics (2003) Pharmacogenetics: ethical issues; Meltzer, Raven et al. (2003) My Very Own Medicine: What Must I Know?; The Royal Society (2005) Personalised medicines: hopes and realities.

[3] Martin et al (2006) False Positive? The commercial and clinical development of pharmacogenetics (available at: www.york.ac.uk/res/pgx/publications), The UK pharmacogenetics study group (2006) Policy Issues in Pharmacogenetics (available at: www.york.ac.uk/res/pgx/publications), Martin and Morrisson (2006) Realising the Potential of Genomic Medicine (available at: http://www.rpsgb.org.uk/pdfs/genommedsrept.pdf) and IPTS (2006) Pharmacogenetics and Pharmacogenomicss: state-of-the-art and socio-economic impact in the EU (available at http://ftp.jrc.es/eur22214en.pdf).

development (IPTS 2006, Martin et al 2006). Although I support the specific policy recommendations made by Martin et al (2006), and conclusions drawn in IPTS (2006), my response here draws mainly from personal reflections following my experiences as a researcher studying the implementation of genetic testing services. The five points I wish to make (below) are disparate and, if deemed relevant, would have implications for a number of sections in the draft report.

1. Intellectual property – an essential incentive and unmeasured barrier

It is clear that SNPs, mutations, gene alleles and splice variants are the subject of patent applications and can legitimately find patent protection when applications fulfil the basic criteria for patentability.[4] There is some evidence to suggest this is already creating barriers to the development of comprehensive DNA diagnostic tools where licensors holding key patents are not forthcoming. Whether this is preventing novel products (rather than competing products) from coming to market or restricting the numbers of patients that can access tests is a question that requires dedicated and sophisticated research studies (c.f. Page 28 of SACGHS report).

2. PGx dosing information – involves more than *translating* existing research

In many cases the differential dosing of a patient following a PGx test is likely to reduce, but not eliminated, the chance of an ADR.[5] Furthermore it is difficult to fully implement differential dosing with current data. For example TPMT testing prior to thiopurine dosing has a demonstrated value in protecting non-metabolisers. However, tailoring of regimes to gain better treatment efficacy in high metabolisers and low metabolisers remains a technical challenge due to lack of data, especially using molecular analysis rather than more direct measures of metabolic phenotype.

When evidence for appropriate drug use has been described in an accepted codified manner in clinical guidelines or if a drug is being used 'off label', ultimate responsibility for administering drugs should rest with the prescribing physician. At present information on drug labels or in the literature remains ignored (as suggested by Zineh, Pebanco et al. 2006) because it is incomplete. In most cases drawing clinical utility from this information is not just a question of *translating* existing PGx research (which implies the information is present but some how unreadable). Instead disparate experimental results need to be integrated and transformed into comprehensive and reliable guides through extension and repetition.

Dosing advice, whether on the label or in clinical guidelines, must be suitably detailed to be relevant and reliable in a wide range of clinical circumstances. Utility will therefore be dependent on wide ranging studies to characterise genetic factors in

---

[4] See Hopkins, M.M., Mahdi, S. Patel, P., and Thomas, S. M. (2007) DNA patenting: the end of an era? *Nature Biotechnology* vol. 25 (2) February 185-187. For more depth see also Hopkins M.M., Mahdi, S. Thomas, S. M., and Patel, P. (2006) *Global trends in the granting, filing and exploitation of DNA patents*. A report for the European Commission. Brighton: SPRU (available at: www.sussex.ac.uk/spru/documents/patgen_finalreport.pdf)

[5] It is important not to overstate the role of PGx in eliminating ADRs even in the often cited case of TPMT testing, ADRs might only be reduced by 50% (See Van den Akker-van Marle, et al (2006) Cost-effectiveness of pharmacogenomics in clinical practice: a case study of thiopurine methyltransferase genotyping in acute lyphoblastic leukemia in Europe *Pharmacogenomics* 7(5) July. 783-792.

different populations (i.e. identify all relevant mutations and SNPs), the penetrance of these factors, as well as their inter-actions with other genetic and non-genetic factors to produce clinically informative risk indices.

The funding of comprehensive studies may not be of commercial interest without incentives, especially for off-patent drugs. As an independent party it will likely remain the government's role to provide funding for these studies. A grant programme could be established to this end. This grant programme should be open to commercial and non-commercial research groups.

3. Guidelines by professional bodies – an underestimated milestone for PGx tests

The draft SACGHS report has already accepted the importance of the role of professional bodies in the diffusion of genetic tests. Professional bodies are indeed the key institutions involved in the basic education of health professionals as well as maintaining standards for continuing professional development. However, it remains to emphasise the central role that these organisations play in the production of guidelines as well as in education and the central role guidelines play in diffusion (page 72-74).

The development of accepted clinical guidelines could form a solid foundation for assessments of clinical utility (even beyond those physicians under jurisdiction of the professional body), reimbursement decisions, efforts to encourage diffusion, and as tools for education. Similarly accepted practice as described in clinical guidelines could become important in ascribing liability in cases where ADRs occur in the absence of a test result.

More should be done to encourage cross-disciplinary discussion between groups of professionals to avoid the 're-inventing of the wheel' by different groups of practitioners using similar drugs, or delays in the application of knowledge developed for one group of professionals that may have relevance to another.

Government grants could be used to encourage the timely writing or re-writing of guidelines in response to new PGx associations or dosing information coming to light. Where comprehensive studies are undertaken as described in (2) above, a separate adjunct to any supporting grants might be arranged to ensure guidelines issued by a professional body are an output.

A multidisciplinary council of professionals could be appointed to ensure guidelines developed by one group of professionals are disseminated to those with responsibility for updating and issuing guidelines in other groups where the same drugs are used.

4. Genetic discrimination – no protection, no trust in PGx

The absence of protection against the threat (real or imagined) of genetic discrimination is a real threat to the uptake of pharmacogenetic testing services as well as a real threat to clinical studies that rely on large scale voluntary participation. The implementation of anti-genetic discrimination measures may not sit easily alongside current practice in insurance due to the issue of 'genetic exceptionalism' as identified in the report (Page 91-92). However this logic does not preclude the validity

of public concerns. In this respect PGx may become yet another reason for a fundamental re-think of the current system of differential fees for healthcare insurance in the USA and elsewhere.

Greater trust in regard to PGx technology may be gained from the public by legal protection against descrimination and this is likely to provide a more firm basis for the development of positive associations with PGx in the public consciousness. If protection is in place, less emphasis may be placed on schemes to 'educate' the public. The focus of education should remain on the healthcare professionals, whose role is, to some degree, education of the patient (although I accept may be less so in the USA than in the UK).

5. Keeping the 'technogical fix' of PGx in perspective

The report is right to suggest PGx may not always reduce the cost burden of healthcare at the level of the clinic, the payor, or even at the societal level (Page 86-87). However PGx may well improve outcomes of particular medical episodes from the perspective of the patient. The challenge for policy makers is to set explicit policies to encourage PGx use when it is desirable from the patient's perspective, as far as is socially acceptable.

The report rightly suggests addressing socioeconomic concerns may be a more worthy use of limited resources than targeted medicines in some cases. Similarly, socioeconomic factors play a role in adverse drug reactions. The recommendations of the report should not neglect the non-genetic components of ADRs[6] (e.g. age, educational status of the patient, ability to follow medical instructions written in non-native languages) or patient stratification (e.g. socioeconomic stratification due to educational status, or insurance status) and place proportionate emphasis on understanding and negating these factors.

[6] Existing non-genetic information may often be sufficient to explain most ADRs. For an important study demonstrating how often this is the case see Pirmohamed M, James S, Meakin S *et al.*: Adverse drug reactions as cause of admission to hospital: prospective analysis of 18,820 patients. *BMJ* 329(7456), 15–19 (2004).

June 1st 2007

Comments regarding the SAGHS document *"Realizing the Potential of Pharmacogenomics: Opportunities and Challenges"*

HumGen International is a multidisciplinary research team that focuses on the ethical, legal and social aspects of human genetics. It is located within the *Centre de recherche en droit public* of the Université de Montréal and is directed by Canada's Research Chair in Medicine and Law, Bartha M. Knoppers. HumGen International, as co-investigator in the Genome Quebec/Genome Canada "Pharmacogenomics of Drug Efficacy and Toxicity in the Treatment of Cardiovascular Disease" project, is grateful for this opportunity to comment.

The Promise of PgX

While indeed, we agree that the inclusion of pharmacogenomics into clinical trials and eventually clinical practice is a promising goal, we at the same time recognize that this goal will only be realized some time in the future. The positive and upbeat perspective presented in this paper is perhaps premature, as there are still many scientific, legal, ethical and social issues that must be addressed before the introduction of pharmacogenetic testing into health care system and decisions.

That being said, this document does an excellent job canvassing the opportunities and challenges associated with the expansion of pharmacogenomic research. The following are suggested additions or modifications, dealing mostly with the ethical, legal and social consequences of the development of this domain.

Recommendation 1, 6 & 3:

In the data-sharing and data base interoperability policy section, beginning on page 21, we recommend that at the very least any NIH-conducted basic research be made available for use by all working in the field. While current policies recommend this, it would be more beneficial if they required it. The document does a good job highlighting the difficulties of data-sharing as a result of intellectual property protection; however, it should nonetheless be essential that all publicly funded basic research is made available for widespread use without undue delay. While we would hope that positive examples of the reduced research costs associated with the sharing of basic research results would influence the private sector to follow suit, we question whether this could ever encourage more sharing on their part.

We also agree that a key to achieving the positive impact of pharmacogenomics is the interoperability of research and data sharing of information derived from clinical trials. To this end, we suggest reviewing some of the tools to promote harmonization already developed by the P3G Project. P3G is a not-for profit international data-sharing project that was launched with the mission of developing "in an open and transparent manner,

research tools for effective collaboration between biobanks so as to enable the international research community to share expertise and resources and facilitate knowledge transfer for the health of populations." http://www.p3gconsortium.org/

Recommendation 7 & 14:

As the issues of confidentiality and discrimination are interrelated, we suggest discussing them together, rather than separately. As it currently stands, recommendation 7, starting on page 42 seems incomplete until it is justified in the discussions about stigma and discrimination, starting on page 91. They should both be included under the rubric of ethical, legal and social issues related to pharmacogenomics.

Informed Consent:

While the issues related to informed consent are adequately canvassed, we believe that a document, such as this one, should go further to explain the implication of this important issue. A recommendation on this matter would be welcomed firstly to guide researchers, and secondly, to contribute to the emergence of a consensus. We question why you decided to refrain from making a recommendation on this issue?

Recommendation 8:

Recommendation 8 is a positive acknowledgement of the often mistaken conflation of race with genetics. The document provides excellent anecdotal evidence of the hazards of perpetuating this assumption, however, the recommendations could go further in finding ways to reduce this tendency is research and marketing. As recommended by HapMap, it has been suggested that ethnicity be denoted according to location of birth rather than according to race. While we agree that researchers should identify other factors, environmental, behavioural, etc, that may account for the differences in drug response, we believe that the evidence presented here suggests that this should be considered fundamental, rather than merely encouraged. Moreover, we also believe that the evidence presented suggests that along with behavioural and environmental factors, the recommendation should include the requirement that upon any discovered correlation between ethnicity and drug response, research into responses of other ethnic groups should be conducted to ensure that the correlation is actual rather than merely perceived.

Recommendation 11:

We believe that public communication about pharmacogenomics should be more active and inclusive. The current recommendations seem to suggest that one-way dissemination will be sufficient to engage the public, however, we believe that two-way communication is essential so that researchers, doctors and policy makers can respond to the real concerns the public faces in relation to the inclusion pharmacogenomics into treatment. As you recommended in your document *"Policy Issues Associated with Undertaking a*

New Large U.S. Population Cohort Study of Genes, Environment, and Disease" on page 54, we must ensure that "public engagement occurs throughout all aspects and stages of the research process, from conceptualization through design, planning, implementation, conduct, and data analysis and reporting."

Recommendation 14:

In the discussion of liability for the use of pharmacogenetics to treat patients, the predictive nature of pharmacogenetics should be addressed. For example, how does one treat a pharmacogenetics-certified 'poor-responder' when there are no alternative treatment options? What do you tell such a patient? The issue of the discovery of secondary information (pleitoria) that can be uncovered when one undergoes a pharmacogenetic test should be addressed as well. What do you do when the test reveals a much more severe susceptibility that the one that the patient has agreed to be tested for? The introduction of pharmacogenetics into patient treatment may raise the need of genetic counselling to better enable patients to make informed decisions about the course of their treatment. Recommendations for these situations are necessary.

Finally the social and psychological implications of pharmacogenomic terminology, such as "personalized medicine" and "poor-responders" are likely to be an issue as well. In fact, at the recent Human Genome Organization (HUGO) conference held in Montreal in May 21-24 2007, a speaker, David R. Cox from Perlegen Science explained that term personalized medicine is misleading and should not be used on account of the fact that pharmacogenomic medicine is not personalized by individual, rather it is classified by groups of responders. Similarly, presentation of responders in terms of non-responders and good responders makes it seem like clear cut demarcation, when in fact, it is more probabilistic. To this end, we feel that terminology should be addressed under the ethical legal and social issues section of this document.

We hope that these comments will be helpful in revising the draft document.

HumGen International, Centre de Recherche en Droit Public: Faculty of Law, Université de Montréal

Denise Avard PhD
Yann Joly LLM
Tina Silverstein BA
Yanick Farmer PhD

DRAFT

International Society of Nurses in Genetics, Inc. (ISONG) Public Comments to the Secretary's Advisory Committee on the *Draft Report on Pharmacogenomics*

Background

The International Society of Nurses in Genetics, Inc. (ISONG) is pleased to provide public comments on the SACGHS *Draft Report on Pharmacogenomics*. As a global nursing specialty organization whose vision is caring for people's genetic and genomic health, ISONG supports SACGHS' identification of pharmacogenomics as a high priority recognizing that pharmacogenomics will most likely initiate wide-spread application of genomics into every arena of health practice.

ISONG recognizes genomics as a central science for all nursing practice and that healthcare for all persons will increasingly include genetic and genomic information, including pharmacogenomics. The 2.5 million practicing nurses are on the frontline of healthcare delivery and will increasingly use genetic and genomic-based interventions and information to improve patient outcomes. Nurses work in collaboration with other healthcare providers in providing genetic and genomic healthcare, including performing pharmacogenomic interventions tailored to patients' genetic and genomic healthcare needs (Jenkins, Calzone, Lea & Prows, 2006). To achieve the clinical integration of pharmacogenomics into practice, ISONG offers the following public comment.

Public Comments

- To assure that all patients receive appropriate pharmacogenomic interventions, ISONG supports SACGHS intent to focus on the education and training for physicians, and other clinicians as this is essential to ensure their competence with pharmacogenomic technologies and their ability to counsel patients and families. ISONG members have had a central role in developing *Essential Nursing Competencies and Curricula Guidelines for Genetics and Genomics*. These *Competencies* include the use of pharmacogenomics in nursing care, stating that the registered nurse "performs interventions/treatments appropriate to clients' genetic and genomic healthcare needs" (p.13). ISONG strongly recommends that SACGHS include nurses from a variety of practice arenas in these educational efforts.

- As evidence accumulates from government agencies, ISONG strongly supports SACGHS intent to disseminate pharmacogenomic guidelines to professional organizations. ISONG agrees with SACGHS recommendations that HHS assist professional organizations in their efforts to help their membership achieve competencies on the appropriate use of pharmacogenomic technologies. We recommend that HHS engage with ISONG, the American Nurses Association, and other nursing organizations that have developed and endorsed *Essential Nursing Competencies and Curricula Guidelines for Genetics and Genomics (2006)* to further these efforts.

- ISONG strongly recommends that SACGHS include nursing and other health professional organizations in any public meeting regarding educating health professionals about pharmacogenomic guidelines. ISONG would be happy to offer input and support in creating strategies for dissemination of pharmacogenomic guidelines and clinical feedback.

- ISONG recognizes that the success of pharmacogenomic interventions may rely on database links of clinical, pharmaceutical and payer information. As many institutions move forward to utilize an electronic medical record system, we strongly encourage further SACGHS' input into this critical area of genetic information and the electronic record.

ISONG nurses have long been on the frontier of genetic and genomic healthcare that promotes individualized and tailored interventions. We support and value SACGHS' *Report* addressing the important area of pharmacogenomics, and the recommendations of novel ways that HHS can contribute to the development of evidence base to measure the economic and medical value of pharmacogenomics.

Thank you for the opportunity to comment on this *Draft Report on Pharmacogenomics*..

To: Reed Tuckson, M.D.
SAGHS Chair
Secretary's Advisory Committee on Genetics, Health & Society
NIH Office of Biotechnology Activities
6705 Rockledge Drive, Suite 750
Bethesda, MD 20892

From: Carol Isaacson Barash, Ph.D.
Principal, Genetics, Ethics & Policy Consulting
317 Lamartine Street, Suite 200
Boston, MA 02130
Tel: 617.848.9080
Fax: 617 933.8907
cbarash@gepci.com

Re: Comments on the Draft Pharmacogenomics Report

Dear Committee,
I am writing to strongly support the Committee's Draft Pharmacogenomics Report which I believe is thorough and necessary. I would like to add some comments about patient access, particularly regarding those who are under or un insured. Access is a particularly vital issue when access to pharmacogenomics can mean the difference between life or death.

As we know, advances in personalized medicine and companion diagnostics are marvelous but if they are unaffordable, except for a very few, the anticipated benefits will not be realized. Patient access, particularly for the under and un insured remains a core issue and yet patient advocacy as it relates to personalized medicine has been far from highly visible. There are many reasons why. For one it's early. Personalized medicine is far from widely available. Moreover, there's usually a time lag between the availability of an innovation and advocacy efforts to ensure widespread access. If, or when, consumers lack access however, patient advocacy is likely to be a particularly potent force.

Patient concerns as they relate to personalized medicine is a data poor domain but starting to develop. 2003 arguably represents a landmark in patient advocacy because a court established a patient's right *to access*. In that year, Dan Greenberg, his wife and several other families, similarly affected by Canavan's Disease and who had helped to develop a genetic test, sued Miami's Children's Hospital and Research Institute, including Dr. Reuben Matalon, alleging breach of informed consent, fraud, unjust enrichment and misappropriation of trade secrets. The group of families had spearheaded the effort to identify the genetic mutation responsible, by enlisting Dr. Matalon, raising research funds and helping to collect skin, blood and urine samples from affected children and their parents. Once the test became available, the company, (including Dr. Matalon) won a patent and established licensing requirements. The Greenbergs, and their allies, sued to make the newly developed test available to the public by ensuring that labs were able to

perform the test without paying licensing fees. They prevailed and in doing so won not the right to royalties but rather the right to remain active participants in the advancement of research and access to the public.

Patient access is ultimately mediated by provider availability and knowledge. As the primary access point provider preparedness to practice personalized medicine is key. The data on provider preparedness, though, suggests real concerns for patients. The supply of capable providers is insufficient to meet patient demand[1]. There continues to be a steady decline in the number of certified medical geneticists which began in 1993. More importantly, the number of professionals entering the genetics workforce is significantly decreasing. Competency is also a key concern, as physician knowledge deficits remain substantial despite genetics education initiatives. While continuing medical education in personalized medicine might help to improve competency levels, it is not required by State medical boards. Physician attitudes influence patient access. A recent German study[2] found that physicians appreciate the availability of pharmacogenomic testing for asthma, which could imply that physicians could appreciate the clinical benefit of pharmacogenomic testing. However, the study also found that general practitioners were worried that patients might be pressured into testing or disadvantaged by health insurers, which implies a reluctance to adopt.

Fear of genetic discrimination is a real deterrent to patient access. Individuals will not take tests if insurance or employment exclusions are perceived as a real threat. Moreover, if, or when, a pharmacogenetic lab result is tied to basic needs/necessary care, barrier to access will be critical.

A better informed patient is more likely to take a pharmacogenetic test and comply with indicated treatment. However, data on consumer knowledge raises concerns about consumer preparedness to advantage themselves. The genetic, scientific and medical literacy of the general public is currently very low[3][4]. A 2007 study of patient comprehension of complex diagnoses (asthma, diabetes, cardiovascular disease, all of which we know have genetic contributions) showed consumer knowledge hasn't increased since 2002.[5] While literacy in all three areas is a highly desirable requisite to

---

[1] Secretary's Advisory Committee on Genetics, Health & Society Testimony Judith Cooksey, October 22, 2003.

[2] Roguasch, A., et. al., Patients' and physicians' perspectives on pharmacogenetic testing. Pharmacogenomics. 2006 Jan; 7 (1): 1-3.

[3] Genetics and Public Policy Center Survey 2002 p://www.dnapolicy.org/research/index.html.

[4] Miller, Jon. 1998. *Public Understanding of Science* 7:203-223; Harvey, E., et. al., Providers' Knowledge of genetics: A survey of 5915 individuals and families with genetic conditions. Genetic Med. 2007 May;9 (5):359-267.

5 Calsbeek, H., et. al., Knowledge and Attitudes Towards Genetic Testing: A Two Year Follow-Up Study in Patients with Asthma, Diabetes Mellitus and Cardiovascular Disease. J Genet Couns. 2007 Feb 23.

appropriate use of personalized medicine, consumers do not need to fully comprehend the medical and scientific technicalities in order to achieve benefit. Data show that consumers want to know about advances in personalized medicine, that they want new tests and drugs, suggesting that demand for new genetic technologies continues to rise[6]. This implies that access is limited by a patient's ability to pay out of pocket costs not covered. Having insurance does not guarantee coverage, and patients who are under or un insured have little if any access.

Access to reference and specialty laboratory tests is an important issue because the business models of these labs minimize reimbursement risk, thereby limiting access. Informal research I recently conducted showed that while some labs may offer patient assistance, patients are typically unaware that assistance is possible because such is not stated upfront. It is not surprising therefore that labs report few requests for assistance. Assistance, if it exists, tends to be available only after assertively inquiring and determined on a case by basis with patient income details a base line requirement. In some cases, if a physician has waived his/her professional fees they will ask that the lab do the same, in which case a clinic contract is informally established. In a few cases, one state has covered pharmacogenetic testing for individuals on state assistance. But laboratories do not generally accept out-of-state Medicaid.

Consumer advocacy may face special challenges to driving access in the area of personalized medicine. It's hard for consumers to push for access if they don't know what specialized tests and treatments are available and if they might be beneficial. More importantly, individuals don't know if they are part of a group (of similar genetically predisposed and phenotypically responsive) until at least they've been tested. That is, at least until they've had access.

When getting the right drug in the right dose is a matter of life or death, access for the under and un insured is crucial, and attendant with ethical and policy implications. It's too early to gage whether corporate profitability will support access to this population and if so how broadly. How much pressure will be put on pharma and insurers is for now uncertain.

Corporate consumer collaborations which are emerging in various areas within genetics may well, though, represent a successful approach to permitting access and meeting other patient concerns. A number of different approaches suggest possible strategies for meeting the personalized medicine needs of the un and under insured. Several years ago The Komen Foundation teamed up with Myriad to provide BRCA testing for high risk under privileged women who otherwise would not have been able to get tested. Here The Komen Foundation negotiated a lowered test price and funded testing and related expenses. The program lasted only one year and was not replicated. The relatively new Coordination Education & Test Translation (CETT) Program (www.cettprogram.org) is a collaboration of clinical and/or research labs, clinicians and disease specific advocacy groups who collaboratively develop the best possible molecular test and ensure that it is available to the target population. Patient participation is key because it provides

---

[6] Evaluation of Genomic Applications to Prevention & Practice (EGAPP)

important feedback to clinical lab and researchers about individual's and family needs that play a role in developing the best possible test as well as ensures that educational materials are appropriate. The Cystic Fibrosis patient group and the Solvay Pharmacy display a more traditional type of collaboration. Solvay provides free digestive enzymes and vitamins to all CF newborns through 2 years of age, funds twenty four year college scholarships to students with CF and has donated substantial fund for CF's Great Strides program that raises money for research. (http://www.cff.org/aboutCFFoundation/NewsEvents/index.cfm?ID=6387&TYPE=1670) Lastly, the Center for Excellence in Environmental Toxicology (CEET) (http://www.med.upenn.edu/ceet/index.shtml) program reaches out to four high risk communities in Philadelphia providing laboratory testing and education for non-routine toxicology tests, including but not limited to chronic beryllium disease and beryllium sensitivity, which we know can be influenced by genotype).

Public-private collaborations of this kind can go far to increasing access to personalized medicine. Patients value corporate involvement particularly if companies provide items that consumers would not otherwise have. Reciprocally, companies can gain recognition and generate greater internal loyalty by engaging employees in the societal importance of their work.

Finally, the right test and right drug are only part of an infrastructure that is required to ensure appropriate uptake. Regulatory uncertainty requires resolution. Racial/ethnic disparities need to be eliminated. The number of capable practitioners needs to be increased, as does patient involvement in test and therapeutic development. Educational materials need to be improved. Regulations that move towards greater international harmonization can help fulfill the promise globally. The path from promise to adoption is more likely jagged than linear, and along that path patients have an important role in helping to drive the field forward.

From: Kalman, Lisa V. (CDC)
Sent: Tue 3/27/2007 10:27 AM
To: Goodwin, Suzanne (NIH/OD) [E]
Subject: Re: Realizing the promise of pharmacogenomics document

Hi,

Very nice document!! Very complete and informative!

I have some corrections to make to this paragraph on page 113.

2. The *Genetic Testing Reference Materials Coordination Program* facilitates and coordinates information exchange between users and providers of quality control (QC) materials, and coordinates efforts for contribution, development, verification and distribution of QC materials for genetic testing. The program is currently working with the genetic testing community to define the QC material needs of PGx testing. Data on cell lines with known PGx genotypes has been collected and we are beginning to assess potential targets for QC material development.
http://www.phppo.cdc.gov/dls/genetics/qcmaterials/

Could you edit this to read:

The Genetic Testing Reference Materials Coordination Program (GeT-RM, formerly GTQC) facilitates and coordinates information exchange between users and providers of quality control (QC) and reference materials (RM), and coordinates efforts for contribution, development, characterization and distribution of RMs for genetic testing. This CDC-based program is currently working with the genetic testing and pharmacogenetics community to define the RM needs of pharmacogenetic testing. Data on cell lines with known pharmacogenetic genotypes has been collected and we are beginning to assess potential targets for RM development.
http://www.phppo.cdc.gov/dls/genetics/qcmaterials/default.aspx

Thanks!

