Personalized Healthcare Workgroup Recommendations Letter

June 3, 2008

The Honorable Michael O. Leavitt

Chairman

American Health Information Community

200 Independence Avenue, S.W.

Washington, D.C. 20201

Dear Mr. Chairman:

The American Health Information Community (AHIC) has given the following broad charge to the Personalized Health Care Workgroup:

Broad Charge for the Workgroup: Make recommendations to the American Health Information Community for a process to foster a broad, community-based approach to establish a common pathway based on common data standards to facilitate the incorporation of interoperable, clinically useful genetic/genomic information and analytical tools into electronic health records to support clinical decision-making for the clinician and consumer.

The Workgroup's deliberations have highlighted a number of key issues regarding the broad charge, including the following:

1. Genetic/Genomic Tests

2. Family Health History

3. Clinical Decision Support

4. Confidentiality, Privacy, and Security

This letter provides both context and recommendations for how the issues of pharmacogenomic laboratory test information and the interface of electronic health record (EHR) systems with clinical research can be addressed in the next twelve months.

BACKGROUND

Personalized Health Care (PHC) represents a systems approach to support patient-centric health care by integrating genetic/genomic test information and health information technology (IT). Pharmacogenomics is defined as the study of variations of DNA and RNA [genes and gene products] characteristics as related to drug response; pharmacogenetics is a subset of pharmacogenomics and is limited to variations in DNA. EMEA, November 2007, ICH Topic E15, Note for guidance on definitions for genomic biomarkers, pharmacogenomics, pharmacogenetics, genomic data and sample coding categories, EMEA/CHMP/ICH/437986/2006. , FDA Guidance for Industry, E15 definitions for genomic biomarkers, pharmacogenomics, pharmacogenetics, genomic data and sample coding categories http://www.fda.gov/cder/Guidance/8083fnl.pdf Pharmacogenomics has the potential to inform therapeutic choices, clarify dosing decisions, reduce adverse drug reactions, and optimize prescribing patterns of providers.

Despite the promise of pharmacogenomics, its integration into routine clinical practice has been slow due to several issues, including: lack of an evidence-base and information on clinical utility; lack of clinical guidelines for the use and interpretation of pharmacogenomic tests in pharmaceutical selection and treatment decisions; impediments to reimbursement for the performance of laboratory tests; and a paucity of clinical practice experience with pharmacogenomic test applications.These may be overcome through the interface of pharmacogenomics with clinical decision support (CDS) tools and clinical research for incorporation into clinical care. The Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) recently released a report on pharmacogenomics, Realizing the Promise of Pharmacogenomics: Opportunities and Challenges http://www4.od.nih.gov/oba/sacghs/reports/SACGHS_Pgx_report.pdf, which identifies three recommendations relating to health information technology: studying how clinically validated pharmacogenomic test results are being incorporated into EHRs; ensuring infrastructure is in place to support pharmacogenomics data in EHRs for CDS tools; and exploring development of pilot studies that examine the impact of CDS tools for pharmacogenomic technologies at the point-of-care.

Because of the complexity of pharmacogenomic data relative to other types of laboratory data, structuring pharmacogenomic information in the EHR and providing filtered interpretations with CDS tools are likely necessary for its optimal use in informing drug selection and dosage at the point-of-care by clinicians. This input at the point-of-care may be built on already existing electronic prescribing infrastructure. Additionally, overcoming some of the barriers for incorporating pharmacogenomics into clinical practice may enhance clinical research on pharmacogenomics and its potential to improve patient health. This research may be leveraged by utilizing EHRs to match potential research participants with clinical study requirements, such as being naïve-to-therapy where pharmacogenomic data may inform dosing or alter therapeutic choice, or to provide clinically meaningful outcomes of pharmacogenomic testing.

In summary, it is recognized that the adoption of EHRs and pharmacogenomics in health care practices are at an early stage, but their integration may achieve meaningful clinical improvements and benefit from implementation of a standard format for collection and exchange of pharmacogenomics information prior to widespread deployment. Increased

or improved EHR functionality may help motivate clinician adoption of electronic tools and pharmacogenomics.

