Finalization of SACGHS Report on Pharmacogenomics

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SACGHS Task Force on Pharmacogenomics

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- Jim Evans
- Andrea Ferreira-Gonzalez
- Julio Licinio
- Steve Teutsch

- Emily Winn-Deen (ad hoc)

- AHRQ - Gurvaneet Randhawa
- CDC - Muin Khoury
- FDA - Steve Gutman, Liz Mansfield, Allen Rudman
- NIH - Greg Feero, Rochelle Long

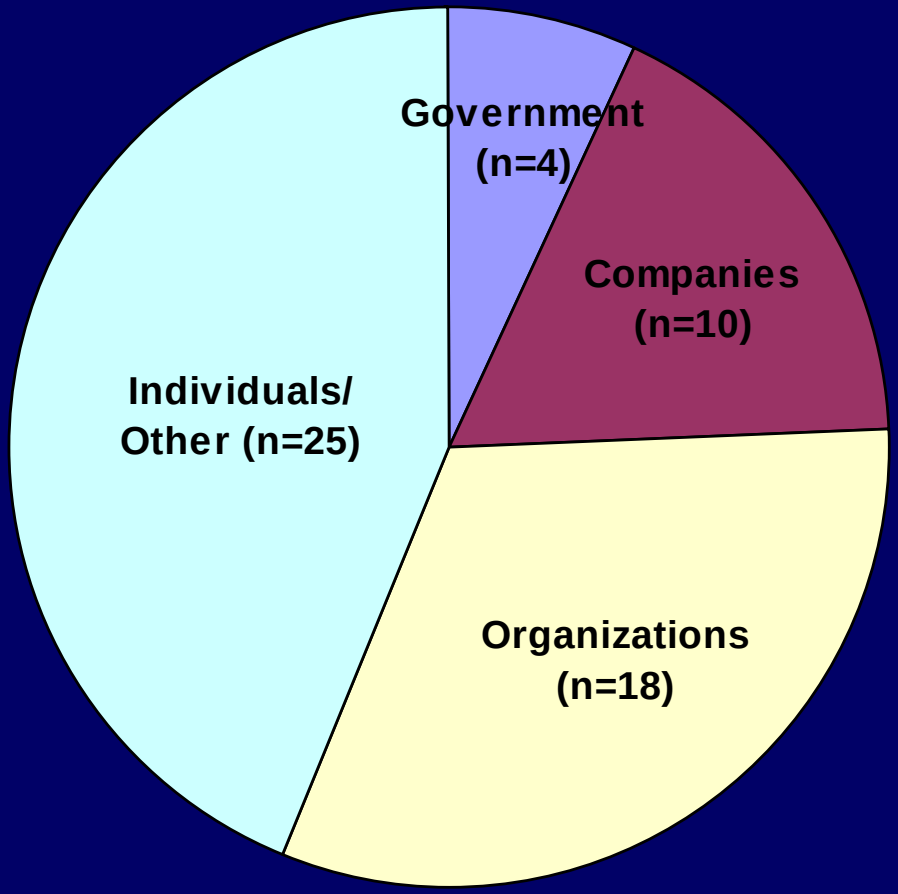
SACGHS PGx Efforts to Date

- Informational sessions
- Compilation of Federal PGx activities
- Review of literature
- Development of and revisions to draft report and recommendations
- Interviews with key experts
- Public comments
- Review and consideration of public comments

Request for Public Comments

- Public comment period: March 23 – June 1, 2007
- Dissemination of request
  - March 23 PMC event: Secretary's announcement of Personalized Health Care Initiative
  - SACGHS website
  - SACGHS listserv (n=936)
  - Targeted "Dear Colleague" mailing (n=283)
  - Targeted request for dissemination to organization membership (n=31 orgs)