-Lisa

Lisa Kalman, Ph.D.
Laboratory Practice Evaluation and Genomics Branch
National Center for Preparedness, Detection and Control of Infectious Diseases
Centers for Disease Control and Prevention
1600 Clifton Road
Mailstop G23
Atlanta, GA 30333
(404) 718-1011
LKalman@cdc.gov

-----Original Message-----
From: Laurence S. Kaminsky [mailto:lsk06@health.state.ny.us]
Sent: Wednesday, May 23, 2007 1:18 PM
To: Goodwin, Suzanne (NIH/OD) [E]
Subject: Comments on SACGHS Report on Realizing the Promise of Pharmacogenomics
Importance: High

Reed V. Tuckson, MD
Chair
Secretary's Advisory Committee on Genetics, Health, and Society
NIH Office of Biotechnology Activities
6705 Rockledge Drive, Suite 750
Bethesda, MD, 20892

Comments on Draft Report of the SACGHS

Dr. Laurence Kaminsky

Comments in response to questions posed:

Are the discussions of topics and issues accurate and complete?

Page 3, line 6: The statement is very limiting in the diversity of disease areas that could potentially be affected. Change to "….response for many diseases including cancer….".

Page 4, para 4, line 2 and Page 17, para 5, line 4: Change to "variation in the functions of drug transporters….".

Page 4, para 4, line 5: Use of the term "variants" to describe the various forms of cytochrome P450 in the context of this report, is potentially confusing. Change to "….cytochrome P450 (CYP) and particularly some of its forms such as CYP2D6 and CYP2C19,….".

Page 4, para 4, line 12: CYP2D6 occurs in many variant forms, some of which are associated with slower drug metabolism in much higher percentages of African Americans and Asian Americans than is indicated here. Thus this statement is an understatement of the extent of the problem.

Page 17, para 3, line 5: Change to: "…excreted, not necessarily in that order."

Page 21, para 2, line 3: It would probably be more accurate to change this sentence to: "….identifying groups of single…".

Page 21, para 2, line 5: By focusing only on CYP2D6 and CYP2C19, the estimates of 25-30% of currently available drugs that are metabolized by cytochromes P450 is underestimated by approximately 3-fold.

Have any significant opportunities, challenges or other issues been missed?

Page 5, B. Challenges and Key Considerations: A key challenge to the development of PGx applications is inadequate available details of the basic mechanisms of the pathways leading to drug efficacy and drug toxicities. Addition of such a statement would make this section more

consistent with the following section, section C. Recommendations, 1) Basic Research.

Page 9, 10) Use of PGx Technologies in Clinical Practice: Please consider adding the following to the list: HHS should support studies to determine whether physicians will alter their normal drug prescribing practices when provided with their patient's genotypes, and the potential consequences of genetic variants.

Page 22, A. Basic Research: Please consider adding that studies to assess the functional consequences for the gene products, arising from SNPs and haplotypes in genes are important for developing genotype - phenotype correlations.

Laurence Kaminsky, Ph.D.
Director, Office of Environmental Research Development
Wadsworth Center, P.O.Box 509, Albany NY 12201
and
Chairman, Department of Environmental Health Sciences
University at Albany, State University of New York.
Ph: 518-474 4920
Fax: 518-486 1505
email: kaminsky@wadsworth.org

-----Original Message-----
From: Howard McLeod [mailto:hmcleod@unc.edu]
Sent: Sunday, June 03, 2007 11:20 PM
To: Goodwin, Suzanne (NIH/OD) [E]
Cc: rochelle_long@nih.gov; hmcleod@email.unc.edu; 'Kathy Giacomini'
Subject: PGRN response to SACGHS Pharmacogenomics report

Suzanne, thank you for your positive response to Rochelle Long's request for a few more hours to complete the Pharmacogenetics Research Network response to the SACGHS report on pharmacogenomics. I have attached the response as a word document. Please feel free to contact myself or Rochelle with any questions regarding this response. The PGRN appreciates the efforts of your group and look forward to the positive changes that should result from this work.

Best regards

Howard

Dr. Howard L. McLeod
Fred N. Eshelman Distinguished Professor
Director, UNC Institute for Pharmacogenomics and Individualized Therapy
University of North Carolina, Chapel Hill
Campus Box 7360
3203 Kerr Hall
Chapel Hill, NC 27599-7360
telephone: 919-966-0512
E-mail: hmcleod@unc.edu

Reed V. Tuckson, MD
Chair, Secretary's Advisory Committee on Genetics, Health, and Society
NIH Office of Biotechnology Activities
6705 Rockledge Drive, Suite 750
Bethesda, MD, 20892

The NIH-funded Pharmacogenetics Research Network (PGRN) is a multi-disciplinary network intended to interpret and understand, as well as discover, pharmacogenetic information. Ultimately, this information can be clinically tested and, where appropriate, translated into safe and effective drug therapies designed for individual patients. In the past seven years, PGRN scientists have explored the contribution of genetics to the effects of medications for diseases such as asthma, depression, cancer and heart disease (www.pharmgkb.org). On behalf of the PGRN investigators we appreciate the opportunity to review the SACGHS's draft report on pharmacogenomics. The wide availability of clinical genomics technology and the critical health economic situation provide great impetus for making pharmacogenomics of broad use for patient care. We commend the Committee on this vast undertaking and welcome the chance to comment on this report. Below are section-by-section minor and major considerations for the Committee's review.

Executive Summary

A. There is a heavy emphasis on drug metabolizing enzyme (DME) pharmacogenomics. There are certainly important examples of clinically relevant DME polymorphisms. Equal, if not more, emphasis should be given to drug target pharmacogenomics.

B. Recommendations: In the recommendation section, the Committee suggests that NIH should require FDA's quality of evidence standards in grant submissions. This is vague and should be clarified in the final draft. Specifically, what requirements does the Committee support, as the FDA evidentiary standards differ depending on the regulatory circumstance. In addition, the major current limitation of pharmacogenomics is the insufficient clinical evidence, rather than quality of clinical test standards.

As a research network, we also strongly endorse recommendations 1 and 2, which call for enhancing basic and translational research. We would like to endorse the recommendation that more funds are made available from NIH and other agencies for research in basic and translational pharmacogenomics. We also would like to add that there needs to be specific recommendations about funding translation (T1 level) of basic mechanisms to clinical drug response. We also suggest that under recommendation 3, Clinical Trial Design, that the NIH require that all clinical drug trials (that it sponsors) include collection of DNA.

In section 5C., it is stated that "Drug and diagnostics manufacturers should conduct studies and disseminate results on the clinical validity and clinical utility of PGx (e.g., through publication in peer-reviewed journals), including statistically non-significant and negative findings." However, this is unrealistic in the context of the current publication policies for most major journals. One way forward would be to encourage the deposit of ALL pharmacogenomics data in a public database such as PharmGKB, as a mechanism for public data sharing that would include neutral or negative findings.

In section 5D., we urge the Committee to comment on the importance of model consent language in human subjects research. In addition, we believe that all human trials should have a provision for collecting, at minimum, germline DNA. So rather than "adding field to the ClinicalTrials.gov database to identify clinical trials that could incorporate PGx study Components," we suggest a field in ClinicalTrials.gov that identifies which studies are collecting germline and/or tissue-specific (e.g., tumor) DNA.

Section 10 highlights the need for HHS to become more of a leader in the integration of pharmacogenomics into clinical practice. HHS contains some of the major initial 'winners' from individualized therapy (CMS, VA, etc), so they need to become more active in helping drive the pharmacogenomics opportunity to fruition.

In section 15, it is stated that an "interdepartmental work group should be established to review SACGHS's PGx recommendations, assess whether and how to implement them, monitor HHS's progress, and report back to SACGHS. The work group also could serve as a forum for discussion of other PGx activities." We strongly encourage this group to include constituents/members beyond the immediate purview of HHS departments.

General Aspects of the Report

In the section on "Application of pharmacogenomics to existing drugs", the PGRN is apprehensive about the statement: "The application of pharmacogenomics to existing drugs, however, may not always add value. Where ADRs associated with a drug are considered minor and alternative drug treatments exist, it may be more practical and convenient to provide the drug and observe the patient's response than to use a pharmacogenomics test to rule out the drug". The ultimate goal is for pharmacogenomics to offer a preemptive strategy for the selection of 'best' therapy as initial therapy. The current approach that allows knowledge of drug effect to be learned through patient misfortune should be discouraged, even in situations where the committee feels the ADR is 'minor'.

In the section on "The Role of PGx in Addressing Unmet Health Needs", there is no mention of improving the drug development process as an unmet health need. Drug development is funded to a large extent by the public in the hopes of creating new drugs for what by definition are unmet health needs. We encourage a section on how the pharmaceutical industry has failed to bring to market many drugs in which the public has invested.

For Recommendation 2, it is suggested that "One of the foci of this translational research should be the development of more rapid, cost-effective genotyping technologies." Rarely will the pharmacogenomics decision need to be made in minutes and there are more pressing issues than small incremental improvements in current technology. Rather money should go to funding independent academic researchers, and to build consortia to facilitate economy of scale. Technology is not the rate limiting step to translation. Lack of incorporation of collection of germline DNA and lack of genetic studies incorporated into large Phase III clinical studies is the major obstacle.

In the discussion regarding industry in the "Gate-Keepers" section, this section is short and does not call on industry to help facilitate Pgx translation. The Committee should consider

stronger recommendations for industry here. As it stands, this section can be seen as justifying a perceived inaction on the part of industry, leaving SACGHS vulnerable to criticism that the Committee is not acting in the fiduciary public interest.

On page 16, the report reads, "Providers will face additional costs of education and an increase in the amount of time needed to use and interpret diagnostic results." This seems overstated in that this requirement is in no way different from currently mandated continuing education requirements for maintenance of licensure in good standing. In addition, in the post–genomic era, if this time is not taken, it will ultimately not be within the standard of care that will be shortly developing due to increased genetic information and understanding. Laboratory medicine departments and electronic medical record providers will need to act, but the level of education for clinicians and patients will typically not be greater than that needed for most current tests.

Pharmacists and other health professional who work with patients and their medications should be explicitly involved in patient education programs.

Finally, Networks between healthcare systems, clinicians and scientists should be established to further research in the pharmacogenetics of drug response and adverse drug reactions. Such partnerships are needed for research on the genetics of response and adverse drug reactions in real-life large patient populations. This recommendation could be placed under translational research or a stand alone.

CENTER FOR PUBLIC HEALTH AND COMMUNITY GENOMICS

UNIVERSITY OF MICHIGAN SCHOOL OF PUBLIC HEALTH

2675 CBPH SPH-I Tower 109 S. OBSERVATORY ANN ARBOR, MI 48109-2029
TELE: (734) 615-3141 FAX: (734) 936-0927 E-MAIL: MOD@UMICH.EDU

May 31, 2007

Reed V. Tuckson, M.D., Chair
Secretary's Advisory Committee on Genetics, Health, and Society
NIH Office of Biotechnology Activities
6705 Rockledge Drive, Suite 750
Besthesda, MD 20892

Dear Dr. Tuckson and the Secretary's Advisory Committee on Genetics, Health, and Society,

The SACGHS is to be commended for its thoughtful review and recommendations for the growing field of pharmacogenomics. Both industry (health care, the pharmaceutical industry) and the public are devoting increasing attention to pharmacogenomic tests and drugs as a real possibility. The draft report mentions the field is moving from the take-off stage. Not only do educational and dialoguing opportunities exist now, but spread of balanced information about this field is likely to be an actual tool in accelerating decision making about research and applications. Seeking public comment is useful because it brings out a variety of viewpoints and novel perspectives.

The most frequently cited advantage of pharmacogenomics (PGx) is that it will enable identification of individuals who are either more likely to benefit from pharmaceutical compounds, or likely to develop adverse drug responses (ADRs) when a given compound is administered. Identifying individuals appropriate for treatment will speed regulatory marketing of needed compounds. While pharmaceutical companies might eye these diagnostic virtues advantageously, they are probably also aware that in some respects market share could also be reduced since a smaller group, compared to blind administration to the population, will be receiving the compounds for which testing is performed. It is hard to judge the outcome from an industrial perspective, since financial and legal pluses and minuses for a range of variables exist, but this double-edged aspect might be considered one reason PGx applications have not expanded more rapidly than they have.

At our institution, Gus Rosania (College of Pharmacy, University of Michigan) has suggested that pharmacogenomics will have an even greater utility in drug discovery than in clinical product development. Pharmaceutical companies universally consider the therapeutic:toxicity window in developing drugs. Recommended dosages are often kept on the low side (unintentionally reducing the therapeutic effect) to minimize toxicity in the range of users. Dr. Rosania argues companies will continue to search for compounds

having the highest therapeutic ratio for the largest portion of the population. Their mission is geared towards large population numbers. One natural use of PGx harmonious with this population-oriented character of the industry is to utilize the technology to implement ADR drug screening assays early in the drug discovery process. In addition to using genomics to identify potential therapeutic efficacy and minimal toxicity of compounds for particular groups based on their genetic variability, which requires personalized testing and more selective drug administration, companies might also wish to use pharmacogenomics to screen-out drugs that early on show variability in response between individuals. The utility of PGx lies in its capacity to be used in industrial ADR screening assays that check to see in the test tube whether a given drug is broken down by candidate pharmaceuticals. In this way, the drug is made more safe and effective early in the drug development process, before it is moved through the clinical trial phases.

Working in a school of public health, I am especially appreciative the SACGHS has mentioned PGx applications for conditions that impact large portions of the population, such as stroke and other vascular thromboses. Use of PGx for managing warfarin in those at risk of harmful blood clots would have widespread benefits. It should be noted that many public health benefits come from primary and secondary prevention, not just tertiary prevention. Genetic tests can be especially useful at the outset before a chronic disease has visibly or significantly manifested. The attempt to maximize population benefit would place PGx at the susceptibility testing stage when prophylactic therapy and disease monitoring could be applied. PGx has a role in preventive just as much as restorative medicine.

One controversial role of PGx that has already become instituted to some degree is targeted use for particular racial-ethnic groups, the arterial drug BiDil being the most prominent example. Other suggested race-based applications can be found for conditions like glaucoma and asthma. Concerns arise because means for establishing correlations between drug function and polymorphisms prevalent in a particular racial-ethnic group are often not part of the original study design. In the case of BiDil, special benefits in African Americans were postulated after an incidental finding that led to a second study and the more group-specific conclusion. Post-hoc analyses require greater statistical power to maintain validity, and are subject to arguments that the correlation found is spurious. Further, secondary studies of this kind tend to focus on one racial-ethnic group, with the consequence that benefit to other racial-ethnic groups is not equally examined. SACGHS is quite right in its recommendation that NIH in conjunction with the FDA should promote valid study design of clinical trials and that HHS should facilitate the use of improved methodologies in cogent observational studies.

Race-based pharmaceuticals represent an intermediate stage during which discovery of specific polymorphisms should proceed so that genetic testing can replace use of racial-ethnic grouping (itself subject to variable definition) as a proxy. I would caution that level of acceptance of race-based pharmaceuticals by members of specific racial-ethnic groups is neither simple nor predictable. It is equally true that in the past particular groups have been harmed by participation in ethically unsound research studies, and ignored by other studies from which they could have benefited. Oftentimes in the medical

and bioethics journals medical authorities and ethicists will assume polar positions, the one embracing genetic developments, the other viewing them critically. In the real world truths are often more centrally located.

Despite ethicists' criticisms of BiDil, the NAACP has teamed up with NitroMed, the makers of BiDil, to advocate for the use of the drug in African Americans suffering heart failure. In our own "Genetics and Racial/Ethnic Identity" Research Community discussions, we heard white bioethically adept discussants criticizing the use of BiDil, while an African American university professional argued its use should be considered in terms of effectiveness in helping African Americans. Genetics Policy Project community dialogues held in Michigan and Alabama showed that while participants of varied racial-ethnic background were strident about avoiding discrimination as a consequence of genetic applications, they also held therapeutic value to be a major priority in accepting particular technologies. To whatever extent the relevant studies are well-designed, this aspect of test and drug development removes itself from casting the findings about a particular pharmacogenomic regiment in doubt or mistrust. The argument about whether race-based genomics will be found provisionally acceptable by particular groups follows a complex rather than linear dynamics, calling for dialogue with the groups potentially impacted, at the start and as developments evolve.

In the SACGHS draft report the sections on "Translational Research" and "Development and Co-development of PGx Products" are almost back-to-back. Laboratory test kits and bottles of medications come with labeling. Were genetic test kits to be used to identify genetic polymorphisms or enzyme levels in one racial-ethnic group especially, or pharmacogenomic medications to be used for such a purpose, instructions should be included that both explain usefulness and avoid stigmatization or exclusion. Wording should be sensitive to racial-ethnic concerns. Explanation should be given that a given disease is not associated with just one group, and that members of other racial-ethnic groups may benefit as well.

My best wishes to SACGHS in its review of public comments and the finalization of its timely *Realizing the Promise of Pharmacogenomics: Opportunities and Challenges* report.

Sincerely,
Stephen Modell

Stephen M. Modell, M.D., M.S.
Dissemination Activities Director
Center for Public Health and Community Genomics
University of Michigan School of Public Health

THE GEORGE WASHINGTON UNIVERSITY MEDICAL CENTER
WASHINGTON DC

SCHOOL OF PUBLIC HEALTH AND HEALTH SERVICES
DEPARTMENT OF HEALTH POLICY

5/31/07

Reed V. Tuckson, MD
SACGHS Chair
NIH Office of Biotechnology Activities
6705 Rockledge Drive, Suite 750
Bethesda , MD , 20892

Dr. Reed V. Tuckson, SACGHS Chair:

Thank you for allowing the public to comment on the recent draft report generated by the Secretary's Advisory Committee on Genetics, Health and Society entitled *Realizing the Promise of Pharmacogenomics: Opportunities and Challenges.* The comments I have on the document are brief and focused. I am available to provide more details regarding these comments at any time.

General Comments

1. Add timeline and deadline

Overall, the document provides one of the best available reviews of the key policy issues related to realizing the promise of pharmacogenomics and should guide work in this area for years to come. The document could be strengthened by adding a timeline of suggested steps which should be taken by the private and public sector in order to reach the point at which pharmacogenomics is improving health outcomes of the public. The timeline should be accompanied by a particular deadline year, such as the year 2020, when various stakeholders will begin to realize the promise of pharmacogenomics on a wider scale. Another approach may be to set a unique set of dates for different stakeholders, such as 2010 for FDA policy improvements, 2012 for CMS policy improvements, and so on. The Healthy People 2010 and other similar government campaigns are a good example of how an established deadline along with a vision and clear objectives can inspire innovation and progress. The document currently provides a variety of objectives to achieve, but does not offer an overall time frame which integrates these objectives and shows how they relate to one another in a temporal manner.

2. Provide evidence to support the need for pharmacogenomics.

Another general aspect of the report which could be improved is the explanation for why there is a need for pharmacogenomics. The explanation of the promise of pharmacogenomics does not provide a great deal of evidence to demonstrate the need that exists for this technology. For example, although pharmacogenomics would appear to quite useful in decreasing adverse reactions to drugs, the document does not provide a list of which adverse reactions are potentially linked to genetic variation, whether these adverse reactions are clinically important, how many people are affected by these adverse reactions, and whether these adverse reactions are so financially burdensome and unable to be managed that new technology, such as pharmacogenomics, is needed to prevent them. If this information is unknown, the report should indicate this fact and encourage research to understand the need for pharmacogenomic technologies to prevent adverse drug reactions. Similar examples apply for the other applications of pharmacogenomics – diagnostic, improving clinical trials, etc. A stronger case for the need for pharmacogenomics in various areas of medicine and how this technology is better than competing technologies will help insurers– public and private – understand why they should pay for this technology in the future.

Comments on Executive Summary

1. Typo

This section does contains a small typo on page 8. The phrase "such collaborations by adding field to the . . " should be changed by inserting "a" or "the" before the word "field."

2. Suggested change to recommendation on subgroup differences in drug response – recommendation 8A

In Recommendation A, I suggest changing "may be" to "are." To date, there are hundreds if not thousands of papers demonstrating the role of genomics in drug response and none which demonstrate that race/ethnicity affects drug response. Papers linking race/ethnicity to drug response are using race/ethnicity as a proxy for unknown or known genomic and environmental factors. Thus, the argument is whether to use a proxy or use the genomic and environmental factors which actually matter for human disease and health outcomes. Also, "FDA" should be changed to "FDA and NIH" since both agencies provide guidance to researchers regarding how they should use race/ethnicity in their studies. The section of the report which is linked to this recommendation should include a section about NIH's policy on race/ethnicity. In addition, the statement "other biological factors" should be changed to "other biological, social, behavioral and environmental factors." This approach mirrors the second recommendation and is a better

reflection of factors which researchers should consider instead of using a proxy such as race/ethnicity.

3. Suggested change to recommendation on subgroup differences in drug response – recommendation 8B

Based on the growing body of evidence that race/ethnicity are proxies and not factors impacting human physiology directly, the statement by SACGHS in this report that race/ethnicity are only proxies, the negative market response received when BiDil was labeled as being for self-identified African Americans only, and the clear statement by the Office of Management and Budget's Directive 15 that these categories are not scientific but only sociopolitical constructs, the end of recommendation B should include a statement that clearly opposes the use of race/ethnicity as an indication for any diagnostic tests/drugs, and supports the use of factors which impact human physiology (genomic and environmental) instead of using race/ethnicity. A potential statement is: "Based on the evidence that race/ethnicity is a proxy and not a factor which impacts human physiology directly, FDA should develop a policy which inhibits the use of race/ethnicity as an indication for future drugs or diagnostic tests." The lack of a clear recommendation on this issue and thereby *implied acceptance* of the opposite approach (using race/ethnicity as an indication for drugs/diagnostic tests) could hinder the translation of pharmacogenomic technologies into clinical practice where racial/ethnic drug labeling is confusing and unlikely to affect clinical decisions.[1]

Comments on Introduction

1. Need clear definition of pharmacogenomics

On page 12, the report states:

> "In the present document, the term "pharmacogenomics" (PGx) refers to the study of how differences in gene expression affect an individual's response to drugs. This encompasses differences in DNA sequences related to an individual's metabolism of drugs (pharmacokinetics) or physiological response to drugs (pharmacodynamics)."

The definition used for pharmacogenomics is not consistent with the focus of the report. The definition uses the term "gene expression." However, the document focuses on genetic tests that analyze genomic differences among humans and not gene expression differences. A better definition would indicate that this field is the study of how "genetic differences that exist between every human makes their responses to drugs unique."

[1] Brody H, Hunt LM. BIDil: Assessing a Race-Based Pharmaceutical. Ann Fam Med, 2006 Nov-Dec;4 (6):556-560.

2. Need proof for claims of PGx impacting compliance

On page 15, the report states:

> "Rational therapy selection using PGx could diminish some compliance problems and increase treatment effectiveness, as well as yield economic benefits to consumers, payers, and the broader health care system."

Is there any evidence to support this statement? None is provided. A discussion of the reasons that people decide not to comply would be quite helpful in understanding whether PGx technologies are likely to make a difference in this area.

3. Explain whether missing PGx data on drug labels is important for patients

On page 20, the report indicates that "findings suggest that much of the available PGx data in the literature is ignored in prescribing information included in package inserts." However, there is no discussion regarding whether this data would likely impact the care being received by patients or their outcomes. There is also no discussion of the quality of this data. A key question is whether there is any reason to include this data. There are likely to be a number of factors related to drugs which are not included in their labeling because of the lack of relevance to treatment or outcomes.

Comments for Research and Development Section

1. PGx researchers must understand how insurers will evaluate the products developed from their research

A useful addition to this section would be a discussion of how to educate researchers (bench science and clinical) about cost constraints downstream which may prevent overly expensive products from reaching consumers who need them the most. Academic and industry researchers must have an awareness of the financial needs of private and public payers in order for pharmacogenomics to affect the health of patients. For example, payers can provide information regarding where they see excessive expenditures that may be relevant areas of innovation for pharmacogenomics (i.e .expenditures on adverse drug reactions for certain drugs).

2. Typo

There is a typo on page 28. The report states: "which traditionally do not traditionally require the same level of external. . . " This should be changed to "traditionally do not require the same level of external . . ."

3. Lack of evidence for statement regarding self-reported race

On page 48, the report states that "In most cases, these data [race and ethnicity] are self-reported . . . " No evidence is provide to support this statement. In fact, one recent study opposes this statement by demonstrating that the vast majority of studies (over 70%) do not provide an explanation of how race/ethnicity is determined.[2] The statement should be changed to reflect the best available evidence or provide some source of evidentiary support which shows why the current literature is not correct.

Comments for Implementation of PGx to Improve Outcomes in Clinical and Public Health Practice Section

1. George Washington University Bachelors Degree in Pharmacogenomics

On page 73, in the discussion of the integration of pharmacogenomics into pharmacy schools, the report should mention the only existing bachelors degree in pharmacogenomics which exists at George Washington University (GWU).[3] This is a unique collaboration between the pharmacology department at GWU and the pharmacy school at Shenandoah University.

Comments on Federal Efforts

1. Addition to Health Disparities Section
The section which discusses efforts related to health disparities, should provide details about the NIH Intramural Center for Genomics and Health Disparities.

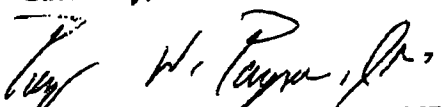
2. Adding ELSI Program to various sections
In the two areas with no federal efforts (genetic exceptionalism and unintended consequences), the report should mention past and ongoing research on these issues being funded by the NHGRI ELSI Program. In addition, the report should mention the existence of Centers of Excellence in ELSI Research which address these issues and most of the ethical, legal, and social implications listed in this section of the report. Currently, there is no explicit statement regarding the work of this valuable component of the NHGRI which is an outgrowth of the foresight of James Watson and other notable scientists concerned about the misuse of their scientific discoveries. Given that Watson's genome was recently sequenced, it would make sense to point to the government's effort to make sure

[2] 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 Dec; 32(12): 724-728.
[3] George Washington University Pharmacogenomics Program, available at http://www.gwumc.edu/healthsci/programs/pharmacogenomics/ (accessed on June 1, 2007).

his genetic information is not used against to harm him, even though it was made available to the public.[4]

Thank you for your taking time to consider these comments.

