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NHGRI Genomic Medicine X: Research Directions in Pharmacogenomics Implementation
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<u>**Welcome, Introductions and Goals of the Meeting**</u>
Genomic Medicine X has convened leaders in genomic medicine and pharmacogenomics (PGx) to survey the landscape of PGx implementation and assess projects that are ripe for clinical use. Although variant and drug-gene interaction discovery is essential for generating the evidence to move implementation forward, the purpose of this meeting is to identify and address the gaps and limitations that have hindered the implementation of PGx and its incorporation into clinical care.

A pre-meeting survey was distributed to 73 CPIC implementers and eMERGE, ClinGen, and IGNITE members with 49% responding. 51% implemented PGx reactively in relation to treatment and 49% implemented preemptive testing. There was diversity in the genotyping platforms and 63% reported that they have or will file for third party reimbursement. Obstacles reported included lack of funding and test reimbursement, lack of institutional support, challenges with Information Technology (IT)/Electronic Health Record (EHR)/Clinical Decision Support (CDS), challenges in laboratory/genotyping technology, lack of education of clinical staff and patients, and lack of clinician buy-in.

<u>**Session 1: The Pharmacogenomics Landscape**</u>
Paul Anderson set the tone for the meeting to focus on clinical care and the real needs of real patients and families. He highlighted the need for more research on adverse drug reactions (ADRs), by sharing the story of his 22-year old daughter who died from Stevens-Johnson Syndrome (SJS) in December 2015.

Variation in response to a drug is frequent and widely recognized, but fatal ADRs are fortunately so rare that it is difficult to recognize and correctly identify them. An estimated one-third of drugs that cause ADRs have some genetic component involved. As an example, warfarin dosing varies by ancestry, due largely to variations in *CYP2C9* and *VKORC1*. An RCT compared genotype-guided versus conventional dosing for warfarin and showed that the genotype-guided group had less than half the rate of major bleeding compared to the clinically-guided group. Another trial, the Genetic Informatics warfarin Trial (GIFT), began in 2012 and randomized 1650 patients post hip/knee surgery and receiving warfarin to PGx-guided or conventional therapy. Results were reported in March 2017 showing that the PGx-guided group had fewer cases of major bleeding. The patients are primarily of European ancestry, and African ancestry variants were not considered. SJS is a disorder manifesting on the skin and mucous membranes most commonly triggered from ADR. SJS has been shown to manifest on patients with HLA-B*1502 alleles which are more frequent in SE Asian populations. Genetic testing needs to be done in an educational way to aid people in understanding PGx.

In preparation for GM X, NHGRI held a meeting of representatives from other NIH Institutes to survey the PGx landscape supported by NIH and identify potential common efforts. PGx resources, networks,

and clinical trials were identified and the group discussed challenges and potential synergies. A major unmet need is the standardization of nomenclature and drug metabolism phenotypes across data resources. There are also many existing PGx resources which may have overlap and duplication across them. As with other genomic programs, population diversity is a challenge in PGx studies. Representation of non-European populations is inadequate and more detail is needed beyond the five overarching Census-defined U.S. race/ethnicity groups. Another barrier is that ADRs have not been adequately studied. Studies are typically small and thus few predictors of responses have been identified, with limited evidence of heritability of a drug response. Epigenetic changes affected by drugs are another knowledge gap. Future directions include immunopharmacology, which should be explored beyond cancer and infectious diseases, and defining biological markers for psychiatry drug responses through the EHR. The NIH IC representatives concurred that they have common interests and could collaborate on projects such as sharing samples and databases and iPSC models of drug responses.

Discussion

It is true that the study of any specific PGx variant will only benefit a small portion of the population, but the culture of clinical practice needs to shift from focusing on the "middle" to the "tails" of the distribution of responses. Physicians' lack of attention to the extremes of the response curve is one of the main barriers of PGx implementation.

Many completed clinical trials of drug efficacy could yield significant PGx-related results if the data were re-analyzed with the present knowledge. Combining all the known drug-gene interactions in a trial can expand the sample size and ability to detect significant results. The COAG clinical trial was noted as an example of a negative trial because of its design. The non-genetic control arm in this trial used a very aggressive clinical algorithm for warfarin dosing that was far more advanced than the standard of care.

