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# Genomic Medicine X: Research Directions in Pharmacogenomics Implementation
## May 2-3, Silver Spring, MD
## Executive Summary

The tenth in NHGRI's series of Genomic Medicine meetings convened leaders in genomic medicine and pharmacogenomics (PGx) to identify and address the major challenges in pharmacogenomics (PGx) implementation. Specifically, the meeting aimed to: 1) survey national landscape of research programs in PGx implementation, 2) review current advances and clinical applications of PGx implementation, 3) discuss limitations and obstacles in PGx clinical implementation, 4) identify evidence gaps and studies that are needed to address them, and 5) discuss strategies for large-scale evaluation and implementation of PGx in clinical care in the United States.

The meeting participants examined barriers to implementation and discussed whether more discovery is needed to generate further evidence, or more emphasis should be placed on adoption of PGx evidence already available. Undoubtedly both are needed but there was wide agreement that available evidence is not being effectively disseminated and implemented. Lessons learned, recommendations, and future research opportunities for moving PGx implementation forward include:

**<u>Lessons Learned</u>**

Implementation:

- Implementing PGx will most benefit a small proportion of population for each drug considered individually, however more than 95% of patients have at least one PGx variant
- Quality of genetic tests and variant interpretation can be vastly improved by requirement to submit to ClinVar and face peer review
- Local data on frequency of poor drug response, either adverse drug reactions (ADRs) or non-response, can be very helpful in convincing clinicians that there is indeed a problem to address
- Adoption of PGx is greatly advanced by a local "clinical champion", to pioneer, lead, and set an example for other care providers
- Electronic health record (EHR) standardization and enhancement are disruptive but will likely be largely completed in the next ten years and should facilitate PGx implementation nationwide
- Genome-wide approaches are most effective for implementation research, given the collective prevalence of individually rare PGx variants, while the sharp focus on one gene and one drug at a time is needed for association discovery
- Support of implementation through grants, while important for initiating implementation programs, is not sustainable or scalable
- Implementation research generally works best logistically if the unit of implementation (or randomization) and of analysis is an entire clinical site, not individual patients within sites
- Capturing outcomes needs advanced planning and incorporation in study design from the start
- Extrapolation of adult data to children and of European ancestry data to non-EA populations is imperfect; better data resources in these special population groups are needed
- Robust generic models can be developed to study cost-effectiveness using local input values to tailor each study; such models are more efficient, faster and simpler than trying to develop individual models *de novo*

Education:

- Appropriate clinician education is essential for successful implementation, as illustrated by mistaken prescribing of higher risk alternative drugs as in the Hong Kong carbamazepine case
- Training programs are needed at multiple experience levels and for multiple health professions, both incorporated in medical/pharmacy/etc. school curricula or as separate certificates
- Education, dissemination and implementation work best when aligned with new guidelines and the popular press

**Recommendations**

Clinical Practice and Education:

- Educate clinicians regarding the misperception of high cost of genetic tests; many genetic tests including exomes and genomes can cost less than an MRI
- Improve turnaround time and user-friendliness of reports of genetic tests
- Educate clinicians fearful of liability from unacted-upon genetic results that they are liable whether they search for and report those results or not
- Promote multidisciplinary training at various levels of complexity and intensity such as a one-month clinical rotation for residents, boot camp for practicing clinicians, full year fellowship
- Change our approach to individualized prescribing by working backwards from response to dose; reverse the typical "dose to exposure to response" paradigm
- Avoid returning genes/variants that cannot be updated until the proper infrastructure is in place
- Provide users with data on what gene/drug pairs are not clinically actionable based on available evidence, to counteract potentially harmful over-marketing
- Identify minimum quality standards for PGx testing such as minimum set of variants to be tested and sequencing depth achieved, to improve quality and consistency of clinical PGx testing
- Develop new coding approach for tracking and reimbursement of gene testing potentially building upon the Genetic Testing Registry, to augment or replace the current 200 CPT codes

Bioinformatics:

- Improve standardization and updating of clinical decision support (CDS) implementation per evolving CPIC guidelines using tools and resources such as CDS-KB, ClinGen, DIGITizE
- Find ways to update and annotate genomic data in EHR as new knowledge accrues
- Encourage development of robust "plug-in" modules for identifying drug-gene interactions building on models currently available for drug-drug interactions
- Engage clinical IT personnel more directly in research, grants, conferences and programs
- Develop national system for PGx and other genomic data to follow patient as they move across healthcare systems, as well as infrastructure for storage and accessibility
- Continue and enhance efforts to develop standardized terminology for PGx genetic results and phenotype designations, and promote their adoption in clinical care and research

Research:

- Leverage opportunities for data re-use by re-analyzing existing genotyping data from past trials to generate new PGx associations
- Involve patients in study design of research programs and facilitate patient-driven contribution of data and samples
- Capture patient data throughout integrated healthcare system including partner and satellite sites, record their treatment outcomes and use compiled experience to develop best practices and evidence for payers and regulators

- Harness existing quality improvement projects to generate evidence
- Diversify approaches to implementation studies by including community-based practitioners/ pharmacists and diverse tools such as PGx cards and QR codes
- Expand PGx studies to include underserved populations including children and persons of non-European ancestry
- Require the use of standardized outcomes, including standardized patient-reported outcomes, across multiple studies so data can be pooled and jointly analyzed
- Work on generating other measures of benefit in addition to cost
- Develop better methods for identifying and studying outliers in drug response
- Create registries of patients who've undergone PGx testing that allow follow-up for outcomes
- Create effective nationwide systems for identifying and studying patients with rare ADRs
- Address barrier of lack of evidence by systematically comparing PGx testing to other routinely accepted testing in relation to the lack of randomized clinical trials
- Convene working group including PGx skeptics to examine ethics of and approaches to large-scale trials that include randomization to no PGx genotyping, and consider approaches such as staggered roll-out where waves of PGx implementation are separated by time
- Link data from sources like IMS Health (now QuintilesIMS http://www.imshealth.com/) on drug use frequency with allele frequencies to estimate potential impact of PGx implementation
- Leverage for research existing self-insurance plans at some institutions that allow PGx-genotyping of all their employees at < $50 apiece
- Continue discovery research to identify additional genetic variants affecting drug response, particularly for commonly used drugs