Sincerely,



Perry W. Payne, Jr., MD/JD/MPP

Assistant Research Professor

[4] Wade, N. Genome of DNA Discoverer is Deciphered, NY Times, available at http://www.nytimes.com/2007/06/01/science/01gene.html?_r=1&oref=slogin (accessed on June 1, 2007).

-----Original Message-----
From: Matthew D. Pegorari [mailto:mpegorari0600@wsc.ma.edu]
Sent: Thursday, May 31, 2007 10:21 PM
To: Goodwin, Suzanne (NIH/OD) [E]
Subject: pharmacogenomics

Dear Suzanne Goodwin,

I am concerned that the pharmaceutical industry will have too great an influence upon public education (Recommendation 11). All health care professionals including physicians, nurses, pharmacists, and other professionals will be a very large part of PGx and they need to be very educated on the subject. These professionals need to be more educated on the topic of PGx, yet there is no information explaining the way in which these current health care professionals will be updated and educated. It seems to me that these professionals will not want to take the time to go back to school and learn more about PGx with their busy schedules. Since physicians must complete CME's to maintain licensure, I understand that many physicians rely very heavily upon pharmaceutical company representatives for information about drugs. It seems that they would be more likely to listen to the pharmaceutical representatives that come to give them the new medications rather then take the time to go get more educated at a university. These pharmaceutical representatives are one of the main sources of information on the products that they are restocking Doctor's office shelves with. If the Doctor's are going to listen to these representatives as their main source of information, is this a credible source to get such important information or should they be getting the ideal information from a professional on the subject? It is unknown to tell within this article where that information would be coming from.

It seems as though there is also some misleading information on the way in which common citizens will be educated on the topic of PGx. It is the responsibility of the health care professionals to educate their patients on this topic of PGx. It seems as though it would not be probable that most Doctors and other such professionals would have the time to spend on each other their patients on PGx. There needs to be a better system in which the Doctor's practice could use in order to educate their patients. Most people are now computer literate and use the internet. Although this is true many are still unclear or unwilling to go online and teach themselves about such things as PGx. It is unlikely that a person that has gone through PGx testing and has been told briefly about the topic by his or her Doctor would go home and look up information on the subject to fully understand it. It is not the responsibility of the patient to teach themselves on such a topic but it would be beneficial to them. As a result I thought of an idea that would not only educate the people about PGx but would also be easy for them to do. The Doctor's practice should get the emails of all of their patients and send them links to web sites that are information intensive on the subject of PGx. Because most people check their email regularly, this would give them the opportunity to easily click on the link that would bring them right to the page. Most people will read something that is easily accessible to them. This will educate the public while not forcing them to do any work at all besides reading the information.

I feel that if such simple things were introduced then it would make PGx a more known and educated topic to not only professionals but to patients as well. This will ensure that Doctor's will be educated by more credible sources about information on the topic. This will result in more accurate results and diagnoses and allow Doctor's to do so faster and more efficiently. By educating the public it allows them to feel more comfortable with PGx and allow them to understand what the Doctor or professional is saying to them when they are addressed on the topic.

Thank you for your time,

Matthew Pegorari

Undergraduate Biology Major at Westfield State College

From: Carol Pena [mailto:carol.pena.b@bayer.com]
Sent: Fri 3/30/2007 10:50 AM
To: Goodwin, Suzanne (NIH/OD) [E]
Subject: Comments on SACGHS Pharmacogenomics Report

Dear Dr. Tuckson,

I am writing to comment on the draft pharmacogenomics report prepared by the SACGHS.

I am a scientist with extensive genetics and genomics experience working in the pharmaceutical industry. I currently work on biomarkers in clinical trials for oncology drugs, so my comments stem from my experience in this arena. I have 2 topics that I think the report should cover a bit more:

- 1) Developing practices for **reliably obtaining sufficient samples in clinical trials** to perform genetic/genomic testing; and
- 2) Clarifying additional **issues on informed consent** for genetic/genomic testing in clinical trials - i.e. what extent of informed consent is needed (recommended wording would be very helpful), what is covered in genetic/genomic informed consent (i.e. what types of tests), what extent of testing is ethical to perform (even with informed consent), and what timeframe the genetic/genomic testing must be performed in under the informed consent.

1) Practices for obtaining adequate samples for genetic/genomic testing in clinical trials

While it is true that there is a dearth of marketed genetic and genomic tests, in large part this is not due to lack of interest by the pharmaceutical industry (at least in my personal experience). One of the largest hurdles that pharma companies must overcome in using genetics/genomics in the course of clinical drug development is the practicality of obtaining adequate samples. While every clinical protocol (all oncology) that I write requests the diagnostic paraffin-embedded tumor sample (or slides made from the tumor sample) to be submitted to biomarker and genetic/genomic testing (with proper consent), typically we receive such samples from only ~30% of the patients enrolled in the trial. It is not that the patients don't have such a sample - depending on the tumor type, almost all have had a diagnostic biopsy that does exist somewhere (we're not requesting fresh biopsies; it's even harder to get these). The difficulty is in actually obtaining the sample. This may stem from a number of practical issues - maybe the biopsy was taken and evaluated by a different doctor than the study doctor and so resides in a different hospital, or maybe the pathologist does not want to surrender the material. But the inability to obtain such material for genetic/genomic testing is a large blockade to being able to utilize penetics/genomics in a clinical trial or to co-develop a PGx-based diagnostic test. This report should cover the development of guidelines that encourage physicians and pharma companies to work together to evaluate this important material.

2) Additional issues on PGx informed consent

Some open questions on informed consent for genetic/genomic testing:

A) Is a separate consent form required for both genetic (i.e. gene sequencing) and genomic (i.e. RNA anlaysis) testing? These have very different ramifications - i.e. RNA testing cannot identify an individual, while DNA sequencing can. Also FISH or DNA methylation status would not identify an individual. Should RNA analysis, FISH, and DNA methylation require the same stringent level of consent as DAN sequencing?

B) Should germline PGx testing have a different level of consent from somatic testing? Again, these 2 types of tests have very different implications - a germline genetic test may speak to overall health and potentially the health of offspring; however, somatic mutations only reflect upon the status of the region - i.e. the tumor itself. A mutation in a tumor will not be passed to the next generation, and, other than the cancer at hand, will have no other effects on the patient's health.

C) How broad can a genetic consent form practically be? At the beginning of a clinical trial the genes or genomic tests to be performed can be defined very specifically - but, in trials lasting years, the state of the art can change by the end of the study. At the end of the clinical trial we would like to perform the tests which are scientifically most sound. While I recognize that PGx consent cannot be complete open-ended, there should be some practical way to obtain consent to do the tests that will make most scientific sense at the conclusion of the study.

D) Timeframe of testing - Again, the state of science is continually evolving. It would be beneficial to determine guildelines on how samples collected in clinical trials can be stored and saved for future testing as new knowledge emerges (potentially over a long timeframe).

Conclusion

Pharmacogenetics and pharmacogenomics do hold much promise for improving the treatment of diseases such as cancer and for individually-tailored treatment. However, scientists in clinical drug development continually face a series of practical challenges that often precludes the performing of "the right experiment". Clearer guidelines on 1) how academic physicians and pharma companies can work together to obtain adequate samples for PGx testing in clinical trials, and 2) PGx informed consent would allow scientists to focus more clearly on the scientific challenges with fewer logistical distractions.

Sincerely,
Carol Pena

Carol E. A. Pena, Ph.D.
Biomarker Scientific Coordinator
Clinical Pharmacology
Bayer Healthcare, Pharmaceuticals
400 Morgan Lane
West Haven, CT 06516
carol.pena.b@bayer.com
(203) 812-5866

PMC Personalized Medicine Coalition

June 1, 2007

Reed V. Tuckson, M.D.
Chair
Secretary's Advisory Committee on Genetics, Health, and Society
National Institutes of Health, Office of Biotechnology Activities
6705 Rockledge Drive, Suite 750
Bethesda, MD 20892

Re: Draft Report to the Secretary of Health and Human Services (HHS), *Realizing the Promise of Pharmacogenomics: Opportunities and Challenges*

Dear Dr. Tuckson:

The following comments are submitted on behalf of the Personalized Medicine Coalition (PMC). The PMC represents a broad spectrum of academic, industrial, patient, provider, and payer communities that seek to advance the understanding and adoption of personalized medicine concepts and products for the benefit of patients. We thank the Advisory Committee for the opportunity to actively engage in this process, and applaud its work in this arena.

Comments:

We congratulate the Advisory Committee for drafting this thoughtful review of important issues in the future of health care related to the emergence of pharmacogenomics. A few specific comments follow.

Public Education. We agree with the Advisory Committee that the public needs to be educated and, as noted in the report, the PMC is dedicated to public education on all topics related to personalized medicine including PGx. The PMC currently is writing a proposal for the development of a national model for a medical education program in pharmacogenomics.

Resources. As the field develops, federal entities responsible for advancing PGx should be funded appropriately. The report highlights the importance of basic and translational PGx research programs at the National Institutes of Health (NIH). PMC supports full-funding of the NIH and encourages the NIH to increase its efforts in understanding the genetic basis of disease.

1225 New York Avenue, NW, Suite 450
Washington, DC 20005

Phone 202-589-1770
Fax 202-589-1778

PersonalizedMedicineCoalition.org
info@PersonalizedMedicineCoalition.org

PMC Personalized Medicine Coalition

The Critical Path Initiative also facilitates co-development of Dx/PGx products. PMC strongly endorses greater funding of the Critical Path Initiative, which has enormous potential to improve health care in the future.

Reimbursement. As the report clearly outlines, federal payers have a leading role in the adoption of PGx as the largest single health care payer in the United States. Third party coverage and reimbursement are essential to ensure appropriate access to personalized medicine products and services, and payer coverage and payment decisions should make use of the best available evidence. In situations where payers seek additional evidence, they should work collaboratively with innovators to ensure that evidence requirements are appropriate and do not create barriers to patient access to new personalized medicine technologies. In addition, we recommend that the report be broadened to suggest coverage and adequate reimbursement of the costs of the relevant pharmaceutical and the validated diagnostic test as well.

The report suggests that adding "prevention" as a Medicare benefit category would expand payer coverage and PMC supports the development of new policies and legislation to expand payer coverage and reimbursement of PGx and services focused on disease prevention.

Health Information Technology (HIT). The PMC strongly supports the creation of a national health information network that enables the interoperable exchange of electronic health records securely among stakeholders in the healthcare system. Such a system will improve health outcomes and increase efficiency in health care research. As the report notes, widespread adoption of electronic health records will empower patients and physicians with the information they need to make optimal treatment decisions. PMC suggests that as the infrastructure develops, it should take into account the unique needs of the basic, clinical, and translational research communities. Providing the research community with secure, consented clinical outcomes information will enable HIT to accelerate new personalized medicine breakthroughs into practice.

Collaboration. PMC appreciates the Committee's recognition of the importance of public-private collaborations to advance the field of pharmacogenomics, and the recognition of the role the PMC can play in advancing the field. We suggest that the report be revised to recognize some of the recent collaborations that have been established, such as the FDA/C-Path Institute Predictive Tox and Molecular Assays and Targeted Therapeutics consortia. These and other initiatives are directly using large-scale electronic health records to identify putative biomarkers for genomic analysis including the C-Path Institute/University of Utah/Intermountain Healthcare cardiovascular safety project.

PMC Personalized Medicine Coalition

In addition, the Foundation for the National Institutes of Health (FNIH), the FDA, the NIH, and the Pharmaceutical Research and Manufacturers of America (PhRMA) recently announced the launch of The Biomarkers Consortium, a public/private research partnership. The consortium will discover, develop, and qualify new biological markers to support new drug development, preventative medicine, and medical diagnostics. Results from consortium projects will be broadly available to researchers worldwide.

We hope that as policy develops, the PMC will become a partner in the process of integrating the promise of pharmacogenomics into healthcare. The PMC has the power to convene stakeholders who can speak to these issues in a clear and constructive way. We hope also to help produce sound policy that addresses the needs of patients, providers, manufactures of both pharmaceuticals and diagnostics, as well as the federal agencies that oversee them.

Thank you for your consideration.

Respectfully submitted,

Amy M Miller

Amy M. Miller, Ph.D.
Public Policy Director

Pfizer Inc
Worldwide Regulatory Affairs and Quality Assurance
50 Pequot Avenue
New London, Connecticut 06320

Pfizer Global Research & Development

May 29, 2007

Reed V. Tuckson, M.D.
SACGHS Chair
SACGHS, Office of Biotechnology Activities
National Institutes of Health
6705 Rockledge Drive, Suite 750
Bethesda, MD 20892

Dear Dr. Tuckson:

Pfizer is pleased to offer the following comments on the draft report of the Secretary's Advisory Committee on Genetics, Health and Society (SACGHS) entitled *Realizing the Promise of Pharmacogenomics: Opportunities and Challenges*.

The document provides an excellent overview of the opportunities and challenges presented by pharmacogenomics and will serve as a useful and well referenced resource document. The committee has provided a very thoughtful and comprehensive assessment of the many facets involved in delivering the true promise of pharmacogenomics and should be applauded by stakeholders for the extensive nature of the review. The report summary rightly emphasizes safety; however, we believe that in the near term, pharmacogenomics holds particular promise in relation to drug development productivity and efficacy. The document would benefit from a more extensive discussion of the challenges involved in applying pharmacogenomics to safety issues, the complexities of which help explain why realizing the potential of pharmacogenomics in this area may be a longer-term goal.

We feel that in many areas DHHS can bring its strengths and expertise to advance the state of knowledge for pharmacogenomics. Specifically, areas such as research on the genetic basis of disease, the translation of basic research findings into clinical trials, and the standardization of data to enable data sharing and database interoperability, would benefit from the department's active input. Areas such as the development of genotyping technologies for example, may be better enabled by other sectors.

The report reflects a comprehensive assessment of many areas, resulting in over 30 recommendations, relevant to the advancement of PGx in health care. In addition to providing this broad perspective, we recommend that DHHS identify a small number of actions as priorities, that warrant particular focus, commitment and action by DHHS.

Recognizing how rapidly this area is evolving and that standardization of terminology will be critical to advancing this area, this document can play a leading role by ensuring consistent use of terms. The present definition of pharmacogenomics found on page 12 of the Introduction for example-- "the study of how differences in gene expression affect an individual's response to drugs"--is not consistent with commonly used definitions.

We have the following specific comments within the document.

Executive Summary.

pp. 4 and 24: "The use of PGx in clinical trial design and patient accrual could lead to reductions in the time needed to develop a drug from 10-12 years to perhaps as little as 3-5 years."

This statement taken from reference 7 (page 4) is speculative in nature and without further elaboration risks overselling pharmacogenomics while underestimating the complexity of the drug development process. We recommend removing it or expanding the section to insure a more measured conclusion of the current state of the art and its potential for impact on the drug development process.

pp. 5, 19-20, and 75-76: "Much existing information on PGx for guiding available therapies appears to be ignored... PGx data were available in the literature for 71.3% of these drugs, but that information appeared in the package inserts of only a few of these drugs. Much of the valuable information about PGx that is available remains to be put to work."

Again this statement from reference 14 (page 5) needs added discussion for perspective. These statements do not take into account the paucity and sometimes poor quality of the evidence surrounding clinical utility that is available. At the present time, the majority of pharmacogenomics studies in the literature provide signals warranting follow-up, but the data do not reach the standards for label inclusion. In particular there are very few publications of prospective, adequately powered studies designed to evaluate the clinical utility of pharmacogenomics applications. The report should reflect that the current status of pharmacogenomics research is largely exploratory, and is not yet consistently informative for guiding the use of drugs in a clinical setting. These statements also conflict with other statements in the report which are more truly reflective of the current state of pharmacogenomics applications, e.g. the 2nd paragraph of Executive Summary on p.3; "...clinical use has been limited by a lack of evidence of clinical validity and utility and other barriers", on p. 18; "Converting PGx science into useful tests will entail establishing and conveying matters of analytic validity, clinical validity, clinical utility and accompanying ethical, legal and social implication of the test.", on p. 33; and "... the body of research on the clinical validity and on page 85; utility of PGx tests is still small".

Recommendation 1 (Basic Research)
p. 6 and 21-22.

In addition to what is recommended, NIH should be encouraged to direct increased resources toward understanding the genetic basis of disease and to allocate sufficient resources to meet this need.

Recommendation 2 (Translational Research)
pp. 6-7 and 23-24

As noted above DHHS's efforts in translational research should be focused on endeavors other than the development of rapid, more cost effective genotyping technologies, which will be driven by external technology providers in the private sector.

Recommendation 5C (Analytic Validity, Clinical Validity, Clinical Utility, and Cost-Effectiveness)
p.7- 8 and 34-37

We agree that publishing PGx studies (either positive or negative) is important.

As noted above, an area in which DHHS could help progress PGx is promoting a standardized terminology and definitions for analytic validity, clinical validity and clinical utility.

Recommendation 6A (Data Sharing and Database Interoperability)
pp. 8-9 and 30-41. A. "HHS should encourage private sector entities (including academic institutions) to voluntarily share proprietary data to advance the development and co-development of PGx products."

This statement regarding the sharing of proprietary data needs clarification. Does this refer to sharing between private and public entities—in which a role for DHHS would be envisioned—or sharing between private sector entities—in which the role of DHHS is not clear.

Recommendation 6C (linking databases)
pp 8 and 41-42.

We strongly agree with Recommendation 6C that linking data and interoperability are critical for the advancement of the field of PGx. This is a very challenging area, and any recommendations in this report should be closely aligned with recommendations will emerge from the Personalized Healthcare Workgroup of the American Health Informatics Community (AHIC).

Recommendation 10D (Use of PGx Technologies in Clinical Practice)
p. 10 and 74-77 (Product labeling).

The recommendation should reflect that there is a need to define the criteria for when it is relevant to include PGx information in a drug label. Currently, a standard of evidence is lacking. The development of such standards of evidence though are closely linked to the development of standards for biomarker validation and qualification.

Recommendation 14 (ELSI Research)
pp 11 and 90 -94

We support the continued efforts to ensure that data generated using pharmacogenomic tools be used both ethically and legally. We believe that the DHHS can play a role in this by the generation of guidelines for appropriate conduct of studies, interpretation and use of data.

Introduction
a) Improved patient safety, paragraph 3 p.14

In this paragraph describing CYP2D6, the document implies a single genetic variant is responsible for slow metabolism. In fact, there are several variants which contribute to this phenotype and together result in the population prevalences of poor metabolizers which are cited.

Research & Development
p. 21 and p. 41

Perlegen and Affymetrix are also collaborators in GAIN, and should be listed.

Research & Development
p. 21

Since this report both summarizes the current status of the field of PGx and also is forward-looking in anticipating potential future applications, a discussion of whole genome scans should reflect the likelihood that sequencing the entire genomes of individuals (patients and/or healthy people) will be practical in the near future, and the implications of this development.

Research & Development
p. 23

In discussing the Pharmacogenetic Research Network (PGRN), there should be a general encouragement by the National Institute of General Medical Sciences (NIGMS) to reach out to industry scientists to join and expand the remit of the PGRN.

Gatekeepers, A. Industry
p.50-51.

The contribution of scientists from Industry should be recognized for leadership in advancing the field of pharmacogenomics, both via investments in internal research and also through cooperative activities with other Gatekeepers. Some examples include the industry's participation in the development of The SNP Consortium; the series of workshops conducted jointly by Industry and the FDA to develop the approach to voluntary genomic data submission; and the Pharmacogenomics Working Group has developed and published standardized terminology and recommended elements of informed consent for pharmacogenomics research. In addition numerous PGx studies conducted by Industry have been published in the scientific literature. As currently written, the report underestimates the industry's strong role in driving the development of pharmacogenetics in partnership with academia and FDA but rather seems to suggest that Industry is only reacting to FDA encouragement

Sincerely,

Lea C. Harty, Ph.D.
Associate Director, Translational and Molecular Medicine
Pfizer Global Research and Development

Marie A. Vodicka, PhD
Assistant Vice President
Biologics & Biotechnology
Scientific & Regulatory Affairs

PhRMA

Reed V. Tuckson, MD
Chair
Secretary's Advisory Committee on Genetics, Health, and Society
NIH Office of Biotechnology Activities
6705 Rockledge Drive, Suite 750
Bethesda , MD , 20892

By email to Suzanne Goodwin: goodwins@od.nih.gov

Re: **Comments on the Draft Report of the Secretary's Advisory Committee on Genetics, Health and Society:** "Realizing the Promise of Pharmacogenomics: Opportunities and Challenges," prepared by PhRMA Genomics Technical Group.

May 31, 2007

Dear Dr. Tuckson:

The Pharmaceutical Research and Manufacturers of America (PhRMA) welcome the Secretary's Advisory Committee on Genetics, Health and Society (SACGHS) Draft Report entitled "Realizing the Promise of Pharmacogenomics: Opportunities and Challenges." PhRMA considers the report to be a comprehensive and thoughtful assessment of the current field of Pharmacogenomics (PGx) and believes that it makes many potentially useful recommendations which could help advance the science and its application to critical healthcare challenges. We appreciate the opportunity to comment on the Draft Report as Pharmacogenomics (PGx) represents a cornerstone in the complex process of making personalized or individualized medicines a reality and involves multidisciplinary expertise, diverse knowledge and wide-ranging applications.

PhRMA represents the country's leading research-based pharmaceutical and biotechnology companies, which are devoted to inventing medicines that allow patients to lead longer, healthier and more productive lives. PhRMA companies are leading the way in the search for new cures. PhRMA members alone invested an estimated $43 billion in 2006 in discovering and developing new medicines. Industry-wide research and investment reached a record $55.2 billion in 2006.

General Comments:
The challenges of implementing PGx which is fundamental to delivering 'the right medicine to the right patient at the right time' should not be underestimated. The report recognizes the diverse stakeholders in the field, but does not fully acknowledge the complexity of the scientific challenges inherent in integrating PGx into the development of new medicines. Translation of new knowledge gained in the realm of basic science into practical clinical applications is a long, multi-step process. The report does not

reflect a full appreciation of the length and complexity of the drug discovery and development process, a process fundamental to development of personalized medicines. It is well established that to develop a drug can take on average 10-15 years at an average cost of 802 million dollars (estimated on 2000 dollars)[1]. PhRMA respectfully suggests that adding members with experience in drug development to the SACGHS could help to address these gaps in understanding and would add value to this and future reports.

It is imperative that PGx tests that are used for clinical decision making be based on robust scientific data. The report does not discuss collaborative efforts currently underway in industry/academic/government consortia to move the science of PGx forward. It also does not recognize the amount of this kind of research actively conducted and supported by the pharmaceutical industry, nor the industry's instrumental role in developing relevant global research standards in collaboration with regulatory authorities and academia. We feel that the introduction of the report should acknowledge

- The complexity of the science involved in PGx, and the central role of industry in advancing that science.
- Progress to date with development of regulatory guidance in the field, both in the US and globally.
- The importance of developing guidance on biomarker validation to bring these efforts forward.

PhRMA believes that building a framework conducive to research and collaboration will facilitate the development of the knowledge base upon which clinical applications can be grounded.

It is also important that the potential of PGx not be overstated. It is stated on Page 4:

> "The use of PGx in clinical trial design and patient accrual could lead to reductions in the time needed to develop a drug from 10-12 years to perhaps as little as 3-5 years."

This statement is highly speculative (coming from a consultant's report on Pharmacogenomics) and nowhere in the report is it critically evaluated. As a result it

---

[1] J. A. DiMasi, "New Drug Development in U.S. 1963–1999," *Clinical Pharmacology & Therapeutics* 69, no. 5 (2001): 286–296; M. Dickson and J. P. Gagnon, "Key Factors in the Rising Cost of New Drug Discovery and Development," *Nature Reviews Drug Discovery* 3 (May 2004): 417–429; and J. A. DiMasi, R. W. Hansen, and H. G. Grabowski, "The Price of Innovation: New Estimates of Drug Development Costs," *Journal of Health Economics* 22 (2003): 151–185.

oversells PGx while encouraging the reader to underestimate the complexity of the drug development process, where PGx is only one component of the many datasets and knowledge bases that must be built up to develop a new medicine. This statement should be modified or the source of the statement and its speculative nature made clear. Also, while pharmacogenomics holds promise for reducing adverse drug reactions it is only one component of the risk benefit profile of a drug and the complexity and long term nature of this endeavor should not be underestimated.

It is critical that the report not base recommendations on anecdotal information. PhRMA is also concerned with the statement, made on page 5 of the document (Section A), that:

> "Much information on PGx for guiding available therapies appears to be ignored. A recent review of package insert information for the top 200 drugs prescribed in 2003, found that PGx data were available in the literature for 71.3% of these drugs, but that such information appeared in the package inserts of only a few of these drugs. Much of the valuable information about PGx that is available remains to be put to work."

These statements do not take into account the paucity of the available evidence surrounding clinical utility. It should be noted by the authors that labeling text, developed by FDA in conjunction with sponsors, must be based on solid statistical evidence provided in regulatory submissions. Casual or anecdotal reports of PGx correlations with clinical outcomes are not now and should not in the future be included on product labels.

We encourage the use of a more generally accepted definition of pharmacogenomics in the document suggest that reference be made to the definitions included in the ICH E15 Step 3 Consultation on: Terminology in Pharmacogenomics: Definitions for genomic biomarkers, pharmacogenomics, pharmacogenetics, genomic data and sample coding categories.[2]

As this report is for a US governmental agency, it is reasonable to focus on the US landscape. However many of the issues discussed in this report have global implications, and there are ongoing efforts toward harmonization being conducted by regulatory authorities around the world. We recommend that this report include a section discussing global implications of PGx and promoting global collaboration in research, development and clinical utilization. This is particularly important given the

---

[2] Federal Register Notice: Vol. 72, No. 4/Monday January 8, 2007. International Conference on Harmonization; E15 Draft Guidance on Terminology in Pharmacogenomics.

global nature of modern drug development. Establishing the required research framework – for example sample collection – requires dealing with the challenges of interactions with multiple countries each operating under different regulations and standards.

Comments on the specific recommendations:

Recommendation 1:
Basic Research
We agree that more NIH investment in basic research on biochemical pathways associated with drug metabolism and drug action is beneficial; however, we suggest that the recommendation is restated to "increase funding of basic research determining which genes have an impact on safety and efficacy of drugs." The recommendation as currently stated appears to suggest focusing on those pathways or targets already known to be related to safety and efficacy of drugs yet there are only a few genes (e.g. CYPs) known to impact safety and even fewer examples for efficacy. Our recommended change in the wording would ensure that the broader research intent is emphasized.

