PERSPECTIVE

Global Pharmacogenomics Within Precision Medicine: Challenges and Opportunities

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This commentary focuses on challenges to the widespread adoption of pharmacogenomics, outlining issues that need to be addressed ranging from basic pharmacogenomics research through to implementation. Goals addressing each challenge are also presented, which aim to increase understanding, assessment, interpretation, accessibility, and adoption of pharmacogenomics in routine clinical practice.

Despite the established role of pharmacogenomic variation in drug efficacy and safety, prompting the creation of treatment guidelines by the Clinical Pharmacogenetics Implementation Consortium (CPIC) and Dutch Pharmacogenetics Working Group (DPWG), the application of this information into routine clinical care remains limited. In this commentary, we identify and attempt to address 10 challenges (**Table 1**, **Figure S1** (PowerPoint version)) that impede the widespread availability of genomics-guided precision medicine.

CHALLENGE 1: THERE IS NO GLOBAL NETWORK OF EXPERTS TO HELP DRIVE BASIC PHARMACOGENOMICS RESEARCH AND CLINICAL IMPLEMENTATION

The creation of a unified network comprised of researchers, clinicians, patients, and professionals from academia, government, and industry would increase the visibility and relevance of pharmacogenomics within the genomics and implementation science communities. The network could create data quality and implementation standards, which would improve adoption. Network members would have access to existing and new consortia and data sets and could attend regular meetings. To fund network activities (including the ongoing curation of pharmacogenomic information), sponsorship or partnership with industry, national guideline organizations, regulatory bodies, and/or scientific societies that foster global initiatives while ensuring arms-length involvement could be considered. While several networks exist that focus on pharmacogenomics, each has its own mission, meetings, and membership, usually within a single country (e.g., Pharmacogenomics Research Network (PGRN), UK Pharmacogenomics and Stratified Medicine Network, and Global Genomic Medicine Collaborative (G2MC)[1]).

CHALLENGE 2: MECHANISTIC UNDERSTANDING OF PHARMACOGENOMIC PHENOTYPES IS HINDERED BY THE LACK OF LARGE DATA SETS AND AVAILABLE BIOSAMPLES

Compared with data sets for complex human diseases, pharmacogenomic data sets are less widely available due to infrequent DNA sample collection and the need for more detailed phenotypic information. To assess drug response, it is essential to have phenotypic information off drug (i.e., at baseline) and on drug. Large, publicly available data sets of carefully collected DNA, RNA (including miRNA (microRNA)), endogenous metabolites, and data on drug adherence, dose, concomitant medications, and clinical outcomes would enhance both pharmacogenomics and comprehensive multi-omics research.

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Table 1 Ten identified challenges that currently limit the widespread clinical implementation of pharmacogenomics