If accepted by the AHIC, the recommendations from the PHC Workgroup should be considered for adoption by the Department of Health and Human Services (HHS) as HHS policy regarding current and future federal activities as they relate to the Workgroup's charge.

RECOMMENDATIONS

1. Fostering EHR Data Standards to Enable Clinical Research and Development Activities

Currently, EHRs may be used for matching potential research participants with clinical study requirements, such as naïve-to-therapy where pharmacogenomic data may inform dosing or alter therapeutic choice. A recent development in health information technology, Personally Controlled Health Records (PCHRs), may provide another route for electronic matching of eligible participants with clinical studies. Mandel, K.D. et al. "Tectonic Shifts in the Health Information Economy." N Engl J Med, 2008, 358, 1732-1737. In the current system, upon enrolling in the study, pharmacogenomic testing is performed and analyzed as relevant to the purpose of the study. However, in the future health system, the EHR or PCHR may already contain pharmacogenomic information, as well as other genomic and phenotypic data. With appropriate permission, oversight, and authorized access to information, approved entities (such as clinical researchers) could receive the genomic data from an EHR, clinical study case report forms (CRFs), or other databases linking genotype and phenotype for clinical studies. This access may require affirmative patient consent and must conform to appropriate patient consent, security, and privacy safeguards, including the Genetic Information Nondiscrimination Act, H.R. 493 Genetic Information Nondiscrimination Act of 2008: To prohibit discrimination on the basis of genetic information with respect to health insurance and employment, passed by Congress, was recently signed by the President. the Common Rule (45 CFR 46), Americans with Disabilities Act (Public Law 101-336) and the Health Insurance Portability and Accountability Act of 1996 (HIPAA; Public Law 104-191), FDA rules for Protection of Human Subjects (21 CFR 50), and any applicable state laws. These have been enacted to protect the rights of individuals with regard to the access and use of sensitive personal information and to reform group health insurance, respectively. Regulations such as the Privacy Rule and the Security Rule have been promulgated pursuant to HIPAA to address issues regarding shared health information. Several other Federal Advisory Committees are considering issues related to oversight of genetic testing, http://www4.od.nih.gov/oba/SACGHS/reports/SACGHS_oversight_report.pdf identification of evidentiary gaps,3 and inclusion of data in EHRs. http://www.hhs.gov/healthit/ahic/ This future system would provide data for safety assessments, clinical outcomes analysis, http://effectivehealthcare.ahrq.gov/healthInfo.cfm?infotype=nr&ProcessID=63 best-practice guidelines development, and identification of potential genetic causes for

adverse events. Although this system may take years to develop completely, steps can be taken now to enable this future.

Current efforts are underway to address the need for common terminology, data fields, and formats for exchange of pharmacogenomic data, for example from clinical research to the Food and Drug Administration (FDA) through a voluntary data submission program. http://www.fda.gov/cder/mapp/4180.3.pdf - http://www.fda.gov/cder/genomics/VGDS.htm The Clinical Data Interchange Standards Consortium (CDISC), FDA, and National Cancer Institute (NCI) are working together through Health Level Seven (HL7) to develop standards for exchanging data based on the HL7 Reference Information Model to enable the clinical care standards of HL7 to have semantic interoperability with those standards used in research. Additionally, recent workUllman-Cullere, M.; Babb, L.; Heras, Y.; Joshi, V.; McDonald, C.; and Huff, S. "Structured genetic data in the medical record by usage of HL7v2, LOINC, SNOMED, RxNORM and Bioinformatic Standards" submitted. has been done to leverage and extend existing clinical standards (HL7 version 2, Logical Observation Identifiers Names and Codes (LOINC), and Systematized Nomenclature of Medicine (SNOMED)) to support genetics data. The use of LOINC and SNOMED standards should provide linkage of genetics data to other clinical data (e.g., phenotype), as well as speed development of CDS. Standards for the exchange of pharmacogenomic data and submission of such data to FDA are becoming quite mature and available through the collaborative efforts of the HL7 Clinical Genomics Special Interest Group.

