Research directions in the clinical implementation of pharmacogenomics - An Overview of US programs and projects

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Abstract

Response to a drug often differs widely among individual patients. This variability is frequently observed not only with respect to effective responses but also with adverse drug reactions. Matching patients to the drugs that are most likely to be effective and least likely to cause harm is the goal of effective therapeutics. Pharmacogenomics (PGx) holds the promise of precision medicine through elucidating the genetic determinants responsible for pharmacological outcomes and using them to guide drug selection and dosing. Here, we survey the US landscape of research programs in PGx implementation, review current advances and clinical applications of PGx,

summarize the obstacles that have hindered PGx implementation, and identify the critical knowledge gaps and possible studies needed to help to address them.

Introduction

Patients' responses to pharmacological treatments are highly variable, ranging from effective treatments to fatal adverse drug reactions (ADRs). Some of this variation is attributable to inherited genetic differences, and many genomic variants influencing responses to frequently used drugs have been identified (1). Pharmacogenomics (PGx) is the science of identifying and validating genomic variants influencing drug response and implementing strategies to use such genomic information to inform treatment decisions. It has become one of the leading and potentially most actionable areas of precision medicine.

Translating PGx discoveries into clinical care remains a challenge for a number of reasons, including limited evidence that implementing PGx-guided drug therapy improves patient outcomes. Several projects initiated by academic medical centers and hospital systems have approached PGx-implementation projects as quality-improvement initiatives, demonstrating the high frequency of pharmacogenetically-relevant genomic variants and the potential value of PGx-guided drug selection (2–4). Such patient-safety programs provide a useful pathway for moving PGx information into clinical practice, but the role of further research efforts to inform this translation remains poorly defined.

Research into the functional effects of PGx variants and their relationships to drug response has been conducted for decades (1), while PGx-implementation research focusing on adoption or uptake of clinical interventions by providers and/or healthcare systems is in a relatively early stage. Here, we survey the US landscape of research programs in PGx implementation, review current advances and clinical applications of PGx, summarize the obstacles that have hindered PGx implementation, and provide recommendations for moving forward. These areas were highlighted in a May 2017 symposium convened by the National Human Genome Research Institute (NHGRI) (5) that was attended by ~40 clinicians and PGx researchers.

Illustrative Examples of Resources of Value for PGx Implementation

Several resources are available to support PGx discoveries and clinical implementation, such as the Pharmacogenomics Knowledgebase (PharmGKB), its affiliated Clinical Pharmacogenetics Implementation Consortium (CPIC), and Supporting Practice through Application, Resources, and Knowledge (SPARK) toolbox of the Implementing Genomics in Practice (IGNITE) network (Table 1). PharmGKB, CPIC, and other resources are expertly curated and annotated, providing valuable information on gene-drug associations important for clinical care. The Pharmacogenomics Clinical Annotation Tool (PharmCAT), the Displaying and Integrating Genetic Information Through the EHR (DIGITizE) program, and the Clinical Decision Support KnowledgeBase (CDS-KB) provide open-source tools and guides for clinical annotation of PGx-relevant genomic variants and clinical decision support (CDS) models for use in clinical care.