Public Comments Received



TOTAL=57

Government – e.g., NIH, OCR, VA

Companies – e.g., Abbott, Amgen, Eli Lilly, Genzyme, GSK, Pfizer

Orgs – e.g., AMP, ACLA, AHIP, BCBSA, AMA, ANA, BIO, ISONG, PhRMA, PMC

Individuals/Other – e.g., academics, health care providers, researchers

Overview of Public Comments

- Comments ran the gamut and addressed every aspect of report and recommendations
- Comments on report text
  - Corrections to some inaccurate statements
  - Updates to mentioned activities
  - Ideas for improvements
- Comments on recommendations
  - Modifications to existing ones
  - Thoughts on which recommendations should be of highest priority
  - New recommendations to consider adding

Recurring Themes of Public Comments

- Report overly optimistic about long-term potential of PGx
- Need more discussion of international efforts and public-private collaborations currently underway
- Need better definition of PGx
- Desire for SACGHS to address oversight of genetic tests

Recurring Themes of Public Comments

- Call for Federal govt to encourage collection of DNA samples in clinical trials to facilitate PGx research
- Need criteria to define what PGx information should be included in a drug label
- More emphasis on the need for more clinical effectiveness evidence to secure payer reimbursement
- Call for value-based approach to reimbursement of PGx products
- Disagreement about whether PGx will necessitate genetic counseling

Review of Public Comments

- PGx TF members received full set and summary of comments in June 2007
- Each TF member assigned 8 comments to review
- Up to 2 TF members reviewed each comment
- Staff reviewed all 57 public comments

Review of Public Comments

- TF member/staff review of public comments
  - What comments should be addressed in the next draft of the report?
  - Of the comments that should be addressed, which warrant TF discussion, and which can be addressed by staff without TF discussion?
  - Of those that warrant TF discussion, how do you suggest it be addressed?

Review of Public Comments

- Two TF conference calls (6 hours total)
  - August 16 and September 10
  - Reviewed discussion guide compiled by staff
    - Comments organized by section of report/recommendation
    - Recommended action – based on TF member/staff input
  - Discussed items which TF members flagged as warranting TF discussion
  - Made decisions about whether and how to address comment in report

Review of Public Comments

- Lewin and staff revised report and recommendations based on decisions made during TF calls
- Revised report in Tab 3 of briefing books

Goals of Today's Session

To finalize recommendations

* Edits to report content can be given to Suzanne Goodwin

Next Steps with PGx Report

Nov 2007	Report and recommendations revised to reflect today's discussion
Dec 2007	"Final" report sent to SACGHS by email
Dec 07 - Jan 08	Copy-editing, preparation of "camera-ready" report, and printing
Feb 2008	Final report transmitted to Secretary
March 2008	Final report released to public

Organization of Report

- Report and recommendations organized into three overarching themes
  - Research and development
  - Gatekeepers
  - Implementation of PGx to improve outcomes in clinical and public health practice
- Total of 15 recommendations (37 subparts)

Organization of Report: Research and Development Section

- Research and development
  - Basic research
  - Clinical research
  - Translational research
  - Infrastructure enabling research and development
  - Ethical, social and legal issues in research and development

➢ Recommendations 1-8 (20 subparts)

Organization of Report: Gatekeepers Section

- Gatekeepers
  - Industry
  - FDA
  - CMS and other third-party payers
  - Clinical practice guideline developers

  ➢ Recommendation 9

Organization of Report: Implementation of PGx Section

- Implementation of PGx to improve outcomes in clinical and public health practice
  - Education and guidance
  - Information technology and PGx
  - Economic implications of PGx
  - Ethical, legal and social issues in clinical implementation of PGx
  - Coordination of HHS PGx activities

➢ Recommendations 10-15 (16 subparts)

Structure of Discussion

- For each section of report
  - Review key issues
  - Review current language of draft recommendations
  - Propose modifications to current language
- At end, vote on final recommendations *in toto*

Questions to Consider

- Are these the recommendations SACGHS should make to the Secretary?
- Are they the best way to address the opportunities and challenges addressed in the report?
- Are you satisfied with the wording of the recommendations? If not, what changes do you suggest?