To enable the envisioned scenario and build on current examples, standard terminology, standard metrics, and structured information for outcomes analysis and research are needed to allow data exchange, interoperability, and integration of pharmacogenomic tests into clinical decision-making. Current approaches to Current Procedural Terminology (CPT) codes do not provide sufficient specificity to be utilized in evidence development and health outcomes data analysis. The following areas may also require attention: gene expression data from the various platforms and systems; clinical research information (clinical study CRFs); safety assessment information; and adverse event information.

Given the information described above, the PHC Workgroup makes the following recommendations:

Recommendation 1.0: HHS agencies should maintain existing relationships with appropriate standards development organizations (SDOs) and industry stakeholders to expand the standards development process for documenting pharmacogenomic data and for submitting to other databases.

Recommendation 1.0.1: HHS agencies and the National Institute of Standards and Technology (NIST) should work together to clarify and determine the role that each will play in developing standards for pharmacogenomic data.

Recommendation 1.1: FDA, National Institutes of Health (NIH), and other federal agencies involved in clinical research should convene a workgroup and develop a document or checklist that clarifies best practices for use of informed consent between patients and caregivers and for data use by physicians, pharmacists, regulators, researchers, and other relevant stakeholders when pharmacogenomics data is submitted to research databases. Issues to consider include: national privacy standards; de-identification of data; appropriate use of data; and educational information to provide to research participants.

The most important function for EHRs and electronic health information exchange is to facilitate communication between the laboratory, clinician, and patient to support patient care.In order for the clinical implications to be appropriately integrated into clinical workflows, leveragable by CDS, and supplemented with clinical guidelines, health care informatics standards need to be defined to support the transmission of genetic data in highly structured form into EHRs and personal health records (PHRs). While patient care is the principal focus, data in EHRs may serve an important function through supporting clinical research in the unidirectional flow of clinical care information from the EHR into CRFs, data registries, or other research records. Unidirectional flow of information from EHRs into research applications is important, asclinical research data is not appropriate for populating EHRs or PHRs for use in clinical practice. An integration profile called Retrieve Form for Data Capture (RFD), developed through Integrating the Healthcare Enterprise (IHE), enables an EHR to support many reporting needs, such as extract and populate a CRF for research, exchange laboratory and X-ray data, provide biosurveillance and safety reporting, and register clinical trials.

Research discoveries enhanced by consented data from EHRs may result in identification of new pharmacogenomic associations and increased clinical utility and validity of existing genetic tests. For example, the NIH National Cancer Institute-supported Cancer Central Clinical Database collects clinical study data using standard CRFs based on common data elements. The NCI’s Center for Cancer Research is using EHR information linked to laboratory data that is incorporated into the CRFs in the Cancer Central Clinical Database. Other Cancer Central Clinical Database adopters also submit laboratory data that is loaded into the appropriate study in the Cancer Central Clinical Database. The utility of these information exchanges is that data is captured once, thereby improving efficiency and accuracy. In addition to CRFs, the cancer Adverse Event Reporting System monitors laboratory reports to identify any adverse events and aids in the rapid reporting of critical events that may require an adjustment of treatment.Systems such as this may be utilized to enhance pharmacogenomic research and patient health.

Given the information described above, the PHC Workgroup makes the following recommendations:

Recommendation 1.2: Coordinated by the Agency for Healthcare Research and Quality (AHRQ), HHS agencies, including FDA and NIH, should identify a core set of data elements relevant to the outcomes of clinical interventions driven by pharmacogenomic tests that need to be captured in EHRs.HHS should facilitate development of standards

for coding these outcomes data and standards that enable exchange of pharmacogenomic test results and/or interpretations from different EHR platforms and other databases that collect relevant outcomes data, while ensuring the confidentiality and privacy of a patient's information. HHS should facilitate standardization of methodologies to analyze and report outcomes of pharmacogenomic tests.

