Lessons Learned

- Behind every statistic is a patient like Angela
- Implementing PGx will have greatest benefit for a small proportion of population (for each drug)
  - One *TPMT* study showed striking difference in toxicity but mainly in risk allele carriers, not enough to affect overall results; also impt in non-risk allele carriers
  - How to get clinicians to focus on outliers
- > 95% of pts will have at least one PGx variant
- Must implement with appropriate education to avoid Hong Kong experience
- Quality can be vastly improved by requirement to submit to ClinVar and face peer review (Aetna)

Lessons Learned (cont)

- “Not a problem” problem– data on drug use critical
- Key hook is solving existing clinical problem
- Importance of clinical champion
- Align education, implementation with new guidelines and popular press– codeine
- EHR upheavals will likely subside– or recur every 10 years?
- Address perception that genetic tests will be thousands of dollars; improve turnaround time
- Address MD fear of liability from unacted-upon genetic results by education, exhortation

Lessons Learned (cont2)

- Arguing for patient safety may obviate some evidence barriers; focus on mitigating risk
- Genome-wide approaches best for implementation research; gene-by-gene and drug-by-drug best for association discovery
- Frequent opportunities for data re-use
- Don’t return genes/variants you can’t update until infrastructure in place
- Support of implementation through grants is not sustainable or scalable
- NIH supported resources for implementation have been widely used; need for them continues

Lessons Learned (cont3)

- Unit of analysis likely needs to be entire clinical site, not individual patient
- Plan in advance to capture outcomes
- Work backwards from response; reverse typical "dose to exposure to response"
- Very imperfect extrapolation of adult data to kids
- Very imperfect extrapolation of European ancestry data to non-EA populations
- Generic approach to cost-effectiveness enables use of local input values; efficient, rapid, simple

Research Opportunities

- Analyze genotype data from past trials
- Patient-driven contribution of data, samples; involve in design of research programs
- Harness existing QI projects to generate evidence, request non-HS designation
- Study diverse approaches to implementation
  - Community-based practitioners/pharmacists
  - PGx card vs. QR codes
  - Children vs. adults
  - Non-EA, underserved populations
- Require use of standardized outcomes including pt-reported outcomes, across multiple studies so data can be pooled
- Need other measures of benefit than cost

Research Opportunities (cont)

- Develop methods for studying outliers
- Create system for pulling together rare ADR patients nationwide
- Create registries of “PGx-ed” patients (Sentinel-like)
  - Capture pts at partner sites, treatment outcomes, use to develop best practices and evidence for payers and regulators
  - CDRN of PCORI, tie Sentinel to *All of Us*
- Systematically compare PGx testing to other routinely accepted testing re lack of RCTs
- Provide users with data on which gene/drug pairs aren’t actionable

Research Opportunities (cont)

- Link IMS data on drug use frequency with allele freqs to estimate PGx impact
- Home institutions' self-insurance plans could PGx-genotype all their employees at < $50 apiece
- Need discovery research for additional gene-drug pairs, particularly for commonly used drugs

Objective 4: Design strategy for large-scale evaluation and implementation of PGx in clinical care in the U.S.?

- Ethics of randomizing to no genotyping– more acceptable in 99% not being genotyped at all
- White paper on ethical aspects of randomization
- Also need to understand when trials needed
- Debated strategy: pragmatic trials to randomize to genotype-guided rx vs. standard clinical care
  - Include key secondary outcome of risk allele carriers as subgroup analysis
  - Identifying risk allele carriers before randomizing likely unethical

Opportunities for Building and Disseminating Consensus

- Need standardized terminology developed and adopted for genetic results and phenotype designations– partly solved?
- Ever-changing panels can be addressed by set of minimum variants for specific condition– CPIC-like consensus group?
- Inability to code for quality and reimb. with 200 CPT codes and 65K tests is major barrier
  - Develop new coding approach to address genomics– build upon GTR?
  - Would also support CDS and outcomes research
- Debate on PGx RCT with naysayers in room?
- Engage USPSTF in evidence review

Opportunities for Building and Disseminating Consensus

- How to build/assure quality in PGx testing
  - Develop guidelines for best practices: identify drugs you “must” test, perhaps in tiers
  - Minimum quality/coverage standards for specific genes: *CYP2D6* only testing *4 and not CNV doesn’t meet standard
  - Identify technologies and standards needed for specific genes and drawbacks of each

Clinical Informatics Needs

- Improve standardization and updating of CDS implementation per CPIC guidelines, CDS-KB, ClinGen, DIGITizE
- EHR data need to be updatable with new knowledge
- Plug-ins for drug-drug interaction can be bought, why not for drug-gene interactions?
- Engage clinical IT personnel more in grants, conferences and programs
- Can’t manually curate haplotype/phenotype assignment– PharmCAT underway
- Need national system for data to follow patient

Clinical Informatics Needs (cont)

- Related to data quality: infrastructure for storage and accessibility
- Aggregate/point to all “big” PGX tools in one mega-site for users
- Point of care and just in time education, can also drive development of standardized data so can be captured

Education and Workforce Development

- Key role of pharmacist, need to educate them:
  - Clinicians contact them
  - Who'll be available to consult– PharmDs with PGY2 year in PGx, viable career path
- Include nurses and patients in education efforts
- Engage community pharmacists
- Value of multidisciplinary training in "Clinical Genomic Action Cmte" (molecular tumor board)
- "Plus one" year for completed clinical pharm or molecular path trainees
- Various levels– 1 mo clinical rotation, boot camp for practicing clinicians, full year fellowship

Education and Workforce Development (cont)

- Various levels of complexity– 1 mo clinical rotation, boot camp for practicing clinicians, full year personalized medicine fellowship
- Include compelling case reports to grab clinicians, also valuable for convincing payers
- Publish lessons learned in implementation
- Consider webcast Cases in (P)Genomic Medicine
- Provide sustained online forum following courses similar to City of Hope
- Include clinicians and professional educators in design; identify what they need to know
- Sneak education into things already happening
- Avoid focusing too much on “genomic” medicine

Intriguing Question: What is the 1-, 3-, and 5-Year Projection for PGx Implementation?

- Useful for all stakeholders (payers, systems, clinicians, *All of Us*) to model future needs, reimbursement, education, infrastructure
- Break into
  - Availability of data
  - Use of data
  - Capture of outcomes of implementation
- Break down by
  - Technology/data lens
  - Consumer lens
  - Disease-specific lens– more useful in some conditions than others, especially those with large amounts data and research

Session 6 – Role of NHGRI and Community in PGx Implementation Research

- Dafdasf

Session 1 – PGx Landscape (cont)

- What's needed (Dan):
  - Comprehensive biology
  - Methods to identify, accumulate, study outliers
  - Accurate tests
  - IT infrastructure
  - Data on diverse approaches (pre-emptive/ reactive, card/QR)
  - Education
  - Medical and economic outcomes
  - Partner engagement

Session 1 – PGx Landscape (cont2)

- Challenges and synergies (Simona):
  - Standardize allelic nomenclature
  - Identify and assess current PGx resources, improve synergies and reduce duplication
  - Increase population diversity
  - Identify and study ADRs
  - Genomic approaches rather than gene-by-gene and drug by drug
  - Reduce costs and turnaround time with pre-emptive testing
  - Engage payers