Session 2: Resources for PGx Implementation

Valuable features of the Pharmacogenomics Knowledgebase (PharmaGKB) include pages on variant annotations and drug labels as well as pharmacokinetic and pharmacodynamic pathways of the drugs. Clinical annotations come from an automated and curated review of the literature and drug label information is summarized as provided by the FDA. Dosing guidelines can be sorted by drug or by gene and are updated on a regular basis. In a survey of PGx experts, the top challenge of implementing PGx was translating the knowledge to clinical practice. The Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines were produced to address this challenge. The freely available guidelines are designed to help clinicians understand how available genetic test results should guide prescribing., CPIC tables allow translation of genetic test results to actionability and variants are phased to assign diplotypes for pharmacogenes. Drugs with strong or moderate recommendations for prescribing are termed level A or level B, respectively. CPIC is endorsed by professional organizations, interacts with various groups like ClinGen, links its guidelines to PubMed, and has members internationally.

The Clinical Genome Resource (ClinGen) aims to create an authoritative central resource that defines the clinical relevance of genes and variants for use in medicine and research. ClinGen curates validity, pathogenicity, and clinical utility of variants involving over 500 participants across the globe. ClinGen links out to, and draws from, a variety of other resources, including PharmGKB and public submissions to

ClinVar, the NCBI database on which ClinGen is built. Over 45 different clinical significance terms have been submitted to ClinVar, highlighting that the use of common standards and language is vital for curation efforts. ACMG and ClinGen have produced guidelines on standardizing language for pathogenicity and actionability which have been widely adopted. ClinGen also works to resolve inter-laboratory conflicts on variant classification. A major publication was able to resolve 87% of differences in interpretation within four ClinVar submitters through data sharing and collaborative work. ClinGen includes a PGx working group to liaise with PharmGKB and CPIC and address challenges specific to submitting PGx variants such as defining haplotypes, star (*) alleles, and biallelic information. To date, ClinVar's PGx content includes 579 assertions on 337 variants in 126 genes from 13 submitters. Users can link to PGx information in CPIC guidelines or ClinGen through decision support tools in the EHR. An important distinction is that ClinVar is categorizing variants across the germline whereas PharmGKB separates its submission based on responsiveness to therapy. A new template has been designed for ClinVar submissions efforts are underway to represent CPIC variants in a more user-friendly way.

The "Displaying and Integrating Genetic Information Through the EHR Action Collaborative" (DIGITizE AC) has been organized through the National Academies of Science, Engineering, and Medicine. Its purpose is to facilitate the development and roll-out of genetics-guided CDS. Two focus areas are 1) developing guides for CDS implementation, and 2) enabling collaborations to get these guidelines into use. In general, most hospitals start on a legacy EHR, migrate to a commercial EHR, and ultimately enhance the commercial EHR over time. Once the transition is complete, new innovative projects like PGx implementation compete with other projects needed for maintaining basic standards of care. The first CDS guides developed by DIGITizE AC focused on abacavir and azathioprine as these were two areas of strong consensus. Key lessons from this project include the need for dedicated and paid effort for project management, analysis, and coordination; for consistency, a limited number of individuals should play these coordinating roles. In addition, DIGITizE AC has learned that competition for IT resources is extreme and prioritizing resources and tasks has been challenging. The need to engage clinical IT expertise in NHGRI's consortia was highlighted. Some preliminary efforts have been made to include IT representatives in NIH grants. Finally, SMART on FHIR apps help reduce the cost of building and integrating the various applications in the different hospital systems.

Genomic testing companies have algorithms in place for single-variant associations but many of these scripts are proprietary and often contradict one another. To address the lack of a freely available resource, the PGx Clinical Annotation Tool (PharmCAT) was developed to automate the annotation of VCF files with appropriate haplotypes or diplotypes from the current 28 CPIC guideline genes, and generate a report with the corresponding CPIC prescribing recommendations. The PharmCAT workflow starts with the sample genotypes in VCF or gVCF formats that go through preprocessing to generate a normalized genotype and sample metadata. The normalized genotype then goes through the haplotyper which automates the conversion of VCF to allele calls. The output is sent to the data reporter which produces the final report by incorporating all pipeline outcomes (sample metadata, exception logic etc.). The project is intended to be open-source so any code script generated by PharmCAT is posted in GitHub. The first version of the tool is now in testing and will be released soon to solicit feedback.