The symposium participants and investigators from other known PGx implementation projects provided information on the use of these resources and other aspects of the PGx-implementation landscape (Table 2). The goal was to collect information for each major clinical PGx-implementation project via a survey. Recipients of the survey were identified as the Principal Investigators of major genomic implementation projects such as the IGNITE, Clinical Sequencing Evidence-Generating Research (CSER), electronic Medical Records and Genomic (eMERGE) consortium and sites implementing the CPIC guidelines [https://cpicpgx.org/implementation/]. In total, information on 40 projects was obtained from 36 participants, with some reporting on more than one project. The survey yielded a 49% response rate (36 of 73 invited). In 57% of the projects, PGx was implemented in both clinical and research environments; in 28%, it was implemented in clinical environments only. Respondents reported conducting projects in the following research settings: 53% reported that it was conducted in an academic institution, 22% in a non-academic setting, 14% in a hospital, and 11% in other healthcare settings. Roughly one-third of projects were implementing reactive PGx testing, in response to treatment plans, and the remainder implementing preemptive testing involving genotyping and/or DNA sequencing. CDS strategies prompting PGx testing orders or notification of PGx test results included both active (information and online ordering algorithms automatically presented to the clinician) and passive (information available to clinicians if sought and opened online) approaches for most projects. Submitting claims for third-party reimbursement for PGx testing was quite common, with 60% of projects having submitted in the past, submitting currently, or planning to do so in the future. Nearly all respondents used CPIC as a resource, followed by PharmGKB, IGNITE SPARK, and ClinVar. There was diversity in the genotyping platforms used by the projects, including Real-Time PCR Systems to characterize "Absorption, Distribution, Metabolism, and Excretion" genes (ADME; e.g., Sequenom iPLEX® ADME pharmacogenetic Panel and Illumina VeraCode® ADME Core Panel) and "Drug Metabolism Enzymes and Transporters" (DMET; Affymetrix DMET™ Plus) gene panels. The most common PGx gene-drug pair tested in the projects surveyed was *CYP2C19*-clopidogrel, followed by *SLCO1B1*-simvastatin, *CYP2C9/VKORC1*-warfarin, and *TPMT*-thiopurines. Reported obstacles included lack of a sustainable business plan; poor test reimbursement; lack of institutional support; challenges integrating with the electronic health records (EHR) ecosystem (such as EHR vendor changes by healthcare systems, lack of EHR infrastructure to support CDS alerts, and widespread use of PDF-based reporting that is often poorly suited for CDS integration); challenges in genotyping technology (including lengthy turn-around time for test results and the need to update panels as new testing information becomes available); need for education of clinical staff and patients; and lack of clinician acceptance.

Factors Affecting PGx Implementation and Illustrative Research Projects

Stakeholder Alignment and Transdisciplinary Teams

Key elements for healthcare systems to successfully adopt and sustain evidence-based PGx testing include the alignment of clinical and administrative stakeholders (e.g., senior administrative and clinical leadership, pharmacy and therapeutics committee members, laboratory directors, health information technology leaders, patients and patient advocates,

and third-party payers). The power of advocacy groups and social media to promote PGx-research initiatives is exemplified by the Metastatic Breast Cancer Project "Count Me In," in which patient self-registration has been far more effective than relying upon physician referrals (6). Alignment of common interests and concerns within and across these groups, especially aligning education and dissemination with new guidelines and reports in the popular press, is essential for adopting a given PGx initiative into routine clinical care. An example of this approach is represented by The INdiana GENomics Implementation Opportunity for the UnderServed (INGENIOUS) project, which studies the effect of prospective and reactive PGx genotyping on healthcare costs and ADR (7).

Availability of PGx genetic testing

Another factor is the availability of rapid, reliable, and low-cost PGx testing in a clinical environment. Implementation projects such as the African American Cardiovascular PGx CONsorTium (ACCOuNT) and the Genomic Prescribing System at Northwestern University (8) successfully use pre-emptive testing to provide PGx information to the clinician at the point of prescribing. Pre-emptive testing of patients likely to receive a drug with established PGx guidance obviates the need for rapid turnaround time but requires that the PGx test results and PGx guidance be readily available once the drug is actually ordered. The fragmentation of healthcare delivery in the US hinders the successful storage, portability, and actionability of such preemptive tests on a scalable basis.

Clinical tools for genomic implementation of PGx variants

Implementation tools and workflows to allow clinicians to order and act upon PGx tests are also important for PGx implementation. The six-hospital Mission Health System has developed system-wide CDS alerts to efficiently implement their test ordering. Vanderbilt University Medical Center also uses CDS linked to EHR as a quality-improvement initiative to show the impact of PGx-guided prescribing on patient care. Vanderbilt's PGx Resource for Enhanced Decisions In Care and Treatment (PREDICT) program began with a specific implementation effort of *CYP2C19*-testing prior to clopidogrel use (4) and later expanded to include several other genes and drugs. The PREDICT program highlighted the variability in implementation among providers, and noted that provider acceptance depended on their belief in clinical efficacy, familiarity with alternatives, and perceptions about the ease of implementation (9). Acceptance was maximized by presenting test results that were easy to understand and that included recommendations based on clinically validated guidelines. Appropriate alternative medication use was maximized by having PGx results available at the time of initial prescribing.