Research and Development Section

- Research and development
  - Basic research
  - Clinical research
  - Translational research
  - Infrastructure enabling research and development
  - Ethical, social and legal issues in research and development

Basic Research

- More basic research is needed to:
  - Identify biochemical pathways and related biomarkers involved in drug metabolism and drug response
  - Refine and improve sensitivity of high-throughput methods for detecting gene expression and drug response
  - Gene-loci specific variability in drug response
- e.g., Genetic Association Information Network

Translational Research: Basic to Clinical

- “T1” translational research is performed to validate basic research findings and apply that knowledge to the development of PGx products
- e.g., PGx Research Network

Clinical Research

- PGx can enable smaller, more efficient clinical trials by:
  - Using PGx test results to screen out subjects more likely to experience adverse drug reactions
  - Identifying subjects more likely to respond well to a drug

Development of PGx Tests

- Incentives to develop PGx tests depend on numerous factors
  - Projected market utilization and expected return on investment
  - Clinical impact of test results
    - Contribution of genetics relative to other non-genetic factors
    - Prevalence and severity of ADRs
  - Gene patents and licensing practices

Co-development of PGx Drugs and Diagnostics

- Some resistance by industry to co-develop drugs and diagnostics, although this is changing
  - Concern about market segmentation
  - Uncertainty about FDA regulation of co-developed products
  - Requires new collaborations between drug and diagnostics companies and coordination of development processes
- Can result in expedited FDA approval, fewer label changes, and greater likelihood for provider uptake

Application of PGx to "Rescue" Drugs

- PGx may help "rescue" drugs found ineffective during drug development in a broad population or withdrawn from market due to serious ADRs
- Post-hoc analysis of clinical drug trial data could distinguish subset of "good" responders

Application of PGx to Existing Drugs

- PGx testing has the potential to improve the safety and efficacy of drugs already on the market
- Incentives for pursuing identification of new indications for existing drugs are mixed

	More Incentive	Less Incentive
Patent status	under patent	off patent
ADRs	severe	mild
Availability of alternate treatment	no	yes

PGx and Small Target Populations

- Special provisions for orphan drugs and humanitarian use devices may encourage development of PGx products targeted to small populations
- Differences in disease prevalence thresholds for drugs and diagnostics
  - Orphan drug: ≤200,000
  - Orphan diagnostic: ≤4,000
  - ➢ Could favor development of PGx drugs but not their companion diagnostics

Translational Research: Development to Clinical Practice

- Adoption of PGx technologies will hinge on evidence demonstrating the value of using PGx products in clinical and public health practice
  - Clinical utility/clinical effectiveness/improved health outcomes
  - Cost-effectiveness
- Paucity of evidence on the clinical utility of most PGx products
  - Few incentives to produce this evidence

R&D Infrastructure

- PGx R&D could benefit from sharing and linking of research and clinical databases, repositories and records
- Challenges to data sharing and interoperability
  - IP concerns
  - Variation in data formats
  - Electronic health records in early stages
  - Different funding streams, stakeholders, administrative protocols, and organizational cultures
- Signs of improvement
  - e.g., PharmGKB, dbGaP, GAIN, C-Path initiatives

ELSI Issues in PGx R&D

- Privacy and confidentiality concerns associated with sharing of genetic information
  - Data access and utility may be lost in exchange for gains in data protection
- Discrepancies between human subjects research regulations for coded specimens (Common Rule vs. FDA regs)
- Concerns about using race/ethnicity as basis for inter-individual differences in drug response
- Liability risks associated with questionable marketing claims, labeling omissions, or incorrect or misinterpreted test results

Basic Research
Draft Recommendation 1

NIH should put more resources into:

1) Basic research on the biochemical pathways associated with drug metabolism and drug action, the genes and gene variations involved in these pathways, and the functions of those genes related to the safety and effectiveness of drug treatments; and

2) Non-hypothesis-based approaches to the understanding of the relationship between genetic variation and individual's response of drugs.

