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New Pharmacogenomics Research Network:

An Open Community Catalyzing Research and Translation in Precision Medicine

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Abstract

The goal of pharmacogenomics research is to discover genetic polymorphisms that underlie variation in drug response. Increasingly, pharmacogenomics research involves large numbers of patients and the application of new technologies and methodologies to enable discovery. The Pharmacogenomics Research Network (PGRN) has become a community-driven network of investigators spanning scientific and clinical disciplines. Here we highlight the activities and types of resources that enable PGRN members to enhance and drive basic and translational research in pharmacogenomics.

ORGANIZATION

The mission of the new PGRN is to catalyze and lead research in precision medicine for the discovery and translation of genomic variation influencing therapeutic and adverse drug effects.

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The Pharmacogenomics Research Network (PGRN), which is coordinated by the PGRN-Hub (see pgrn.org), has adopted a new approach to sponsor activities and develop shared resources to enhance research in pharmacogenomics. The PGRN is community-driven and is open to all scientists, where participating researchers' needs drive its activities.

The PGRN includes major multidisciplinary centers, which each conduct independent research programs; enabling resources, which provide tools and information for the pharmacogenomics community; and a coordination site for leadership, the PGRN-Hub, which sponsors meetings, a website, and other strategic activities (Figure 1a). The PGRN now includes over 300 members worldwide, with scientific interests distributed broadly in pharmacogenomics (Figure 1b). The PGRN members have access to the rich information and valuable collaborative resources provided by the PGRN to enhance their research programs.

PGRN-HUB

The PGRN-Hub serves as the coordinating body of the network, with the aim of catalyzing communications and collaborations among pharmacogenomics researchers worldwide. The PGRN-Hub engages in various activities, including but not limited to: (1) sponsorship and organization of scientific webinars and meetings; (2) maintenance of a website that disseminates information about the network and pharmacogenomics research; and (3) oversight and management of enabling research resources, made available to PGRN members. The Hub also maintains an active social media presence.

The PGRN-Hub, together with members of the PGRN, facilitates the organization of large scientific conferences, thus far co-located with the annual meeting of the American Society for Clinical Pharmacology and Therapeutics (ASCPT) and the American Society for Human Genetics (ASHG). Among the recent meetings are the PGRN-ASHG Annual Symposium in 2016 and the Clinical Pharmacogenetics Implementation Consortium (CPIC) meeting in 2017, held as pre-conferences to the annual meetings of the ASHG and ASCPT, respectively. Future meetings with ASHG are being planned.

The PGRN-Hub established and maintains pgrn.org to unify, organize, and display PGRN resources and activities (Figure 1a). The website was developed and iteratively evolved to have a modern look, communicative scientific illustrations, and has an easy to navigate interface. The PGRN-Hub aims to create an engaging web experience that focuses on recruiting a diverse new membership, enhancing collaborations, and providing outreach to the broader scientific, medical and public communities (Figure 1a). Pages on pgrn.org contain descriptions of pharmacogenomics projects and resources, publications, event calendars, meeting registration tools and archives.

The PGRN-Hub arranges Research in Progress Seminars (RIPS) featuring scientific presentations by members, which are held each month via video conferencing mechanisms (Figure 1a). A PGx Tools page provides a categorized list of links to helpful resources and databases (Figure 1a). The Hub is currently offering to build web pages for any PGRN members with infographics that efficiently describe the member's project (http://

www.pgrn.org/apply-for-a-webpage.html). Members also gain access to a searchable Member Directory, and can have their publications added to the automatically updated publications page (http://www.pgrn.org/all-pgrn-publications.html).

