Title

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Journal

Clinical Pharmacology & Therapeutics, 110(3)

ISSN

0009-9236

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Publication Date

2021-09-01

DOI

10.1002/cpt.2340

Peer reviewed

Published in final edited form as:

Clin Pharmacol Ther. 2021 September ; 110(3): 559–562. doi:10.1002/cpt.2340.

Advancing Precision Medicine Through the New Pharmacogenomics Global Research Network

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Abstract

The new Pharmacogenomics Global Research Network (PGRN) is an independent society that builds on the National Institutes of Health (NIH)–funded Pharmacogenomics Research Network

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CONFLICT OF INTEREST

A.A.M. is the current President of the PGRN and a member of the PGRN Board of Directors. J.J.Y. is the President-Elect and L.B.R. is the Treasurer-Elect of the PGRN. K.M.G. is a past president of the PGRN and a past member of the PGRN Board of Directors. All authors are PGRN members.

DISCLAIMER

As Deputy Editor-in-Chief of Clinical Pharmacology & Therapeutics, Kathleen M. Giacomini was not involved in the review or decision process for this paper.

that was established in 2000. Leveraging the original PGRN's previous success, the new network continues to be a leader in the field of personalized medicine focusing on research, discovery, and translation of genomic variation influencing drug efficacy and adverse events, while simultaneously increasing inclusion in the field and expanding globally.

The original Pharmacogenomic Research Network (original PGRN) has been the crucible of pharmacogenomics (PGx) research since its initial NIH funding in 2000. The original PGRN brought together students and PharmD, PhD, and MD experts to improve drug safety and effectiveness through scientific discovery. PGRN research has spanned the translational spectrum: from genomic discovery studies, such as genome-wide association studies (GWASs) that reveal pharmacogenomic basis of drug response and toxicities,[1] to mechanistic pharmacogenetic projects, such as a zebrafish model that identified genomic determinants of human QT prolongation,[2] to clinical trials that estimated warfarin dose using clinical and PGx data.[3] The original PGRN supported the conduct of many GWASs including several focused on drug toxicities (e.g., platinum-induced ototoxicity) through a major collaboration with RIKEN in Japan. Summary statistics for many of these GWASs are available through a pharmacogenomic toolkit for PGRN members.[4] Additionally, the PGRN has been involved in the development of multiple PGx resources, discussed below. The success of the PGRN is measured in the impact of the science that hones clinical practice. PGx testing was once available only through research laboratories; now patients can obtain testing through direct-to-consumer companies, leading to a profound increase in PGx information available clinically. Despite these advances, new PGx discovery is not optimized, given the genetic tools available. Data sets are often not racially or ethnically diverse, rare variants are seldom studied, and implementation trials are not performed in large enough cohorts.

The original PGRN successfully transitioned from an NIH-funded endeavor to an independent scientific society in April 2020. The new Pharmacogenomics Global Research Network builds on the foundational pillars of education, research, and clinical care while expanding the network globally. Membership has already grown to include members with expertise in many therapeutic areas who are from all over the world, including over 40 countries (Figure 1a). The PGRN aims to expand the PGx research coalition, increase inclusion, and improve the care for all patients. Its mission is to "catalyze and lead research in precision medicine for the discovery and translation of genomic variation influencing therapeutic and adverse drug effects."[4] To do so, the PGRN has established a committee structure, with six committees each led by co-chairs.[4] These committees support the PGRN mission through organizing and hosting scientific meetings, webinars, publications, and tutorials. Support for early-career investigators is important to the network along with an emphasis on developing countries; both help increase the number of investigators and diversity in data sets. The Publications Committee has established a relationship with *Clinical Pharmacology and Therapeutics*, which will consider PGRN-branded manuscripts. Below we briefly describe the PGRN community and some of the PGRN's regular activities and resources.

RESEARCH IN PROGRESS SEMINARS

The Scientific Program Committee facilitates the Research-in-Progress Seminar series (RIPS), a monthly online webinar to discuss advances in PGx, many of which came from PGRN members. These lectures cover diverse topics ranging from genomic discovery studies, mechanistic research of specific pharmacogenes, statistical and computational methodology, and clinical implementation of PGx. Since the start of the new PGRN, we have organized 15 RIPS presentations given by some of the most recognized international leaders in PGx from academia, government, and industry. As one of the most attended scientific activities of the PGRN, the RIPS will continue to serve as the main platform to engage the PGx research community, with the goals of promoting high-quality science and fostering collaborations to advance the field.

EARLY CAREER RESEARCH IN PROGRESS SEMINARS

The mission of the Early Career Committee is focused on facilitating engagement and visibility of trainees and early-career scientists in the field of PGx. This committee has developed programs that will enhance the careers of these trainees and early-career scientists, including establishment of Early Career Research in Progress Seminars (EC-RIPS). These seminars feature emerging research presented by predoctoral and postdoctoral scientists as well as investigators at the starts of their careers. Similar to RIPS, the EC-RIPS are hosted virtually and afford early-career researchers valuable opportunities to promote their accomplishments and increase the visibility of their scientific work.