Discussion

There is no seamless way to integrate CPIC or other PGx guidance in the myriad CDS systems in clinical uses. A valuable first step would be to establish CPIC as the reliable source for information and standardize the test names and terminology to facilitate the continuous update and improvement of the guidelines. The CDS KnowledgeBase (CDS-KB) is a joint program between eMERGE and IGNITE where groups can upload their CDS artifacts and flow diagrams in an effort to generate consistency across implementations. What is missing from these tools are nuanced interpretations and updates including drug-drug-gene interactions and more complex polypharmacy scenarios. Other variables not currently considered include history of surgery and allergies. Integrating all these variables is a challenging task and a resource gap, but from an IT perspective the largest challenge is making the data accessible.

Disseminating these resources to community clinical pharmacists could increase application of reliable CDS-guided recommendations since clinical pharmacists are on the front line receiving real-time feedback from patients. Training and engaging them in the development of CDS is essential. In addition, patients should receive educational materials which will help in generating awareness that can then be passed to clinicians by the patients themselves. With respect to training professionals, Children's Mercy in Kansas City has a pediatric pharmacology program that has experienced difficulty in recruiting trainees. Marketing the program differently, by downplaying genomics and including some machine learning and analytics language, enhanced the enthusiasm and recruitment.

To date, successes in implementing PGx have largely been through projects funded by the NIH but this is not scalable or sustainable. Furthermore, EHRs are constantly being updated which necessitates hospitals to spend more money on keeping their systems up to date. Plug-in applications are available for drug-drug interactions; potentially they could be developed for drug-gene interactions. Ways to create the necessary CDS infrastructure include incorporating it in funding opportunities related to clinical implementation, or approaching industry to build a standardized commercial product.

Session 3: Implementation Research Projects

For PGx to be implemented widely, it must have clinical value and be economically viable. PGx economic research requires an interdisciplinary approach by engaging informaticians, economists and geneticists. The INdiana GENomics Implementation Opportunity for the UnderServed (INGENIOUS) project studies the effect of prospective and reactive PGx genotyping on healthcare costs and adverse events. The study initially began in Eskenazi Health in Indianapolis and expanded to Indiana University (IU) Health, with 2,000 patients randomized to receive genotype-guided therapy and 4,000 receiving the standard care. A significant number of actionable results in 13 CPIC Level A genes— 25% of patients were recommended a change in selection or dose of their drug— are being reported to Eskenazi providers and 20% of actionable results have required clinical pharmacologist engagement. INGENIOUS has also worked with the Indiana University Precision Genomics Oncology Clinic to study patients with refractory cancers or tumors of unknown origin to extract PGx results from germline whole genome sequencing. Results are presented to physicians in an intuitive way using a color-coded schematic indicating poor, intermediate, or normal responses for each gene.

The study of outliers has been very informative in cancer treatments. Studying the small number of patients with exceptionally good responses to drugs has identified genes that can help develop methods for optimally matching patients to drugs, highlight effective uses for "failed" therapies, and aid with development of new therapies. However, relying on physicians referring these patients for study is not effective, and tumor samples may not be readily available for study. One approach takes advantage of social media and advocacy groups. The Metastatic Breast Cancer Project (MBCP) enables patients to register themselves for the study online; 3500 patients from around the US have signed up in the last 18 months. The process includes an online consent form on which patients provide contact information for their doctor. MBCP collects saliva via mail, contacts their physicians to obtain medical records, and calls the pathology labs to ask for tumor tissue. Whole exome sequencing (WES) and cell-free DNA analyses are performed on the saliva and tissue. The data are de-identified and available to anyone for research. So far more than 1200 patients from 992 institutions have submitted saliva. Patient advocates have been key in encouraging patients to register via social media. Facebook and Twitter advertisements from the first 1000 registrants encouraged a large spike in registration. Partnering directly with patients through social media enables rapid identification of large numbers of candidates willing to share their data for research. A similar project on angiosarcoma was launched 6 weeks ago with 200 patients already signed up. The Dana Farber Cancer Institute will launch a third project on prostate cancer soon.