It would be beneficial to specifically mention support for basic research on the genetic basis of disease, as advances in this area could translate into defining disease subsets and understanding the biological variation in disease pathways, both of which are critical for realizing the potential of pharmacogenomics. We also suggest that this recommendation encourage NIH to partner with the pharmaceutical industry and academia to assure NIH efforts are not duplicating ongoing work in industry/government consortia. There is much work to be done and collaboration may be the only way to address key clinically meaningful outcomes to which PGx can contribute.

Recommendation 2:
Translational Research
We agree that HHS agencies should help facilitate the development of clinically useful PGx technologies. However, we believe that the work of technology development and validation is best pursued by those companies developing the diagnostic platforms that PGx tests are run on, and that HHS agencies are best positioned to fund clinical trials, particularly with generics and disease research that encompass the use of these developing technologies.

Recommendation 3:
Clinical Trial Design

We suggest that the first sentence "NIH should encourage sponsors and researchers to consult with FDA early in the study design phase..." should be re-worded as follows: "Sponsors and researchers should be encouraged to consult with FDA early in the study design phase..." NIH does not play a major role in guiding the drug development strategies undertaken by industry as this recommendation implies; thus the beginning of the section should be reworded. We do believe that sponsors should consult with FDA early in the study design phase so that meaningful study results can be used to support a pre-market review application. We also believe that clinical trials should be conducted with appropriate scientific methodology and rigor to answer the clinical trial's (or experiment's) hypothesis and thus be 'fit for purpose.' Specifically stating that "studies should have sufficient statistical power and that quality controls should be in place" implies a level of precision not warranted in a general recommendation.

We agree that NIH should consider including FDA's quality-of-evidence standards in their assessments of the scientific merits of grant submissions that propose to advance scientific evidence around a biomarker's clinical validation.

Recommendation 5:
Analytic Validity, Clinical Validity, Clinical Utility, and Cost-Effectiveness

A. PhRMA believes that while observational studies may have utility, particularly for serious adverse effects, evidence-based clinical decision-making is better supported by prospectively-designed studies.
B. We agree that facilitating collaborations between public and private entities to advance generation and sharing of knowledge on biomarkers' analytic validity, clinical validity, etc is important. It will be especially beneficial to focus upon engaging payers to better define test characteristics that will make PGx desirable from a cost-effectiveness perspective. We believe that demand created by payers for cost-effectiveness may result in accelerated adoption and utilization of biomarkers in routine clinical medicine.
C. We believe that it will be beneficial for HHS to encourage collaboration among industrial concerns to develop biomarkers in non-competitive spaces, e.g. markers for staging or subtyping disease, or predicting non-specific adverse events like QT prolongation.

PhRMA would welcome HHS commitment to the development and adoption of a common terminology for the concepts of analytic validity, clinical validity and clinical utility, and suggests this be added to Recommendation 5.

Recommendation 6:
Data Sharing and Database Interoperability

We agree that interoperability of PGx technologies and databases will facilitate research and support building the necessary evidence base. Uniform genomic data standards, harmonization and development of an infrastructure to enable data exchange are all beneficial. We also support current efforts towards standardization (e.g. the work of the Microarray Gene Expression Data Society http://www.mged.org/ on gene expression arrays) and encourage that these efforts be effectively leveraged. Considerations of informed consent and patient confidentiality are key in this area.

Recommendation 7:

Protection of Personal Data

There are already substantial measures and guidelines in place for confidentiality and privacy on handling data of study participants, particularly in the pharmaceutical industry. We believe that rather than stronger data security measures, the most pressing need is for practice standards associated with PGx research to become more uniform regarding interpretation of patient consent to the use of the data, especially as regards genomic/genetic data. It is also important to note that while data sharing is often used to refer to data at the patient level, many types of anonymous data summaries can be made available that will facilitate research while reducing or eliminating concerns about confidentiality.

Recommendation 8:

Population Subgroup Differences in Drug Response

We agree that is important to understand the complexity of the interplay between genomic and racial or ethnic factors. As more data become available, and genomic tests are more commonly used by the medical community, establishing genomic factors as the basis of differential dosing strategies will contribute significantly towards improving patient outcomes.

Recommendation 9:

PGx-informed Prescription Drug Coverage

We believe that, in those instances where a validated PGx test with proven clinical utility is available, health plans, including Medicare prescription drug plans, should not only cover the cost of the most clinically appropriate drug but also reimburse the cost of the validated PGx test. In addition, PGx-informed optimization of drug therapy is predicated on availability of the range of different drugs related to the validated PGx test or tests. Thus, it will be important for plans to provide coverage for an adequate range of treatment options, so that the optimal therapy can be selected by the physician and patient (as informed by PGx test information and other factors). It also will be important for coverage and payment policy to apply PGx test information in flexible, clinically sensitive ways, since PGx test results often will provide information on likelihood of

individual response that will be combined with other information to inform the most clinically appropriate treatment regimen for the individual patient.

Recommendation 10:
Use of PGx Technologies in Clinical Practice
We believe that relevant PGx information may be appropriate to include in drug and PGx test labels, particularly those data relevant to analytical validity and clinical validity. However, there may be instances where some or **all** PGx data may not necessarily be appropriate for inclusion into product or test kit labels. For example, should all available relevant data for a given analyte, potentially including both commercial and "home-brew" kits, be required for inclusion? Will all published (or potentially even unpublished) validity/utility data be included?

Recommendation 10 is focused on increasing the inclusion of *relevant* PGx information in drug labels. We believe a critical element for accomplishing this is the establishment of a clear definition of when PGx information is sufficiently mature and robust for label inclusion. In other words, setting standards of evidence required for PGx information to be considered "relevant" for use in drug labels will be a critical step.

Another issue that is often overlooked in discussions of PGx is how the information may affect all aspects of clinical practice. The spectrum of consequences of truly integrating PGx information into clinical practice is a topic for further research. The types of studies needed to understand clinical utility will require in-depth considerations and collaborative efforts across different disciplines (academics, practitioners, pharmaceutical researchers, and so on) to establish the place of PGx in clinical practice.

Recommendation 11:
Public Education and Engagement
Please clarify this recommendation. Is "the assessment of the public's perceptions of and receptiveness to PGx" intended to evaluate the effectiveness of the public consultation mechanism or the public willingness to participate in clinical research studies?

Patients must be appropriately informed about the information a PGx test will provide to them and their health care providers. For example, what are the consequences of taking or not taking the test with regard to treatment options and the likely clinical outcomes entailed in each scenario? Patients must also be provided with information to allow them to differentiate between the various medical applications that use genetic information e.g. pharmacogenomics vs. disease diagnosis vs. genetic screening vs. prenatal diagnosis and so on.

Recommendation 12:
Health Information Technology
We propose that the Committee's recommendations for modernizing and optimizing the management and utilization of all secured medical information should be a priority for HHS.

Recommendation 13:
Economic Value of PGx
Pharmacoeconomic models for evaluating the outcomes of PGx testing should be designed to carefully explore the impact of differing assumptions regarding hypothetical future policies of private payers towards PGx use and reimbursement.

Recommendation 14:
ELSI Research
The SACGHS, recommendation focusing on "limits access to health care" and "results in genetic discrimination" may be misinterpreted and have a detrimental effect on the advancement and acceptance of PGx testing. Therefore, PhRMA believes that NIH should instead focus on formulating and championing practice guidelines based on already existing and 'experience-checked' practices that have evolved to *avoid* undesirable (but in many cases unlikely) outcomes of PGx. We recognize that this report is focused on PGx, however, we suggest that the recommendations made for PGx should be in line with other markers/assays/tests already used, and where generation of a wide range of medical information is routinely managed, i.e. PGx utilisation should not be more restrictive than necessary.

Recommendation 15
Co-ordination of Pharmacogenomic/Pharmacogenetic Activities
Co-ordination of activities resulting from SACGHS recommendations will be important if activities are to be prioritized and focused. PhRMA suggests that HHS consider liaising with key stakeholders in other countries who are also seeking to maximize the potential of PGx, so that a framework conducive to global drug development is achieved

Additional Comments:

Page 12: We suggest including a glossary section to clearly define the terminology used in the document. We believe that the explicit definition of PGx offered on page 12 is too narrow and is in conflict with usage of the term elsewhere in the document. For clarity we suggest the term 'pharmacogenetics' should be defined and used in accordance with the draft ICH E15 guideline. The report also states that 'pharmacogenetic tests frequently employ high throughput technologies such as microarrays or gene chip..' (p12), we suggest that the report should have a balanced

view on use of technologies with a broad range of throughputs as appropriate to the specific application.

Pages 19-20: The following statement should be omitted as it is inaccurate and misleading:
"These findings suggest that much of the available PGx data in the literature is ignored in prescribing information included in package inserts"

Page 21: Perlegen and Affymetrix need to be added to GAIN

On page 40 of the SACGHS under Data Sharing (paragraph 4), the document states:

> "Industry is unlikely to share what it considers proprietary data without some assurances that any patents and data they have specified as confidential are protected before restatement or publication. Additionally, companies may seek legal arrangements stipulating that they would share intellectual property or commercial product development and still retain the ability to pursue and market the product independently. Even with such agreements, industry may remain circumspect about sharing their data with others."

This paragraph does not accurately summarize the primary issues that the pharmaceutical industry faces with regard to data sharing. Specifically, samples collected during global drug development programs must comply with multiple countries' individual restrictions and regulations regarding sample usage and data protection. Therefore, although US law may allow limited data sharing for pharmacogenomics databases, the same standards will not apply to the whole of any company's sample database. In order to ensure that all countries will continue to allow collection of PGx samples, the pharmaceutical industry must carefully comply with even the most restrictive of data sharing guidelines.

Page 41: Perlegen should be added to the list of GAIN companies.

PhRMA appreciates this opportunity to comment and please feel free to contact me if you have any questions about PhRMA's response.

Best regards,

/S/

Marie A. Vodicka, PhD

Steering Committee
Pharmacogenomic Evaluation of Antihypertensive Responses (PEAR)
University of Florida Health Science Center
Box 100486
Gainesville, FL 32610

Reed V. Tuckson, MD
Chair, Secretary's Advisory Committee on Genetics, Health, and Society
NIH Office of Biotechnology Activities
6705 Rockledge Drive, Suite 750
Bethesda, MD, 20892

Pharmacogenomic Evaluation of Antihypertensive Responses (PEAR) is multi-center, cross-discipline research group within the National Institutes of Health (NIH)-funded Pharmacogenetics Research Network (PGRN). In general, the goal of the PGRN is to aid all researchers in understanding how genes vary among individuals, and how this variability affects drug safety and efficacy. The PGRN hopes to set standards for future research studies, and make scientific recommendations that will ultimately impact the clinical use of drugs. The specific aims of PEAR are to elucidate the genetic contribution to antihypertensive response variability, with a goal of translating pharmacogenetic findings to patient care.

On behalf of the PEAR investigators we appreciate the opportunity to review the SACGHS's draft report on pharmacogenomics. Given the ever increasing affordability of genomic technologies and the rapidity with which translatable pharmacogenetic associations are being uncovered, we feel the time is right to formalize the discourse on pharmacogenomics at the researcher, "gate-keeper", health care provider, and patient levels. We commend the Committee on this vast undertaking and welcome the chance to comment on this report. Below are section-by-section minor and major considerations for the Committee's review.

Comments/suggestions regarding the report

A. The Promise of PGx: In this section, promising (i.e., translatable) Pgx examples include TPMT and HER2, well known and clinically utilized genetic diagnostics. However, the Committee also includes warfarin among these examples. We believe that translation of genotype-guided warfarin therapy is possible, but complicated by issues likely to be worked out in a large prospective clinical trial, which is being planned. We believe that including warfarin among the validated and clinically utilized cancer examples may be a bit overstated. We suggest removing this example in this section.

In this same section, the emphasis on drug metabolizing enzyme (DME) Pgx is a bit overstated as DME polymorphisms are only likely to be relevant to a small subset of drugs with narrow therapeutic indices. While many of the examples that are in or near translation to practice are DME, we believe the the majority of new cases in the future are likely to not revolve around DME. Equal, if not more, emphasis should be given to drug target Pgx, or more generally stated,

those pharmacogenetic examples that influence drug efficacy or toxicity through non-pharmacokinetic mechanisms.

B. Challenges and Key Considerations: We agree that there are many challenges to Pgx implementation. However, we do not believe that the current health information infrastructure is not suitable for onsite clinical decision making based on Pgx. Rather, there has been a paucity of clinically relevant examples to implement in health care settings. Health care settings such as Medco, Kaiser, and the VA Medical Center systems are incredibly sophisticated in terms of information infrastructure and are ideal settings in which to pilot clinical Pgx. There should be consideration for the extensive effort being put forward by the Roadmap to help utilize clinical data warehouses to help implementation of either pharmacogenomics studies or to determine if the predicted genetic contribution plays a role in patient outcomes. Currently, there are institutions that have placed large amounts of financial and bioinformatic resources to allow this type of study, and NIH's CTSA support will in the future help to move this type of program forward.

C. Recommendations: In the recommendation section, the Committee suggests that NIH should require FDA's quality of evidence standards in grant submissions. This is vague and should be clarified in the final draft. Specifically, what requirements does the Committee support, as the FDA evidentiary standards differ depending on the regulatory circumstance. Furthermore, we submit that it is not a lack of evidentiary standards in research that currently limits Pgx translation into practice, but rather difficulty in accessing large datasets for validation of genetic associations.

For Recommendation 2, it is suggested that "One of the foci of this translational research should be the development of more rapid, cost-effective genotyping technologies." We feel this is not the best use of resources; rather money should go to funding independent academic researchers, and to build consortia to facilitate economy of scale. Technology is not the rate limiting step to translation. Rather lack of access to large genetic databases to allow replication in multiple cohorts, such as those available in large Phase III clinical studies, is the major obstacle to translation at present.

We have serious concerns regarding the section leading up to Recommendation 3. This recommendation, in part, calls for NIH to consider making FDA's quality-of-evidence standards a component of their assessments of the scientific merits of grant submissions. This seems an inappropriate recommendation as the quality of Pgx science is largely of the highest caliber. Rather, the report is surprisingly silent of the role of the pharmaceutical industry in Pgx research. The report should take a stronger stand on requiring collection of DNA in clinical studies. HHS should consider making genomic data collection mandatory for all HHS-funded studies (including pharmaceutical industry studies) with an opt-out for participants. In recommendation 5B, specific mention should be made encouraging pharmaceutical industry to collaborate with academic researchers in order to validate Pgx findings.

In section 5C., it is stated that "Drug and diagnostics manufacturers should conduct studies and disseminate results on the clinical validity and clinical utility of PGx (e.g., through publication in peer-reviewed journals), including statistically non-significant and negative findings." However, we submit that neutral findings are unlikely to be published in high-impact journals given the

current editorial policies of requiring replication cohorts (even for neutral findings). We urge the Committee to comment on this editorial policy or aid in development of non-traditional methods of dissemination of non-published Pgx findings.

In section 5D., we urge the Committee to comment on the importance of model consent language in human subjects research. In addition, we believe that all human trials should have a provision for collecting, at minimum, genomic DNA. So rather than "adding a field to the ClinicalTrials.gov database to identify clinical trials that could incorporate PGx study Components," we suggest a field in ClinicalTrials.gov that identifies which studies are collecting germline and/or tissue-specific (e.g., tumor) DNA.
In section 6, we encourage the Committee to discuss the importance of standardizing phenotypes for clinical studies in order to facilitate testing and replication of genetic associations.

In section 10, we recommend that HHS should have a greater presence at society meetings where practice models, test performance, and other issues can be addressed.

In section 12, we strongly advocate taking steps to "ensure the inclusion of clinically validated PGx test results into patient records, along with decision support systems and tools to enhance appropriate test use and interpretation." We suggest that these systems should be piloted within the VA medical center system because of its already evolved electronic medical record.

In section 13, the scope of the economic considerations of Pgx are narrowly focused on cost-effectiveness.' For Pgx per se, cost-utility and cost-benefit might be even more important economic models for consideration.

In section 15, it is stated that an "interdepartmental work group should be established to review SACGHS's PGx recommendations, assess whether and how to implement them, monitor HHS's progress, and report back to SACGHS. The work group also could serve as a forum for discussion of other PGx activities." We strongly encourage this group to include constituents/members beyond the immediate purview of HHS departments.

General Aspects of the Report
In the section on **"The Role of PGx in Addressing Unmet Health Needs"**, there is no mention of improving the drug development process as an unmet health need. Drug development is funded to a large extent by the public in the hopes of creating new drugs for what by definition are unmet health needs. We encourage a section on how the pharmaceutical industry has failed to bring to market many drugs in which the public has invested, and that through use of pharmacogenomic-guided drug development, some of these drugs might be successes.

In the section on **"Current State of the PGx Field"** it is noted that "enhancements in post-marketing surveillance methods can generate information about benefits, risks and costs of PGx products. However, current post-marketing surveillance techniques and infrastructure may be inadequate for the collection and analysis of such data." We agree with this assessment. Furthermore, there needs to be a tremendous amount of resources dedicated to revamping the FDA AERS to allow for adequate samples, precise case definition and identification, and collection of genomic DNA. This should be crafted into a specific recommendation.

On page 40, the report reads "Industry is unlikely to share what it considers proprietary data without some assurances that any patents and data they have specified as confidential are protected before restatement or publication. Additionally, companies may seek legal arrangements stipulating that they would share intellectual property or commercial product development and still retain the ability to pursue and market the product independently. Even with such agreements, industry may remain circumspect about sharing their data with others." The report is particularly soft on industry here. As previously mentioned, the public in large part finances industry studies, and is therefore entitled to exploration of Pgx within industry-sponsored research. The Committee should consider specific recommendations on how we can leverage relationships between academia and industry to validate genetic biomarkers (or diagnostics—both categories should be developed simultaneously as the FDA has different approval paths for both) for clinical translation.

In the discussion regarding industry in the "Gate-Keepers" section, this section is short and does not call on industry to help facilitate Pgx translation. The Committee should consider stronger recommendations for industry here. As it stands, this section can be seen as justifying a perceived inaction on the part of industry, leaving SACGHS vulnerable to criticism that the Committee is not acting in the fiduciary public interest.

On page 88, there is tremendous emphasis on the need for cost-effectiveness studies of Pgx tests. We are unclear on why this emphasis. For example, cost-benefit and cost-utility analyses may be more relevant for Pgx. In addition, there is no requirement for cost-effectiveness for many molecular diagnostics to be clinically important; this cost-effectiveness stipulation may serve as a barrier to implementation of genetic-based therapeutic decision making on a broad level.

Specific Points of Clarification

- In its introduction (Page 12), the definition of Pgx seems imprecise as genetic variations that may not lead to altered gene "expression" may be important in Pgx.
- On page 14, CYP2D6 is given as an important Pgx gene because of its role in drug metabolism. The committee lists several drugs metabolized by CYP2D6 and the reader infers that CYP2D6 polymorphisms may be important determinants to response of these drugs. We urge the Committee to use this example with caution, as we and other have previously demonstrated CYP2D6, while a determinant of variable drug concentrations, may have no impact on response to many drugs.
- On page 14, the report states "While current methods of "trial and error" prescribing for determining the appropriate drug and dosage for particular patients is adequate and minimally harmful..." We submit that "minimally harmful" is not precise since it could be argued that putting someone on non-effective therapy is the same or worse than putting someone on a drug that will cause an adverse drug reaction.
- On page 16, the report reads "Even with these benefits, the average consumer likely will experience a net increase in drug costs, particularly in the short-term, due to adoption of new PGx drugs and technologies and greater burden of patient cost sharing for drugs." This is not necessarily true. Costs of drugs are also driven by failed drugs in phase III. As Pgx begins to be used in drug development, the cost of development will likely go down and diagnostics might not be that expensive. In addition, identifying those most

likely to respond or not respond lessens the number of interactions needed with the health care system.

- On page 16, the report reads, "Providers will face additional costs of education and an increase in the amount of time needed to use and interpret diagnostic results." This seems overstated in that this requirement is in no way different from currently mandated continuing education requirements for maintenance of licensure in good standing. In addition, in the post–genomic era, if this time is not taken, it will ultimately not be within the standard of care that will be shortly developing due to increased genetic information and understanding
- On page 49, Recommendations 8A and 8B are not specific enough.

Respectfully submitted by:
The PEAR Steering Committee: Drs. Issam Zineh, Julie Johnson, Stephen Turner, Eric Boerwinkle, Arlene Chapman, Kent Bailey.

From: Alice_Rathjen [mailto:alice.rathjen@dominga.com]
Sent: Monday, June 04, 2007 2:21 PM
To: SACGHS
Subject: Re: Public Comment Invited on Draft SACGHS Report on Pharmacogenomics

Dear SACGHS,

Sorry to miss the cutoff date.

Here's my comments:

The implications of the mapping of the human genome warrant that a system of checks and balances be brought to bear to guide us into the future. The major determining forces at play within the United States is as follows: the courts, our democratic processes, our constitutional right to privacy, and the open market.

What's currently needed is a mechanism that allows individuals to act on the basis of their own self-interest in the open market place. To issue a policy that attempts to control an individuals rights to ownership of their own intelligence or idenity will only result in those rights of ownership being exercised via an entity that exists outside of the United States.

Companies will exist to provide individuals access to their own genetic data via the Internet. It's only a question of which countries the labs and servers will reside in.

The best we can hope for is that these entities will be responsible to the individuals that have entrusted them with their data.

Regards,

Alice Rathjen

Robert Reinhard
425 Market Street, 32nd floor
San Francisco, CA 94105
May 17, 2007

Via email: goodwins@od.nih.gov

Reed V. Tuckson, MD
Chair, Secretary's Advisory Committee on Genetics, Health and Society (SACGHS)
NIH Office of Biotechnology Activities
6705 Rockledge Drive, Suite 750
Bethesda, MD 20892

RE: Realizing the Promise of Pharmacogenomics: Opportunities and Challenges (Report)[1]

Dear Dr. Tuckson and Members of the SACGHS:

Thank you for the opportunity to comment on the cited draft Report to realize promises of pharmacogenomics. I comment from the perspective of a patient/community advocate, with experience advising investigators and agencies especially in the development of HIV/AIDS vaccines or other prevention methods and HIV treatment. The draft report was very welcome in its thoughtful layout and scope of the diagnostic, treatment, data collection, privacy, ethical and cost issues connected with this field of research. These comments provide suggestions to round out that discussion.

The Report's use of recent "case study" type examples of patient care improvements is useful to evaluate some of the particular medical cautions, safety concerns, insurance issues, reimbursement and sensitivities for drug development. In the case of HIV/AIDS drug treatments, those issues have recently been the subject of elaborate study also with the potential introduction of CCR5 antagonists and especially regarding effects of viral tropism in patients of different genetic background. Treatment with this class of drugs may involve sophisticated and potentially costly diagnostics as well as careful safety followup. A high level collaborative forum of multiple stakeholders examined these problems, and I cite their work product in footnote with request you include lessons learned from it in the Report.[2]

Further improvements in the draft Report would expand its subject matter scope – which focuses almost exclusively on therapeutic drugs – to evaluate similar and related issues for biologics and vaccines, which have novel and complex pharmacogenomic/genetic research questions attached to them. Individualized host/virus interactions have been the subject of important recent study in the development of candidate HIV/AIDS vaccines. I describe some of this current effort in comments submitted last year to the NIH genome wide association study proposal, and for ease

---

[1] http://www4.od.nih.gov/oba/SACGHS/SACGHS_PGx_PCdraft.pdf
[2] Collaborative Approaches to HIV Drug Development: Planning for Long-Term Monitoring of Safety in CCR5 Antagonist Development. Report of a Joint FDA/FCHR Joint Public Meeting http://www.hivforum.org/uploads/CCR5/FCHR%20FDA/FDA%20FCHR%20FINAL%20REPORT%202.pdf

of reference and comment I attach the comments in pdf here – see especially footnotes 3-5 of the attachment. I request those comments and policy suggestions be incorporated by reference and considered in review of the SACGHS Report.

The comments/policy suggestions previously submitted to the NIH GWAS proposal have dual application for the SACGHS purposes. I won't retype them because they are attached in full, but I will list them in this letter. They include:

1. Adoption of specific extra safeguards or protections to secure privacy protection, maintain special standards when recruiting vulnerable populations in trials, and prohibitions on certain data disclosures;[3]
2. Use of standard boilerplate language when using or publishing results to inhibit misuse or misappropriation of data for uses never intended by professionals in designs of research studies; such language would reduce potential for unjust stigmatization of individuals or classes based on genetic traits
3. Development of novel means to increase true benefits to participants in trials involving genetic research;
4. Required use of open or public access publishing when research results are disseminated in peer review journals recording studies partially or wholly funded by the government; and
5. Development by NIH of a responsive and robust intellectual property policy sensitive to concerns in recent cases involving patents based on associations; also requested is a detailed statement from NIH to allow review of "premature claims on pre-competitive information."

The SACGH's work efforts are much appreciated. I can be reached at tel: 415/268-7469 or email at rreinhard@mofo.com if you have any questions about this letter or its attachment.

Sincerely,

Robert Reinhard

Robert Reinhard
Member, Community Advisory Group, San Francisco Department of Public Health Research Section

w/att.

[3] I also appreciate the mentions in the SACGHS draft Report of legislation in the Senate to secure nondiscrimination from use of genetic information. That legislation deserves serious consideration and efforts to implement.

425 Market Street, 32nd floor
San Francisco, CA 94105
October 27, 2006

By email to GWAS@nih.gov
Hardcopy to follow

NIH GWAS RFI Comments
National Institutes of Health (NIH)
Office of Extramural Research
6705 Rockledge Drive, Room 350
Bethesda, MD 20892-7963

Re: Request for Information(RFI):Proposed Policy for Sharing of Data Obtained in NIH Supported or Conducted Genome-Wide Association Studies(GWAS)-NOT-OD-06-094 [1]

To the NIH Office of Extramural Research:

Thank you for the opportunity to comment on the proposed GWAS policy. We comment from the perspective of patient/community advocates, individually or on behalf of AIDS service organizations, with experience advising investigators and agencies especially in the development of HIV/AIDS vaccines or other prevention methods and HIV treatment. We are supportive of but also cautious about the effort to create a centralized NIH GWAS repository. The prospect of utilizing data to accelerate design of effective biomedical interventions is encouraging, but the potential for misuse or abuse of data and other ethical concerns to insure appropriate benefits require careful thought.