Workforce Education

An educated multidisciplinary workforce (including physicians, pharmacists, nurses, and others interacting with patients and their medications) is another important component for effective PGx implementation. Healthcare providers must clearly understand what PGx testing is available, whether the results are available preemptively (and, if not, when and how to order them), and what to do in the event of receiving an actionable result or "clinical alert." The IGNITE University of Florida (UF) Personalized Medicine Program has observed a lack of appropriate training and clinical experience with PGx in both pharmacy

and medical schools (personal communication, J. Johnson). To test the effects of active learning and personal genotyping on student knowledge, a control group of students was enrolled in a required PGx course, and another group (the intervention group) enrolled in the required PGx course as well as an elective clinical PGx course and had the option to undergo their own panel-based genotyping and to use PGx data in working through case examples. Post-course knowledge test scores from the intervention group were higher than the control group, suggesting that confidence and knowledge needs to go hand-in-hand. Their study showed that post-course knowledge test scores are higher when knowledge and practical applications are given at the same time and that in general when more instruction on a topic is given students tend to receive better test scores (unpublished data) (10).

Cost-effectiveness of PGx implementation

Demonstration of PGx cost-effectiveness would facilitate acceptance and implementation by hospital systems and payers. The eMERGE-PGx Project implemented a PGx-sequencing panel at multiple sites (11), and explored diverse approaches to designing and implementing PGx-based CDS alerts and collecting outcomes. Although no cost-effectiveness analyses were conducted in this preliminary effort, the collection of clinic/facility-level economic outcomes and expanded development of well-validated instruments to assess implementation outcomes particularly relevant to PGx should be considered in the future. In the meantime, the sites are collaborating to report descriptive metadata and define quantitative and qualitative outcomes across many domains pertinent to cost-effectiveness analyses.

In addition to prospective data collection, cost-effectiveness can be estimated using economic modeling. An example from Geisinger Health System examined the use of *IL28B* genotyping to inform the use of triple therapy for Hepatitis C viral genotypes 2 and 3 (12). Threshold analysis predicted a high likelihood of cost-effectiveness if *IL28B* genotyping results were routinely used; this was subsequently implemented clinically. More extensive economic analyses for pharmacogenomics is underway at Vanderbilt (unpublished data) (13, 14).

Clinical effectiveness of PGx implementation

Finally, it is clear that new approaches for demonstrating the clinical effectiveness of PGx implementation would be helpful. It is not feasible to generate randomized clinical trial evidence to test the benefits of PGx-guided prescribing for every gene-drug pair in every population (15). Members of the IGNITE Network utilized a pragmatic study design (16) to examine outcomes with *CYP2C19* genotype-guided antiplatelet therapy in patients undergoing percutaneous coronary intervention; this was performed while awaiting the results of an ongoing traditional randomized clinical trial with an estimated completion date of 2020 (17). Each of the 7 participating sites had implemented *CYP2C19*-variant testing in clinical practice and recommended alternative antiplatelet therapy over clopidogrel for patients with a non-functional *CYP2C19* allele indicative of reduced clopidogrel effectiveness. The team reviewed medical records for genotyped patients to identify major adverse cardiovascular events in the year following percutaneous coronary intervention. Fewer events occurred when genotype results were available early after coronary

intervention and alternative therapy was prescribed in patients with a non-functional *CYP2C19* allele (18).