African American (AA) populations have more genetic variation and carry actionable variations at higher frequencies than persons of European ancestry. Despite this, the great majority of genome-wide association studies in PGx are in populations of European descent. Non-European populations are still in the phase of discovery; PGx-guided therapies cannot yet be implemented because the appropriate genes and variants to target have not been identified. The African American Cardiovascular pharmacogenomics CONsorTium (ACCOuNT) is a U45 collaborative grant funded by NIMHD in DC and Chicago to accelerate discovery and translation in African Americans. Data that will be collected include clinical response, DNA and mRNA data. Drugs studied include warfarin, clopidogrel, and new oral anticoagulants (NOACs). Participants with significant AA ancestry can be identified using a pre-emptive SNP panel. The study at present does use self-identified race but hopes to shift to the computational method in the future. All the de-identified data will be deposited into a publicly available AA Data Commons which will include tools for admixed population analyses. Another project by Northwestern University, the Genomic Prescribing System (GPS), is an online portal by which physicians can receive PGx results; it was built out of the 1200 Patients Project, a pre-emptive PGx genotyping project to give the physician PGx information at the point of prescribing. Several patient engagement groups have been involved in moving these efforts forward and advocating for more minority-centered PGx.

The Mission Health System (MHS) serves North Carolina and includes a tertiary care regional center, five smaller hospitals, and a very stable patient population. 75% of their patients are on Medicaid, Medicare or self-paying. Mission Health's Personalized Medicine Program includes a focus on predicting responses to chemotherapy drugs where testing is already standard of care. In the non-cancer realm, the program focuses on drug –gene associations with the highest levels of evidence, where testing is emerging as a best practice. Major projects in the cancer realm have included developing an integrated tumor marker program at Mission Cancer Center, enhancing access to genomic profiling, providing clinical

consultation/interpretation for genomic profiling, and starting in-house testing for leukemia. Non-cancer projects include removing codeine from the MHS pediatric formulary to minimize risk of lethal response due to genetic variations. They have also developed CDS alerts system-wide in inpatient and outpatient records and the NC Medicaid office is adopting their policies. In 2016, MHS launched a pilot feasibility study to bring PGx to primary care and developed a Personalized Medicine clinic for adults with non-cancer conditions at the Fullerton Genetics Center. Lessons learned from these projects include the importance of both "top down" and "bottom up" physician support of personalized medicine, the significance of timing with regards to emerging national and regional concerns that have leadership support, aligning education and dissemination with new guidelines and popular press, and the knowing what motivates a researcher's hospital and community.

Vanderbilt University projects use the EHR to incorporate research in implementation and show how these experiences matter to the patients, primarily as a quality improvement initiative rather than a research project. Vanderbilt's BioVU is a de-identified DNA data repository with more than 235,000 samples that has allowed research into PGx effects. The Pharmacogenomic Resource for Enhanced Decisions In Care and Treatment (PREDICT) program began with an implementation effort on *CYP2C19* loss of function (LOF) variants and clopidogrel prescribing and later expanded to include other genes and drugs. Among patients predicted to be at high risk of receiving a PGx-relevant drug, 65% received a PGx-relevant medication within the first year. Of the first 10,000 patients tested, 91% of patients had at least one actionable or high-risk variant. In addition, 121 VU providers were surveyed about PGx prescribing. The vast majority agreed that a person's genome may influence their drug responses, particularly to clopidogrel or warfarin. The factors on whether they would consider ordering a genomic test included the strength of evidence on how it could affect their patient. Providers did respond to genotype information in a dose-dependent fashion: poor metabolizers of antiplatelet therapies (LOF homozygotes) were more likely to be switched to alternative therapy than were intermediate metabolizers (heterozygotes). Nevertheless, warfarin remains the most commonly prescribed anticoagulant, except at the VA, and clopidogrel remains the most commonly prescribed anti-platelet drug. Lessons learned from the PREDICT study highlight the variability in implementation projects among different sites and note that local provider buy-in is dependent on belief in clinical efficacy, ease of use, and familiarity.

The compelling case of a 57-year old patient was presented to highlight the meaning of personalized medicine. The patient was diabetic, had a family history of heart disease and elevated cholesterol, and was admitted for chest pain. At that point, she received a stent and was prescribed clopidogrel. Within the span of a year the patient was re-admitted 9 times, received 5 interventions and 9 stents, only after which she was genotyped and was found to have the *CYP2C19*2/*2* allele, a poor metabolizer for clopidogrel. She was switched to prasugrel and has been stable without restenting in the 3 years since.