PGRN RESEARCH CENTERS

Center for Precision Medicine in Leukemia, St. Jude Children's Research Hospital, Tennessee and University of California, San Francisco, California

The aims of the Center for Precision Medicine in Leukemia (CPML) are to elucidate the inherited and somatically acquired genomic variation that account for interindividual differences in effectiveness of, sensitivity to, and adverse effects from the antileukemic agents used to treat acute lymphoblastic leukemia (ALL). Because outcomes are generally worse in adults than in children with ALL, the CPML is studying the role of genetics as well as non-genetic covariates in adults and children enrolled on front-line clinical trials for ALL. The ultimate goal is to implement precision medicine approaches to optimize the chance for cures while minimizing adverse effects [1].

Pharmacogenomics Of Statin Therapy Center, Children's Hospital Oakland Research Institute, California and University of California, Los Angeles, California

Statins are the most widely prescribed class of drugs to prevent coronary heart disease and stroke. There is however, considerable interindividual variation in efficacy of statins for reducing disease risk, as well as in susceptibility to the most common adverse statin effects, myopathy and type 2 diabetes. The goal of Pharmacogenomics of Statin Therapy (POST) is to apply complementary investigative approaches and multidisciplinary expertise for the discovery and validation of genetic and metabolic factors responsible for this variability. This information has the potential for optimizing use of statins in clinical practice and for identifying new pathways that underlie the diverse biologic actions of this drug class.

Improving Prediction of Drug Action, Vanderbilt University, Tennessee

The three projects in the Improving Prediction of Drug Action (IPoDA) program at Vanderbilt aim to reduce the burden of severe adverse drug reactions (ADRs) by improving prediction in an individual subject, repurposing available drugs, and providing new tools to the drug development process to reduce risk. Two projects, studying the QT interval and HLA-related skin reactions, deploy novel cellular assays in subjects with and without ADRs to develop predictors of patients at risk. The third project uses phenome-wide scanning in electronic health records to refine prediction of long QT-related, HLA-related, and other ADRs and to repurpose drugs.

PGRN RESOURCES

Below we describe the two categories of resources that PGRN supports to enable pharmacogenomics research. The first category includes independent resources that generate information and share knowledge freely to enable research and translation in pharmacogenomics. The second category includes collaborative resources available only to PGRN members to support research in pharmacogenomics; collaborative resources involve

an application and a peer-review process, which are supported by the PGRN-Hub. Collaborative resources necessarily involve an agreement between the PGRN members and the group providing the resources.

Resources that Generate Pharmacogenomics Information and Knowledge

Clinical Pharmacogenetics Implementation Consortium—The CPIC began in 2009 as a shared project between the Pharmacogenomics Knowledgebase (PharmGKB) and the PGRN. CPIC's goal is to facilitate the clinical implementation of pharmacogenetic tests [2]. One of its main activities is to create, curate, and post and update peer-reviewed gene/drug clinical practice guidelines that facilitate translation of genetic test results into prescribing actions (Table 1). A key principle is that CPIC guidelines focus on how to use available genetic test results, not on whether to order genetic tests, with the assumption that genomic testing is becoming widespread. Standardized terms and formats are being developed with others in the clinical community to facilitate uptake into electronic health care records [3].

PharmGKB—The PharmGKB (pharmgkb.org), established in 2000, is the online knowledge resource of human genetic variations that impact drug response phenotypes. The PharmGKB offers information as variant annotations (research-level annotations of individual publications describing the relationship between genetic variants and drugs; these are created on a paper-by-paper basis), drug-centered pathways, very important pharmacogene summaries, clinical annotations (genotype-based pharmacogenomic relationships summarizing all variant annotations regarding the same genetic variant-drug association), pharmacogenomics-based drug-dosing guidelines, and drug labels with pharmacogenomic information [4].

Functionalization of Variants in Clinically Actionable Pharmacogenes—The Functionalization of Variants in Clinically Actionable Pharmacogenes (F-CAP) aims to provide a series of fully annotated datasets describing the functional consequences of most single mutations in each gene, facilitating the interpretation of variants observed in the clinic. Genetic variation in pharmacogenes is extensive with small number of variants unambiguously linked to alterations in drug response. The F-CAP is addressing this problem by leveraging new technology to test the function and stability of nearly all possible substitutions at all positions in some of the most clinically important pharmacogenes, beginning with CYP2C9, CYP2C19, CYP2D6, TPMT and VKORC1. The in vitro findings are disseminated to the pharmacogenomics community in partnership with the CPIC and PharmGKB.