Population Diversity

Inadequate characterization of PGx-relevant genomic variants across persons of diverse ancestry, while largely a gap in discovery and validation of PGx-relevant variants, also contributes to major gaps in PGx implementation. Addressing this problem is critical for ensuring that all groups benefit from PGx implementation (19). Several minority patient-engagement groups have been involved in advocating for additional minority-centered PGx initiatives. In addition, data for implementing PGx in pediatrics are modest, and extrapolating adult PGx data to children has some limitations (20). To address this disparity in pediatric PGx knowledge, Kansas City's Children's Mercy Hospital created the GOLDILOKs (Genomic and Ontogeny-Linked Dose Individualization and cLinical Optimization for Kids) Initiative (21), which includes stage of physical development in addition to genomic variation as a key determinant of drug selection and dosing. Providers focus on educating children and families about how dosing might differ; this has produced creative explanatory material (22) that are more understandable to children.

Lessons Learned

Stakeholder Alignment and Transdisciplinary Teams

Implementation research requires transdisciplinary teams that include expertise in genomics, clinical engineering, informatics, health services research, economics, and organizational science, as well as operational partners including administrators, clinicians, HIT professionals, payers, and patients. The adoption of PGx, as with many aspects of genomic medicine implementation, is often best advanced by identifying a local "clinical champion"; such an individual can help develop clinically relevant knowledge that can be widely applied beyond the individual system under study and encourage (and set an example for) other providers (23). The role of pharmacists as clinical champions deserves more study, given that several of the most successful clinical PGx programs are led by senior pharmacists and pharmacologists.

Availability of PGx genetic testing

Implementation of PGx testing is rarely cost-effective when performed in a 'one gene at a time' fashion (24, 25) because such testing only benefits the small portion of the population that both receives the particular drug and carries a variant associated with a super-, non-, or adverse response. Detecting meaningful differences in clinical outcomes with PGx testing for a single gene-drug pair is inefficient compared to multi-gene testing because the latter is relatively inexpensive and because more than 90% of the population carries high-risk alleles for multiple pharmacologically relevant genes ("pharmacogenes")(8) and many will be prescribed multiple pharmacogenetically actionable drugs in their lifetimes (26). A more genomic approach, assessing most or all known drug-gene interactions via well-designed PGx panel testing, is more likely to assess fully the impact of a broader implementation that would involve multiple drugs. Such an approach is currently being used in the European

Ubiquitous Pharmacogenetics (U-PGx) trial (27) as well as at Vanderbilt University (13, 14) and Mission Health (28) and others (8).

Clinical tools for Genomic Implementation of PGx Variants

Successful implementation also depends on integration of structured PGx test results and electronic CDS delivered through EHR ecosystems, which is complicated by the rapid evolution, incompatibility, and heterogeneity in both reporting laboratory and clinical EHRs. Competition for informatics resources can be intense when basic clinical care needs must take priority, and providing dedicated funding for PGx health information technology (HIT) support can help reduce this bottleneck. Rather than customizing "one-off" solutions for each system, more "off-the-shelf," transportable solutions [similar to the plug-in application program interfaces (APIs) available for drug-drug interactions] would provide more options for EHR integration of PGx information. Implementation would also be facilitated by establishing laboratory-to-provider and provider-to-provider interfaces to automate transfer of standardized, structured PGx test results. CPIC has led a modified-Delphi process to develop standardized terms for PGx results that is being adopted for clinical use (29). Rapid transfer of structured data would enable the development and dissemination of CDS to translate and integrate genomic information into existing clinical workflows, allowing clinicians to make PGx-informed decisions at the point of care.

Workforce Education and Patient Engagement

Detailed advice to clinicians on making PGx-informed decisions needs to include education as a key component, especially for those serving high-risk populations. The potential for inappropriate action on PGx results by clinicians is well illustrated by the mistaken prescribing of high-risk drugs as alternatives to carbamazepine in the Hong Kong experience of *HLA-B*15:02* testing (30), which resulted in fewer ADEs to carbamazepine but more ADEs to the alternatively prescribed drugs (e.g., phenytoin). System-wide training programs are needed at multiple levels and for multiple health professions; incorporation in medical/pharmacy school curricula is an important step, but by itself will take decades to permeate care, so is not a tenable approach on its own. Separate certificate programs, stand-alone courses, online courses, and webinars, where discussion and interaction around relevant PGx cases are facilitated, all have roles to play. Examples of such courses include the UF's Precision Medicine Conference (31) and the City of Hope's Intensive Course in Cancer Risk Assessment (32), both of which could be replicated and disseminated nationwide. However, while necessary, these traditional approaches to education are not sufficient to enable appropriate use of PGx information. In particular, information available at the point of care and "just in time" to support clinician decision-making is also necessary (33).