COMMUNITY

The PGRN community is diverse in terms of membership from various sectors, including educational institutions; diagnostics, biotechnology, and pharmaceutical industries; and clinical practitioners. Driven by the common goal of improving precision medicine, academic, industry, and regulatory researchers are invested in PGx. For example, PGx research grants supported by the NIH are awarded to many academic investigators, especially those affiliated with pharmacy and medical schools. These funds support research in PGx ranging from functional genomics to large clinical genome-wide association and next-generation sequencing studies. Numerous academic institutions now house PGx-focused clinical centers and graduate-level training programs. Pharmaceutical industry and regulatory agencies have recognized PGx as a key player in drug development and postmarketing drug optimization. By stratifying patient populations based on genetic polymorphisms or somatic cell mutations in tumors, drug developers can improve clinical trial response rates. In the postmarketing setting, identification of genetic subgroups at risk of reduced efficacy or increased toxicity can considerably improve outcomes. Of note, over 300 Food and Drug Administration (FDA)–approved medications include pharmacogenomic biomarkers on labeling found on the FDA website (https://www.fda.gov). The FDA also offers a table of pharmacogenetic associations and a cloud-based platform (precisionFDA) to promote sharing of next-generation sequencing data. These three sectors (academia, industry, and regulatory) are well represented across current PGRN membership. Several industry sponsorships that were established over the past year provide opportunity for future

research collaboration. The PGRN remains committed to promoting cross-sector cohesion toward the advancement of PGx.

EDUCATIONAL PROGRAMS

The Education Committee has a mission to develop educational programs and content focused on research and clinical implementation of PGx. The educational programs are targeted to investigators and practitioners across all career stages, and to individuals with diverse interests ranging from research to implementing pharmacogenomic testing in patient care settings. Some of the planned programs will include information for the public at large. A recent survey of PGRN members asking which resources would be most helpful resulted in the creation of educational resources, which are posted in the members section on the PGRN website. These include links to resources for investigators and practitioners, including implementation resources, PGx-based dosing applications, PGx competencies for educators, patient education, and links to educational programs such as master's degree programs in PGx. In addition, a host of research tools can be found through links that were developed by the NIH-funded PGRN. Collectively, these resources support members in the teaching, research, and practice of PGx.

RESOURCES

While the Education Committee provides research tools to PGRN members, multiple resources found on the PGRN resources section of the website are available to the general public. These are large NIH-funded resources that provide value to the PGx community and were created in partnership with the PGRN. (Figure 1b) The Pharmacogenomics Knowledge Base (PharmGKB; pharmgkb.org)[5] was originally funded along with the PGRN in 2000 and is the leading publicly available curated PGx knowledge resource. PharmGKB offers annotated summaries of PGx literature, genotype-based prescribing guidelines, and drug labels, along with pharmacokinetic and pharmacodynamic drug-centered pathways. The Clinical Pharmacogenetics Implementation Consortium (CPIC; cpicpgx.org)[6] began in 2009 as a collaboration between the PGRN and PharmGKB to address barriers to clinical implementation by creating free, peer-reviewed, evidence-based gene–drug clinical practice guidelines. CPIC guidelines include neuropsychiatric, oncologic, cardiovascular, and other disease areas. In another collaboration between PharmGKB and the PGRN, the Pharmacogenomic Clinical Annotation Tool (PharmCAT; pharmcat.org)[7] was developed to extract variants from a genetic data set, determine PGx haplotypes, and report corresponding guideline recommendations. The Pharmacogene Variation Consortium (PharmVar; pharmvar.org)[8] catalogs allelic variation of pharmacogenes and provides a standardized nomenclature critical for facilitating the interpretation of pharmacogenetic test results to guide precision medicine. These resources are relevant to basic research, translation, and implementation, and are beneficial to routine users as well as new learners interested in PGx.

GLOBAL OUTREACH

Global human genetic diversity, including variation in clinically important pharmacogenes, has been shown to contribute to differential pharmacotherapeutic effects.[9,10] The full characterization of this worldwide diversity and its association with drug response phenotypes is important to all populations. In light of this need, the PGRN has expanded its membership globally and established affiliations with several Europe-based consortia (including the UK Pharmacogenetics and Stratified Medicine Network, Dutch Pharmacogenetics Working Group, and Ubiquitous Pharmacogenomics). These efforts have undoubtedly stimulated PGx research and education worldwide.

However, there remains a dearth of scientists from developing countries conducting PGx research, which contributes to the lack of representation from these geographic regions in published PGx studies. To tackle this issue, the PGRN has enriched the seminars with a diversity of speakers and established a Developing Countries & Global Pharmacogenomics Committee. Future endeavors may include collaboration with research consortia of developing countries such as the NIH-sponsored Human Heredity and Health in Africa (H3Africa) initiative.[11] Altogether, the PGRN is devoted to ensuring that all populations benefit from the advances in health that PGx research promises to offer.

