Update on Development of SACGHS Report on Pharmacogenomics

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SACGHS Task Force on Pharmacogenomics

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- Steve Gutman, Joe Hackett, Allen Rudman, FDA
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- Muin Khoury, CDC
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Personalized Medicine & PGx

- **Personalized medicine** - using information about a person's genetic makeup to tailor strategies for the detection, treatment or prevention of disease

- **Pharmacogenomics** (PGx) – study of genes responsible for the variability in individual responses to drugs

  - Delivering the right drug at the right dosage to the right patient at the right time

Drivers of Personalized Medicine & PGx

- Research & development
- Health care system
- Public interest
- Public policy
  - Secretary's Personalized Health Care Initiative

PGx Opportunities and Challenges

- PGx has significant promise
  - Improve productivity of the drug pipeline
  - Increase safety and effectiveness of drugs (fewer ADRs)
  - More efficient use of drugs
- Many challenges must be addressed before PGx becomes integrated into clinical and public health practice

SACGHS's Role in PGx

- Identifying the opportunities and challenges associated with the integration and application of PGx into clinical and public health practice

- Advising the Secretary on how the Federal government can help to advance the opportunities in this field and address the challenges

  - Development of PGx report and recommendations to Secretary

SACGHS PGx Efforts to Date

- Informational sessions – June/October ‘05
- Approval of report outline – October ‘05
- Compilation of Federal PGx activities – March ’06
- Development of draft recommendations – Mar/Jun ’06
- Review of literature – June ‘06
  - Building toward the development of PGx report and recommendations to Secretary

PGx Task Force Activities Since June 2006

- Following June SACGHS meeting
  - Staff revised draft recommendations based on SACGHS discussion and guidance from TF Chair
  - Lewin developed draft report
- September 28 in-person meeting
  - Reached consensus on overall organization of report
  - Identified priority topics/issues to address in recommendations

Goals of Today's Session

- To ensure that all major opportunities and challenges associated with PGx have been identified
- To ensure that draft recommendations address high-priority issues
- To ensure that draft recommendations are the appropriate solutions for addressing the issues

  - To reach consensus on whether draft report and recommendations are ready for public review and comment

Planned Next Steps on PGx

- Revise report and recommendations based on input received during today's discussion
- Lewin to seek input of 15 federal and non-federal experts/stakeholders on various PGx issues (Winter 2006)
- Seek public comments (Winter/Spring 2007)
- Finalize report and recommendations (Summer 2007)
- Release final report (Fall 2007)

Organization of Report

- Report and recommendations organized into three overarching themes
  - Research and development
  - Gatekeepers
  - Implementation of PGx to improve outcomes in clinical practice

Organization of Report: Research and Development Theme

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

➢ Recommendations 1-5 (14 subparts)

Organization of Report: Gatekeepers Theme

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

  ➢ Recommendation 6 (3 subparts)

Organization of Report: Implementation of PGx Theme

- 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

➢ Recommendations 7-11 (14 subparts)

Structure of Discussion

- Walk through each issue within the 3 overarching areas
- Consider the draft recommendations addressing some of the identified issues
- Identify recommendations that should be of highest priority to Secretary
  - Task Force identified 12 high-priority recommendations (of 31 total, counting subparts)

Points of Discussion

- Issues
  - Does the report cover the major issues?
  - Are there any issues that have not been but should be raised in the report?
  - What issues are of highest priority for the Federal government to address?

Points of Discussion

- Recommendations (see Executive Summary on pp. 5-9)
  - Do the recommendations as currently worded sufficiently address a high-priority issue?
  - Are there any recommendations that have not been but that should be included?
  - Are there any recommendations that should be deleted (e.g., because they address a low-priority issue, will not have enough of an impact on the problem, are not implementable)?

Prioritization of Issues & Recommendations: Questions to Consider

- To what extent will addressing this issue via this recommendation advance the goals of PGx?
- Is the Federal government in a position to act upon this issue/recommendation?

