Comments to the Secretary's Advisory Committee on Genetics, Health, and Society on pharmacogenomics

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.

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 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: 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 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 HHS to 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: We recommend that the SACGHS 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 SACGHS 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 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; 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 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 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 SACGHS 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