Challenge[a]	Goals for Improvement
#1: There is no global network of experts to help drive basic pharmacogenomics research and clinical implementation	• Create a global pharmacogenomics network comprising researchers, clinicians, patient representatives, and other professionals from academia, government, and industry • The goal of the network is to advance pharmacogenomics research and implementation in both developed and resource limited countries • Provide network members access to existing and new consortia, data sets, and regular meetings • Create a list of standards for data quality and implementation to improve the adoption of clinical pharmacogenomic testing • Consider sponsorship by or partnership with industry, national guideline organizations, regulatory bodies, and/or scientific societies to provide the infrastructure needed for network activities while ensuring arms-length involvement • Increase the visibility of pharmacogenomics within human genomics circles
#2: Mechanistic understanding of pharmacogenomic phenotypes is hindered by the lack of large data sets and available bio-samples	• Increase the availability of publicly available data sets that include drug adherence, doses, and concomitant medications along with before-drug and on-drug phenotypic information from patients from multiple ethnic groups, and particularly non-Europeans • Accumulate large samples of individuals with DNA, RNA (including miRNA), endogenous metabolites, and kinetic assessments to allow for comprehensive -omics research • Assemble a pharmacogenomics sample bank, which includes appropriately banked samples such as blood and urine from individuals from multiple ethnic groups on drugs, and control individuals • Consider collection of real-world data from patients to supplement pharmacogenomics research
#3: Compared with common genetic variation, less is known regarding the impact and clinical actionability of rare genetic variation	• Conduct studies in founder populations and populations with high rates of consanguinity that are enriched for homozygous rare variation • Acquire sufficiently large samples (e.g., blood, urine, tissues) and optimize methods to examine the functional and clinical impact of rare and common variation together • Use multi-omics approaches to better assess *in vivo* functional consequences • Use machine-learning approaches to improve functional prediction for rare variants, beginning with important pharmacogenes • Use innovative experimental approaches to examine mechanistic consequences of rare variants *in vitro*
#4: Models are underutilized to understand pharmacogenomic variation	• Use knock-out, knock-in, and humanized rodent models to understand functional variation, including identifying the physiologic and pharmacological roles of transporters and enzymes • Consider humanized mouse models as a tool to improve pharmacological studies, especially when ligand specificity of the encoded protein differs by species • Investigate organ-specific and cell-specific impacts of genetic variants using animal models • Use patient-derived tumor xenograft models to elucidate pharmacogenomic variation in various cancer types
#5: Validated biomarkers are an untapped resource to improve pharmacogenomic discovery and implementation	• Recruit drug-naïve populations to study and validate specific metabolic biomarkers as surrogates for genotypes, especially in instances where genetic testing is not available • Perform genome-wide association studies of drug and metabolite levels to identify predictors of treatment response • Study endogenous metabolites to improve understanding of enzyme and transporter function • Create a set of criteria to determine which biomarkers are specific and valid for which genes • Determine the relative utility of pharmacogenomic testing vs. biomarker assessments, while taking into consideration the disease, clinical setting, treatment selection, dosing, and medication adherence • Through measured biomarkers, determine the relative contribution of genetics and environment to functional variation
#6: Special and diverse populations are understudied	• Investigate genomic variation in multiple world populations to increase the power for genetic discovery, increase clinical relevance, and ensure democratization and accessibility of pharmacogenomics • Develop tailored pharmacogenomic algorithms that consider population differences in allele frequencies and functional variation • Support local pharmacogenomic research capacity in developing countries through Western training initiatives • Ensure diverse and special populations derive benefit from conducted research and avoid invoking further inequalities • Harness machine learning to improve functional variant prediction to reduce reliance on clinical studies • Consider special populations (e.g., children, elderly) to elucidate the contribution of genetic variation and nongenetic factors (e.g., development, comorbid illness) to interindividual variability of expression and function of pharmacogenes

(Continued)

Table 1 (Continued)

Challenge[a]	Goals for Improvement
#7: Many pharmacogenomic tests are not standardized, reimbursed, or regulated, limiting their clinical utility	• Collaborate closely with the medical technology industry to drive the creation of reliable and affordable pharmacogenomic tests, with universally accepted standards • Educate test manufacturers regarding the complexity of pharmacogene variant calling due to the presence of pseudogenes, copy number variation, and structural variation • For pharmacogenes, optimize the use of whole gene sequence vs. precise calling in regions containing actionable variants • Identify scenarios where strand-specific haplotyping would be useful • Create laboratory standards for the source and quality of DNA • Administer pharmacogenomic tests preemptively or with rapid turnaround time to promote utility in hospital-based medicine • Create a set of clinical decision support guidelines and train healthcare practitioners to both administer and interpret test results • Develop infrastructure to link one-time genetic test results to longitudinally available electronic health records and ensure data protection • Increase adoption and accessibility by ensuring costs are reimbursed by ministries of health or insurance companies • Develop a uniform set of regulatory standards for testing to ensure universal acceptance

#8: Successful widespread pharmacogenomic implementation is limited by a lack of evidence of clinical utility and cost-effectiveness studies	• Create multidisciplinary teams of medical leads, scientists, laboratory technicians, and pharmacists
	• Promote learning health systems through prospective empirically based implementation trials
	• Encourage health systems to become early adopters of pharmacogenomics
	• Develop health economic models to show cost-effectiveness of implementation
	• Improve the usability of electronic health records
	  ○ Introduce standardized phenotypes and harmonized data reporting
	  ○ Include relevant follow-up data
	  ○ Consider creation and adoption of alert-based system searchable by drug or gene name which may be improved by machine-learning approaches
	  ○ Update clinical decision support as more information becomes available regarding functional consequences of variants
	  ○ Provide support, e.g., via a clinical research coordinator, to healthcare providers to reduce the time burden of entering information

#9: Education and advocacy initiatives are needed to increase the adoption of pharmacogenomics	• Develop educational materials, fact sheets, and training programs concerning the health and economic benefits of implementing genomics-guided medicine • Educate all relevant stakeholders (e.g., patients, providers, ministries of health, healthcare insurance companies, etc.) regarding the benefits of pharmacogenomic implementation, using N-of-1 to phase IV studies and postutilization evidence • Educate stakeholders regarding the difficulty of proving that a pharmacogenomic intervention has improved care: treatment has generally improved over time (historic controls may not be appropriate), withholding pharmacogenomic testing from a control group is not ethical, and it is impossible to track the prevention of poor outcomes • Highlight the unmet need by emphasizing the high prevalence of actionable pharmacogenomic variation in the context of current prescribing and drug-use patterns
#10: Additional Challenge: The threshold for clinical actionability based on cell-free DNA testing is unknown	• Investigate the promise of cell-free DNA testing, including regarding epigenetic mechanisms (i.e., DNA methylation), as a complement to germline DNA testing • Determine the threshold of mutational burden in cell-free DNA reads to consider clinical actionability • Consider tumor antigen load together with mutation load to optimize immune therapy in cancer treatment • Determine how to differentiate normal mosaicism from tumor DNA • Optimize the detection and functional prediction of minor clones