Discussion of Research and Development Theme

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

Points of Discussion

- Issues
  - Does the report cover the major issues?
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Basic & Translational Research

- More basic research is needed to advance understanding of the biochemical pathways associated with drug metabolism and drug action, the genes involved in these pathways, and gene functions related to the safety and effectiveness of drug treatments
- More translational research is needed to apply this knowledge to the development of clinically useful PGx technologies
- Translational research studies, if designed carefully, can be a source of data for downstream studies of the clinical validity and clinical utility of PGx tests

Co-development of PGx Drugs and Diagnostics

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

Application of PGx to Abandoned Drugs

- Many drugs have been “abandoned” because they have failed to detect a significant treatment effect in the broader population
- Post-hoc analysis of clinical drug trial data for which genotype information is available can enable the rescue of abandoned drugs for use by smaller populations of high responders

Application of PGx to Currently Marketed Drugs

- 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 Rare Disease Drug Development

- 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 accompanying diagnostics
- Unclear whether FDA would consider a PGx-based drug an orphan product if it confers large benefit to an orphan-sized population but a modest benefit to a large population

Clinical Validity and Clinical Utility

- Most PGx research has yet to be translated into clinical practice
- Adoption of PGx technologies will hinge on evidence of their clinical validity and clinical utility
- Little evidence of clinical validity and clinical utility currently exists

R&D Infrastructure

- PGx research could benefits from integration of research and clinical databases, repositories and records
- Data collection, storage, modeling and transfer within and among PGx databases create challenges to infrastructure and support
  - Variation in data formats
  - Electronic health records in early stages
  - Different funding streams, stakeholders, administrative protocols, and organizational cultures

ELSI Issues in PGx R&D

- Privacy and confidentiality concerns relating to research records
  - Data access and utility may be lost in exchange for gains in data protection
- PGx test results may reveal secondary information
- Discrepancies between human subjects research regulations (Common Rule vs. FDA regs)
- Not requiring PGx testing as condition for drug treatment could increase drug companies' liability risk

Use of Race/Ethnicity in PGx R&D

- PGx promises to advance the development of personalized medicine by identifying individual differences in drug response
- Continuing to stratify subgroups by race in drug development (e.g., BiDil) or associating molecular subgroups with race may reinforce race as a biological construct and may limit availability of PGx-based drugs to certain subpopulations

Points of Discussion

- Issues
  - Does the report cover the major issues?
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  - What issues are of highest priority for the Federal government to address?

Points of Discussion

- Recommendations
  - Do the recommendations as currently worded sufficiently address a high-priority issue?
  - Are there any recommendations that have not been but that should be included?
  - Are there any recommendations that should be deleted (e.g., because they address a low-priority issue, will not have enough of an impact on the problem, are not implementable)?

Prioritization of Recommendations: Questions to Consider

- To what extent will addressing this recommendation advance the goals of PGx?
- Is the Federal government in a position to act upon this recommendation?

Basic & Translational Research
Draft Recommendation 1A

NIH should invest more resources into basic research on the biochemical pathways associated with drug metabolism and drug action, the genes involved in these pathways, and gene functions related to the safety and effectiveness of drug treatments.

Basic & Translational Research
Draft Recommendation 1B

NIH should support more translational research focused on the development of clinically useful PGx technologies.

Basic & Translational Research
Draft Recommendation 1C

NIH should encourage and provide mechanisms for basic and translational researchers to coordinate with clinical trial and outcomes researchers as they design their studies and identify endpoints and data elements to be measured.

Basic & Translational Research
Draft Recommendation 1D

Research that could to lead to the development of a PGx test requiring FDA review should be planned with the goal of meeting FDA quality-of-evidence standards so that the results can be used in support of a pre-market review application.

NIH should encourage investigators to consult FDA when their research reaches a pivotal stage.

NIH could encourage the conduct of methodologically sound and statistically rigorous studies by giving higher priority scores to studies that are designed to satisfy FDA quality-of-evidence standards.

Development of PGx Products
Draft Recommendation 2A

HHS should provide FDA with the necessary resources to develop guidance documents about best practices for the co-development of PGx drugs and diagnostics. This guidance should promote collaboration between the drug and diagnostics industries and 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.

Development of PGx Products
Draft Recommendation 2B

FDA should identify research opportunities relating to the co-development of PGx products. FDA could encourage and facilitate the conduct of this research through its Critical Path Initiative.

Development of PGx Products
Draft Recommendation 2C

HHS should advance the further development of "abandoned" drugs by facilitating access to information about such drugs.

Incentives will be needed to encourage the voluntary submission of proprietary data by pharmaceutical companies.

Development of PGx Products
Draft Recommendation 2D

FDA should amend the Humanitarian Device Exemption regulation so that incentives for the development of orphan drugs are extended to PGx tests that are intended to be used in conjunction with the orphan drugs.