Translational Research
Draft Recommendation 2

As knowledge of the underlying biology accrues, further research will be needed to translate this knowledge into the development of clinically useful PGx tests and technologies and to assess their clinical validity and clinical utility.

HHS agencies should facilitate the development of clinically useful PGx technologies by investing more resources into all components of translational research (including the translation of basic research findings into clinical trials, as well as the translation of clinical research findings into clinical and public health practice and policy). One of the emphases of this translational research should be to foster the development of more rapid, cost-effective genotyping technologies.

Clinical Research
Draft Recommendation 3A

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

Clinical Research
Draft Recommendation 3B

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

Clinical Research
Draft Recommendation 3C

NIH should encourage grantees and contractors to participate in FDA's Voluntary Genomic Data Submission program to ensure consistency in data standards that may affect drug prescribing.

Clinical Research
Draft Recommendation 3D

**** New recommendation proposed by comments****

HHS should enable the investigation of biomarkers associated with drug response by encouraging sponsors of federally-funded clinical drug trials to request appropriate biological samples from research participants.

Development and PGx Products
Draft Recommendation 4A

HHS should ensure that sufficient resources are available to FDA to build on and implement the agency's efforts to develop guidance on the co-development of PGx drugs and diagnostics. 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. It also should promote collaboration between drug and diagnostics manufacturers.

Development of PGx Products
Draft Recommendation 4B

FDA's Office of Combination Products should coordinate the review of PGx tests and drugs among the various FDA centers/offices, to minimize delays in approvals of co-developed PGx products and to ensure timely access to such products.

Development of PGx Products
Draft Recommendation 4C

HHS should identify and provide incentives to the private sector to encourage the development of PGx products for smaller markets.

Establishing an Evidence Base
Draft Recommendation 5A

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

Establishing an Evidence Base
Draft Recommendation 5B

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

Establishing an Evidence Base
Draft Recommendation 5C

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

Establishing an Evidence Base
Draft Recommendation 5D

NIH should provide mechanisms to promote interactions among basic, translational, clinical and outcomes researchers for the identification of endpoints and data elements to be measured. The goal of these interactions would be to maximize the value and utility of basic and translational research data for downstream assessments of the clinical validity and clinical utility of PGx tests.

Data Sharing and Database Interoperability
Draft Recommendation 6A

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

Data Sharing and Database Interoperability
Draft Recommendation 6B

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).

Data Sharing and Database Interoperability
Draft Recommendation 6C

Research, regulatory, medical record and claims databases need to be interoperable to facilitate research on PGx technologies and build the necessary evidence base. Interoperability of these databases will facilitate the study of the molecular pathogenesis of disease, the identification of targets for drug development, validation of PGx technologies, assessment of health outcomes associated with use of PGx technologies and determination of the cost-effectiveness and economic impact of using these technologies.

HHS and other relevant Departments (e.g., DVA, Department of Defense [DOD]) should work with the private sector to improve data sharing and interoperability among databases. Specifically, HHS should work with existing organizations to create uniform genomic data standards, explore ways to harmonize data analysis methodologies and develop an infrastructure to enable data exchange.

Data Sharing and Database Interoperability
Draft Recommendation 6D

FDA should identify, initiate and facilitate research opportunities and public/private partnerships to encourage the development and co-development of PGx products, e.g., through the Critical Path Initiative.

Protection of Personal Information
Draft Recommendation 7

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.

Population Stratification in Drug Response
Draft Recommendation 8A

Because genomic factors may be more meaningful predictors of drug response than race and ethnicity categories, FDA should develop guidance that encourages the collection and analysis of genetic and other biological factors that may better explain differences in drug response.

Population Stratification in Drug Response
Draft Recommendation 8B

When drugs are shown to be effective in certain racial and ethnic subpopulations (e.g., BiDil), FDA should encourage manufacturers to conduct additional postmarket studies to identify biological, social, behavioral and environmental markers that may underlie the differential drug response.