To express general cautions applicable to this RFI, please note we agree with much of the comment summary NIH already received on its related Request for Information: Modifications to NHLBI Policy for Distribution of Data from Clinical Trials and Epidemiology Studies.[2] Specifically, we agree with the comments NIH received on the topics of 1) privacy and confidentiality, 2) IRB approval, 3) quality of the research, 4) liability for misuse of the data, 5) trust/continued participant cooperation, and 6) effects on response rate. We would like to add other thoughts on NIH's new individual questions below. Replies to the first two questions are combined.

---

[1] http://grants.nih.gov/grants/guide/notice-files/NOT-OD-06-094.html
[2] http://grants1.nih.gov/grants/guide/notice-files/NOT-HL-06-116.html and http://www.nhlbi.nih.gov/funding/policies/rfi-genome.htm

RFI Questions and Responses

1. What are the potential benefits and risks associated with wide sharing of phenotypic and genotypic data where identifying information has been removed?
2. In addition to removing personal identifying information, what protections are needed to minimize risks to research participants whose phenotypic and genotypic data are included in a centralized NIH data repository and shared with qualified investigators for research purposes?

It is well recognized that human genetic variability, HLA diversity and other ethnic difference factors can pose significant challenges in the design of potentially effective preventive or therapeutic HIV vaccines.[3] Recently an important new research consortium was developed to explore these factors in greater detail and to understand particularly beneficial polymorphisms. Appropriate human cohorts are needed.[4] A GWAS-type data repository may help overcome some of these research challenges and/or provide other important data to understand epidemiology, viral transmission or design of other effective treatment.[5]

However, risks associated with personal identification may be incurred if, as NIH proposes, the information is coded and subject to code breaking. Despite measures or promises of confidentiality protection, legal means are available to compel identification. For example the privacy protections expected under the U.S. Health Insurance Portability and Accountability Act (HIPAA) are subject to a number of exceptions, including for law enforcement, lack of control over all potential downstream data users or other reasons. Even with a person's authorization to disclose information under HIPAA, the complexities and long term use associated with GWAS may frustrate attempts to achieve meaningful comprehension of disclosure risks through informed consent or HIPAA explanations to patients. Use of data for purposes other than

---

[3] See for example Leslie A, Price DA, Mkhize P, Bishop K, Rathod A, Day C, Crawford H, Honeyborne I, Asher TE, Luzzi G, Edwards A, Rosseau CM, Mullins JI, Tudor-Williams G, Novelli V, Brander C, Douek DC, Kiepiela P, Walker BD, Goulder PJ. Differential selection pressure exerted on HIV by CTL targeting identical epitopes but restricted by distinct HLA alleles from the same HLA supertype. J Immunol. 2006 Oct 1;177(7):4699-708; Brander, C. HLA and HIV: Implications for HIV Vaccine Design ASHI Quarterly 2004 Vol.28 (2):58-9 http://www.ashi-hla.org/publicationfiles/ASHI_Quarterly/28_2_2004/HLA_HIV.pdf ; Ward FE,Tuan S, Haynes BF.Analysis of HLA Frequencies Population Cohorts for Design of HLA-Based HIV Vaccines (1995) http://hiv-web.lanl.gov/content/hiv-db/REVIEWS/articles/Ward.html The HIV Sequence Database reviews article set also lists several other descriptions of potential benefits from this effort http://hiv-web.lanl.gov/content/hiv-db/REVIEWS/reviews.html

[4] CHAVI Announces International Search for Genes Affecting HIV Response http://dukemednews.duke.edu/news/article.php?id=9752 ; Talenti A and Goldstein DB. Genomics meets HIV-1. Nat Rev Microbiol, November 1, 2006; 4(11): 865-73.

[5] Javanbakht H, An P, Gold B, Petersen DC, O'huigin C, Nelson GW, O'brien SJ, Kirk GD, Detels R, Buchbinder S, Donfield S, Shulenin S, Song B, Perron MJ, Stremlau M, Sodroski J, Dean M, Winkler C. Effects of human TRIM5alpha polymorphisms on antiretroviral function and susceptibility to human immunodeficiency virus infection. Virology. 2006 Oct 10;354(1):15-27; Bashirova AA, Bleiber G, Qi Y, Hutcheson H, Yamashita T, Johnson RC, Cheng J, Alter G, Goedert JJ, Buchbinder S, Hoots K, Vlahov D, May M, Maldarelli F, Jacobson L, O'brien SJ, Telenti A, Carrington M. Consistent effects of TSG101 genetic variability on multiple outcomes of exposure to human immunodeficiency virus type 1. J Virol. 2006 Jul 80(14):6757-63. Shrestha S, Strathdee SA, Galai N, Oleksyk T, Fallin MD, Mehta S, Schaid D, Vlahov D, O'Brien SJ, Smith MW. Behavioral risk exposure and host genetics of susceptibility to HIV-1 infection. J Infect Dis. 2006 Jan 1;193(1):16-26. Carrington M, O'Brien SJ. The influence of HLA genotype on AIDS. Annu Rev Med. 2003 54: 535-51.

pharmaceutical product development or biomedical interventions would be an abuse in these circumstances resulting perhaps in travel restrictions, discrimination or enforcement consequences.

For these reasons, a number of extra safeguards or even outright prohibitions should likely be added to a GWAS system. These could include:

- Securing amendments to HIPAA or other similar nonUS requirements to prevent nonmedical health access to personal identification information;
- Special restrictions on or safeguards for recruitment of populations especially vulnerable to disclosure risks such as prisoners or immigrants;
- Prohibitions on disclosure to or use by employers, insurors or third party payors to deny medical coverage, assign differential premium risks, restrict access to therapies or unfairly discriminate in employment.

Although some of these risks could be eliminated by removing personal identity information completely without any linking or coding, there may be situations where participants could beneficially be alerted to genetically attributable health risks. Participants should be fully informed about and able to learn of such health risks in the most confidential and secure manner possible, considering practical issues with active contact or the willingness and ability of researchers to initiate those discussions.

Another risk from creation of a GWAS repository – with or without risks from personal identification disclosure – is the potential for unjust stigmatization of individuals, groups or families.[6] A workable GWAS program would state clearly that the data are appropriate, scientifically and ethically, ***only*** for limited public health purposes involving product development or professionally derived biomedical intervention, are unreliable and insupportable for other use or by political or nonmedical entities.

It would be appropriate to require any researcher using or publishing results based on the data to state affirmatively some kind of boilerplate recognition of the misuse and abuse potential for stigmatization directly in every associated publication, paper, abstract or presentation. This mechanism could prevent others from the wayward misappropriation of data for purposes other than those intended by professionals in the stated and IRB approved biomedical designs of their research study. The boilerplate could read, for example:

> Conclusions derived from the genotypic or phenotypic characterization of individuals, groups or families in this [publication] are meaningful or supportable only for the purpose of biomedical intervention or treatment and are unethical, insupportable or

---

[6] See for example the Council for International Organizations of Medical Sciences current draft "Special ethical considerations for epidemiological research," p. 7; http://www.cioms.ch/special_ethical_consideration.pdf accessed October 12, 2006. The draft states: "One must also remember that potential "harm to subjects" may not be restricted to them, but may extend to their family members or, more generally, to a group to which they belong; for instance, findings of a higher than average prevalence of certain genetic traits or diseases among the study subjects may stigmatize the family or the group in the eyes of others."

> inappropriate for use in other purposes. Use of the data to support any result of stigmatization, discrimination or adverse social harm would constitute a misuse or abuse of the data.

This boilerplate is offered merely for illustration and most likely could be improved upon by others.

As with any study recruiting participants, ethical norms require that GWAS research be conducted – individuals placed at risk – only in populations that may benefit from the research. This guiding principle could be difficult to embody when the data collection effort may realize beneficial results indirectly or long after it is collected. To increase the connection of benefits to participants from the GWAS, individuals should be given personal opportunities to follow the long term progress of the research efforts, receive news reports if they wish and learn of particular clinical trials directed at their characteristics. Users of the data to develop pharmaceutical products should also be directed to plan and explain early on how targeted populations may have reasonable access to treatment or therapy if successfully brought to market.[7]

3. What are the advantages and disadvantages of the proposed:
Approach to scientific publication?

We do not disagree with the proposed policy to allow preferred publication rights to investigators who submit data to the repository or the instructions to acknowledge Contributing Investigators. However, again, as a means to return benefit from data analysis back to volunteer individual participants and patients and to respect *their* contribution to the work, we request that NIH *require* that public or open access publication be used to disseminate research results. Participants should also be given opportunities to learn about research results consistent with the reply to questions 1 and 2.

Approach to intellectual property?

We have limited experience with all issues relating to intellectual property concerns and their potential to accelerate or inhibit innovation. Intellectual property schemes should be evaluated so as to maximize innovation and R&D for the benefit of public health. But it seems the policy would benefit from more concrete discussion and evaluation of issues that are currently raised in some pressing litigation such as that in *Laboratory Corporation of America Holdings v. Metabolite Laboratories Inc.*, U.S., No. 04-607 or other examples where innovations are based on capitalizing on associations.[8] The NIH could also call for specific comment on the issues of utility or patent stacking as they affect application for gene related patents.

The policy mentions NIH preferences regarding premature claims on precompetitive information. We request that NIH provide more specifics for comment to evaluate or avoid

---

[7] The comments reflected in these replies appear consistent with the program outlined by Senator Barack Obama in his proposed legislation, S. 3822, the Genomics and Personalized Medicine Act of 2006. http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=109_cong_bills&docid=f:s3822is.txt.pdf

[8] See also Genetics and Patenting http://www.ornl.gov/sci/techresources/Human_Genome/elsi/patents.shtml

ambiguity as to who would decide and under which parameters claims would be considered premature and that NIH define "premature claims on pre-competitive information" further.

4. What specific resources may investigators and institutions need to meet the goals of this proposed policy?

No reply provided for this question.

Finally, although not responsive to a particular question, it is our opinion and we request your concurrence, that participation in, submittal to, the data repository not be considered mandatory in order to obtain grant funds for other studies or data collection.

The chance to offer suggestions on the NIH policy was very welcome. Although experiences with HIV informed the writing of these comments, the letter is not meant to attribute any less importance or priority to the potential benefits and uses that may accrue for other serious medical concerns. The wide application and potential for the program seem poised to contribute to the common good. Please refer to Robert Reinhard as the contact person for these comments at tel: 415/268-7469 or by email at rreinhard@mofo.com if you have any questions.

Sincerely,

Robert Reinhard

Robert Reinhard, Community Advocate (and also signing for):

AIDS Foundation of Chicago http://www.aidschicago.org
AIDS Vaccine Advocacy Coalition http://www.avac.org
Steve Wakefield, Community Advocate
Dr. David Crawford

CC: Senator Barack Obama
713 Hart Senate Office Building
Washington, D.C. 20510

Reply fax: 973-235-2981

1 June 2007

Reed V. Tuckson, MD, Chair
Secretary's Advisory Committee on Genetics, Health, and Society
NIH Office of Biotechnology Activities
6705 Rockledge Drive, Suite 750
Bethesda , MD , 20892

Comments from Roche Pharmaceuticals and Diagnostics on the Draft Report from the Secretary's Advisory Committee on Genetics Health and Society: "Realizing the Promise of Pharmacogenomics: Opportunities and Challenges."

Dear Dr. Tuckson:

Roche is grateful for the efforts of SACGHS to create an important and comprehensive document on Pharmacogenomics, and appreciates the valuable opportunity to provide comments. Roche welcomes the existence of an authoritative document outlining the opportunities and challenges surrounding PGx, and therefore supports the promulgation of concepts which incorporate balanced views. Because of the many, often contradictory viewpoints surrounding pharmacogenomic issues, the assertion of a consistent message is challenging; a credible and respected document will therefore minimize discrepancies while incorporating as much consensus as possible.

The field of PGx will require collaboration among the sectors, which, in turn necessitates fundamental comprehension of the various vantage points. The current draft would benefit from a better understanding of the drug and device development processes and what is actually occurring in the marketplace. The general sense that industry is uninterested in co-development is inaccurate and outdated as recent co-development initiatives would demonstrate. Examples, in addition to the Herceptin case, and their associated companion diagnostics, exist and need to be included in this analysis. Furthermore, a global perspective of regulatory agencies should be included. Finally, the report fails to address a number of collaborative efforts currently underway. The Foundation for NIH's Biomarkers Consortium and C-Path Institute initiatives provide evidence of the potential for collaboration.

The report contains several unsubstantiated statements which are later contradicted. For example, the statement on page 15 ("Health care spending continues to increase faster than the economy at large, with little improvement in health care") represents a generalization with no supporting evidence. Page 18 then contrasts this statement by highlighting the benefits of Herceptin, which brings about a response in 25-30% of women with metastatic breast cancer - clearly an improvement over the previous state-of-the-art treatments. Another inconsistency can be found on page 29, where "Herceptin might have been approved earlier had there been a coordinated co-development effort", yet Herceptin serves as an example for how "careful coordination.... can result in expedited drug approvals." Finally, page 16 claims that "personalized medicine may reduce health care costs over the long-term", but page 87 states that "net cost savings from new technologies are rare." These generalizations and other inconsistencies require resolution if this report is to be taken as a credible and reliable source on Pharmacogenomics.

Recommendation 2
The development of new technologies for point of care diagnostic tests would be better left to the IVD industry and to the makers of laboratory developed tests. The H5N1 diagnostic test was a special case, where test development was hindered by the very limited availability of clinical specimens.

Recommendation 3
The need for FDA oversight of diagnostic tests that guide drug prescribing is not well addressed. Regarding encouragement of consultation with FDA, sponsors already do consult early with FDA in addressing the premarket submission requirements, gaining input on study protocols and planning for clinical studies. Developers of IVD test systems, including pharmacogenomics tests, routinely utilize the pre-IDE process available from CDRH's Office of In Vitro Diagnostics for review of their tests offering, its intended use and associated clinical protocols. In addition, the early review of pharmacogenetic studies is a focus of FDA's Voluntary Genomic Data Submissions program.

Recommendation 4
The draft Drug-Diagnostic Co-Development Concept Paper serves as a starting point for the development of such a guidance. However, it represents an idealized approach to co-development of drugs and diagnostic tests. Issuance of the Co-Development Guidance is expected to be a useful tool in helping to facilitate the development process and the premarket submission review for co-developed products.

Recommendation 5
Manufacturers are unable to promote information on product performance that is not described in the approved labeling. Publications from third party investigators are obviously in the public domain, but the manufacturer's ability to promote such information is limited. Statistically non-significant findings are unlikely to be publishable. Finally, tests without established clinical applications are considered research use only assays and are not effective IVDs intended for clinical diagnostic use.

Recommendation 6
An interoperable database would certainly facilitate PGx research, but the funding for such a database, as well as responsibility for its development and maintenance need to be more clearly outlined. Any initiatives should be in close alignment with efforts of the Personalized Healthcare Workgroup of the American Health Informatics Community (AHIC).

Recommendation 9
Criteria for determining the most clinically appropriate drug need to be clearer. Also, the PGx test should also be covered by payers if it is being used in making treatment decisions.

Recommendation 10
Not all PGx data will be appropriate for inclusion in product labels. Criteria should be established for inclusion of only relevant PGx information.

Recommendation 12
Does the Office of the National Coordinator for Health Information Technology have the resources needed to incorporate the additional PGx data?

Recommendation 14

This situation assumes that the associated diagnostic test is a validated assay, with clinical data to support its claimed use for PGx applications.

Additional, specific comments are as follows:
On regulation and FDA's capacity for PGx review, p 5:
The present regulatory framework has been effective in processing PGx submissions. The De Novo 510(k) pathway is being used to clear new PGx assays that historically would have required Premarket Approval Applications. A major concern and issue for FDA has been the lack of regulatory oversight of laboratory developed PGx tests, particularly those that constitute a high risk.

On payer resistance to reimburse PGx products and willingness to innovate, p 6:
For the IVD developer and manufacturer of a PGx test the issue is more basic—reimbursement may be insufficient to support the development and manufacturing costs or simply lacking entirely.

On co-development, p 28-29:
Drugs and companion diagnostics in most cases will not come from the same company and this should not be a concern for FDA. The two applications could still be reviewed concurrently and both products approved at the same time. In addition, the Office of Combination Products would have a role in facilitating this process. This has happened for a number of premarket submissions for drugs and diagnostics including:

- Herceptin (trastuzumab)
- Erbitux (cetuximab)
- Vectibix (panitumumab)
- Gleevec (imatinib mesylate)

On risk of liability for PGx drug and diagnostic manufacturers, if test results are incorrect or misinterpreted, p 49:
This is true for all commercial diagnostic tests and not unique to PGx tests. Liability is related to the intended use, and the risk profile of the assay (i.e., consequence of a false positive or negative result). This may be further aggravated by promotional practices not supported by adequate clinical studies and poor performance in the field when placed into commercial use.

On perceived financial disincentives for drug companies to pursue companion diagnostics, p 51:
It is likely that the development cost of assay development and FDA approval would be small in relative terms as compared to the cost of developing the drug.

On product submission and review process and the requirement of clinical data for IVDs, p 53 :
Clinical utility data are required only for class III (PMA) products.
CDRH has been successfully applying the De Novo 510(k) approach for novel tests (without predicate devices), avoiding the requirement for a Premarket Approval Application.

On CMS regulatory responsibilities, compared to FDA's, p 68:
There is limited comparability between CLIA requirements and FDA requirements for laboratory tests, particularly with respect to FDA premarket review. Similarly, the requirements for Premarket Approval Application are significantly more comprehensive than for Premarket Notification - 510(k) submissions. Clinical utility is required to be demonstrated for PMA products, and not traditionally required for most 510(k) products.

We hope our comments are helpful. We believe our suggestions will help clarify and further strengthen this draft report and increase its usefulness and relevance. We look forward to further consideration of this important document.

Should you have any questions, please contact Dr. Finley Austin at 973-562-5621 or by email at finley.austin@roche.com.

Sincerely,

M. J. Finley Austin, Ph.D.
Director of U.S. External Science Policy
Roche Pharmaceuticals

James F. Kelly, Ph.D.
Senior Director, Regulatory Affairs
Roche Molecular Systems Inc.

From: jean public [mailto:jeanpublic@yahoo.com]
Sent: Tue 4/10/2007 3:47 PM
To: Goodwin, Suzanne (NIH/OD) [E]
Subject: THANK YOU FOR SENDING ME A PAPER COPY OF PHARMACOGENOMICS

I HAVE TWO COMMENTS:

THE STATEMENT IS MADE "134 MILLION AMERICANS ARE GOING TO HAVE CHRONIC CONDITIONS BY 2020". WHAT MAKES THAT STATEMENT ACCURATE.

ARE US TAX DOLLARS BEING USED TO DEVELOP THIS PROCEDURE FOR THE DRUG COMPANIES BENEFIT AND PROFITS?

B. SACHAU
15 ELM ST
FLORHAM PARK NJ 07932

From: jean public [mailto:jeanpublic@yahoo.com]
Sent: Wed 3/28/2007 1:08 PM
To: Goodwin, Suzanne (NIH/OD) [E]; americanvoices@mail.house.gov; comments@whitehouse.gov
Cc: vicepresident@whitehouse.gov
Subject: public comment on federal register olf 3/28/97 vol 72 #58 pg 14577

dhs genetics, health and society

please send me a paper copy of the report that you have on this subject.

in addition, i am very afraid of how the drug companies push their products upon the people these days, without even the people's consent being given. the vaccines that the drug companies pushed on the govbernor and legislators so that eveyr girl should be vaccinated with hpv is disastrous. the drug companies are much too powerful. instead of this agency acting as a brake on this power and making sure it is beneficient and for the people's interests, this agency just rolls over and plays dead for drug profiteers. i do not want to see the superiority of the drug industry over public agencies representing the citizens of this country increase in relation to genetics, etc. it is already awful and seeks to take all rights away from the people.

b. sachau
15 elm st
florham park nj 07932

Schering-Plough

Integrated Therapeutics Group, Inc.
1700 Rockville Pike, Suite 525
Rockville, Maryland 20852
Telephone (301) 770-9524

May 31, 2007

Reed V. Tuckson, MD, Chair
Secretary's Advisory Committee on Genetics, Health, and Society
NIH Office of Biotechnology Activities
6705 Rockledge Drive, Suite 750
Bethesda , MD , 20892

Comments on the Draft Report of the Secretary's Advisory Committee on Genetics, Health, and Society: Realizing the Promise of Pharmacogenomics: Opportunities and Challenges

General Comments

Schering-Plough believes that this report is an excellent beginning to encourage the development of pharmacogenomics as a research, clinical development, and ultimately therapeutic tool. We appreciate the opportunity to comment on the drug development implications of this document.

Additionally, Schering-Plough believes there are global aspects of the drug development process that should be considered when making these recommendations. Schering-Plough currently participates in multiple pre-competitive consortia groups with other pharmaceutical companies who are working to improve our ability to conduct pharmacogenomic studies during the course of our clinical trials. Although this is a US-focused document, the committee should be aware that global drug development is subject to laws and regulations from multiple countries, and must take these into account when developing strategies for sample and data sharing.

Comments on the SACGAHS Recommendations

Recommendation 1 Basic Research

NIH should put more resources into basic research on the biochemical pathways associated with drug metabolism and drug action, on the genes and gene variations involved in these pathways, and on functions of those genes related to the safety and effectiveness of drug treatments.

There is also value in investigating the complex interaction of genetic predisposition to disease and the interaction of these disease-specific genetic markers with pharmacogenomic markers of drug safety and efficacy. This recommendation should be broadened to include complex genetic traits.

Recommendation 7 Protection of Personal Data

As data access and sharing expand, it will be important to strike the right balance between protecting the privacy and confidentiality of personal data and fostering access to these data for PGs research. Stronger data security measures may be needed as more PGx researchers access patient data.

There should also be an effort to educate patients on how current data security measures are executed and enforced.

Recommendation 8B Population Subgroup Differences in Drug Response
When drugs are shown to be effective in certain racial and ethnic subpopulations (e.g., BiDil), FDA should encourage manufacturers to conduct additional post-market studies to identify biological, social, behavioral and environmental markers that may underlie the differential drug response.

If there is an FDA effort to encourage post-marketing pharmacogenomic studies, more efforts should to be made to facilitate the feasibility of collecting genetic samples for study. Education of investigators and IRBs regarding the importance of genetic sample collection to better investigate compounds will be critical for executing these post-marketing efforts.

Recommendation 9 PGx-informed Prescription Drug Coverage
In instances where a validated PGx test is available to guide therapeutic decision-making, health plans, including Medicare prescription drug plans, should cover the most clinically appropriate drug as indicated by PGx test results.

Medicare prescription drug plans should cover the most clinically appropriate drug, and corresponding medical insurance plans should cover the pharmacogenomic test. Please include a recommendation for encouraging payment for pharmacogenomic clinical testing.

Recommendation 10D Use of PGx Technologies in Clinical Practice
FDA and drug and diagnostics manufacturers should focus more attention on ensuring that all relevant PGx information is included in drug and PGx test labels. The information contained in these labels should clearly describe the test's analytical validity and clinical validity and provide adequate and clear information for clinicians to use when making treatment decisions based on PGx test results (e.g., about dosing or drug selection).

Clinical practice guidelines for personalized medicine may be more appropriate than drug labels for communicating how to make treatment decisions based on pharmacogenomic results (e.g. warfarin clinical practice guidelines).

Comments on the Draft Report

(Page 19, first full paragraph), PGx offers certain alternatives to traditional models of drug development, regulation, clinical practice and reimbursement. The prevailing blockbuster model of developing drugs for broad populations, intended to yield annual revenues exceeding $1 billion, is strained due to increases in the time and costs of drug development, rising prices of prominent or truly novel ("breakthrough") drugs, and heightened public awareness of actual or perceived breaches in drug safety.[91] Using PGx-related technologies for drug development can shift the focus to stratified populations and segmenting formerly large target populations. New methods for conducting clinical research have also emerged and are being applied in PGx, such as adaptive clinical trial designs. The resulting PGx-related drugs and test combinations are likely to come 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. The prospect of still-daunting drug

development costs and narrower markets for new drugs could provide further motivation for manufacturers to affix premium prices to these drugs.

This paragraph may oversell the current ability for industry to use pharmacogenomics during drug development in the near future. It is the earlier go / no go decisions based on pharmacogenomics studies that will allow for more effective, streamlined drug development.

(Page 24, C. Clinical Research), Findings from PGx-informed basic and translational research can affect the design of clinical research and the development of new drugs. PGx can be used to select participants based on their genetic predispositions to respond to certain types of therapies, resulting in smaller, efficient, safer and more rapid clinical studies. For example, investigators can use information from preclinical studies that identifies genes linked to drug metabolism to genotype subjects recruited for phase I trials, enabling screening out subjects who are more likely to experience ADRs. Identification of polymorphisms in the drug target gene during phase I and phase II trials and their link to adverse effects or variation in drug response can be used to refine inclusion criteria in phase III clinical trials. Use of PGx in clinical trial design could yield as much as a three-fold reduction in clinical drug development time, from 10-12 years to as little as 3-5 years. This should increase the efficiency and lower the costs of new drug development.

While this type of trial may be feasible for very common polymorphisms, it may be difficult to identify sufficient numbers of homozygous mutant or deficient patients in a reasonable length of study screening. Some of the downsides of PG-informed translational research should be discussed. Additionally, it should be noted that the quoted estimate of decreasing drug development time to 3-5 years may require a paradigm shift for drug development requirements by global regulatory authorities.

(Page 25, third full paragraph), While the use of adaptive trial design has clear benefits, experts in industry and academia have been quick to note potential pitfalls. Controversy remains over the use of adaptive design in later trials, particularly in phase III, because they have less statistical efficiency and the results are difficult to interpret. Adaptive trial design can be logistically complicated and complex to run, requiring a robust and integrated data system to manage information on drugs and trial participants. Some are concerned that these trials could result in unintentional unblinding and bias because they can preferentially select trial participants.

The statistical inefficiency noted for adaptive trial design is primarily the result of improper design. Adaptive trial design is currently being implemented in many drug development programs.