Recommendation 1.3: AHRQ, NIH, and federal health care providers should identify opportunities for and encourage pilot projects to demonstrate the use of EHRs for supporting clinical research and integrating pharmacogenomic data into clinical research databases utilizing existing standards and terminology.

Recommendation 1.4: A multi-stakeholder workgroup, including clinicians, health IT specialists, industry, laboratories developing or performing pharmacogenomic tests, medical device/product reviewers, pharmacists, and researchers, should be formed to develop a core minimum data set (potentially including gene names, gene mutations, coded interpretations, and associated medications) and common data definitions available for inclusion of pharmacogenomics data with demonstrated clinical validity and utility in an EHR.

Recommendation 1.5: The unidirectional information-flow from EHRs to clinical research applications (such as case report forms) should be prioritized for Use Case Development.

II. Clinical Decision Support in Health Care Delivery

The use of CDS capabilities within EHRs and related electronic clinical systems holds great potential to improve health care outcomes in the U.S. CDS provides clinicians, staff, patients, and other individuals with knowledge and person-specific information, intelligently filtered at appropriate times, to enhance health and health care. CDS encompasses, but is not limited to: computerized alerts and reminders to care providers; methods to bring care into compliance with clinical guidelines; generation of order sets, patient data reports and summaries, and documentation templates; advice to promote more accurate and timely diagnoses; and tools that enhance clinical workflow. Osheroff, J. A. et al. "A Roadmap for National Action on Clinical Decision Support." J Am Informatics Assoc, 2007, 14, 141-145.

Over the past several months, numerous AHIC Workgroups have identified these CDS capabilities as a timely and important area of focus. To address this need, a CDS Ad Hoc Planning Group, comprised of representatives from the Consumer Empowerment, Electronic Health Records, Personalized Health Care, Population Health and Clinical Care Connections, and Quality Workgroups, was created in May 2007 to form a common framework through which a coherent and complete set of priorities for CDS could be generated. Recommendations prepared by the CDS Ad Hoc Planning Group were accepted on April 22, 2008 by the AHIC.
http://www.hhs.gov/healthit/documents/m20080422/6.2_cds_recs.html

The recommendation letter mentions the formation of a multi-stakeholder federal CDS Collaboratory. "To coordinate efforts internal to the government, a multi-stakeholder federal CDS Collaboratory, co-sponsored by Agency for Healthcare Research and Quality (AHRQ), the HHS Personalized Healthcare Initiative, and ONC, has been formed. This group will build upon a scan of CDS-related federal agency activities conducted in 2007, and will work to leverage the efforts and knowledge of multiple agencies to expedite development and widespread adoption of effective CDS capabilities." http://www.hhs.gov/healthit/documents/m20080422/6.2_cds_recs.html The CDS Collaboratory is co-sponsored by AHRQ, the HHS Personalized Healthcare Initiative, and the Office of the National Coordinator for Health Information Technology (ONC), and will coordinate CDS efforts internal to the government. In addition, Recommendation 2.2 from the CDS Ad Hoc Planning Group described a public-private CDS entity, working with its stakeholders, that should plan a CDS infrastructure to serve the nation in the long term, and identify actions that its constituents can take to further the adoption of CDS. Looking across existing efforts within the public and private sectors, the public-private CDS entity should identify approaches where coordination, collaboration, and collective action can advance effective use of CDS. Specific deliverables may include:

- Formulate education efforts and business cases that promote integration of CDS within EHR systems and create incentives for use of CDS to support improved patient care quality
- Develop a framework to optimize the delivery of CDS interventions so that advice is delivered at the right time, place, and in a manner that enables consumers and health care professionals to act upon it in a timely manner
- Establish a communication forum for CDS stakeholders to promote identification of common interests and execution of mutually beneficial activities that advance widespread and effective utilization of CDS.

Recommendation 3.3 from the CDS Ad Hoc Planning Group described the development of a minimum data set of personal attributes that contribute to individualized care. Once the minimum data set has been created, the Healthcare Information Technology Standards Panel (HITSP) should develop interoperability standards for the personal attribute minimum data set. Interoperability standards should span EHRs and PHRs and should be added to the criteria for relevant certifications.