Clinical Validity and Utility of PGx
Draft Recommendation 3A

HHS should provide AHRQ, CDC and NIH with additional funds to identify PGx technologies that are important from a public health standpoint and support efforts to address gaps in evidence for which clinical validity and utility evidence is lacking.

CDC's EGAPP Working Group and HuGENet and AHRQ's EPC program may be appropriate mechanisms or models for identifying such technologies and specific evidentiary and research needs.

Clinical Validity and Utility of PGx
Draft Recommendation 3B

FDA should encourage manufacturers to submit clinical utility data as part of their pre-market applications and post-market surveillance, and request manufacturers' permission to make these data available to the public.

Manufacturers should disseminate any significant and non-significant findings on the clinical validity and clinical utility of PGx technologies, e.g., through publication in peer-reviewed journals.

Clinical Validity and Utility of PGx
Draft Recommendation 3C

In certain circumstances, public and private health plans should facilitate the generation of knowledge by conditioning payment of PGx technologies on a commitment by test developers to collect data on the clinical validity and clinical utility of PGx technologies. CMS's draft Coverage with Evidence Development initiative may serve as a model for this practice.

PGx Research Databases
Draft Recommendation 4A

HHS should work with the private sector to improve data sharing and interoperability among research, regulatory, health record and claims databases.

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.

Comparable efforts to standardize phenotypic data are also needed.

PGx Research Databases
Draft Recommendation 4B

As data are shared, the privacy of patients and research subjects should continue to be of paramount concern, and HHS should take steps to ensure that the confidentiality of their data is not compromised.

FDA Guidance for Population Subgroup Data
Draft Recommendation 5

Race and ethnicity categories should not be used alone when analyzing differences in drug response.

FDA should develop guidance that encourages the collection and analysis of genetic and other biological factors that may better explain differences in drug response.

When drugs are shown to be effective in certain racial and ethnic subpopulations, FDA should require manufacturers to conduct additional studies to identify biological markers that underlie the differential drug response.

Points of Discussion

- Recommendations
  - Do the recommendations as currently worded sufficiently address a high-priority issue?
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Prioritization of Recommendations: Questions to Consider

- To what extent will this recommendation advance the goals of PGx?
- Is the Federal government in a position to act upon this recommendation?

Discussion of Gatekeepers Theme

- "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

Points of Discussion

- Issues
  - Does the report cover the major issues?
  - Are there any issues that have not been but should be raised in the report?
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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 profitability
  - 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 (afternoon session)
  - Extent to which genetic data submissions will be required
  - Pre-market review of 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 information)
  - 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 providers
- Evidence-based practice guidelines for PGx products are lacking

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Prioritization of Recommendations: Questions to Consider

- To what extent will addressing this recommendation advance the goals of PGx?
- Is the Federal government in a position to act upon this recommendation?

Coverage of PGx Technologies
Recommendation 6A

CMS should clarify in writing that PGx tests are diagnostic and thus eligible for Medicare coverage.

Coverage of PGx Technologies
Recommendation 6B

Health insurance plans should be more transparent in how they make coverage determinations for PGx technologies by developing guidelines that define the type, quality and standard of evidence that must be met for PGx technologies to be covered.

Whenever a particular PGx technology is denied coverage because it does not meet these evidentiary standards, health insurance plans should inform the test developer what additional evidence is needed.

Coverage of PGx Technologies
Recommendation 6C

HHS should provide resources to relevant agencies to address evidentiary gaps identified by health insurance plans.

Points of Discussion

- Recommendations
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Prioritization of Recommendations: Questions to Consider

- To what extent will this recommendation advance the goals of PGx?
- Is the Federal government in a position to act upon this recommendation?

Discussion of PGx Implementation Theme

- 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

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Provider Education and Guidance

- Genetics education and training by health professionals, payers, regulators is insufficient
- Limited information available (via labeling and practice guidelines) about how to interpret PGx test results and use them to inform treatment decisions

Public Education

- Genetics education needed to help consumers make informed treatment decisions
- Direct access to PGx testing (via OTC sales or DTC marketing) may increase inappropriate use of PGx tests
  - Increased health care costs
  - Potential for misinterpretation of test results
  - Misinformed health decision making
  - Adverse health consequences

Information Technology

- Uptake of EHRs still in early stages
- No consensus on how genetic information should be stored in EHRs and who should have access to stored data
- Lack of harmonized standards for storing and exchanging genomic data
- Need for PGx decision support tools and reminder systems

Economic Implications of PGx

- Use of PGx technologies will likely add to health care costs
- Need to examine the benefits and costs of investments in PGx technologies
- Little research on cost-effectiveness of PGx interventions

ELSI Issues in Clinical Implementation of PGx

- Financial barriers to PGx products (e.g., high copays, underinsurance, no insurance) could result in access disparities
- 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-A23)
- No single, coordinated framework or action plan to address PGx challenges or share information about PGx activities among the Federal agencies

Points of Discussion

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Points of Discussion

- Recommendations
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Prioritization of Recommendations: Questions to Consider

- To what extent will addressing this recommendation advance the goals of PGx?
- Is the Federal government in a position to act upon this recommendation?