Gatekeepers Section

- "Gatekeepers"
  - ❖ Entities that can enable, halt or redirect the course of PGx technologies; affects integration and patient access
  - – Industry
  - – FDA
  - – CMS and other third-party payers
  - – Clinical practice guideline developers

Role of Industry

- Manufacturers' perceptions of risk and return on investment influence whether and how PGx products are developed and marketed
- Disincentives to develop PGx products
  - Segment market → decreased revenues
  - Exacerbated by low reimbursement rates
  - Additional responsibility involved in coordinating co-developed products

Role of FDA

- FDA approval affects manufacturing practices, conduct of clinical trials, market clearance, post-marketing surveillance, access to PGx products, and their use in clinical practice
- Questions about:
  - Adequacy of genetic test regulation (will be addressed in more detail in SACGHS oversight report)
  - Extent to which genetic data submissions will be required
  - Pre-market review process for co-developed products
  - Labeling of PGx products

Role of CMS and Other Third-Party Payers

- Ability to obtain coverage and favorable reimbursement critical to manufacturers' willingness to invest in R&D of new PGx products
- Challenges include:
  - Medicare does not cover preventive services
  - Private plan coverage may be difficult to obtain (e.g., because of limited clinical validity and utility evidence)
  - Reimbursement may not be adequate
  - Uncertainty about and variation in plans' evidence expectations

Role of Clinical Practice Guideline Developers

- Availability of practice guidelines affect coverage of PGx products and their uptake by health care providers
- Evidence-based practice guidelines for PGx products are lacking
  - Tied to limited evidence of their clinical utility and lack of clinical trials to base dosing decisions

Reimbursement for PGx Products
Recommendation 9

In clinical situations where a PGx test has been shown to enhance safety and/or effectiveness of clinical management (i.e., has demonstrated clinical utility compared to alternative management strategies) and provides value comparable to or an improvement over other covered services, public and private health plans should provide coverage and reimbursement for the test and the most clinically appropriate drug as indicated by PGx test results.

PGx Implementation Section

- Implementation of PGx to improve outcomes in clinical practice
  - Education and guidance
  - Information technology and PGx
  - Economic implications of PGx
  - Ethical, legal and social issues in clinical implementation of PGx
  - Coordination of HHS PGx activities

Education and Guidance

- As PGx tests and associated therapies become more widely available, it will be necessary to educate health care providers, payers, policymakers and the public
- Limited information available (via labeling and practice guidelines) about when to test and how use PGx test results to guide treatment decisions

Information Technology

- EHRs and decision support tools can improve PGx research and facilitate use of PGx products in clinical practice
- Uptake of EHRs still in early stages
- Harmonized standards for storing and exchanging genomic data under development
- Questions about who should have access to EHR data

Economic Implications of PGx

- While PGx technologies may improve health outcomes and be cost-effective, they likely will increase total health care costs
- Need to examine the financial consequences of investments in PGx technologies
  - Increased costs without concomitant returns may divert limited resources from other more productive investments in health care and other sectors
- Little research on cost-effectiveness of PGx interventions

ELSI Issues in Clinical Implementation of PGx

- Financial and cultural barriers could result in disparities in access to PGx technologies
- Concerns about genetic discrimination
- Liability risk if provider fails to administer recommended PGx test

Coordination of HHS PGx Activities

- Lots of Federal activities in PGx (see Appendix A on pp. A1-A10)
- No single, coordinated framework or action plan to address PGx challenges or share information about PGx activities among the Federal agencies

Use of PGx Technologies in Clinical Practice and Public Health Practice

Draft Recommendation 10A

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

Use of PGx Technologies in Clinical Practice and Public Health Practice

Draft Recommendation 10B

HHS should assist professional organizations in their efforts to help their memberships achieve established competencies on the appropriate use of PGx technologies. HHS also should encourage and facilitate collaborations between the organizations and the federal government around these activities.