Discussion
From a payer perspective, the fundamental issues regarding reimbursement of genetic tests revolve around three aspects. Firstly, the coding of the tests for reimbursement is not up to date and reflective of the vast number of available tests that exist. About 10 new tests are introduced every day, but only approximately 200 of those are assigned a CPT code. This discrepancy between number of tests and CPT

codes causes a bottleneck in moving reimbursement forward. Secondly, it has been very challenging for payers to get standard measures of what is considered "good quality" in a genetic test. The Association for Molecular Pathology (AMP) has been coordinating efforts to develop new codes for genetic tests but progress has been very slow. The idea is not to generate a code for every test but codes that can be generalized, such as more generic codes that can be applied broadly across PGx and other genetic testing. Lastly, there has not been enough health economics data generation to support reimbursement. This is an area were better communication is needed between scientists and payers as definitions of cost-effectiveness are different between economists and clinicians.

Payers are still making their assessments based on clinical or analytic validity, and are still looking at large, randomized trials and at single-gene variants for PGx. This complicates things when there is need of coverage decision for multi-gene panels. Having both cost and clinical outcomes makes a forceful argument for both hospitals and insurers since medications that cost more and can hurt patients are indisputably to be avoided. Defining these outcomes is challenging as metrics are not consistent across institutions. PGx has a lot to learn from implementation science.

A barrier in generating sufficient evidence for implementation is the difficulty in assessing the accuracy of variant interpretation. There has been considerable improvement in the accuracy of data submitted to ClinVar, which is now also a forum for peer-assessment. This is shown by a correlation between quality and whether labs submit to ClinVar at all; requiring labs to submit to ClinVar might be a way to improve the quality of PGx (and other genetic) variant information. A beneficial move towards this idea was Aetna's decision to require submission of *BRCA* data to ClinVar for reimbursement. There is a need to discuss what type of evidence is convincing and gather the differing opinions across all stakeholders.

Panel Discussion: Research Gaps to be Addressed
Thiopurines, clopidogrel and warfarin are examples where there is some evidence to advocate for nationwide implementation of PGx in clinical care. CPIC has provided guidelines for the genes associated with metabolism of these drugs but the guidelines are not being widely implemented. This contrasts with the impact of drug interactions or poor renal or hepatic function, which have few studies and no randomized clinical evidence, yet are widely adopted. It is unclear whether PGx implementation is lagging because of "genetic exceptionalism" and the demand for compelling evidence, or because of the lack of focused effort to disseminate available guidelines.

To address the evidence gap there is need to distinguish between discovery research and implementation. Discovery research to identify drug-gene associations should focus on one drug and one gene at a time because the more drugs and confounders that are added to each study, the less likely one is to discover gene-drug associations amidst all the noise. Implementation, in contrast, is rarely cost effective or practical done as one gene or drug at a time and a more genomic approach is needed. IGNITE has discussed the idea of a large multi-center clinical trial with common outcome measures. The PGx community needs to engage physicians and payers in the design to identify what evidence will be convincing to them. The idea of preemptive testing for a PGx panel has the most agreement at present so maybe this is where the proof of concept needs to focus.

On the topic of economics, the dramatic drop in cost of PGx tests was discussed. Some of these tests are now much lower cost than an MRI and still we see that MRIs are covered, and PGx tests are not. At present, ordering a test under an indication of a medical problem at a low cost is reimbursable; the challenge is preemptive testing with no medical problem exhibited. This scenario does not pose a "medical necessity" argument but it might be worth considering whether genetic testing could become comparable to vaccination. Luckily, unlike some medical tests, genotyping only needs to be done once, which should significantly minimize its long-term cost and increase its economic value. However, the quality of these tests changes over time and payers do not know whether the test they're reimbursing is "good quality." For genotyping to be implemented preemptively, the right infrastructure needs to be in place to ensure constant data accessibility, another challenge to overcome.

