Title: Global pharmacogenomics within precision medicine: challenges and opportunities

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Conflicts of Interest:

Dr. Giacomini is a co-founder of Apricity Therapeutics, Inc. Dr. Schwab is an unpaid member of numerous scientific advisory boards. Dr. Shuldiner receives compensation as a full-time employee of Regeneron Pharmaceuticals. Dr. Relling receives investigator-initiated research funding from Servier. Dr. Tyndale has consulted for Apotex, Quinn Emanuel, and Ethimos, is an unpaid member of numerous scientific advisory boards, and is an associate editor for CPT. The other authors declare no conflicts of interest.

Funding:

This work was supported by the Dr. Antoni Esteve Foundation. We also acknowledge support from the Canada Research Chairs program (Dr. Tyndale, the Canada Research Chair in Pharmacogenomics), Canadian Institutes of Health Research (FDN-154294 to Dr. Tyndale), the Centre for Addiction and Mental Health (CAMH), and the CAMH Foundation. We also recognize funding from the NIH (CA 21765, GM 115279, HG 010135, and CA 142665 to Dr. Relling; GM 117163 and GM 115370 to Dr. Giacomini), and the UK Medical Research Council (MRC Centre for Drug Safety Science; MR/L006758/1 to Dr. Pirmohamed). Dr. Matthias Schwab was supported in part by the Robert Bosch Stiftung Stuttgart, the German Research Foundation under Germany's Excellence Strategy - EXC 2180 – 390900677, and the Horizon 2020-PHC-2015 grant U-PGx 668353.

Keywords: Pharmacogenomics, personalized medicine, implementation

Word counts:

Introduction: 49/75

Commentary: 1597/1600

Number of inserts: 1 figure, 1 table

References: 10/10

Introduction (49/75)

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.

Commentary (1597/1600)

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 **(Figure 1** and detailed in **Table 1)** 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, datasets, 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 there are several existing networks that focus on pharmacogenomics, each has its own mission, meetings, and membership, usually centered 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 datasets and available bio-samples.

Compared to datasets for complex human diseases, pharmacogenomic datasets are less widely available due to infrequent DNA sample collection and the need for more detailed phenotypic information than in complex disease. Notably, to assess drug response, it is essential to have phenotypic information off drug (i.e. at baseline) as well as on drug. Large, publicly available datasets of carefully collected DNA, RNA (including miRNA), endogenous metabolites, and data on drug adherence, dose, concomitant medications, and clinical outcomes would enhance both pharmacogenomics and comprehensive multi-omics research. 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 to 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 will be required. Sequence data from UK Biobank and other large national programs are examples of such datasets 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 pharmacogenomic variation. For instance, a GWAS of clopidogrel response in ~400 Amish individuals replicated the *CYP2C19*

locus and further 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 to understand their functional role(s) in drug response. A variety of approaches, including knock-out, transgenic, and humanized rodent models can be leveraged to understand functional effects of variants, including their organ- and cell-specific impacts. Humanized rodent models are particularly useful when inter-species 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. An expert working group (see Challenge 1) could develop criteria to determine which biomarkers are specific for which genes and determine the relative contribution 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 and accessibility of pharmacogenomics, studies in ethnically diverse world 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 non-genetic factors (e.g. development, comorbid illness) to interindividual variability of expression and function of pharmacogenes.

Challenge 7: Many pharmacogenomic tests are not standardized, which limits utility of test results.

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 versus precise calling of actionable variants. Because poor quality bio-samples can produce spurious results, laboratory standards for the source and quality of DNA will also need to be created. Groups such as AMP and CAP are working to set minimum standards and proficiency testing.

To improve the use of pharmacogenetic results, testing will need to be performed pre-emptively, at point-of-care or in routine labs with rapid turnaround time of standardized results. Healthcare practitioners will need to be further educated and clinical decision support systems will help in optimizing decision making. The incorporation of point-of-care genotype testing was shown to improve 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 (EHRs), prescribing systems, and laboratory records; this would require a sophisticated informatics infrastructure that ensures patient data protection.

Challenge 8: Successful widespread pharmacogenomic implementation is limited.

In addition to addressing Challenges 1-7, 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 substantial interest in testing cost-effectiveness of implementation. England's NHS is currently determining which gene-drug pairs should be prioritized for country-wide implementation. The criteria will include allele frequency, evidence of clinical benefit, frequency of drug use, polypharmacy, cost-effectiveness, and technical considerations (7). The usability of EHRs 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 health care 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 health care systems (e.g. 100,000 Genomes Project (7)), will provide invaluable insights that will help pave the way for widespread adoption.