Using the framework of the above CDS recommendations, the PHC Workgroup makes the following recommendations for pharmacogenomics:

Recommendation 2.0: When the public-private CDS entity is developing strategies to incorporate accepted CDS technologies into health care information technology and clinical processes, and describing high level, standard workflows and types of CDS interventions that are applicable to health professionals' workflows, the electronic exchange of clinically useful pharmacogenomic and other relevant health information among the patient, pharmacist, and prescribing clinician should be considered.

Recommendation 2.1: When developing a minimum data set of personal attributes that contribute to individualized care, the public-private CDS entity should include pharmacogenomic test information and/or interpretations as part of that minimum data set.

Recommendation 2.2: AHRQ and NIH should continue to work with appropriate agencies and organizations, including clinical laboratories, to evaluate how pharmacogenomics-related CDS tools affect clinicians' and patients' decision-making, and to ensure that developed tools will be utilized by end-users. Clinician expertise and complicating factors such as comorbidities and polypharmacy need to be examined in combination with the CDS tools.

Recommendation 2.3: The public-private CDS entity and CDS Collaboratory should include standards for reporting, annotating, tracking, and updating versions of pharmacogenomic and related algorithms. Algorithms should be stored in a CDS repository and should be continually updated as new variants and/or pharmacogenomic data are developed.

III. Integrating Pharmacogenomics into Medication Prescribing Practices

E-prescribing is one of the most mature forms of health information technology with about 70 percent of the 57,000 community pharmacies having the capacity to receive e-prescriptions, though only about 2% of all prescriptions are submitted electronically. National Progress Report on E-prescribing: http://www.surescripts.com/pdf/National-Progress-Report-on-EPrescribing.pdf The National Council for Prescription Drug Programs has played a significant role in standards development for e-prescribing. By augmenting the information that is provided to pharmacies, pharmacists could become more engaged as a point-of-care resource providing assurances for patient safety, minimizing adverse events and improving health outcomes. Providing pharmacists with clinical data attributes, such as allergy, pharmacokinetic data, and pharmacogenomic results or interpretations, could improve communication, verify proper dosing decisions, and augment consumer education. Including CDS in e-prescribing systems may improve the safety, quality, efficiency, and cost-effectiveness of care. Teich, J. M. et al. "Clinical Decision Support in Electronic Prescribing: Recommendations and an Action Plan: Report of the Joint Clinical Decision Support Workgroup" J Am Informatics Assoc, 2005, 12, 365-376. This will require the development of standard terminology, metrics, and guidelines to optimize the messaging both to and from the pharmacy, examination of the workflow (clinician/prescriber, clinical laboratory, patient, and pharmacy), and identification of the policy and technical issues associated with transmittal of laboratory test results into an EHR.

Recommendation 3.0: HHS should work with stakeholders, including professional associations representing clinicians, clinical laboratories, pharmacists, and others, to develop a white paper on the opportunities and challenges associated with dispensing pharmaceutical drugs based on pharmacogenomic test-derived interpretations in inpatient, ambulatory, and mail-order services. Issues to consider may include:

incorporation into workflow, identification of the party responsible for utilizing the dosing algorithm (which incorporates pharmacogenomic data with other clinical data), identification of contraindications, and ensuring that testing precedes dispensing, where appropriate.

Recommendation 3.1: The information-flows between the clinical laboratory, patient, pharmacist, and prescribing clinician, including pharmacogenomic-based dosing interpretation of clinically validated test/drug combinations, within e-prescribing technology should be prioritized for Use Case Development.