Session 4: Evaluating Outcomes and Cost-Effectiveness
The eMERGE-PGx Project implemented PGRNseq, a targeted capture sequencing panel for PGx research and implementation in multiple sites across eMERGE. A design paper was published early in the study describing how PGRNseq was applied differently in the individual eMERGE sites; sites used different drug-gene pairs, focused on pediatric vs adult patients, and had other variations. Proposed and near-to-completion outcomes include the sequencing of 84 pharmacogenes in more than 9000 participants. Although the study population is predominantly of European ancestry, recruitment included over 1000 participants of African ancestry. The project created the SPHINX (Sequence, Phenotype, and pHarmacogenomics Integration) database, a searchable variant repository that summarizes sociodemographic information and gene frequency but doesn't provide individual-level data due to privacy concerns. The eMERGE-PGx sites have been collaborating to report descriptive metadata and define quantitative and qualitative outcomes across seven domains: recruitment, sequencing, genotype validation, provider education, patient education, EHR integration, and actionable rare variation. There were no systematic efforts in cost-effectiveness analysis and few post-implementation assessments have been made to date; outcome assessments were focused at the individual level and assessed primarily through the EHR. There was significant variation in how PGx CDS alerts were designed and implemented throughout the eMERGE Network, producing a series of natural experiments with a variety of alert design and drug-gene interaction choices. Future directions should take into account the differing natures of clinical and implementation research by including clinic/facility level outcomes as well as individual outcomes and incorporating validated dissemination and implementation instruments to assess outcomes.

Implementing PGx in pediatrics is especially important as it can aid the early and effective intervention which could change the disease over the course of a child's development. At present, however, there is little clinically useful guidance regarding the dose to exposure relationship as a function of genotype in pediatric patients and there are limitations in extrapolating adult PGx data to children. Atomoxetine, a major drug for treating ADHD, includes population-based guidelines for regulatory purposes in the product monograph but these are of limited value for individualizing care. For example, data from a genotype-stratified pharmacokinetic study of simvastatin in adults extrapolated to children replicated the genotype-phenotype associations seen in adults but the magnitude of effect in children was greater. To address this disparity of pediatric PGx knowledge, the Children's Mercy Hospital in Kansas City

created the GOLDILOKs (Genomic and Ontogeny-Linked Dose Individualization and cLinical Optimization for Kids) Initiative which includes stage of development as an important factor in addition to genomic variation. This initiative follows the "response to exposure to dose" paradigm which focuses on the individual's drug target genotype to determine the right exposure for that genotype and the dose required to achieve the desired exposure, rather than the "dose to exposure to response" paradigm so often followed in clinical care. Providers in GOLDILOKs also focus on educating children and families about how dosing might differ and have produced creative tools that are more understandable to children.

The University of Florida (UF) IGNITE site has designed pragmatic studies around PGx implementation and has collaborated with other institutions to examine outcomes with pharmacogenetic implementation. The initial pharmacogenetic implementation at UF Health focused on *CYP2C19* genotype-guided antiplatelet therapy for patients undergoing percutaneous coronary intervention (PCI). The genotype test was placed on the post-PCI order set, with the test run in the UF Health pathology labs and results placed in the EHR. Recommendations for alternative therapy are provided for LOF allele carriers and are built into the CDS. There is an ongoing clinical trial, "Tailored Antiplatelet Initiation to Lessen Outcomes Due to Decreased Clopidogrel Response After Percutaneous Coronary Intervention" (TAILOR-PCI) assessing the efficacy of genotype-guided antiplatelet therapy after PCI. This trial was initiated in May 2013 and has a targeted enrollment of 5270 participants undergoing PCI. The genotype-guided strategy arm uses ticagrelor for patients with the *CYP2C19*2* or **3* allele and in the control arm all patients are treated with clopidogrel. The primary outcome is major adverse cardiovascular events (MACE) within a year of treatment and the estimated completion date is March 2020. In the meantime, the UF Health team led a multi-institutional examination of outcomes of *CYP2C19*-clopidogrel testing as part of clinical care. Data were included from 7 participating sites in IGNITE. Twelve-month rates of MACE after PCI were significantly lower among LOF allele carriers treated with alternative antiplatelet therapy, e.g. ticagrelor or prasugrel vs. clopidogrel. The next step is to conduct an economic analysis based on the outcomes data. The UF implementation study showed that a genotype-guided approach to antiplatelet therapy in the clinical setting is feasible and in patients with *CYP2C19* LOF, cardiovascular outcomes can be improved when the clinical genotype is made available and alternative therapy is prescribed early after PCI.