Collaborative resources available to PGRN members by application

Resources for PGRN members are coordinated by the PGRN-Hub. Major collaborative research resources, which are coordinated by the PGRN-Hub, involve collaborations with RIKEN Integrative Medical Science (IMS), BioBank Japan, and Kaiser Permanente Northern California (KPNC). The PGRN-RIKEN Global Alliance (PGRN-RIKEN) collaboration, which was launched in 2008, represents a large international genomewide association study (GWAS) resource. Over 40 pharmacogenomics GWAS projects are

supported by this mechanism. The PGRN-Hub organizes two PGRN-RIKEN meetings each year to enable submission and review of new proposals for pharmacogenomics GWAS and sequencing [5]. Once accepted, the PGRN-RIKEN collaborative projects provide genomewide genotyping or targeted sequencing at RIKEN (http://www.pgrn.org/pgrn-riken.html). Resources provided by KPNC (http://www.pgrn.org/rpgeh.html) and BioBank Japan (http://www.pgrn.org/biobank-japan.html) enable multi-disciplinary research in pharmacogenomics with a focus on multiple ethnic groups. For the KPNC resource, the PGRN member may propose a pilot pharmacogenomics project based on the Research Program in Genes and Environment on Health (RPGEH) resource, which includes 100,000 patients at KPNC with genomewide genotyping and phenotypes from the electronic medical records. This resource is particularly useful for investigators seeking preliminary data or information to enable National Institutes of Health (NIH) research proposals. Similar processes are available for the BioBank Japan, which includes GWAS and phenotype data [6].

In addition to the resources described above, the Pharmacogenomics induced pluripotent stem cell (iPSC) Library and Services (PiLS) provides PGRN members with the ability to access and contribute towards an induced pluripotent stem cell (iPSC) library to facilitate pharmacogenomics research. This resource, which is under construction, will encompass a rationally sized iPSC library with an integrated single-nucleotide polymorphism (SNP) database, providing practical and accessible methods for the broader PGRN community to rapidly and accurately study the potential impact of SNPs on drug response. Different types of services are offered depending upon the experience of the investigators in working with iPSCs. The services include providing iPSC clones with SNP database information, and facilitating efficient gene editing/differentiation protocols. Investigators wishing to use this resource can find information at http://www.pgrn.org/pgrn-pils-resource.html.

PGRN GOING FORWARD

We invite all scientists interested in participating to join the PGRN at http://www.pgrn.org/join.html. In addition to establishing affiliations with other pharmacogenomics consortia such as Ubiquitous Pharmacogenomics (U-PGx), the UK Pharmacogenetics and Stratified Medicine Network, and the PGRN-RIKEN, the PGRN is seeking to grow its membership of researchers interested in collaborative, multi-disciplinary research in pharmacogenomics on a global scale. The new PGRN offers opportunities, enabling resources, scientific meetings, and a rich community of scientists to enable new discoveries in pharmacogenomics.