Cost-effectiveness of PGx implementation, Reimbursement and Insurance Coverage

One barrier to payer engagement and reimbursement is the lack of useful CPT (Current Procedural Terminology) codes for genetic/genomic tests. There are currently over 50,000 such tests in the Genetic Testing Registry GTR, including 45 for PGx, (34) but there are only about 200 CPT codes for these tests, (35) making it challenging for payers to know what is being ordered. Imprecision in coding not only produces a bottleneck in moving reimbursement forward, but can hinder research on the use and outcomes of specific PGx

tests. Despite several coordinated efforts to develop CPT codes for such tests, progress has been very slow. Some have argued that more generalized codes are needed, that could be applied to panels of pharmacogenetic tests (36). Improved coding may also facilitate generation of health economics data needed to support reimbursement for PGx.

PGx variant interpretation and Common Data Models/Measures

The success of the clinical use of PGx tests depends heavily on the accuracy and consistency of genomic-variant interpretation. Significant improvement in that interpretation has been demonstrated by data sharing and consensus approaches to adjudication of variants' pathogenicity (37). Sharing of multiple laboratories' interpretations in ClinVar and PharmGKB has provided transparency and permits accumulation of experience to resolve conflicting classifications that arise during community curation. To improve data quality, some payers are now requiring testing laboratories to submit their data to ClinVar as a condition for reimbursement (38). Peer-reviewed, curated, and documented assignments of function to PGx-relevant variants is part of CPIC guidelines, and will facilitate efforts of DIGITizE and other groups to standardize PGx-test results.

It would be helpful to use a common data model to facilitate data sharing, such as that developed by the Observational Medical Outcomes Partnership (OMOP) (39). Standardized outcomes, such as those being developed in IGNITE, CSER, and eMERGE, are also essential (40). This highlights the need for defining key outcomes at the outset and incorporating them in the study design. Engaging physicians, patients, and payers to develop those designs, select outcomes, conduct research, and disseminate results is critical to producing evidence that will be relevant to stakeholders. While standardization of data and outcomes is important, local factors (e.g., population, clinician workflow, and resources) must be considered if implementation is to be successful. Collection of data on dissemination and implementation from early sites of adoption using validated frameworks [e.g., Reach, Effectiveness, Adoption, Implementation and Maintenance (RE-AIM) (41)] is essential to lowering the barriers to implementation in settings with fewer resources.

Recommendations for Implementation and Research

Standards to Guide PGx Implementation

Steps to promote PGx implementation include improving PGx testing by reducing turnaround time, increasing the user-friendliness of PGx reports, standardizing PGx test reports, and sharing interpretations of PGx-relevant genomic variants across clinical laboratories for open peer review via deposition in ClinVar and PharmGkB (along with supporting observations). High standards for PGx testing should be established by the scientific community, such as establishing a minimum set of genomic variants to be tested (42) in each pharmacogene and the minimum DNA-sequencing quality metrics to be achieved. Efforts to promote standard terminology for alleles and drug response phenotypes (such as poor-, extensive- or ultra-metabolizer) (29) represent an opportunity where a consensus can be reached and uniform terms among PGx experts can be adopted.

Development of PGx guidelines by CPIC and other authoritative sources is critical for PGx implementation. Improving standardization and updating CDS programs using tools produced by CPIC and other resources such as CDS-KB, ClinGen, IGNITE, and DIGITizE would also promote implementation, and avoid each adopting site needing to interpret and implement guideline content individually into proprietary EHR systems. Rapidly evolving knowledge requires that systems are in place to facilitate updating of variant interpretations and guidelines for their use.