Acknowledgements

These topics were examined during the ninth Dr. Antoni Esteve Foundation Discussion Group entitled “Pharmacogenomics: Advances and Challenges” held in S’Agaró, Spain in May 2019.

References

(1) Volpi, S. *et al.* Research Directions in the Clinical Implementation of Pharmacogenomics: An Overview of US Programs and Projects. *Clin Pharmacol Ther* **103**, 778-86 (2018).

(2) Bergmeijer, T.O. *et al.* Genome-wide and candidate gene approaches of clopidogrel efficacy using pharmacodynamic and clinical end points-Rationale and design of the International Clopidogrel Pharmacogenomics Consortium (ICPC). *Am Heart J* **198**, 152-9 (2018).

(3) Backman, J.D. *et al.* Genome-wide analysis of clopidogrel active metabolite levels identifies novel variants that influence antiplatelet response. *Pharmacogenet Genom* **27**, 159-63 (2017).

(4) Chu, X.Y. *et al.* Clinical Probes and Endogenous Biomarkers as Substrates for Transporter Drug-Drug Interaction Evaluation: Perspectives From the International Transporter Consortium. *Clinical Pharmacology & Therapeutics* **104**, 836-64 (2018).

(5) Jorgensen, A.L. *et al.* Implementation of genotype-guided dosing of warfarin with point-of-care genetic testing in three UK clinics: a matched cohort study. *BMC Med* **17**, 76 (2019).

(6) Henricks, L.M. *et al.* DPYD genotype-guided dose individualisation of fluoropyrimidine therapy in patients with cancer: a prospective safety analysis. *Lancet Oncol* **19**, 1459-67 (2018).

(7) Turnbull, C. *et al.* The 100 000 Genomes Project: bringing whole genome sequencing to the NHS. *Bmj-Brit Med J* **361**, (2018).

(8) Perry, C.G. *et al.* Educational innovations in clinical pharmacogenomics. *Clin Pharmacol Ther* **99**, 582-4 (2016).

(9) Bush, W.S. *et al.* Genetic Variation Among 82 Pharmacogenes: The PGRNseq Data From the eMERGE Network. *Clinical Pharmacology & Therapeutics* **100**, 160-9 (2016).

(10) Del Re, M. *et al.* The Detection of Androgen Receptor Splice Variant 7 in Plasma-derived Exosomal RNA Strongly Predicts Resistance to Hormonal Therapy in Metastatic Prostate Cancer Patients. *Eur Urol* **71**, 680-7 (2017).

Figure Legends

Figure 1. 10 identified challenges that currently limit the widespread clinical implementation of pharmacogenomics. These challenges range from not having a global unified network to help drive pharmacogenomics initiatives, to gaps within discovery research and our poor understanding of genomics within special and diverse populations. There is also a lack of available standardized tests and reports, poor integration of pharmacogenomic information within existing electronic health and laboratory records, a need to incentivize early adoption of pharmacogenomics and outcome studies in the context of a learning health care system, and few initiatives to foster pharmacogenomics education and training.

1	**Organization** • Lack of unified, global pharmacogenomics network
2-4	**Discovery** • Lack of widely available bio-samples and large datasets • Poor understanding of rare variation • Underutilization of models
5	**Biomarkers** • Untapped resource to improve discovery and implementation
6	**Special and Diverse Populations** • Poor understanding of genomic structure
7-8	**Implementation** • Lack of standardization of tests, point-of-care testing and reports • Few clinical sites routinely implement pharmacogenomic information
9	**Education and Advocacy** • Few initiatives currently exist
10	**Additional challenge** • Threshold for clinical actionability based on cell-free DNA testing is unknown

Challenge	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, datasets, 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 datasets and available bio-samples	• Increase the availability of publicly available datasets 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 to 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 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 versus 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 non-genetic factors (e.g. development, comorbid illness) to interindividual variability of expression and function of pharmacogenes
#7: Many pharmacogenomic tests are not standardized, which limits utility of test results	• 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 versus 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 pre-emptively or with rapid turnaround time to promote utility in hospital-based medicine • Create a set of clinical decision support guidelines and train health care 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
#8: Successful widespread pharmacogenomic implementation is limited	• 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 o Introduce standardized phenotypes and harmonized data reporting

	o Include relevant follow-up data o Consider creation and adoption of alert-based system searchable by drug or gene name which may be improved by machine learning approaches o Update clinical decision support as more information becomes available regarding functional consequences of variants o Provide support, e.g. via a clinical research coordinator, to health care 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 post-utilization 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