Perspectives are important in studying the pragmatic application of economic and cost-effectiveness analysis of genomic medicine implementation projects. Most economic analyses are performed from the societal perspective but this perspective does not translate well to decision making at the health system level. Geisinger used an economic model to look at the cost of different protocols for implementing universal tumor screening for Lynch Syndrome (LS) and used these as different input variables. Using different approaches didn't impact the number of LS cases identified, but showed a significant difference in cost per case (range from $10,730 to $13,555). For *IL28B* genotyping and protease inhibitors in hepatitis C virus (HCV) infection, administering triple drug therapy only to patients with resistant *IL28B* genotype requires an improvement in sustained viral response (SVR) of slightly greater than 2% to cross the cost-effectiveness threshold. Treating all patients, in contrast, requires an improvement of over 11%. PGx-informed warfarin dosing showed the importance of using a patient

perspective in prospective data from Intermountain Healthcare, which showed that tested patients required 2-3 fewer blood tests to get to a stable dose. The patient-centered perspective would strongly favor PGx testing based on the reduced number of visits for blood draws. Developing an economic model requires significant expertise and resources and most models are created for a specific use with customized inputs that limit reuse. This leads to the question of whether a generic model could be created to allow stakeholders to enter relevant key parameters and generate results relevant to decision making. A case using generic modelling was introduced at the Personalized Genomic Medicine Program at UF on a project for PGx prevention of Stevens-Johnson syndrome. The use case was HLA-B*15:02 testing prior to use of carbamazepine to reduce the risk of severe cutaneous adverse reactions. A conceptual framework and decision tree were generated; required input variables included prevalence, cost, cost of disease treatment, ceiling ratio and threshold value and there were options for populating probabilities, utility, treatment duration and discount rates. The model performed reasonably well and efficiently, showing that enabling use of local input values on a generic cost-effectiveness model is feasible and can offer an efficient and timely value-based decision making tool. Implementing this approach demonstrates that cost-effectiveness analyses can be rapidly performed without extensive training in decision modeling to provide useful evidence for decision making.

Discussion

The best approach to generate compelling evidence of PGx effectiveness are likely to be obtained from a pragmatic study design where patients are assigned to be genotyped or receive standard care. Designing a randomized clinical trial has been especially challenging because of the uncertainty of whether the evidence that is already present has eliminated clinical equipoise, making randomization unethical. This could be an opportunity to research the ethical aspects of addressing evidence, implementation and adoption gaps and inform the decision as to what needs to be done next in PGx. We also need to agree when and if a clinical trial is necessary and when it might be unethical. It will be important to include "naysayers" or those unconvinced of PGx effectiveness as well as zealous proponents.

Many believe that the evidence is already clear and it would be a waste of resources (and potentially unethical) to conduct randomized clinical trials (RCTs) rather than simply use what is already available. One way to address concerns about randomization is to recognize that PGx cannot be implemented everywhere at once, and if there is a plan for a phased roll-out across a series of care settings one could randomize them to be early vs. late adopters. Even if we agree that the evidence is sufficient, there is still room for implementation research to determine *how best* to implement PGx. Evidence generated from that might be the key to changing practitioner behaviors. In addition, physicians place a great emphasis on whether a test will be reimbursed. Clinical guidelines also need to inform the payment practices—another area on which we need to focus. This time gap for adoption could be related to clinician anxiety about becoming the first person to enact new procedures. Cost of the change is also an issue.

Session 5: Multidisciplinary Approaches and Training PGx Practitioners

Educating students, clinicians, patients and practitioners is important for implementing PGx and a current barrier to its success. Data from the IGNITE University of Florida (UF) Personalized Medicine

Program show there is lack of appropriate training and clinical experience with PGx activities and tools in pharmacy and medical schools. UF identified the need to train its students on how to apply the knowledge in the clinical setting in a manner that accommodates the diverse educational needs. To test the effects of active learning and personal genotyping on student knowledge and self-efficacy, a control group of students was enrolled in a required PGx course, and another group (intervention group) enrolled in the required PGx course as well as an elective clinical PGx course, and had the option to undergo panel-based genotyping and use genetic data in patient cases. Teaching strategies differed between the control and intervention groups; the elective clinical course included more interactive, case-based studies with emphasis on clinical applications, while the required course followed the more standard didactic model. Post-course knowledge test scores were higher in the intervention group than the control group. No correlation between students' confidence and knowledge was shown in the control group pre- or post-course, but confidence and knowledge were correlated in the intervention group post-course. A total of 950 participants have enrolled in this study in the past five years. This shift towards *how* to implement is reflected in change in content of the UF Precision Medicine Conference, which has recently allocated more time to interactive approaches with patient cases and implementation medicine in comparison to 2016 where the majority of the time was didactic.