Use of PGx Technologies in Clinical Practice

Draft Recommendation 7A

As evidence of clinical validity and utility for a PGx technology accrues, HHS should support the preparation of meta-analyses and technology assessments summarizing the evidence base.

These analyses and assessments should be disseminated to professional organizations to facilitate their development of clinical practice guidelines.

Use of PGx Technologies in Clinical Practice
Draft Recommendation 7B

HHS agencies should collaborate with federal, state, and private organizations to develop, catalogue and disseminate case studies and practice models in the use of PGX technologies.

Use of PGx Technologies in Clinical Practice

Draft Recommendation 7C

HHS should provide resources to professional organizations that will help enable their membership to meet established competencies on the appropriate use of PGx technologies.

Use of PGx Technologies in Clinical Practice

Draft Recommendation 7D

FDA should continue to work with drug and diagnostic manufacturers to provide adequate labeling information so that clinicians can make dosing decisions based on PGx test results. The labeling should clearly describe the test's analytical and clinical validity and provide dosing guidelines based on test results.

Use of PGx Technologies in Clinical Practice

Draft Recommendation 7E

FDA and NIH should continue their efforts to provide up-to-date, real-time prescription drug label/package insert information. The Internet-based DailyMed project currently underway will be wide-reaching, but to ensure that all sectors of the public have access to this information, these agencies should develop other ways to reach members of the public who may not have internet access.

Use of PGx Technologies in Clinical Practice

Draft Recommendation 7F

The Office of the National Coordinator for Health Information Technology should promote the incorporation of PGx test information into electronic health records as well as decision support systems and tools that can notify providers about PGx tests and labeling information that could help them make appropriate treatment and dosing decisions.

Use of PGx Technologies in Clinical Practice
Draft Recommendation 7G

Until the electronic health record becomes a universal feature of the health care delivery system, HHS should identify other ways to make best PGx practices more readily available to health providers.

Information for the Public
Draft Recommendation 8A

HHS should fund studies of public awareness of the benefits, risks and limitations of PGx technologies.

Information for the Public
Draft Recommendation 8B

HHS should ensure that educational resources are widely available through federal websites and other appropriate media to inform decisions about the use of PGx technologies.

Information for the Public
Draft Recommendation 8C

HHS should dedicate resources to public consultation activities to gauge the public's receptiveness to and concerns about these technologies and their willingness to participate in clinical research studies involving PGx.

Economic Value of PGx
Draft Recommendation 9

HHS should determine the economic value of investments in PGx research and development relative to investments in other health and non-health-related areas.

This assessment should analyze the effects on society as a whole as well as each individual stakeholder.

ELSI Research
Draft Recommendation 10

NIH should fund more research on the ethical, legal and social implications of PGx.

Gaps in current knowledge include questions about whether integration of PGx into clinical and public health practice will exacerbate health and health care disparities, limit access to or decrease the quality of health care, increase medical liability, or result in genetic discrimination.

Steps should be taken by HHS to address any problems identified through this research.

Coordination of HHS PGx Activities
Draft Recommendation 11A

An interagency work group should be established to review SACGHS's PGx recommendations, assess whether and how to implement them, monitor the Department's progress, and report back to SACGHS. At the request of the agencies, the work group also could serve as a forum for discussion of specific PGx activities.

Coordination of HHS PGx Activities
Draft Recommendation 11B

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 current and future gaps and opportunities can be addressed.

Points of Discussion

- Recommendations
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Prioritization of Recommendations: Questions to Consider

- To what extent will this recommendation advance the goals of PGx?
- Is the Federal government in a position to act upon this recommendation?

Next Steps with PGx Report

- Is the draft report and recommendations ready for public review and comment?
  - Revise report and recommendations based on input received during today's discussion
  - Lewin to seek input of 15 federal and non-federal experts/stakeholders on various PGx issues (Winter 2006)
  - Seek public comments (Winter/Spring 2007)