A PowerPoint slide containing this information in figure form is available in the **Supplementary Information**.
miRNA, microRNA.
[a]The relative importance of each of these 10 challenges depends on many factors including the specific drug, disease/disorder, and population; thus they are not necessarily listed in any ranked order.

Access to bio-samples could be facilitated through the creation of a pharmacogenomics sample bank. Large epidemiologic and population-based studies and the collection of real-world patient data should be used to supplement findings from clinical studies with controlled drug administration and carefully selected phenotypes.

CHALLENGE 3: COMPARED WITH COMMON GENETIC VARIATION, LESS IS KNOWN REGARDING THE IMPACT AND CLINICAL ACTIONABILITY OF RARE GENETIC VARIATION

To identify rare variants relevant to drug response and/or adverse outcomes, very large sample sizes from general populations are required. Sequence data from UK Biobank and other large national programs are examples of such data sets that are becoming increasingly available. Another approach is to study genetic founder populations and those with high rates of consanguinity to facilitate the identification of important rare variation. For instance, a GWAS

(genome-wide association study) of clopidogrel response in ~ 400 Amish individuals replicated the *CYP2C19* locus and identified nominal associations at other loci which can be validated through follow-up investigations in additional populations.[2] *In silico* studies, including the use of machine learning, together with *in vitro* characterization and *in vivo* animal models, could be used alongside clinical studies to improve the functional prediction of rare variants, beginning with important pharmacogenes.

CHALLENGE 4: MODELS ARE UNDERUTILIZED TO UNDERSTAND PHARMACOGENOMIC VARIATION

Once significant genes are identified in GWAS, a major challenge is understanding their functional role(s). A variety of approaches, including knock-out, transgenic, and humanized rodent models can be leveraged to understand functional effects of variants, including organ-specific and cell-specific impacts. Humanized rodent models may be particularly useful when interspecies variation in ligand specificity for enzymes, transporters, or other gene products exists. In oncology, patient-derived tumor xenograft models could help elucidate the impact of pharmacogenomic variation in various cancer types.

CHALLENGE 5: VALIDATED BIOMARKERS ARE AN UNTAPPED RESOURCE TO IMPROVE PHARMACOGENOMIC DISCOVERY AND IMPLEMENTATION

Biomarker studies including GWAS of active drug and/or metabolite levels can lead to the identification of novel variation associated with treatment response.[3] Moreover, GWAS of endogenous metabolite levels can facilitate our understanding of the endogenous role of enzymes and transporters and identify specific metabolic biomarkers for predicting drug–drug interactions, as has been shown for the solute carrier transporters.[4] Validated metabolic biomarkers, which capture environmental along with genetic influences, can be used as a surrogate for genomics in situations where genetic testing is unfavorable due to disease status, clinical setting, and/or requirement for therapeutic drug monitoring. A network of experts could develop criteria to determine which biomarkers are specific for which genes and determine relative contributions of genetics and environment to functional variation. The consideration of environmental influences and additional patient factors will enable the development of more comprehensive tailoring algorithms.

CHALLENGE 6: SPECIAL AND DIVERSE POPULATIONS ARE UNDERSTUDIED

To increase the power for genetic discovery, enhance clinical relevance, and ensure the democratization of pharmacogenomics, studies in ethnically diverse populations are essential. To meet the goal of implementing tailored treatment algorithms, a comprehensive understanding of genomic variation is required; initiatives such as the African Genome Variation Project (https://www.sanger.ac.uk/science/collaboration/african-genome-variation-project) aim to reduce the existing information gap. Local pharmacogenomic research capacity should be fostered in developing countries using the support of Western training initiatives. Special populations such as children, the elderly, and pregnant women should also be considered to elucidate the contribution of genetic variation and nongenetic factors (e.g., development, comorbid illness) to interindividual variability of expression and function of pharmacogenes.