Steps to fill critical data gaps through research include experimenting with diverse approaches for delivery of test results, such as PGx-information cards (43) provided to the patient and scannable Quick Response (QR) Codes (27) linked to a website with drug-dosing recommendations tailored to a specific patient based on PGx-test results. Creating a national or international registry of patients who have undergone extensive PGx testing and are willing to share their PGx results and outcome information could be a low-cost and efficient means for studying rare ADEs and obtaining needed outcome data. Additional studies are needed to understand PGx-relevant variation and its clinical impact in underserved populations, such as non-European ancestry populations, children, and patients with limited access to care and financial capacity. Better methods are needed for identifying and studying outliers in drug response, as are systematic approaches to standardization of study outcomes, including patient-reported outcomes. Identifying additional genomic variants and genes influencing responses to commonly used drugs are still needed, and could capitalize on large-scale clinical trials of drug efficacy; it is recommended that such trials include collection of DNA from participants with appropriate consent for future PGx research.

Creation and testing of software applications or "plug-ins" for delivering information about gene-drug interactions and activation of CDS rules could build on models currently available for drug-drug interactions, but would need to support updating as new genomic variants are characterized. Research to enhance the role of community clinical pharmacists in PGx dissemination and implementation and to evaluate their effectiveness could shed light on this valuable and underutilized resource at the front line of patient interactions. Training and engaging this valuable community of providers in the development of CDS is essential. Engaging HIT personnel more directly in research or quality improvement would support more rapid implementation, not only of standardized terminology but also of more robust interfaces to transfer structured PGx test results and CDS rules. Ensuring such support and engagement of HIT experts will be critical to development of interoperable, potentially nationwide systems for PGx and other genomic data that could follow patients as they move across healthcare systems.

The Benefits of PGx Implementation

It is important to study whether PGx testing has direct patient-care benefits. Outcomes of interest would include decreasing common and rare ADRs, lowering the need for outpatient visits, reaching intended therapeutic effects faster or in a greater percentage of the population, and reducing the cost of care. Trial designs will be challenging, given that the

most severe ADEs and the most penetrant pharmacologically-relevant genomic variation are likely to be rare (15).

If costs of PGx testing continue to decline and reimbursement can be improved through more precise coding and evaluation of outcomes, demonstration of cost-effectiveness may become less of a barrier; however, it is important to measure other benefits, such as reduced need for outpatient visits or other monitoring. Clinicians and payers must also be educated on the falling costs of PGx tests and the efficiency of multigene panels, especially since panel-based PGx testing can cost as little as $150. Clinicians fearing liability for not acting upon PGx results as recommended by the American College of Medical Genetics and Genomics (ACMG) (44) should also be educated that comprehensive genome sequencing might reveal high-risk genomic variants for disease susceptibility or management for other conditions, and they might be liable whether they search for and report those results or not. Preemptive genotyping of patients likely to receive PGx-relevant drugs represents the most efficient method of PGx implementation and obviates the need for clinicians to initiate the testing.

In addition to physicians, multidisciplinary teams trained in PGx-based drug selection and dosing (including industry partners) can be very effective for improving and disseminating PGx experience. Partnerships among community-based practitioners, pharmacists, and genetic counselors – rather than reliance on a single health professional – will be needed for delivery of comprehensive PGx services (45), just as they are for the research to develop these services. The potential role of motivated patients in educating their clinicians should not be overlooked; providing educational resources to them will help in generating awareness that can then be transferred to clinicians by the patients themselves.