CONCLUSIONS AND FUTURE

Though in its first years, the new PGRN as an independent society continues to develop since its inception in 2020. It offers a large portfolio of resources from webinars to educational tutorials and tools to support early-career investigators interested in the research and practice of PGx. For the developing world, the PGRN strives to support educational and research efforts and to build a community of scientists, well equipped for the research, education, and practice of PGx. Increased diversity of investigators and data sets paired with research collaboration available through the PGRN will improve drug effectiveness and safety.

ACKNOWLEDGMENTS

We sincerely appreciate the valuable input and feedback from Anu Ramamoorthy.

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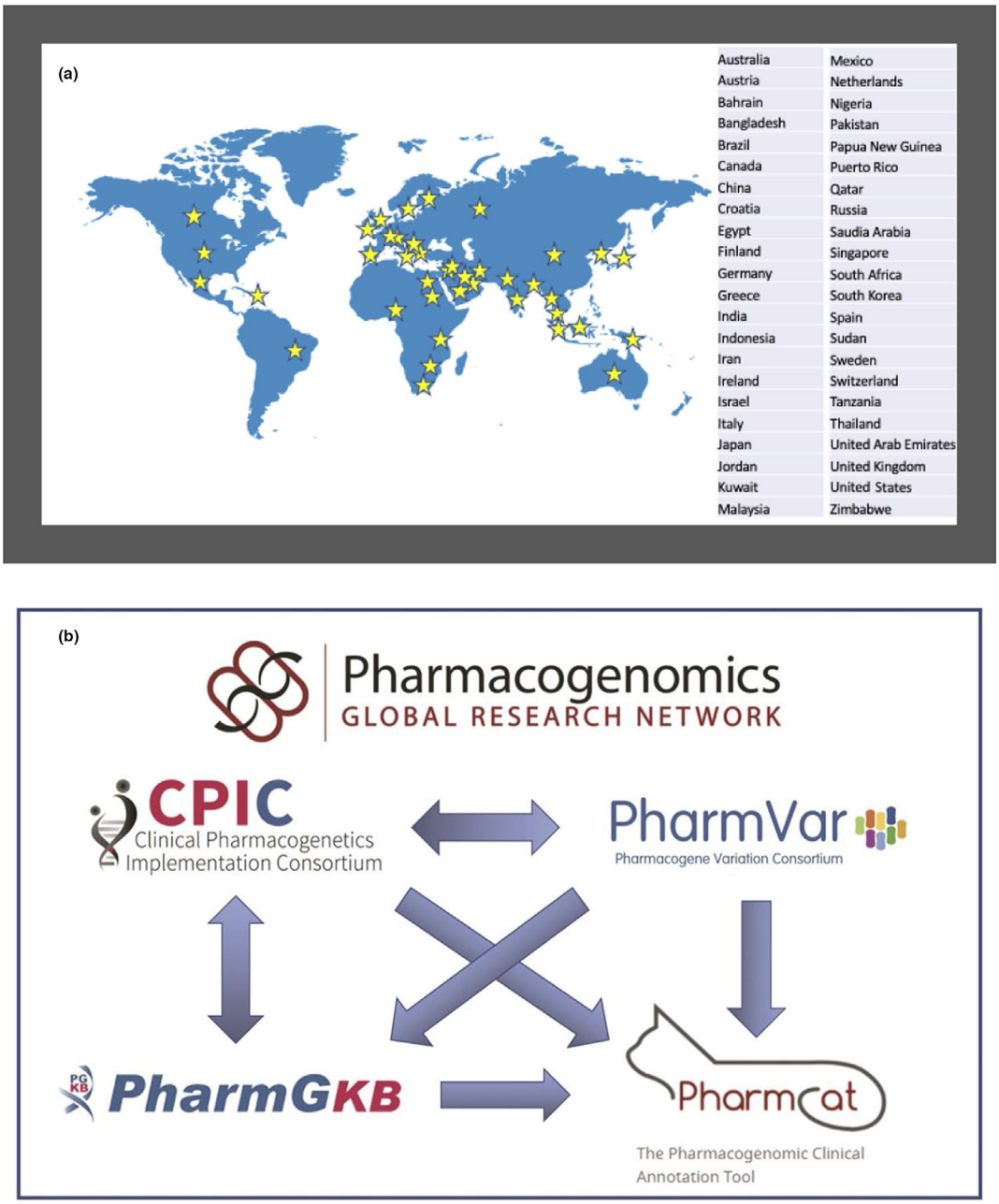

Figure 1.

The PGRN provides multiple resources to its global community (**a**) Global map showing locations of PGRN members along with a list of specific countries in which members are located. PGRN, Pharmacogenomics Global Research Network. (**b**) PGx resources in the PGRN community. These resources are somewhat interdependent, and pharmacogenomic information flows across them consistently and transparently. PGRN, Pharmacogenomics Global Research Network; PGx, pharmacogenomics; PharmGKB, Pharmacogenomics Knowledge Base.