(Page 40, first full paragraph), Industry is unlikely to share what it considers proprietary data without some assurances that any patents and data they have specified as confidential are protected before restatement or publication. Additionally, companies may seek legal arrangements stipulating that they would share intellectual property or commercial product development and still retain the ability to pursue and market the product independently. Even with such agreements, industry may remain circumspect about sharing their data with others.

The primary concerns for industry to share data in a pre-competitive space are much more focused in feasibility rather than concerns about proprietary data. The pharmaceutical industry faces many issues with regards to global legal and regulatory differences in genetic sample and data usage. We recommend that these be acknowledged. Because industry must comply with the

most stringent global requirements imposed on subsets of samples contained in a global sample set, sharing of data is therefore made extremely difficult. The pharmaceutical industry must ensure that these stringent requirements are met in order to ensure that it will be feasible to continue collection of genetic samples globally.

(Page 44, Informed Consent, first full paragraph), PGx may raise special concerns related to informed consent. For instance, PGx testing may be a condition of treatment, as set forth by clinical practice guidelines or payment policies (e.g., in the form of prior authorization or utilization review). Some consider this to be coercive, since consenting to a PGx test may be required to gain access to a treatment. This issue can also arise when PGx testing is a condition of enrollment in a clinical trial of an investigational drug. Subjects may feel compelled to consent to genotyping in order to gain access to the study agent.

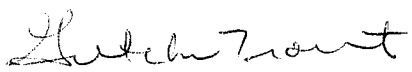
The comment that requiring pharmacogenomic samples on a clinical trial may be coercive is not applicable to healthy volunteer studies. Differentiation between patient and healthy volunteer studies should be made.

(Page 45, final paragraph), Achieving the appropriate level of informed consent for a given research or clinical scenario is an important consideration in PGx research; broad consent may lead to uninformed choice on the part of research subjects, while narrow consent can hinder research. Additional guidance may be needed to help investigators design consent processes that maximize benefits from research while preserving adequate levels of choice.

The value of broad consent during a lengthy drug development process cannot be overemphasized. Sponsors do not have the benefit of clinical safety or efficacy data during early drug development, making narrow consents extremely difficult. The overall strategy for collection of pharmacogenomic samples must be taken into account when deciding if consent can be narrow or must necessarily be broad.

If you have any questions concerning Schering-Plough's comments, please contact Dr. Amelia Warner at 908-740-5497.

Sincerely,



Gretchen Trout
Director
Regulatory Policy and Intelligence
Global Regulatory Affairs
Schering-Plough Corporation

Duke Clinical Research Institute
DUKE UNIVERSITY MEDICAL CENTER

Dr. Kevin A. Schulman, MD
Director, Center for Clinical and Genetic Economics

June 4, 2007

Reed V. Tuckson, MD
Chair, Secretary's Advisory Committee on Genetics, Health, and Society
NIH Office of Biotechnology Activities
6705 Rockledge Drive, Suite 750
Bethesda, MD 20892

Dear Dr. Tuckson:

Enclosed are comments on the draft report of the Secretary's Advisory Committee on Genetics, Health and Society, entitled "Realizing the Promise of Pharmacogenomics: Opportunities and Challenges". I am happy to respond to any questions that may arise during review.

Thank you for this opportunity to provide feedback.

Sincerely,

Kevin A. Schulman, MD
Professor of Medicine and Business Administration
Director, Center for Clinical and Genetic Economics
Associate Director, Duke Clinical Research Institute
Duke University Medical Center

Tel: 919-668-8101 Fax: 919-668-7124
E-mail: kevin.schulman@duke.edu

Enclosure: Public Comment on draft report titled "Realizing the Promise of Pharmacogenomics: Opportunities and Challenges"

Duke Clinical Research Institute
DUKE UNIVERSITY MEDICAL CENTER

Personalized Medicine and Current Technologies

In terms of personalized medicine, although this is an exciting area of technology development, we need to hold the technology developers accountable for the development of evidence in both private and public areas.

Technologies mentioned in this report are not the first diagnostic technologies to be brought to market; they are merely the latest innovation of advancing technology. As of yet, they do not represent a new paradigm requiring separate consideration. From the payer perspective, there are 2 potential uses of these technologies: 1) screening or risk prediction, 2) treatment.

Payment and Reimbursement

In many health plans (including the Medicare program), prognostic technologies with no obvious therapeutic intent are not considered a covered benefit. This means that consumers will have to pay for these technologies out-of-pocket unless the private sector and government decides to expand the scope of the covered benefit to include prognostic technologies (which is unlikely). We need to uphold technologies with therapeutic intent to the same standard of accountability and evidence as other technologies in this same category. Such a hurdle may compromise current business models in the private sector, which would be unfortunate.

Therefore, a compromise proposal would set out to treat these technologies as a special category for conditional reimbursement, such as Medicare's Coverage with Evidence Development (CED) determination. This would allow for payment of such novel technology in the context of more rigorous data collection efforts around the value of the technology (e.g. clinical trial, registry). We are likely to face multiple generational iterations of technology in this space and a robust platform for real-time data collection and assessment seems to be a reasonable approach for spurring innovation as well as assuring the public that they will have evidence to support the use of these technologies on an ongoing basis.

A separate issue is the appropriate payment for diagnostic tests incorporating these new technologies. The current payment structure for the diagnostic market was established in the mid 1980's and may be woefully inadequate for this new paradigm. Currently, the Medicare program, which has major responsibility for determining payment for these technologies, has only three full-time equivalent staff assigned to this area. Thus, the Secretary should create a task force to develop an appropriate construct for coding and payment for this new generation of technology.

Guidelines for Use

Guidelines for use of new technologies are generally evidence based. Currently, the evidence to support most of the personalized medicine technology is the lowest grade of clinical evidence (grade C, observational or cohort studies). It may be premature to

Duke Clinical Research Institute
DUKE UNIVERSITY MEDICAL CENTER

develop guidelines for technology until the evidence to support their use rises to higher levels of scientific rigor.

Nomenclature

The nomenclature used in most personalized medicine technologies is not appropriate for wide-spread clinical use. There are several nomenclature schemes, all of which are based on genomic haplotype and not related to the functional significance of the information

- For example: a *2 variant may be a rapid metabolizer when assessing one enzyme and a slow metabolizer when assessing another.
- Also, "wild-type" represents the most common variant, in the context of the population being studied but does not represent a universal construct. It goes without saying that most patients would prefer not to be identified as "wild-type" or "variant" when they merely have different, single-gene coding regions that have no more functional significance than variation in hair color, which is observable in the general population

Thus, it is critical that we develop a clinical nomenclature that correlates with the functional significance of personalized medicine information so that the significance of the genomic information becomes immediately apparent to the practicing community.

Cost of Technology

For many drug targets there is likely to be genetic variation that is related to dose-response or even responsiveness to specific medications. In the current environment, manufacturer returns from investments in new products are a function of the size of the market as well as the price per unit. To the extent that market size for any specific product is reduced by segmentation as result of personalized medicine, the price of those products will be greater (as long as the price was determined with the eventual market size projection). This results because manufacturers will have a constant cost of clinical development and a much smaller market size from which to generate a return.

Current initiatives that must be altered for personalized medicine to be affordable include the FDA Critical Path Initiative and the NIH Roadmap. The FDA Critical Path is focused on spurring the efficiency of the drug development process. The NIH Roadmap is targeted towards building a clinical research infrastructure that could reduce the cost of drug development. For personalized medicine to be affordable, we may have to augment both of these efforts in order to ensure that the fixed costs of drug development are reduced—thus decreasing the price of these tailored products. Since marketing and distribution also represent substantial fixed cost burden, we may need to consider ways to use public policy to help offset these fixed costs, again, in order to reduce the eventual costs of these products.

- For example: Federal support of a personal health record with embedded personalized medicine tools would ensure that manufacturers do not have to bear the burden of developing this type of infrastructure support for their products.

Duke Clinical Research Institute
DUKE UNIVERSITY MEDICAL CENTER

Personal Health Record

It is unclear how any of these technologies can be implemented in the absence of a personal health record. There is a unique solution to most genotyping analyses that would be performed for an individual; a record of those test results needs to be enduring if it is to be valuable and be accessible at all points of care where therapeutic strategies are being discussed or recommended for the individual. The Health Record Network Foundation or the Dossia effort should be explored as potential models for such a national personal health record effort.

SATSU
Science and Technology Studies Unit

THE UNIVERSITY of York

Science and Technology Studies Unit (SATSU)
Department of Sociology
University of York
York YO10 5DD UK
email: gl12@york.ac.uk
www.york.ac.uk/res/cpr

31 May 2007

Reed V Tuckson MD
Secretary's Advisory Committee on Genetics, Health, and Society
NIH Office of Biotechnology Activities
6705 Rockledge Drive, Suite 750
Bethesda , MD , 20892
USA

Dear Dr Tuckson,

Realizing the Promise of Pharmacogenomics: Opportunities and Challenges *Draft Report of the Secretary's Advisory Committee on Genetics, Health, and Society*

We appreciate the opportunity to contribute to the public consultation on the SACGHS draft report on Realizing the Promise of Pharmacogenomics: Opportunities and Challenges.

The Science and Technology Studies Unit (SATSU) at the University of York, UK, has conducted a number of research projects on pharmacogenomics since 2001, focusing in particular on regulatory and clinical uptake issues, and the challenges how to realise the promise of this new technology – and are pleased to note that you have referred to some of this work in the Draft Report. This research has been funded by the Wellcome Trust, UK Economic and Social Research Council, the UK Department of Health, and the European Commission, and has included fieldwork in the US.

Our response to the Draft Report consists of:

1. Brief comments on issues in the Draft Report which we wish to question or elaborate upon. These comments draw upon a recent ESRC-funded project on 'Pharmacogenomics. diagnostic tests, and clinician acceptance', the findings of which are currently being drafted for publication. Details of this, and other SATSU research on PGx, including publications and reports, are available at www.york.ac.uk/res/pgx

2. An appended summary of the recommendations of our own Wellcome Trust funded research undertaken in 2002-2004, and updated for publication in August 2006. This is published as *False Positive? the commercial and clinical development of pharmacogenetics* (ISBN 978-0-9553542-1-2). Available to

download at www.york.ac.uk/res/pgx/publications/ Two hard copies of the report have also been mailed today to you.

We believe our own report provides a comprehensive overview of both the opportunities and challenges presented by the development and potential introduction of PGx-based treatment regimes into clinical settings. Whilst PGx promises to improve patient care in a number of ways, many questions remain to be answered before the promised benefits are realised. Our aim in publishing *False Positive?* is to help frame these questions and to provide an in-depth analysis of the central issues that will need to be resolved before the potential benefits of this important technology can be realised.

I have also included brief biographical details at the end. Please let me know if you have further questions or if I can be of any further help.

Kind regards

Dr Graham Lewis

Realizing the Promise of Pharmacogenomics: Opportunities and Challenges *Draft Report of the Secretary's Advisory Committee on Genetics, Health, and Society* – comments from Dr Graham Lewis, Science and Technology Studies Unit (SATSU), University of York, UK

- **Are the discussions of topics and issues accurate and complete?**

Overall, our impression is that the conclusions are somewhat lacking in substance with regard to certain key issues, and that a more sophisticated analysis of the challenges and potential hurdles that confront introduction into routine clinical practice is required in order to progress the field.

The most pressing of these challenges is: how are we going to generate the evidence base upon which we can determine the benefits, or otherwise, of introducing PGx into routine clinical practice in different therapeutic areas?

A broad range of PGx researchers, from the biosciences, medicine, and social science, are agreed that this is the most important outstanding issue. Much has been written about the 'promise' of pharmacogenetics. What is required now is the prioritisation of the necessary research - coupled with appropriate funding and possibly other incentives - to make available the evidence required to make sensible decisions on if, and in what areas, PGx can provide major benefits to public health.

However, calls for public agencies and private sector companies to 'go out and do the studies and provide the evidence' - which appears to be one of the messages in the draft report – are, we believe, unlikely to bring about the necessary evidence in the near term. Clearly, there are tensions (both scientific and cultural) between 'leaving it to the market' and advocating the injection of public money (particularly in the US context). However, there may be merit in examining a mix of the two through public-private partnerships in order the generate the required evidence on clinical utility, for example.

We also believe that, in practice, there is considerable overlap between the recommendations listed in section C., page 6, listed under 2) Translational Research and 10) Use of PGx Technologies in Clinical Practice.

It is important that "downstream" research is recognised as crucial for clinical uptake – and to include social science research in this area. As our *False Promise?* report concludes: 'By adopting a systemic comprehensive framework, that stresses the co-construction of new technologies, industries, clinical practices, health services and regulatory regimes, new insights can be provided into the process of technical change in medicine. Not only does this help better understand the drivers and barriers that shape adoption, but it also helps identify key issues for policy intervention that more traditional analytical approaches may miss.

We are also pleased to see recognition that the most benefits in terms of public health may reside in the application of PGx to common, generic, products, such as warfarin (although, as we note below, we dispute the implied claim that sufficient evidence is available to justify routine use of PGx in anti-coagulation treatment).

The UK government's Department of Health recognised this possibility in its 2003 White Paper on genetics and the NHS, which included funding for six research projects on PGx. (We are partners in the UK 'pharmacogenetics of warfarin' study, led by Prof Munir Pirmohamed of Liverpool, where we are examining patient and staff attitudes to introduction of PGx-based regimes in anti-coagulation clinics).

Additional on warfarin and PGx
Current evidence is based on retrospective, and not prospective studies. It is debatable if retrospective studies are sufficient in this area, given the huge complexity of warfarin response. Also, interim results from the UK prospective warfarin study (details available at www.genres.org.uk/projectsliverpool2/) suggest that the relationship between stable dose and the genes, CYP2D6 and VKORC, is even less than existing retrospective data suggests. If these interim results are confirmed, they will serve to undermine claims made for the use of retrospective-based data for treatment decisions.

- **Have any significant opportunities, challenges or other issues been missed?**

- **Does the draft report adequately describe the range of perspectives on the issues?**

There is an absence of recognition of the more critical literature on the subject of PGx and personalised medicine – critical in the sense that the claims for PGx are treated with greater scepticism – and which has often been conducted by social scientists. As argued above, support for "downstream" research is crucial to uptake.

Our own research suggests that the introduction of PGx will be evolutionary and not revolutionary, and will be restricted to quite specific areas, and this will be for both clinical, and cost and institutional/organizational reasons. In simple terms, it will not make sense to provide PGx-based treatment services in all therapeutic areas – but we need to collect the evidence to decide which areas will provide real patient and cost benefits - and which should be forgotten about.

- **Are the draft recommendations specific enough?**

In our view, the draft recommendations are not strong enough, given the potential benefits from PGx on the one hand, and on the other, the lack of a sufficient evidence base required to make informed decisions about clinical use etc.

As suggested elsewhere, under this heading we would also recommend that the Committee consider our own recommendations contained in our report: *False Positive? the commercial and clinical development of pharmacogenetics*, which are appended to this submission.

- **Are there other strategies for addressing the issues?**

Our own report's recommendations discuss a number of strategies for addressing the issues (see below).

- **Which draft recommendations should be of highest priority for the Federal government to address?**

The most pressing recommendations are those contained in Section 10) Use of PGx Technologies in Clinical Practice, and which we have covered above. However, a range of strategies will be required in order to progress the field across a number of fronts.

Appendix A of the report identifies major pharmacogenomics activities in the public and private sector. Are there other relevant initiatives that should be included in the list?

Don't know of other US initiatives - but there are several in the UK (see note above on DH PGx research programme, plus several others including our own research at www.york.ac.uk/res/pgx). Also initiatives in Europe, such as recent studies commissioned by the European Commission, may be useful to include.

Other comments on Draft Report

Page 3: reference to warfarin as example of current use of PGx

Whilst PGx-based warfarin treatment has been advocated, and presumably used, by some clinicians, others remain deeply sceptical – and even hostile - with regard to the evidence-base in the context of routine use, and maintain that prospective clinical data and cost effectiveness data are required before an accurate assessment of the merits of large-scale introduction of PGx-based regimes is possible. Hence, the calls for a large prospective trial in the US (which I understand the NIH may fund/sponsor if agreement on design issues can be reached to the satisfaction of NIH).

Also of note is the fact that a prospective research trial is underway in the UK, funded by the UK Department of Health (DH), led by Prof Munir Pirmohamed at University of Liverpool (end date Sept 2007).
http://www.genres.org.uk/prp/projectsliverpool2/) – one of six PGx projects under the DH's Pharmacogenetics Research Programme (www.genres.org.uk).

Interestingly, the FDA has been announcing the imminent inclusion of PGx data on the warfarin label for many months (now years?) - yet this has not happened. One can speculate why this is the case but it suggests that current reliance on retrospective data is insufficient and that, in the case of warfarin, the benefits are not as clear-cut as some suggest when we move from the science to routine clinical use, in either the US or UK context (Ref: Lewis G, Pharmacogenomics, diagnostic tests, and clinician acceptance, ESRC Science in society project - see www.york.ac.uk/res/pgx for details).

FDA labelling/re-labelling
My own research suggests the matter is more complex than "putting available information to work" with regard to both the key aspects relating to uptake: clinical data and cost effectiveness/organizational issues.

The most obvious example of "putting available data to work" is in the FDA's re-labelling initiative, which has been undertaken for several drugs, in different therapeutic areas. However, in a number of cases the PGx data included on the label is 'informational' only (and not "mandatory" as data on cancer drugs and associated tests is).

Labels also say little or nothing about actual use of the information provided on the label. For example, the label does not always tell doctors if a suitable test is actually available - or how they can access the test. Crucially, nor are they informed about how to interpret the results if they decide to prescribe the test.

Whilst such omissions may be explained by the concept of "clinical freedom" in prescribing, they do nothing to encourage clinical uptake. Greater awareness and practical integration of clinical data and organizational and institutional issues is required.

The cynical-bureaucratic interpretation would be that the FDA has done its job within the confines of its statutory duty to include safety and efficacy information on the label, as demanded by Federal law. But whether for bureaucratic, legal or organizational reasons, it appears unable to move beyond this obligation and offer practicable help and advice on the label.

The publication of new or revised FDA guidelines, as promised by an FDA spokesperson in Feb. 2007 (see page 75 of draft report) suggests that the FDA may confront some of these issues in the near future. However, at this point in time, is not possible to know how significant the proposed changes will be – or whether they are indeed possible within the current regulatory framework. Our research suggests this is a key area.

Recommendation 2) Translational research

We would underscore the importance of translational research and the assessment of clinical validity and utility of PGx testing in particular. Furthermore, we believe that it is important to ensure sufficient resources are available to undertake this work.

In addition, research on the "downstream" challenges relating to adoption, including organizational and institutional hurdles to take-up, is also required. The latter refers to more than the usual call for "more genetics education" for doctors, as necessary as this is. The use of what sociologists call the "deficit model" to explain why professionals (or patients for that matter) refuse to adopt a new technology has now been comprehensively called into question, and a more sophisticated description of the factors influencing uptake is required (which we have attempted to provide in our Wellcome Trust funded report: '"False Positive? etc..." by Martin P, Lewis G, Smart A and Webster A., 2006 - available at: http://www.york.ac.uk/res/pgx).

As mentioned above, it is also therefore important to recognize that demonstration of "clinical utility" requires multi-disciplinary research. Whilst this may or may not apply in the US context, our experience in the UK is that there is insufficient recognition of the importance of research on clinical utility and cost effectiveness issues, coupled with a lack of willingness to fund research in this area. This of course begs the question as to who is going to fund such research.

Recommendations from False Positive? The commercial and clinical development of pharmacogenetics

Paul Martin, Graham Lewis, Andy Smart and Andrew Webster, University of York/University of Nottingham (ISBN 978-0-9553542-1-2) (Available to download at: http://www.york.ac.uk/res/pgx)

1. Supporting industrial innovation

In broad terms, policy might aim to steer industry to use PGx in a way that fosters the development of new drugs that have improved safety profiles, greater efficacy, proven utility and meet clinical need. However, from the research the main issue of concern to industry is the need to:

- **Recommendation 1**: *Create greater regulatory certainty* in order to sustain long-term investment in PGx. In particular, this relates to the:
  - Type of data required by regulators and how it will be used within the assessment process;
  - Process of assessing and approving companion diagnostics;
  - Oversight of the use of companion diagnostic tests;
  - Nature of the pharmacovigilance regime associated with PGx;
  - Extent to which PGx tests will be mandated for already licensed medicines and the evidence required to make label changes;
  - Resolution of the ethical issues surrounding the more general use of genetic testing and personal genetic information in healthcare systems.

2. Preventing market failure

A major issue this study has identified is the possibility of market failure for technological options of PGx that offer considerable public health benefits, but that appear to be commercially unattractive (these include developing new drugs for so called 'orphan genotypes'; pre-prescription screening to identity patients at risk of ADRs from already licensed drugs or who will be good responders to already licensed drugs; the use of PGx in post-marketing surveillance). This problem might be addressed through the following measures:

- **Recommendation 2**: *Extend orphan drug legislation* to provide incentives for companies to develop drugs for markets and patient groups segmented by PGx tests that may not otherwise be commercially attractive.
- **Recommendation 3**: *Create public-private PGx partnerships* to develop diagnostic tests for a number of important and widely used already licensed medicines that are currently commercially unattractive.

3. Protecting the safety and rights of the public

There are a number of ways in which the introduction of PGx might be used to improve the safety of medicines (pre-prescription genotyping, improved pharmacovigilance). At the same time, PGx also raises new issues for public safety, including the risk of more widespread and potentially dangerous off-label prescribing and threats to privacy and patient confidentiality through the disclosure of personal genetic information to third parties. To realise the potential safety benefits of PGx and address these concerns public policy might aim to:

- **Recommendation 4**: *Enhance pharmacovigilance systems* to ensure that PGx technology and data are introduced into the monitoring of new medicines and already existing drugs where appropriate.

- **Recommendation 5**: *Improve drug labelling, the oversight of off-label prescribing and the transparency of decision-making* on the inclusion of PGx data on drug labels, including whether such data is made mandatory or not.
- **Recommendation 6**: *Ensure tight statutory regulation and oversight of the third party use of personal genetic information.*

4. Supporting the clinical adoption of PGx

This study has stressed that the clinical adoption of any drug is highly dependent on its clinical profile and its use in specific contexts. However, the research has identified a number of important barriers that appear to be common across case studies and might stand in the way of the widespread adoption of PGx testing in routine clinical practice. These include, the utility of the technology in practice, the lack of evidence (on the benefits of testing, the genotype-phenotype relationship, and cost effectiveness), and how testing will be funded. To overcome these barriers public policy might aim to:

- **Recommendation 7**: *Include data on proof of clinical utility in the approval process for all PGx related diagnostic products.*
- **Recommendation 8**: *Give greater public funding to help create an evidence base on the clinical utility and cost-effectiveness of using PGx testing for important already licensed drugs*. Greater effort should also be made to improve the provision of information to clinicians on test availability and clinical utility.
- **Recommendation 9**: *Support the development of PGx delivery systems* that can be integrated in established patterns of professional practice. The process of translation could be stimulated by providing clear guidance on exactly how PGx tests might be used and interpreted by clinicians. This might be included in the design of the electronic patient record and computer-based decision support systems.

5. Creating a PGx innovation platform in health delivery systems

Any systematic approach that is taken by public health agencies will establish the context within which future drug regimes based on PGx will operate. This includes the policies, practices and infrastructures that support the development, introduction, purchase, use and governance of new and existing medicines – these might collectively be called a 'medicines innovation platform'. As has been stressed throughout this report, the collection of policies and institutional arrangements that constituted such a platform would need to be flexible, foster the creation of innovation niches and reflect on its own actions and the value of new technologies such as PGx. Policies to support a PGx innovation platform might include the following:

- **Recommendation 10**: *Provide further investment in developing the overall structuring of genetic health service delivery* and especially the organisation, funding and governance of genetic testing. However, it must be stressed that it will be neither viable nor rational to adopt PGx in all therapeutic areas.
- **Recommendation 11:** *Explore alternative ways of providing PGx testing services*. It is not clear that the established structure of genetic testing laboratories in the UK either has the capacity or is best placed to carry out

high volumes of routine PGx testing. Policy should explore a range of different service delivery models.

- **Recommendation 12:** *Fund ongoing and systematic evaluation* of the routine use and utility of medicines, the wider cause of ADRs, and the benefits of PGx in this context.

6. The contribution of social science in helping understand the development of pharmacogenetics

This report has adopted an explicit conceptual framework based on current research in the social sciences to describe, analyse and assess the current and future development of pharmacogenetics. By adopting a systemic comprehensive framework, that stresses the co-construction of new technologies, industries, clinical practices, health services and regulatory regimes, new insights can be provided into the process of technical change in medicine. Not only does this help better understand the drivers and barriers that shape adoption, but it also helps identify key issues for policy intervention that more traditional analytical approaches may miss.

Research on the introduction of pharmacogenetics has been supported in the UK by bodies such as the Wellcome Trust and the ESRC, with results from a number of empirical studies now available in the academic literature. This effort needs to continue, along with specific encouragement for dissemination to the wider health care policy community including clinicians. The July 2006 publication *Policy Issues in Pharmacogenetics: a Policy Briefing from the UK Pharmacogenetics Study Group* published by social scientists from several UK universities is a good example of the latter.

- **Recommendation 13:** *Continue to support multidisciplinary social science research on emerging genetic technologies, such as PGx.*

==========

Dr Graham Lewis is a Research Fellow in the Science and Technology Studies Unit (SATSU), University of York, UK and Director-designate of the University's new Centre for Prospective Regulation. Originally trained as a chemist, he worked for many years in the pharmaceutical industry in the UK and USA before obtaining a PhD in science and technology policy at the University of Manchester. He has researched the development of pharmacogenetics for a number of years, focusing on factors shaping clinical adoption and the part played by regulatory agencies. Other interests include international harmonisation of medicines regulation and international bio-repositories. On-going work includes studies on PGx, diagnostic tests and clinician acceptance, part of the ESRC Science in Society Programme, and the pharmacogenetics of warfarin (with M. Pirmohamed and others) for the UK Department of Health. He was a major contributor to the European Commission's Institute for Prospective Technological Studies international comparative study on pharmacogenetics in 2006. Recent publications include articles in *Nature Genetics Review* and *Nature Biotechnology*.