Many efforts in PHC focus on the future health system; however, pharmacogenomics provides current opportunities to improve patient outcomes. For example, recent progress in elucidating the genetic basis for variations in drug metabolism and response has motivated the FDA to modify prescription drug labels (for example, warfarin http://www.fda.gov/bbs/topics/NEWS/2007/NEW01684.html , carbamazepine-containing drugs, http://www.fda.gov/cder/drug/InfoSheets/HCP/carbamazepineHCP.htm and morphine http://www.fda.gov/bbs/topics/NEWS/2007/NEW01685.html) to suggest the use of genetic testing prior to commencing treatment. Timely and complete dissemination of this information to clinicians may be challenging, but existing programs (DailyMed, http://dailymed.nlm.nih.gov/dailymed/about.cfm Structured Product Labeling, http://www.fda.gov/oc/datacouncil/SPL.html MedWatch, http://www.fda.gov/medwatch/ and other FDA programs, such as FDA Alerts, Health Professional Information Sheets, news releases, podcasts, and Continuing Medical Education Programs) provide access for updated safety information on drugs and other regulated medical products and could be bolstered through the use of CDS or other web-based tools. It is likely that similar prescription label changes will follow additional pharmacogenomics research. Pharmacogenomic tests analyze variations in genes that may affect drug targets or drug metabolism, thus enabling optimal drug selection or dosing to avoid adverse events and optimize efficacy. Some of these tests are already used in practice or in clinical studies for a diverse group of conditions such as schizophrenia, de Leon, J. et al. “The CYP2D6 Poor Metabolizer Phenotype May Be Associated With Risperidone Adverse Drug Reactions and Discontinuation” J Clin Psychiatry, 2005, 66, 15-27. Attention Deficit Hyperactivity Disorder, Trzepacz, P. T. et al. “CYP2D6 metabolizer status and atomoxetine dosing in children and adolescents with ADHD,” European Neuropsychopharmacology, 2008, 18, 79-86. cancer chemotherapy (irinotecan), Innocenti, F. et al. “Genetic Variants in the UDP-glucuronosyltransferase 1A1 Gene Predict the Risk of Severe Neutropenia of Irinotecan,” J Clin Oncology, 2004, 22, 1382-1388. - O’Dwyer, P. O, et al. “Uridine Diphosphate Glucuronosyltransferase (UGT) 1A1 and Irinotecan: Practical Pharmacogenomics Arrives in Cancer Therapy” J Clin Oncology, 2006, 24, 4534-4538. and asthma and chronic obstructive pulmonary disease (leukotriene antagonists and theophylline). Weiss, S. T. et al. “Overview of the Pharmacogenomics of Asthma Treatment” Pharmacogenomics J, 2006, 6, 311-326. A white paper commissioned by ONC and HHS published in 2005 provided several guidelines to help federal government activities concerning CDS in e-prescribing and related domains.17 Within the recommended features and elements needed for an e-prescribing system to provide effective, high-value CDS, the white paper suggested that

test results should be integrated with EHRs, and that genomic data, as it becomes available and clinically relevant, should be included as a data element. In addition to label changes, the evidence to support the use of these tests is still being developed. Exploration of standardized electronic methods to communicate these changes in labeling and evidence may increase clinician knowledge and, therefore, improve patient outcomes.

Recommendation 3.2: AHRQ, CDS Collaboratory, and FDA shouldconvene a meeting with various stakeholders, including associations representing clinicians, patients, and pharmacists; clinical laboratories that develop and perform pharmacogenomic tests; commercial drug database industry; EHR vendors; e-prescribing vendors; and other organizations to determine how information from FDA label changes may be integrated into electronic prescribing or CDS tools for point-of-care decision-making.

Recommendation 3.3: National Library of Medicine (NLM)should lead an effort to complete and vet an ongoing activity to integrate structured genetic information, including pharmacogenomic test results and interpretations, into an EHR/PHR. This effort should include necessary normalization and translation of clinical standards into those compatible with the research setting.

These recommendations are supported by information obtained through research and testimony to the Personalized Health Care Workgroup, which is contained in the supporting documents available at http://www.hhs.gov/healthit/.

Thank you for giving us the opportunity to submit these recommendations. We look forward to discussing these recommendations with you and the members of the American Health Information Community.

Sincerely yours,

/John Glaser/

John Glaser, PhD

Co-Chair, Personalized Health Care Workgroup

/Douglas E. Henley/

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