Evidence of benefits and risks of PGx testing is urgently needed, but generating such evidence through traditional randomized clinical trials could present serious ethical dilemmas for clinical investigators already convinced of the value of PGx testing. Many such researchers would have difficulty randomizing patients to receive a drug that the patient was known to be incapable of activating or at high risk of adverse effects. Some advocate instead for pragmatic clinical trials (46) or effectiveness-implementation hybrid designs trials (47). Recognizing that PGx quality-improvement projects cannot be implemented into all clinical systems at once, a phased roll-out could be considered where clinical sites are randomized as to *when* their implementation is begun, allowing sites randomized to late implementation to serve as controls for those randomized to early implementation. In addition, there may be other approaches, such as retrospective analyses and clinical simulations, that can provide platforms for generating evidence of benefits of PGx testing.

Conclusions

Implementation of PGx-guided drug selection and dosing presents many opportunities for improving drug safety, but its real-world clinical- and cost-effectiveness remains largely unproven. Such proof is needed to move PGx implementation from the vanguard of specialized, early-adopter centers to standard clinical care. The evidence base for PGx-relevant genomic variants needs to expand to address many of the challenges highlighted

here, including analytical and clinical validity as well as clinical utility. As PGx knowledge and guidelines improve, along with innovative research designs and changes to healthcare delivery systems, sophisticated CDS systems and multidisciplinary education and collaboration will be needed to move clinical implementation of PGx from the exception to the norm of state-of-the-art patient care.

Acknowledgments

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Table 1

Resources of value for PGx implementation

Resource	Description	URL
Pharmacogenomics Research Network (PGRN)	The mission of the PGRN is to catalyze and lead research in precision medicine for the discovery and translation of genomic variation influencing therapeutic and ADRs adverse drug effects.	http://www.pgrn.org/
PharmGKB	PharmGKB is a publicly available, online knowledgebase responsible for the aggregation, curation, integration, and dissemination of knowledge regarding the impact of genomic variation on drug response. The main goal of PharmGKB is to aid researchers in understanding how variation in a person's genome affects how he or she responds to a drug.	https://www.pharmgkb.org/
PharmCAT	PharmCAT is developing a software tool to extract all CPIC guideline PGx variants from a genomic dataset (represented as a VCF), interpret the variant alleles, and generate a report. The CPIC-pipeline report can then be used to make future treatment decisions. This project was created to address the lack of a freely available resource able to automate the annotation of VCF files with appropriate haplotypes or diplotypes from CPIC guidelines. The project is open-source and any code script is posted in GitHub.	https://github.com/PharmGKB/PharmCAT
Clinical Pharmacogenetics Implementation Consortium (CPIC)	CPIC provides guidelines that enable the translation of laboratory test results into actionable prescribing decisions for specific drugs. CPIC tables, created jointly with PharmGKB, allow translation of PGx test results to actionability. They are peer-reviewed and published in a leading journal with simultaneous online posting with supplemental	https://cpicpgx.org/

Resource	Description	URL
	information/data and updates. CPIC's goal is to address some of the barriers to implementation of PGx tests into clinical practice.	
Dutch Pharmacogenetics Working Group (DPWG)	The objectives of the DPWG are to develop PGx-based therapeutic (dose) recommendations and to assist drug prescribers and pharmacists by integrating the recommendations into computerized systems for drug prescription and automated medication surveillance.	https://www.pharmgkb.org/page/dpwg
Displaying and Integrating Genetic Information Through the EHR Action Collaborative" (DIGITizE AC)	DIGITizE AC is a consortium effort to develop PGx-guided CDS guidelines, enabling other collaborations to freely re-use them. They produce implementation guides to facilitate the incorporation of PGx testing into clinical medicine.	http://www.nationalacademies.org/hmd/Activities/Research/GenomicBasedResearch/Innovation-Collaboratives/EHR.aspx?page=1
Clinical Decision Support KnowledgeBase (CDS-KB)	The goal of CDS-KB is to catalog and share CDS implementation artifacts and to serve as a collection of practical experiences and resources to enable more rapid translation and implementation of genomic medicine.	https://cdskb.org/
IGNITE SPARK	The SPARK Toolbox is an online information resource library focused on the field of genomics. The IGNITE Network reviews, adds, and organizes new information resources to support genomic medicine implementation. The Network was created to enhance the use of genomic medicine by supporting the development of methods for incorporating genomic information into clinical care and exploration of the methods for effective implementation, diffusion, and sustainability in diverse clinical settings. The ultimate goal is to help clinicians incorporate genomics into their practices and researchers study the best ways to use genomics in healthcare.	https://ignite-genomics.org/spark-toolbox/