-----Original Message-----
From: Stanley J. Szefler [mailto:szeflers@njc.org]
Sent: Tuesday, May 29, 2007 12:52 PM
To: Goodwin, Suzanne (NIH/OD) [E]
Subject: Re: Public Comment Invited on Draft SACGHS Report on Pharmacogenomics

Dr. Tuckson - I did review the document in detail and had the following comments in relation to the questions below:

Are the discussions of topics and issues accurate and complete?
-- You might consider how this might fit in with other areas of development, such as biomarkers.

Have any significant opportunities, challenges or other issues been missed?
-- There is quite a bit of work being done in NIH networks including areas, such as asthma. Perhaps these should be disucssed as well and indicate opportunities for interaction.

Does the draft report adequately describe the range of perspectives on the issues?
-- I think so but additional disease states could also be mentioned to give specific examples of applications. If a drug metabolizing gene is identified, how extensive a drug list would be needed for testing?

Are the draft recommendations specific enough?
-- Overall the description is good, but there are not enough specific examples of genes in place and how they were validated. What are the specific steps and criteria needed to establish vaildity and application?

Are there other strategies for addressing the issues?
-- As above, perhaps interaction with NIH networks.

Which draft recommendations should be of highest priority for the Federal government to address?
-- Identification of relevance of specific genes should be the highest priority, so that a template could be established. Then carry through the other layers mentioned.

Appendix A of the report identifies major pharmacogenomics activities in the public and private sector. Are there other relevant initiatives that should be included in the list?
--interaction with NIH clinical research.

As I said, overall, this document reflects a lot of careful thought and planning. Hope my comments are helpful.

Stan Szefler

Stanley J. Szefler, M.D.
National Jewish Medical & Research Center
1400 Jackson Street Room J313
Denver, CO 80206
303-398-1193 phone

303-270-2189 fax
szeflers@njc.org e-mail

BlueCross BlueShield Association

An Association of Independent Blue Cross and Blue Shield Plans

Allan M. Korn, M.D. FACP
Senior Vice President
Clinical Affairs
Chief Medical Officer

225 North Michigan Avenue
Chicago, Illinois 60601-7680
312.297.6840
Fax 312.297.5726
allan.korn@bcbsa.com

June 1, 2007

Reed Tuckson, M.D.
Chair
Secretary's Advisory Committee on Genetics, Health, and Society

Via e-mail to:goodwins@od.nih.gov

Dear Dr. Tuckson:

The Blue Cross and Blue Shield Association (BCBSA) appreciates the opportunity to submit comments on the draft report: *Realizing the Promise of Pharmacogenomics: Opportunities and Challenges*. The BCBSA, an association of 39 independent Blue Cross and Blue Shield Plans, provides health benefits to 100 million members, one in three Americans.

We commend the members and staff of the SACGHS and its PGx Task Force for developing a useful analysis of the potential for pharmacogenomics (PGx) to improve health and the possible challenges to realizing this benefit in clinical practice. BCBSA wishes to underscore the importance of having robust evidence on analytic validity, clinical validity, and clinical utility to support the adoption of PGx technologies. The comments offered below emphasize our key concerns and suggest modifications in some of the discussion and recommendations.

The Promise of PGx

The Executive Summary details early successes of PGx, including Herceptin for metastatic breast cancer, managing the use of thiopurine 6-mercaptopurine (6-MP) for acute lymphoblastic leukemia in children, and managing the use of warfarin. The use of Herceptin is clearly a success. However, we question the application of this description to the management of warfarin and thiopurine

treatment. While TPMT genotyping to predict the likelihood of severe 6-MP toxicity is likely beneficial to some patients, there are gaps in the evidence that limit full delineation of benefits and risks and hinder the development of recommendations for dosing based on genotyping results.

With regard to warfarin management, we are not aware of the existence of evidence establishing an incremental benefit from using PGx testing in lieu of, or in addition to, current monitoring methods. It is clear that a portion of the variability in stable warfarin dose is accounted for by genetic polymorphisms. However, it is not yet clear that the known variation is sufficient to improve initial dosing such that severe bleeding episodes are significantly reduced This is evidenced by the fact that at least three clinical trials are currently underway to address these issues.

Coverage and Third-Party Payment Mechanisms

The Executive Summary, Gate Keeper section, and recommendations make reference to third-party coverage and payment barriers to PGx innovation and adoption. These references imply that difficulty in gaining coverage for PGx products and "payer resistance to the higher drug prices that may come with PGx–based targeted therapies" will limit access to these products. We believe that the major obstacle to coverage and widespread adoption of these products by clinicians is lack of evidence of clinical utility. Health plans require evidence of clinical utility before providing coverage for new technologies. Many costly technologies and drugs with established evidence of clinical value are covered by health plans. Cost is not the barrier to coverage and adoption- lack of evidence of value is.

The report goes on to discuss the challenge PGx "may pose to coverage of prescription drugs" due to formulary structure and tiering. It is true that health plans employ formularies with drugs selected for inclusion based on safety, efficacy, and cost-effectiveness (where a number of drugs are effective for the same indication). It is possible that a drug may not be included in the formulary because it is only effective for a small proportion of a patient population. If a clinically valid PGx test should become available for a condition or drug metabolism variation, members with certain genetic variations may be newly identifiable as appropriate candidates for the non-formulary drug. All health plans have an exceptions process to allow prescribers to provide documentation of their rationale for ordering a non-formulary product. The clinical merits of a request for a non-formulary drug based on pharmacogenomic tests would be handled just like any other request based on medical necessity so long as there is scientific evidence to support the request.

In the section: Potential Reimbursement Challenges to PGx, the report states: "Many emerging technologies, such as gene-based diagnostic tests involving multiple biomarkers and PGx therapies indicated by results of genetic tests, challenge conventional interpretations of medical necessity, and the pace of PGx

innovation can challenge existing mechanisms for determining medical necessity." The report does not explain or show how PGx and the pace of innovation challenge the core tenets of medical necessity that call for the treatment or test in question to: 1) be appropriate; 2) alleviate a problem involving a patient's health, functioning or well-being; and 3) be effective for the treatment of that condition. The statement about PGx challenges to medical necessity mechanisms is completely spurious and must be deleted.

Analytic Validity, Clinical Validity, and Clinical Utility, and Cost-Effectiveness

We fully agree with the statement in recommendation 5 that the adoption of PGx technologies will hinge on the availability of evidence of their analytic validity, clinical validity, clinical utility, and cost-effectiveness. This is key to coverage and widespread use of the technologies. We concur that "HHS should provide resources to identify and address evidentiary gaps." However, we are concerned with the statement that "HHS should facilitate the development of tools to improve the validity of findings from observational studies." (p.7) Given that there are few proven PGx models, observational data may be insufficient to infer improved outcomes from the use of PGx testing compared to the use of conventional methods (or no methods). Early PGx tests may face more stringent evidence requirements in order to generate models for future tests. An example is provided by the ongoing randomized controlled trials comparing PGx testing for warfarin dosing compared to conventional INR testing and observation

We agree that HHS should support the conduct of systematic reviews and technology assessments to summarize the developing evidence base (Recommendation 10). HHS support of the ongoing Evaluation of Genomic Applications in Practice and Prevention project (EGAPP) would facilitate these activities.

Under Research and Development, we strongly agree that determination of clinical validity and utility are essential to inform clinical decision-making. We have concerns with the statement: "Assessing the actual clinical validity and utility of a test in practice should occur while researchers are measuring its analytic validity." (p. 34) We must have confidence in the technical validity of a PGx test before clinical validity and utility can be reliably evaluated. For example, the original HER2 assays used in clinical validation studies of Herceptin could not be developed for commercial use. The development of new commercial assays after clinical validation created controversy regarding which test was optimal.

Co-Development and Co-Marketing of PGx Diagnostics and Drugs

We agree that co-development of PGx diagnostics and drugs will be optimal to assure that clinicians are able to target the drugs to patients most able to benefit from them. However, we do not agree that diagnostics should be bundled with

drugs at the point of sale. Clinicians and payers should have maximum flexibility to meet the needs of their patients and members.

Importance of Reimbursement for Adoption and Diffusion of PGx
The discussion on page 63 of the impact of coverage expectations and payment levels on investment in PGx products should acknowledge the critical role of clinical utility data. Difficulties in obtaining coverage for a new test that directly affects patient management can be expected if evidence linking the test to improved outcomes or management is not available. ***The barrier to adoption is lack of evidence, not lack of coverage.***

We recognize that there is a real concern about developing PGx tests for drugs that are already on the market, particularly if they have lost patent protection. The diagnostics industry has not historically conducted studies to establish clinical utility and may be ill prepared to do so. This deficiency must be remedied if products are to flow smoothly to market.

Regulatory Issues
Genetic testing is not currently recognized as a CLIA specialty area. Given the complexity of genetic testing technologies and results interpretation, and the potential impact on patient management, we believe that it is advisable to institute a genetic testing specialty in CLIA. This recommendation has been supported by the laboratory community.

We disagree with the statement on page 68 that "CLIA requirements for in-house laboratory testing are generally less rigorous than FDA requirements of the 510(k) and PMA premarket review process. CLIA requires that a laboratory demonstrate the analytical validity and reliability of its in-house tests, but does not require demonstration of the clinical validity or utility of these tests. This is in contrast to FDA requirements for IVDs, which require submission of data indicating all four of these attributes "

The SACGHS report correctly defines clinical validity and utility as follows:" A test has clinical utility if the use of the test results (e.g.via informing treatment or patient management decisions) leads to improved patient outcomes. A test has clinical validity if it accurately and reliably differentiates based on the actual presence or level of a risk factor, condition, disease; predicts response to treatment; or predicts health outcomes." The FDA Office of In-Vitro Devices does not use these definitions.

In fact, the FDA does not distinguish between clinical utility and validity. FDA submission guidelines state that "Clinical Validation/Clinical Utility may be based on:

- New clinical trial data prospectively collected in a longitudinal study

- Retrospective studies, which must have appropriate IRB approval and informed consent, well characterized sample control, and standardization of tests across laboratories and
- Review of information in the literature."

A general literature review of studies that suggest an association between test results and intermediate (biochemical) or patient outcomes can satisfy FDA's clinical validity/clinical utility requirement as was done for the Roche AmpliChip. The current FDA approach does not meet the definition of clinical utility used in the SACGHS report.

Potential for Genetic Discrimination

In a number of instances and in Recommendation 14, the report raises the issue of genetic discrimination Recommendation 14 expresses the concern that integration of PGx into clinical and public health practice may exacerbate health care disparities and result in genetic discrimination. The argument appears to be that management of PGx product use by payors through prior authorization or strict reliance on clinical indications and the potential to impose higher patient cost-sharing through increased co-insurance or co-payments (or through non-coverage when evidence is lacking) for PGx-based therapies will result in differential access to care for individuals with genomic variations. It is suggested that this differential access could be viewed as genetic discrimination. It is difficult to see why the potential for evidence-based use management and higher cost-sharing for some PGx products should be viewed differently from comparable practices applied to non-genomic services.

A second area of concern expressed in the Ethics, Legal, and Social Issues realm is that individuals will fear genetic information on their response to a drug could be misused by employers or insurers. Where PGx results can determine who will benefit from a drug or intervention and at what dosage, clinicians and health plans will want to assure that the tests have been performed so that utilization can be adjudged medically necessary and appropriate. For example, Herceptin is medically necessary for patients with an over-expression of the HER-2 protein and use of Herceptin should be contingent on positive test results for HER-2. We hope that the report is not suggesting that requirements for such tests as a condition of coverage and payment would be discriminatory or coercive (p. 42). This issue requires further clarification.

Data Sharing and Database Interoperability

Recommendation 6C states that "Research, regulatory, medical record, and claims databases need to be interoperable to facilitate research on PGx technologies and build the necessary evidence base." The BCBSA supports public-private data sharing and migration to electronic medical records and claims systems. However, we question the recommendation for medical records and claims databases to be interoperable, at least in the short term. Achieving full-blown interoperability will be a very costly and lengthy process.

ICD.10
A discussion of migrating to ICD-10 is ill placed in the discussion of medical necessity on page 67 of the report. This discussion should be removed. The timing of migration to ICD-10 is a highly controversial issue, as evidenced by the coalition of 49 state medical societies and other stakeholders such as BCBSA and AHIP that has urged a more measured implementation. ICD-10 must be implemented carefully to train physicians and other health care providers to take full advantage of the system's granularity of codes.

Thank you for your consideration of our concerns. If you have any questions on our comments, please contact me at 312.297.6840 or Inger Saphire-Bernstein at 312.297.5529.

Sincerely,

Allan M. Korn, M.D., FACP
Senior Vice President, Clinical Affairs
and Chief Medical Officer

UNC SCHOOL OF MEDICINE
DEPARTMENT OF PEDIATRICS

Centers for Education & Research on Therapeutics ™

1 June 2007

Reed V. Tuckson, MD
Chair, Secretary's Advisory Committee on
Genetics, Health, and Society
NIH Office of Biotechnology Activities
6705 Rockledge Drive, Suite 750
Bethesda, MD, 20892
Sent via email to Suzanne Goodwin at goodwins@od.nih.gov

Dear Dr. Tuckson,

On behalf of our pediatric colleagues at The University of North Carolina at Chapel Hill, the North Carolina Children's Hospital, and the UNC Center for Education and Research on Therapeutics (CERTs), the nation's only CERTs devoted to pediatrics, we write to urge the Secretary's Advisory Committee on Genetics, Health, and Society to devote more attention to the future of pharmacogenomics (PGx) – and all its challenges and opportunities – to improve pediatric health care and health outcomes.

The Federal Register Notice accompanying the draft report invites public comment on three sets of challenges: research and development; "gatekeepers," i.e., those who are involved in facilitating the progression of PGx; and implementation of PGx to improve outcomes in clinical and public health practice. The request for public comment particularly asks whether "...any significant opportunities, challenges, or other issues [have] been missed?" We believe significant opportunities are being missed in the exploration of implementation of PGx to improve pediatric outcomes in clinical and public health practice.

We respectfully suggest that the draft report at present does not adequately reflect the significant challenges and opportunities we face in developing and deploying pharmacogenomic tools for pediatric health care, and we request that the Advisory Committee devote more attention to pediatrics in subsequent drafts. At present, the draft makes very few references to children or to pediatric health care. It is very appropriate that the report makes reference to the use of PGx to tailor therapy in pediatric acute lymphocytic leukemia as an example of PGx in present practice, and the report mentions in two footnotes some literature that includes discussion of pediatric challenges. We also note two mentions of the federally funded Pediatric Pharmacology Research Units (of which UNC and Duke are one) and their potential for doing phase I PGx research. PGx research has not yet been a focus of the PPRU program as yet, but it might well be moved forward because of this report.

Because children are, by definition, simultaneously a vulnerable population snf society's future, we think that any discussion of genetics, health, and society should have the wellbeing of children as one of its primary aims. We suggest the following topics for further attention:

From birth on, children are much more likely to be subject to genetic testing than are adults. In 2004, a DHHS Taskforce recommended that newborns be screened for 29 different genetic conditions, and also recommended that policy not stop with screening, but extend to broader plans for diagnosis and treatment as well. By definition, treatment tailored to genomic profiles. The National Conference of State Legislatures estimates that 4.1 million newborns are now screened for genetic disorders, many with clear cut interventions based on altering the metabolic products of abnormal gene products. Although not traditionally viewed as PGx or individualized therapy, we believe that newborn genetic testing will come more and more to be recognized as a part of this broad category, with more individualized streamlining of therapy and better understanding of both the genomic makeup of the child and the in utero environment of affected mothers on outcomes. We believe that issues surrounding genetic testing should be a part of any broad statement. We also see opportunities in PGx research to improve our ability to initiate the treatment that will lead to the best outcomes for newborns with genetic or metabolic disorders. The FDA alluded to such hope in a 2005 article on genomics and devices in its *FDA Consumer Magazine* (http://www.fda.gov/fdac/features/2005/605_devices.html, last visited for this comment on May 31, 2007).

Although most children are healthy most of the time, children routinely encounter the health care system from birth onward via well child care and the treatment of acute illness. Virtually all infants and toddlers receive early childhood immunizations and most are exposed to and contract infectious diseases. Many children experience chronic childhood illnesses (e.g. asthma), where pharmacotherapy is used in more and more targeted ways, without knowledge of the response – or even the ability to respond – to therapeutic agents used at a given developmental stage, much less with a practical ability to apply knowledge of the effects of genetic background on therapeutic response. This is also true for the infectious agents involved in childhood illnesses, with broad rather than targeted antibiotic approaches contributing to our present challenges of community-based antibiotic resistance.

As we have noted above, a small but important proportion of the pediatric population has a genetic disorder or congenital impairment requiring lifelong health care; in some cases, such as that of Cystic Fibrosis, the genetic origins of disease are now partially understood, but highly variable. In some cases, as with childhood cancers, our understanding of the role of genomics is growing rapidly; in others, such as being able to establish population-based pharmacodynamic and pharmacogenomic guidelines for safer dosing, we are likely to be on the verge of significant breakthroughs. Our understanding of genomic influence is in its early stages, and in some of these cases -- perhaps the most vulnerable ones – in utero drug exposures may play a significant causal role in establishing future response to therapeutics by affecting the formative stages of gene expression during fetal development.

Children and adolescents experience a complex array of chronic or acute health conditions, including major chronic ailments such as asthma or diabetes, significant mental and emotional disorders (e.g., attention deficit and hyperactivity disorder, autism, depression, and problems secondary to child abuse and neglect), relatively rare but life-threatening diseases (e.g., renal failure, cancer, pediatric rheumatic disease), and trauma – all typically requiring pharmaceutical or device interventions. One of the great challenges of pediatric health care, however, is that our pharmaceutical interventions usually occur with the rather coarse-grained approach of weight-based dosing; we have few opportunities to take children's rapidly changing developmental stages into account, including developing hepatic and renal function, much less

their PGx profiles. These limitations on current knowledge leave children prey to medication errors compounded by the potential for pharmacogenomic variability in both the individual and his or her developmental stage.

As the advisory committee knows well, what we today call "Individualized Therapy" (IT) aims to help advance the potential progress of emerging knowledge, including genomics, to deliver therapies in a narrow range, tailored by genomic differences, individual patient characteristics and environmental factors. We believe that the promise and challenges of IT may be even greater in children than it is in adults.

IT, including genomics, not only holds promise for better immediate outcomes of pharmaceutical interventions, but for the long-term outcomes of healthier growth and development of children, even children with very serious disease (85% of whom now survive to adulthood), by reducing toxicity's long-term and/or late-emerging effects in adulthood. IT, including PGx, is likely to show its earliest promise in the field of pediatric oncology; this is recognized in the draft report's reference to PGx and ALL.

We see its promise, however, extending much further, to other serious chronic diseases of childhood – for example, by helping to reduce the toxicity of disease-modifying anti-inflammatory drugs used with rheumatic diseases, inflammatory bowel disease, and asthma/allergy that currently are driven from a 'trial and efficacy" approach, not directed by evidence. Certainly the ability to tailor antibiotic use to assure maximum therapeutic effect with minimum production of resistant organisms is an emerging area of critical importance.

On behalf of our pediatric colleagues, we ask the Special Advisory Committee to provide greater emphasis in subsequent drafts of the report to the role of PGx and individualized therapy in pediatric health care.

Sincerely,

Alan D. Stiles MD
Principal Investigator, UNC CERTs
Brewer Professor and Chairperson
Department of Pediatrics
Physician in Chief, NC Children's Hospital

Sue Tolleson-Rinehart, PhD
Co-Principal Investigator, UNC CERTs
Res. Asst. Professor of Pediatrics
Adjunct Professor of Political Science

THE UNIVERSITY OF UTAH

Vice President for Research

201 S. Presidents Circle Rm 210 Salt Lake City, Utah 84112-9011 (801)581-7236 FAX(801) 585-6212

June 1, 2007

Via Electronic Delivery

Reed V. Tuckson, MD
Chair
Secretary's Advisory Committee on Genetics, Health, and Society
c/o Suzanne Goodwin, goodwins@od.nih.gov
National Institutes of Health, Office of Biotechnology Activities
6705 Rockledge Drive, Suite 750
Bethesda, MD 20892

Re: Comments on the Draft Report to the Secretary of Health and Human Services (HHS), *Realizing the Promise of Pharmacogenomics: Opportunities and Challenges*

Dear Dr. Tuckson:

We submit this commentary on behalf of University of Utah faculty engaged in basic, translational and clinical research in the realm of personalized medicine. The University of Utah holds a pioneering legacy and an ongoing dynamic of research progress in several of the disciplines that now contribute to "*the Promise of Pharmacogenomics.*"

We congratulate and support the dedicated and inspired efforts of the Advisory Committee and reiterate our commitment to be a long-term participant in this process and a resource to the broader personalized medicine community. With this commentary we reiterate our support of these efforts and our willingness to help wherever possible.

COMMENTS AND SUGGESTIONS

Basic and Translational Research

We endorse the recommendation of this report calling for ongoing and accelerated levels of support for basic and translational research. Much is being accomplished, but the gap between the research vision and true availability of personalized healthcare tools and treatments remains wide. Universities can contribute to this effort by pursuing research strategies and projects that add to new knowledge that can be commercialized in the private sector.

Public Education and Engagement

The University of Utah respectfully calls attention to our NIH-funded Genetic Science Learning Center, http://learn.genetics.utah.edu, which is the most widely used genetics education resource in the world. We intend to broaden our public information outreach the realm of personalized health care, http://learn.genetics.utah.edu/units/pharma/index.cfm just as we have in the ongoing national discussion regarding stem cell research; http://learn.genetics.utah.edu/units/stemcells/. This widely visited internet portal has been invaluable in helping to disseminate important information, and we are prepared to do more.

In the process of addressing the need to educate citizens and clinicians about the promise of personalized health care, we stress the parallel need to inform and encourage citizens and their health care providers about the importance of personal responsibility in striving to maintain a healthy diet, remain active physically and mentally. The promise of personalized health care will best be realized with an informed and involved citizenry.

Data Sharing, Database Interoperability

Item D. The University of Utah supports the FDA Critical Path Initiative and efforts to increase funding for this important effort as well as increased funding for the FDA at large.

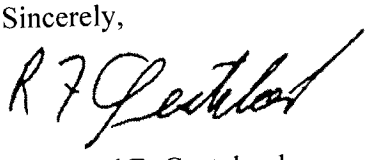
Health Information Technology

The success of personalized health care depends on successful integration of life sciences and information technology and the attendant distribution of knowledge to appropriate parties. The current Health and Human Services leadership is to be congratulated for its sustained efforts to encourage broad implementation of Health Information Technology, including but not limited to electronic medical records. Of great importance in the realm of data sharing, database interoperability, and health information technology is the growing need for advanced data analysis. Equally important are security tools and systems, particularly in light of the denial of service attacks launched in eastern Europe since the HHS document was released in March, 2007. Successful implementation of personalized health care methods depends on the flow of information between authorized parties in secure and reliable ways.

Our Commitment to Participate and Contribute

The University of Utah is well positioned to support the efforts of the Department of Health and Human Services towards the goal of making personalized medicine a practical reality. Our institution embarked down this path decades ago. With unique resources like the Utah Population Data Base (http://www.hci.utah.edu/groups/ppr/), a 101-year-old School of Medicine (http://uuhsc.utah.edu/som/), the first Medical Informatics department in the United States (http://uuhsc.utah.edu/medinfo/), a renowned scientific computing and imaging capability that is used by universities and research agencies nationwide, (http://www.sci.utah.edu/); we are committed to making progress in the pursuit of pharmacogenomic medicine. In that sense we applaud the Report and look forward to ongoing involvement.

Sincerely,



Raymond F. Gesteland
Vice President for Research

Comments on "Realizing the Promise of Pharmacogenomics:Opportunities and Challenges

Submitted by Marc S. Williams, MD, FAAP, FACMG
Member, SACGHS
Director, Intermoutain Healthcare Clinical Genetics Institute
324 10th Ave. Suite 130
Salt Lake City, UT 84103

To Dr. Reed Tuckson, Chair SACGHS:

General comment: All gene symbols throughout the document should be in italics.

Page 3 Section A 1st paragraph. In the sentence discussing early successes of PGx, one of the examples given is managing the use of Warfarin. I don't think this can be used in this context as, at this time, there is not a single study that demonstrates clinical utility in prevention of adverse events. This is confirmed by the information presented in the second paragraph of page 18 that talks only about the effect of variants on final dose. If you are looking for a third example of success I would suggest Gleevec in the treatment of CML and Gastrointestinal Stromal Tumor (GIST)

Page 3 Section A 2nd paragraph. Here and in other places the phrase "trial and error" is used. While this is technically accurate, it is a bit pejorative. My suggestion is use the term empiric as, "Current empiric approaches to pharmaceutical therapy…"

Page 4 paragraph 2. The last sentence indicates that "…PGx may help to reduce costs…" In fairness there is a countervailing argument that PGx could increase costs due to treatments for the untreatable, higher per drug costs (due to smaller market to spread development costs) and hidden costs due to unnecessary repeat testing and unavailability of results across different record systems.

Page 5 Section B paragraph 1. It is stated that, "…few have achieved adequate third-party reimbursement…" How is adequate defined? What data exists to support this contention? I suggest this as an alternative: "…to date, only a small number of PGx products have reached the market and, of these, few have experienced widespread use in practice and the adequacy of reimbursement for these tests at the present time is unknown."

Page 6 second bullet (it's the third bullet of section B) Second sentence. It is stated that, "…the prospect of payer resistance to the higher drug prices…" This statement is specious. If utility is clearer demonstrated, payers will pay for extremely expensive drugs. Examples of this include enzyme replacement therapy for lysosomal storage diseases and disease modifying medications for rheumatoid arthritis as well as a drug held up as the first PGx medication, Gleevec.

Page 7 Section C item 3) Is clinical trial design meant to be one size fits all, or will it vary for rare or 'orphan' conditions? My understanding is that it will be the latter and the executive summary should briefly note this.

Page 9 Section C item 9) This item seems to be implying a coverage mandate. If this is the case, who determines the appropriate standard of validation? What about benefit plans that exclude genetic testing? Would this supersede these benefits? I think this is a very complex and dangerous area and should be approached thoughtfully and carefully. In my opinion once a "validated test" is available to guide therapy, payers will be all over this in order to reduce the downstream costs of adverse drug events and ineffective therapy (assuming the test cost itself is reasonable and available).