CHALLENGE 7: MANY PHARMACOGENOMIC TESTS ARE NOT STANDARDIZED, REIMBURSED, OR REGULATED, LIMITING THEIR CLINICAL UTILITY

Collaboration with the medical technology industry and organizations that create minimum acceptable standards would expedite the creation of reliable and affordable pharmacogenomic tests with universally accepted criteria. Test providers will need to consider the complexity of pharmacogene variant calling (due to homologous pseudogenes and structural variation) to optimize the use of whole-gene sequencing vs. precise calling of actionable variants. Because poor quality bio-samples can produce spurious results, laboratory standards for DNA source and quality will also need to be created. Groups such as Association for Molecular Pathology and College of American Pathologists are working to set minimum standards and proficiency testing.

Pharmacogenomic testing will ideally be performed preemptively, at point-of-care or in routine labs with rapid turnaround time and clinical decision support to optimize decision making. The incorporation of point-of-care genotype testing improved anticoagulation control in patients treated with warfarin;[5] while received favorably by > 90% of patients, staff felt that the turnaround time of 45 minutes increased the length of the clinic.[5] The most efficient procedure would involve linking one-time genetic test results to longitudinally available electronic health records, prescribing systems, and laboratory records; this would require a sophisticated informatics infrastructure that ensures patient data protection. To increase adoption, testing costs will need to be reimbursed by ministries of health or insurance companies. Furthermore, uniform regulatory standards for testing should be developed to ensure universal acceptance, which may be facilitated by a global pharmacogenomics network.

CHALLENGE 8: SUCCESSFUL WIDESPREAD PHARMACOGENOMIC IMPLEMENTATION IS LIMITED BY A LACK OF EVIDENCE OF CLINICAL UTILITY AND COST-EFFECTIVENESS STUDIES

To better assess clinical utility, multidisciplinary teams of medical leads, scientists, laboratory technicians, and pharmacists should be encouraged to become early adopters of pharmacogenomics. We need to create a learning healthcare system through prospective empirically based implementation trials, where data from historical controls can be used when withholding testing is unethical; for example, prospective *DPYD* genotype-guided therapy was shown to reduce the risk of fluoropyrimidine-associated toxicity.[6] The effect of implementation on a system-wide level is currently unknown; Genomics England's 100,000 Genomes Project will pilot and iteratively evaluate the impact of implementing prioritized gene–drug pairs on the whole of England's National Health Service (NHS).[7]

There is also substantial interest in, and requirement for, testing cost-effectiveness of implementation. England's NHS is currently determining which gene–drug pairs should be prioritized. The criteria will include allele

frequency, evidence of clinical benefit, frequency of drug use, polypharmacy, cost-effectiveness, and technical considerations.[7] The usability of electronic health records must also be greatly improved, including the use of standardized phenotypes and harmonized data reports along with relevant follow-up data, and support must be provided to healthcare providers to reduce the time burden of data entry. The creation of an alert-based system searchable by drug or gene name, along with appropriate clinical decision support, is also required.

CHALLENGE 9: EDUCATION AND ADVOCACY INITIATIVES ARE NEEDED TO INCREASE THE ADOPTION OF PHARMACOGENOMICS

Tailored educational innovations for various stakeholders (e.g., patients, clinicians, ministries of health, insurance companies) are required to increase adoption. A training program implementing personalized genetic testing has already been shown to be an effective pedagogical tool among medical students at the University of Maryland School of Medicine.[8] Educational strategies that highlight the high prevalence of actionable pharmacogenomic variation in the context of current prescribing patterns[9] are important.

CHALLENGE 10: ADDITIONAL CHALLENGE: THE THRESHOLD FOR CLINICAL ACTIONABILITY BASED ON CELL-FREE DNA TESTING IS UNKNOWN

In oncology, cell-free DNA testing complements germline DNA testing and may be particularly useful for monitoring treatment resistance.[10] For clinical implementation, a consensus must be reached regarding the threshold of mutational burden in cell-free DNA reads to consider actionability. In immune therapy, assessment of tumor neoantigen load in addition to mutational burden will be required. Methods that differentiate normal mosaicism from tumor DNA are needed to ensure the validity of cell-free DNA testing, as are those that detect and predict the functionality of minor clones.

CONCLUSION

Despite established associations between pharmacogenomic variation and treatment response, the clinical implementation of this information lags. Improving basic pharmacogenomics research, including rare variant analyses and studies in diverse populations, together with initiatives focused on embedding pharmacogenomics within healthcare systems (e.g., 100,000 Genomes Project[7]), will provide invaluable insights that will help pave the way for widespread adoption.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

Figure S1. Ten identified challenges that currently limit the widespread clinical implementation of pharmacogenomics.

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CONFLICTS OF INTEREST

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