An educational barrier relevant to oncology is the inclusion of both germline and somatic genomic variation, as it can be challenging for practitioners to concentrate on more than one genome. Cancer care is constantly evolving and tumor sequencing is being ordered for disease classification and prognosis, FDA-approved therapies, and experimental therapies. The Moffit Cancer Center has formalized a Personalized Medicine Clinical Service (PMCS) program for medical oncology fellows to develop understanding of genomic analysis and incorporation of genomics in clinical practice. PMCS is a required one-month clinical rotation for all second-year hematology/oncology fellows and molecular pathology fellows. 56 physicians have been trained to date as well as more than 120 nurses. The program also provided solid tumor and hematologic malignancies 'boot camps' to expand the Moffitt clinical faculty's test ordering and interpretation expertise.

The Inter-Society Coordinating Committee for Practitioner Education in Genomics (ISCC) aims to improve genomic literacy of physicians and other practitioners and enhance the practice of genomic medicine through sharing of educational approaches and joint identification of education needs. Members of the ISCC include professional societies, NIH Institutes, federal agencies, hospitals and health systems, universities, patient advocates and insurers. ISCC Working Groups (WG) are co-chaired by an NIH representative and an external organization representative. The Competencies WG incorporates PGx by identifying single-gene disorders that may be amenable to targeted pharmacological therapy, discussing PGx implications for future health, creating awareness of PGx variation in systems-based practice, and familiarizing practitioners with available PGx databases and resources. The Educational Products WG utilizes NHGRI's competency-based education resource, the Genetics and Genomics Competency Center (G2C2, http://genomicseducation.net/) that includes specific resources for pharmacists. The Insurer Staff Education WG addresses the growing need for medical staff in the insurance industry to understand genetic testing and hosts a series of webinars, including a Pharmacogenetics video (https://www.youtube.com/watch?v=7LbAtShVtWI).

Discussion

The main challenge in practitioners' education is effectively engaging the audience to convince them to implement PGx in clinical practice. In general, if a resource meets an unmet need then practitioners will become interested and use it, so we need to focus on making the usefulness of tools more obvious and on possibly getting them endorsed by professional societies.

Telling successful stories or case examples in genomic medicine is another way of engaging. Patient and provider interactions, like cases presented in the UDN, are extremely compelling. Professional societies have venues where these case reports could be presented, and if we can assist them in incorporating genomics in their multimedia community outreach platforms, the field will gain momentum. In parallel to clinical cases where actionable results are obvious, the interesting molecular biology observations should also be disseminated to practitioners. Research and clinical implementation should be a continuum, and knowing the basic biology behind the clinical actionability is important.

Training in genomics should begin from medical/pharmacy school. Programs in Florida (UMiami, UF) have introduced Masters programs in clinical genetics that run concurrently with medical school. Other institutions, like UC Denver, are now incorporating in their portfolio online certificates for interactive PGx training or webinars where discussion and interaction around genomic cases are facilitated. City of Hope National Medical Center offers a cancer genetics course where attendees receive intensive hands-on exposure and are provided a forum where they can bring their own cases for discussion. The course organizes an annual symposium where cases and outcomes are discussed, and this initiative could serve as a robust model to be replicated specifically for PGx and adopted nationwide.

Summary and Next Steps (see Executive Summary for more specifics)

It is important to remember that behind every statistic there's a patient like Angela Anderson. Although implementing individual PGx variants will benefit only a small portion of the population for each variant, taken collectively more than 95% of patients will have at least one PGx variant and the great majority of patients will receive a drug relevant to their PGx variants during their lifetime. Evidence of effectiveness of PGx-based dosing in improving patient or system outcomes will continue to be critical in promoting adoption. Emphasizing patient safety, risk mitigation, and quality improvement may overcome resistance to adoption due to perceived lack of evidence, but a randomized trial assessing the impact of PGx-based dosing, involving all or most known actionable PGx genes, would be very valuable. Key secondary outcomes in such trials should include subgroup analyses of risk allele carriers, recognizing that identifying risk allele carriers before randomizing will likely not meet ethical guidelines. A white paper on the ethics of randomizing some patients to no genotyping would also be helpful. Recognizing that PGx cannot be implemented in all clinical settings at once, a pragmatic approach could involve a phased roll-out where sites are randomized to adopt PGx in waves over a period of several years, and where later waves (until they implement PGx) serve as usual care controls for earlier waves.