Page 11 Section 15) I would suggest the following additional considerations:

- Post-market surveillance to assess validity and utility in routine clinical practice.
- Access to and timing of tests and test results to inform therapy. This issue has the following questions:
    - When is information necessary to choose and dose a drug accurately? In the case of Warfarin it may be that the test result is needed at the time of the first dose, meaning in the situation of an acute thrombotic event, point of care testing may be desirable.
    - How will reference labs deal with these issues of turn-around-time?
    - How will the implications of intellectual property impact availability of timely testing?
    - Issues relating to develop, quality and availability of point-of-care genetic/genomic tests.

Page 13 Section A1a Sentence 1. Substitute empiric for trial and error. I would also consider substituting the word inappropriate for incorrect. Incorrect implies the correct answer is known and that is not the case at present.

Page 15 Section A2a paragraph 2 The paragraph implies that PGx will impact issues of lack of implementation of effective treatments and non-compliance. I think this is highly speculative with little if any data to support. I would propose: "Effective treatments for many acute and chronic conditions are grossly underutilized. One aspect of this is the recognition that half of patients with chronic health conditions discontinue use of their medications after one year (66). There are extensive efforts underway in the United States to use guidelines, disease management, quality improvement and clinical decision support tools to improve the use of effective treatments. Incorporation of information derived from PGx could complement these efforts by aiding in selection of medications more likely to be effective and well-tolerated, which would be expected to have higher compliance. These efforts could yield economic benefits to consumers, payers, and the broader health care system."

Page 16 Section A2b first sentence of page: Would add "and severity" after duration. "…diminishing the duration and severity of illness…" Duration is only appropriate for acute or curable illnesses.

Page 16 Section A2b paragraph 2 last sentence Would add after genetic information, "(for tests that are only required to be done once in a person's lifetime)"

Page 17 first paragraph immediately before Section B After the last sentence that discusses underserved populations, I think another sentence has to be added for balance. "Alternatively, limiting the use of new agents to subgroups rather than whole populations could increase the unit cost of drugs, as development costs can only be spread across a portion of patients. If research and development costs don't decrease this would raise a significant concern about access to these drugs for underserved populations.

Page 17 last paragraph sentence 2. Recommend "increased" rather than serious in sentence: "…low TMPT activity, are at increased risk for life-threatening…"

Page 18 first sentence. Recommend replacing avoiding with "reducing" as "…TMPT variants, thus reducing the risk of this life-threatening…" Also, in this sentence, the reference noted (84) does not actually present any data. To my knowledge there has been no study that has demonstrated prospectively that use of this information actually reduces the rate of myelosuppression. The only studies show a correlation between genotype and frequency of myelosuppression. While strongly suggestive, this does not prove that using this knowledge ahead of time will reduce life-threatening myelosuppression.

Page 19 Second full paragraph. While PGx data may well be available in the package insert on 71% of the top 200 drugs, there are few if any data on clinical validity and utility. You note later in the paragraph that there is "…no consensus on the strength of association between genetic variability and drug response for these agents." There is no consensus because of the paucity of data that address this issue. I think this should be explicitly stated rather than simply implied. The last sentence of the paragraph, "These findings suggest that much of the available PGx data in the literature is ignored in prescribing information included in package inserts." To which I would add, "and appropriately so given the lack of clinical data on the impact use of PGx in prescribing."

Page 24 Section C. Paragraph 1 second sentence. Recommend adding "potentially" before "resulting in smaller, efficient, safer and more rapid…" Same paragraph last 2 sentences claim the potential for a three-fold reduction in development time. Is there evidence to support this claim, or is this one author's opinion?

Page 25 paragraph 3 the sentence that talks about the controversy over the use of adaptive design in phase III. The statement is made that "…the results are difficult to interpret." A brief explanation as to the difficulties would be useful, as the answer is not apparent (at least to me).

Page 26 Recommendation 3. The recommendation implies that the FDA must develop this expertise in order to insure fruitful consultations. This should be stated explicitly.

Page 27 Second paragraph. The paragraph discusses the difficulty of predicting the influence of PGx on drug development. Some predictions could be made by looking at the development of drugs for patients with a specific response element that occurs in a subgroup of the population with the disease. Examples could include Herceptin and the EGFR2 inhibitors in non-small cell lung cancer.

Page 28 paragraph under 3) The sentence beginning with "Furthermore, ambiguity remains…" has the word "traditionally" twice.

Page 31 paragraph under 5) sentence 3. This sentence states that "…current dosing decisions for the drug are based primarily on clinical judgment." While technically true, it might be more informative to state "…decisions for the drug based on limited sets of patient characteristics that explain only a small percentage of the variability between patients."

Page 33 Recommendation 4B. Would suggest the word "novel" rather than "greater" before intellectual property protection. Also, this recommendation doesn't address issues of incentives for existing drugs, or drugs that have been removed from the market that might be considered for re-entry based on PGx. Were these out of scope?

Page 34 paragraph under 1) sentence beginning "*Clinical utility* refers to…" recommend adding "improve therapy for a disease" between "inform clinical decision-making" and "prevent adverse health outcomes" Later in the paragraph the statement is made "…indicate that health care providers perceive little evidence to date of the clinical validity and utility of PGx tests…" This statement implies that the evidence exists but the providers don't use it. The reality is that the evidence of clinical validity and utility do not exist at present. The only "evidence" that is reasonably robust is that of retrospective associations with stable dose and/or adverse events, which may or may not be outcomes that answer questions of validity and utility.

Page 42 Recommendation 6C Should the Personalized Health Care Workgroup of the DHHS American Health Information Community (AHIC) be explicitly referenced in this recommendation? AHIC is referenced on page 44 with respect to its role in privacy and protection of information and the Personalized health Care Workgroup is referenced in the bullet on page 83.

Page 49 Paragraph under 4) Suggest modifying the last sentence of this paragraph as follows: "Requiring PGx as a condition for drug treatment, **when data adequately support an association with adverse drug events that can be prevented by using the test**, could further reduce pharmaceutical companies' liability risk. The reason for including the clause is to prevent the application of this type of wording to all drugs in an attempt to shift liability to providers. Any "requirement" needs to be associated with appropriate data that justifies requiring a PGx test.

Page 56 First full sentence that refers to proportion of PGx tests will fit within IVDMIA category. Another important consideration is whether the dosing algorithms that are developed to support appropriate use of medications by practitioners (i.e. clinical decision support algorithms) will be regulated as devices by the FDA. There are some early indications from intensive care protocols that this may be the case.

Page 60 a) Medicare The document does not mention Medicaid, the VA or Tricare. Medicaid in particular is important given the large number of members, the fact that all Medicaid recipients have prescription drug benefits and the variation in policies from state to state.

Page 60 a) Medicare second paragraph. Another issue that may impact Medicare coverage of tests is the application of Medically Unlikely Edits (MUEs) to genetic tests that require multiples of CPT codes. This issue could significantly impact use and reimbursement of tests.

Page 62 Recommendation 9 There is no reference to the role of employers in defining benefit plans. Even if an insurer indicates it would cover a genetic test, employers can still define a benefit plan that excludes coverage of genetic tests. Also many larger companies are providing coverage through a self-insurance mechanism where a payer partner serves only to administer the employer-defined benefit. These plans are exempted from many regulatory mechanisms such as ERISA. The other problem with this recommendation is that it reads like a mandate. While this may be justifiable for tests that have robust validation, the secretary has no regulatory authority over private health plans to devise or enforce such a mandate.

Page 63 When talking about the TEC of the BCBSA the statement is made that these are publicly available. It is my understanding that these reports are only available to those who purchase a subscription. If this is correct the statement should be clarified.

Page 65 first paragraph. I think section 2 c) (beginning on page 64) needs to at least mention the national problem of the un- and underinsured. While this problem is by no means unique to this issue, it is deserving of explicit discussion.

Page 65 Section 2 d) ICD-9-CM is mentioned as a coding system. It needs to be noted that this coding system is not adequate to describe diagnostic indications for PGx testing in most cases, but in particular around the area of genetic disorders. In addition it should be noted that the CPT system currently has codes for genetic tests that are generic and reflect activities such as DNA extraction, PCR etc. There are no level 1 CPT codes that describe the specific test being done. Some genetic modifiers for CPT codes have been added that provide this specificity, but their use is not required and most systems are not using them. Additionally, at present only five modifiers are applicable for Pharmacogenomics. One of these (9L) is a general "not otherwise specified code", and a second (9B) captures all CYP2 genes, so one could not distinguish between a CYP2C9 and CYP2D6 for example. The section has a maximum capacity to accommodate 26

codes which is highly unlikely to be sufficient. (this comment also applies to the statement at the end of the first paragraph on page 67 that talks about the genetic modifiers for CPT codes). References to these specific problems can be found in the SACGHS Report on the coverage and reimbursement of genetic tests, as well as the ACMG Manual on Reimbursement for Medical Genetic Services.

Page 67 paragraph 1 sentence 3, I recommend changing the word "may" to "will" as in: "…coding systems will need to be revised…"

Page 69 Middle paragraph last sentence. Statement made that: "…recognizes the need for more detailed guidelines in the future." No comment is given as to who would own the responsibility for creation and implementation of the guidelines and where funding is for guideline development, not to mention updating and maintenance.

Page 71 Section A1) I would recommend including PharmDs in this category. Even though they may not technically have "prescribing ability" most hospitals extensively rely on PharmDs to manage processes analogous to PGx such as drug-drug interactions and patient-specific dosing based on clinical parameters such as renal function, weight, age, etc.

Page 89 Last paragraph. Reference 527 is cited to emphasize that the savings to the health care system of PGx testing for Warfarin would alone result in savings of $1.1 billion in health care costs. It should be noted that this study used assumption-based models, not actual clinical data, was not published in the peer-review literature and others have serious concerns with the assumptions that were used in this study (Veenstra, personal communication).

WORLD **PRIVACY** FORUM

Comments of the World Privacy Forum

On the Draft Report of the Secretary's Advisory Committee on Genetics, Health, and Society, *Realizing the Promise of Pharmacogenomics: Opportunities and Challenges*

For the Office of the Secretary, Health and Human Services, Secretary's Advisory Committee on Genetics, Health, and Society; the National Institutes of Health; U.S. Public Health Service

VIA e-mail and fax

May 23, 2007

Reed V. Tuckson, MD
Chair, Secretary's Advisory Committee on Genetics, Health, and Society
NIH Office of Biotechnology Activities
6705 Rockledge Drive, Suite 750
Bethesda, MD 20892

Dear Dr. Tuckson:

The World Privacy Forum welcomes the opportunity to comment on the draft report of the Secretary's Advisory Committee on Genetics, Health, and Society titled *Realizing the Promise of Pharmacogenomics: Opportunities and Challenges* published in March 2007. This is a response to the request for comments that appeared in the Federal Register on March 28, 2007, 72 Fed. Reg 14577.

Introduction

The World Privacy Forum is a non-profit, non-partisan public interest research organization. It focuses on in-depth research and analysis of privacy topics, including topics in medical privacy, financial privacy, and other aspects of privacy.[1]

These comments focus on the privacy implications of the draft report. We want to state our basic view as clearly and as simply as we can. Privacy is not a barrier to any aspect of the practice of medicine. It is an inherent part of medical care and has been since the dawn of medicine. Privacy is not something to be evaded, avoided, undermined, dismissed, or overcome. The need for privacy must be accepted and incorporated in any medical setting, including research.

The World Privacy Forum recognizes the value of patient data for research, and we express no fundamental objection. However, the terms of any data use or data sharing for research are

[1] <http://www.worldprivacyforum.org>

important, the effects on privacy must be evaluated, and the fundamental goals of privacy must be incorporated. As with any other secondary use of health treatment records, the sharing of patient data for research affects the privacy interests of patients. That is true regardless of the scope or importance of the research. Data sharing can be justified notwithstanding its negative privacy consequences, but there must be a suitable recognition and accommodation of patient privacy interests.

So we are a bit put off by this recommendation on page 8 of the report:

> HHS should work with the private sector to identify obstacles to data sharing and to develop solutions to overcome these obstacles (e.g., legal and data confidentiality assurances, intellectual property protections).

Our objection is as much to the language as to the policy. We are unhappy that the Department of Health and Human Services in many of its activities already tends to view privacy as a *barrier* to its plans for greater exploitation of patient information for treatment and other purposes. We would much prefer to see an acknowledgement of the inherent necessity of privacy in the health care system that extends beyond lip service. If patients walk away from research activities or from treatment because they do not think that their privacy interests are adequately protected, nothing will be accomplished. Accommodating privacy has costs and consequences that cannot be entirely *overcome*. We readily acknowledge that privacy must compete with other basic health care objectives, but we object when those seeking to attain those other objectives are readily prepared to jettison privacy entirely in pursuit of those other goals.

Our general conclusions about privacy and medicine are true for pharmacogenomics (PGx) just as for any other aspect of medicine. We do not argue here that genetic information inherently requires extra protection beyond that afforded to other health information. We suggest that genetic information, like some other health information, has some characteristics that may call at times for different application of standard privacy policies. For example, conflicts between the interests of related individuals may be more intense with genetics than with most other classes of health information.

We observe that existing protections for all health information have significant inadequacies. We do not expect the SACGHS to fix those problems, but we caution against any assumption that current medical privacy law and policy suitably resolves all health privacy concerns. The HIPAA health privacy rule has many shortcomings, and the existing problems will only grow worse as uses of patient information are expanded through networks and otherwise.

We also caution about too much reliance on HHS to protect privacy interests. The Department has too many other roles in the health care system to be trusted to always strike a fair balance when privacy matters are at stake. Other stakeholders need to be involved when choices are to be made, privacy impact assessments are needed, and balancing of interests is required.

Finally, we reaffirm the importance of Fair Information Principles (FIPs) in establishing policies for the use of any personal information. Fair Information Principles are an internationally accepted set of principles that describe how an information-based society may approach

information handling, storage, management, and flows with a view toward maintaining fairness, privacy, and security in a rapidly evolving global technology environment. We note that the HIPAA health privacy rule is an express implementation of FIPs. While HIPAA has flaws too numerous to address in these comments, its goal of implementing FIPs in any health information activity is a sound one. FIPs must be deeply embedded and fully integrated into any PGx projects and data flows from the beginning.

The Department played a prime role in the original development of FIPs. The first steps toward formally codifying Fair Information Principles began in July 1973, when an advisory committee of the U.S. Department of Health, Education and Welfare proposed a set of information practices to address a lack of protection under the law at that time. The resulting HEW report, *Records, Computers and the Rights of Citizens: report of the Secretary's Advisory Committee on Automated Personal Data Systems*, set forward key foundational ideas for safeguarding privacy.[2]

In 1980, the Organization for Economic Cooperation and Development (OECD) used these core HEW fair information principles and built upon them to create a set of eight Fair Information Principles codified in the OECD Guidelines on the Protection of Privacy and Transborder Flows of Personal Data.[3] The OECD has historically created internationally-agreed upon codes, practices, decisions, recommendations, and policy instruments. The eight principles OECD published in 1980 were agreed upon by member countries, including the United States, through a consensus and formal ratification process. These OECD guidelines form the basis of many modern international privacy agreements and national laws, and these eight principles from 1980 are referred to by the U.S. Government Accountability Office as key principles for privacy protection.[4]

Marketing

We begin our main comments with marketing issues because there is not enough awareness in the health policy world about existing trafficking in health care information. We are encouraged by the Committee's attention (page 79) to the marketing opportunities that may arise if PGx tests evolve into consumer products. We think that there are additional related concerns.

The interest of marketers in personal health information is strong. We suggest that you look up the web site of Direct Magazine at <http://listfinder.directmag.com/market> and enter the keyword *ailments* into the "list finder" search box. You will find page after page of mailing lists that offer the names and addresses of individuals by ailment, including diabetes, Crohn's disease, Lupus, heart disease, asthma, and many others. Purveyors of mailing lists and personal profiles would be happy to add genetic characteristics to their files.

---

[2] <http://aspe.os.dhhs.gov/datacncl/1973privacy/tocprefacemembers.htm>.

[3] Organisation for Economic Co-operation and Development. *Guidelines on the Protection of Privacy and Transborder Flows of Personal Data* (Sept. 23, 1980), <http://www.oecd.org/document/18/0,2340,en_2649_34255_1815186_1_1_1_1,00.html>.

[4] General Accounting Office, *Agency and Reseller Adherence to Key Privacy Principles* 1-2 (April 4, 2006) (GAO-06-421).

We expect that one consequence of the availability of additional genetic information about individuals will be an increase in personally directed advertising hawking expensive prescription medication, new testing methods, and useless treatments. We leave it as an exercise for the Committee to speculate how purveyors of fraudulent weight loss remedies might use new genetic findings and genetic information to sell their wares.

These detrimental activities do not outweigh the development of beneficial uses of PGx. However, they do suggest the need for stronger controls over patient information, restrictions on direct-to-consumer (DTC) advertising, and better enforcement of consumer protections.

Research vs. Treatment

The draft report focuses much, but not all, of its attention on research activities. We want to underscore the major differences for privacy between research and treatment activities. Under current health privacy policies, health information in the hands of those who are not HIPAA covered entities is not subject to HIPAA privacy protections. Thus, records subject to HIPAA in the hands of a treating physician are not necessarily subject to HIPAA when disclosed to a researcher. A registry or other database of health information maintained for research purposes is not likely to be covered by the HIPAA privacy rules.

Under the right circumstances, research records can have significant protections against secondary use through certificates of confidentiality. In general, certificates of confidentiality authorize researchers to resist compulsory legal demands (e.g., subpoenas and court orders) for identifiable research information about individuals. By providing a defense against compelled disclosure, certificates provide a defense against legal obligations to disclose records to law enforcement agencies, private litigants, and others who may have an interest in the records for purposes unrelated to the purpose for which the records were compiled. One statute that establishes a certificate program is 42 U.S.C. § 241.[5]

By contrast, when health research records are maintained by federal agencies and are not protected by certificates, the records can be subject to secondary uses, including for law enforcement purposes. Treatment records covered by HIPAA privacy rules may also be disclosed for numerous secondary purposes without patient consent and without court orders. For example, HIPAA records can be disclosed for law enforcement purposes in response to oral requests with minimal threshold requirements and for national security purposes with no threshold requirements at all.

Patient records held by researchers who are not federal agencies are also at greater risk for secondary use when not covered by certificates of confidentiality. While institutional review boards (IRBs) may impose some conditions on reuse or redisclosure of patient records by researchers, we doubt that all IRBs are knowledgeable enough to impose an adequate set of

---

[5] Other statutes that provide for certificates of confidentiality or the equivalent include: 42 U.S.C. § 242m(d); 42 U.S.C. § 299c-3(c); 42 U.S.C. § 290aa(n); 42 U.S.C. § 3789g(a); 42 U.S.C. § 10604(d); and 44 U.S.C. § 3501 note. See the NIH's Certificates of Confidentiality Kiosk at <http://grants.nih.gov/grants/policy/coc/index.htm>. We do not mean to suggest that existing certificate of confidentiality laws are perfect, but they offer a type of protection not otherwise available for health research records.

rules. We have even more doubts about the ability of IRBs to oversee the enforcement any restrictions that they may impose.

We recommend that all research activities that involve any type of identifiable health information be required to have certificates of confidentiality. We also recommend that all research activities that involve any type of patient-specific genetic information be required to have certificates of confidentiality, whether that information appears identifiable or not. The World Privacy Forum believes that the capability of identifying individuals from subsets of genetic information will expand greatly in the future. Portions of an individual's genetic code that appear to be non-identifiable today may become identifiable tomorrow as a result of new technologies or other data repositories maintained by other researchers or even by law enforcement agencies.

The report needs to pay considerably more attention to the transition from research activities to routine treatment applications of PGx technology. When genetic sequencing becomes a standard treatment activity, the sequences can be readily available to law enforcement under current HIPAA privacy rules. With the looming possibility of a national health network, it is fully conceivable that law enforcement professionals could have virtually unlimited access to patient records through, for example, the ease of a network terminal.

When DNA sequence information becomes a routine part of a health record, that information may leak out of the health care system and end up in the files of employers, insurers, pharmaceutical manufacturers, purveyors of personal health record services, marketers, and others. There is nothing unique here about sequence information. Considerable amounts of patient information leak out of the health care system today.

The jump from research to treatment has enormous implications for privacy, and the non-medical use of genetic sequence information may have negative consequences for individuals. The Committee should not focus too narrowly on the medical applications of PGx technology and ignore the other consequences. We can envision the possibility that routine integration of PGx into medical practice will result in greatly expanded DNA analyses for patients, including the possibility of full sequencing for all newborns. That could result in a DNA database akin to – or even more comprehensive than – the existing FBI fingerprint database. We envision the need for stronger privacy rules and laws, and the Committee should consider what type of additional protections might be needed.

Identifiability

The draft report considers the use of coding or encryption to protect privacy of patients. We support better technical measures to mask identity. Coding identifiable information, if done properly, offers some protection for privacy. However, information that does not have any overt identifiers may nevertheless be capable of reidentification. The work of Carnegie Mellon Professor Latanya Sweeney offers overwhelming evidence on this point. We refer you in particular to B. Malin and L. Sweeney, *How (Not) to Protect Genomic Data Privacy in a Distributed Network: Using Trail Re-identification to Evaluate and Design Anonymity*

Protection Systems.[6] We quote the paper's abstract here because it makes the point that removal or encryption of explicitly identifiable genetic information is not sufficient.

> The increasing integration of patient-specific genomic data into clinical practice and research raises serious privacy concerns. Various systems have been proposed that protect privacy by removing or encrypting explicitly identifying information, such as name or social security number, into pseudonyms. Though these systems claim to protect identity from being disclosed, they lack formal proofs. In this paper, we study the erosion of privacy when genomic data, either pseudonymous or data believed to be anonymous, is released into a distributed healthcare environment. Several algorithms are introduced, collectively called REIdentification of Data In Trails (REIDIT), which link genomic data to named individuals in publicly available records by leveraging unique features in patient location visit patterns. Algorithmic proofs of re-identification are developed and we demonstrate, with experiments on real-world data, that susceptibility to reidentification is neither trivial nor the result of bizarre isolated occurrences. We propose that such techniques can be applied as system tests of privacy protection capabilities.

The enormous amount of personal information available from public and private sources means that the realm of truly non-identifiable personal information is shrinking every day. You should not assume that genetic information will be exempt from this trend. We fully expect that patient genetic information will eventually end up in the possession of commercial data brokers and other private actors who may not be subject to privacy rules. We do not believe that the Committee should casually assume that coding or encryption will provide a broad or permanent solution to privacy concerns.

We are more positive about the use of what the draft report calls *controlled data-release arrangements, where parties must commit to protecting privacy and confidentiality before being granted access* (page 43). Data use agreements of the type described in the HIPAA health privacy rule have a place and can provide a layer of protection. We recommend that data use agreements expressly provide that data subjects are intended third-party beneficiaries of the legal, technical, and administrative protections established by the agreements. Otherwise, data subjects may have rights without remedies, and the intended protections may have little meaning.

Even the most carefully drafted and complete data use agreement has its limits. A data use agreement can have utility in research, public health, and health oversight activities where the need for identifiers is often narrow and the volume of data is typically large. However, data use agreements are not likely to have any applicability in a treatment context where the identity of the patient is always known and where the use of overt identifiers is often essential. Privacy responses that work for research do not necessarily solve treatment problems, and vice versa.

Privacy Solutions

---

[6] 37 Journal of Biomedical Informatics 179-192 (2004), <http://privacy.cs.cmu.edu/dataprivacy/projects/trails/dnaTrails.html>.

We note the recommendation (page 11) for more funding of research on the ethical, legal, and social implications of PGx. We agree, but we think that this is an inadequate response. ELSI research is welcome, but ELSI research in the past has tended to sit on a shelf or in a journal, completely divorced from the policy process. If ELSI activities on PGx result in more of the same, then they may be pointless.

What is needed is a method for assuring that ELSI issues – especially including privacy – are addressed when decisions are made about funding research, approving protocols, establishing databases, and implementing the results of research in treatment activities. Two types of institutions exist for these purposes.[7]

First, the World Privacy Forum recommends that a full time, independent privacy officer position be created for PGx activities. This privacy officer should be properly qualified and have plentiful and long experience with ELSI, the Privacy Act, Fair Information Practices, HIPAA, and other aspects of health privacy. In addition, the privacy officer should be responsible for creating a fair and impartial Privacy Impact Assessment for each proposed or actual major project.

Additionally, the project's privacy officer should:

- be independent from any institution participating in the project's activities;
- serve as an ex-officio member of any PGx ELSI committee;
- have the ability to report directly to the Congress and to the HHS Secretary;
- not be subject to removal from office without cause;
- be authorized to issue public reports, testify before Congress, hold press conferences, and undertake comparable public activities without the need for clearance from project management;
- have sufficient resources and staff to initiate and conduct audits and investigations of compliance with privacy and security obligations.

Because PGx privacy matters will include research, treatment, policy, and other issues, we suggest that the privacy officer should be in the Office of the Secretary. It would be ideal if the position of HHS privacy advocate were reestablished and provided with sufficient resources to carry out a broader mission, including PGx privacy.

Second, privacy impact assessments (PIAs) should be required for significant PGx activities funded by the federal government. Each PIA should be published for public comment, and the comments should be considered by decision makers. The E-Government Act of 2002 requires federal agencies to prepare a PIA under specified conditions. Whether or how the Act may apply to PGx activities should not determine whether a PIA is completed. We recommend that PIAs be required for significant federal PGx activities, including major research databases and policy decisions for PGx. We do not envision that each PGx research protocol will need its own PIA, however.

---

[7] We are intentionally ignoring IRBs here because we do not believe that IRBs generally have the skills or capability of addressing privacy.

We also recommend that the PIA exceed the statutory requirements of the E-Government Act. At a minimum, decision makers must be required to consider the PIA and to respond publicly to its findings and recommendations. The PIA could be conducted by the privacy officer or by a third party with suitable experience and independence from project planners and likely project participants. The need for independence is crucial. Too often, PIAs are prepared by project managers, contractors, or others with too much of a stake in the project to be objective.

Conclusion

Thank you for the opportunity to comment on the Committee's draft report on pharmacogenomics. We have no doubt that it is possible to incorporate new advances in medicine without unduly impinging on the privacy that patients appropriately demand from the health care system. We hope that our suggestions will be helpful in making progress with pharmacogenomics in combination with robust privacy protections.

Respectfully submitted,

Pam Dixon
Executive Director
World Privacy Forum
www.worldprivacyforum.org
+1 760.436.2489