Use of PGx Technologies in Clinical Practice and Public Health Practice

Draft Recommendation 10C

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

Use of PGx Technologies in Clinical Practice and Public Health Practice

Draft Recommendation 10D

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

Use of PGx Technologies in Clinical Practice and Public Health Practice

Draft Recommendation 10E

**** New recommendation proposed by comments****

To inform the development of PGx test and dosing guidelines, HHS should fund clinical trials that provide evidence on whether PGx information is clinically useful and, if so, how to use this information in addition to other relevant factors (e.g., gender and age of patient, other medications being taken).

Use of PGx Technologies in Clinical Practice and Public Health Practice

Draft Recommendation 10F

Professional organizations are encouraged to submit clinical practice guidelines that they develop for PGx testing to AHRQ's National Guideline Clearinghouse, to facilitate dissemination and encourage their implementation and use.

Use of PGx Technologies in Clinical Practice and Public Health Practice

Draft Recommendation 10G

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

Use of PGx Technologies in Clinical Practice and Public Health Practice

Draft Recommendation 10H

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

Public Education and Engagement
Draft Recommendation 11A

HHS should use existing public consultation mechanisms to engage the public in a constructive dialog regarding the potential benefits, risks and limitations of PGx technologies. This dialog should include an assessment of their perceptions of and receptiveness to PGx and their willingness to participate in clinical research studies involving these technologies.

Public Education and Engagement
Draft Recommendation 11B

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.

Health Information Technology
Draft Recommendation 12A

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 records, along with decision support systems and tools to enhance appropriate test use and interpretation. Decision support systems and tools should include information about the availability of PGx tests, patients' test results and relevant information for making treatment and dosing decisions.

As the infrastructure develops, HHS should account for the needs of basic, clinical and translational researchers to ensure that secure, consented clinical outcomes information is available to accelerate integration of PGx breakthroughs into clinical practice.

HHS should support efforts to establish standards for the development of electronic clinical decision support systems and tools. PGx test clinical practice guidelines should be developed in a manner that allows for their integration into such systems and tools.

Health Information Technology
Draft Recommendation 12B

Until electronic health record systems become a universal feature of the health care system, HHS should identify other ways to make best clinical practices for PGx more readily available to health providers as they are developed.

Economic Implications of PGx
Draft Recommendation 13

To ensure that investments in PGx are well-spent, HHS should gather data to assess the economic value of investments in PGx relative to other health-related investments. This assessment should encompass the cost-effectiveness of PGx technologies and take into account their short- and long-term impacts on specific sectors and society as a whole.

ELSI Research
Draft Recommendation 14

NIH, in collaboration with other agencies, should continue to encourage and fund research on the ethical, legal and social implications of PGx. This research should include studies of whether integration of PGx into clinical and public health practice exacerbates health and health care disparities, limits access to or decreases the quality of health care, increases medical liability or results in genetic discrimination.

Coordination of PGx Activities
Draft Recommendation 15A

An interdepartmental work group should be established to review SACGHS' PGx recommendations, assess whether and how to implement them, monitor HHS' progress and report back to SACGHS. The work group also could serve as a forum for discussion of other PGx activities.

Coordination of PGx Activities
Draft Recommendation 15B

HHS should assess the level and adequacy of resources being devoted to support the integration of PGx into clinical and public health practice, to be sure that gaps and opportunities identified in this report are addressed.

Voting

- Are these the recommendations SACGHS should make to the Secretary?
- Are they the best way to address the opportunities and challenges addressed in the report?
- Are you satisfied with the wording of the recommendations?

Prioritization of Recommendations

- Which recommendations should be of highest priority for the Secretary and HHS agencies to act on?
  - In the near term?
  - In the long term?

Executive Summary
(pp. 3-11)

- Does the Executive Summary adequately summarize the key points of the report?
- What, if anything, should be changed?

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Acknowledgements

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- **ASPE**: Sandra Howard, Theresa Lawrence
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- **SACGHS staff**
- **Public commenters**