Resource	Description	URL
Genetic Test Registry (GTR)	GTR provides a central location for voluntary submission of genetic test information by providers; it is a registry that provides information on the methodology behind test results and describes them uniquely. The scope includes the test's purpose, methodology, validity, evidence of the test's usefulness, and laboratory contacts and credentials. The overarching goal of the GTR is to advance the public health and research into the genetic basis of health and disease.	https://www.ncbi.nlm.nih.gov/gtr/
ClinVar	ClinVar is an archival database of interpretations about the clinical significance of genomic variants and their relationship to phenotypes. It facilitates access to and communication about the relationships asserted between human genomic variation and observed health status, and the history of that interpretation. ClinVar processes submissions reporting variants found in patient genomes, assertions made regarding their clinical significance, information about the submitter, and other supporting data.	https://www.ncbi.nlm.nih.gov/clinvar/
MedGen	MedGen is a portal about conditions and phenotypes related to medical genetics. Its goal is to provide information on conditions with a genetic component and practice guidelines, position statements, and recommendations for many conditions. Terms from GTR, UMLS, HPO, Orphanet, ClinVar, and other sources are aggregated into concepts, each of which is assigned a unique identifier and a preferred name and symbol. It organizes information related to human medical genetics, such as attributes of conditions with a genetic contribution.	https://www.ncbi.nlm.nih.gov/medgen/

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Resource	Description	URL
Medical Genetic Summaries	Medical Genetic Summaries is a growing collection of summaries that describe the impact that specific genomic variants have on health. They are concise, structured reviews about genomic variants and drug responses and is integrated with GTR and MedGen. The summaries review genomic variants that underlie inherited conditions, affect the risk of developing a disease in the future, or influence how an individual may respond to a specific drug.	https://www.ncbi.nlm.nih.gov/books/NBK61999/

Table 2

Summary of the pre-meeting PGx implementation survey (36 responding of 73 invited).

Question (N=total)	Percent	
Type of PGx Implementation (N=40)[1]	57	Clinical and Research
	28	Clinical Only
	15	Research Only
Responding Institution (36)	53	Academia
	22	Non-academic setting
	14	Hospital
	11	Other healthcare setting
Triggers Prompting PGx Test Orders (N=40)	35	Reactive
	65	Pre-emptive
Type of Alert Prompting PGx Test Order or Notification of PGx Test Results (N=39)	51	Active and Passive
	31	Active (i.e. alert and/or specific message sent)
	18	Passive (i.e. the test order was available on demand only)
Filing for 3rd Party Reimbursement for PGx Tests (N=37)	60 40	Filing Not Filing
External Resources or Knowledgebases Used (N=36)	94	CPIC
	78	PharmGKB
	19	IGNITE Spark
	17	ClinVar
Genotyping Platforms Used (N=47)*	38	Real-Time PCR Systems
	17	DMET Panel
	13	ADME Panel
	32	Other
PGx Gene-Drug Pair Currently Tested (N=35)	91	CYP2C19-Clopidogrel
	86	SLCO1B1-Simvastatin
	83	CYP2C9/VKORC1-Warfarin
	80	TPMT-Thiopurines
	74	CYP2D6-Codeine
	71	CYPG2C19 and/or CYP2D6-Antidepressants
	60	DPYD-Fluorouracil, capecitabine
	43	UGT1A1-Irinotecan, Belinostat, Nilotinib, Pazopanib, Erlotinib, Atazanavir, Abacavir, Indacaterol
	40	IFNL3-Ribavarin, peginterferon
	34	HLAB-Abacavir
	31	HLA-Allopurinol, Carbamazepine, Phenytoin

[1]Some participants reported on more than one project.

[2]Some projects used more than one platform.