Acknowledgments

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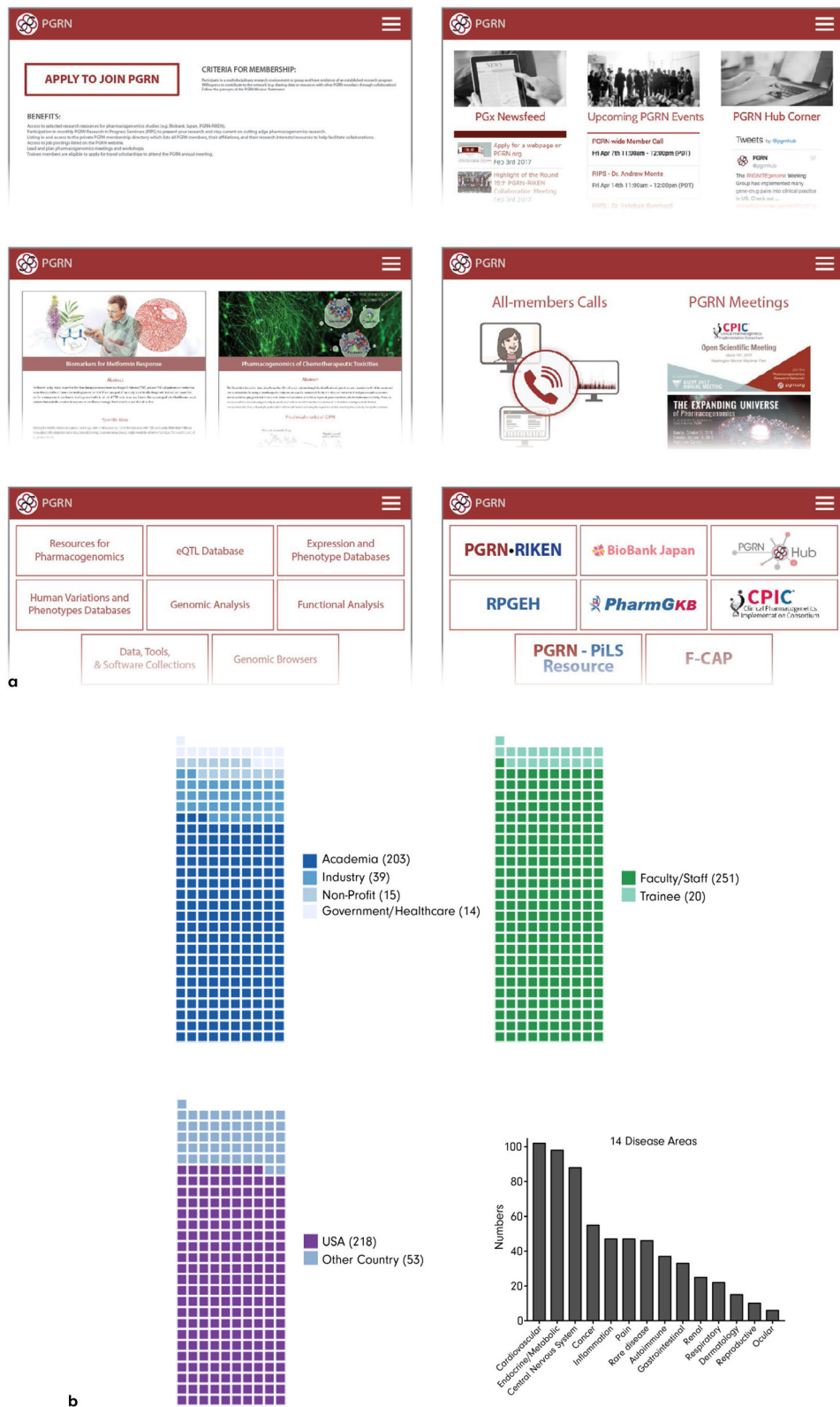
Figure 1.

The mission of Pharmacogenomics Research Network (PGRN) is to catalyze and lead research in precision medicine for the discovery and translation of genomic variation influencing therapeutic and adverse drug effects. (**a**) The main features in pgrn.org includes where members can find important information related to pharmacogenomics research opportunities. (**b**) About our current PGRN Members. To date, the new PGRN includes 271 members (top left panel). The breakdown of the membership shows that 93% of members are faculty at universities or staff in other sectors, and 7% are trainees (top right panel). Though most members are from the United States, 20% are from countries outside of the United States (bottom left panel). Currently, there are 14 main disease areas that are focused by the PGRN members (bottom right panel).

Table 1

The Clinical Pharmacogenetics Implementation Consortium (CPIC) creates, curates, posts and updates peer-reviewed gene/drug clinical practice guidelines to facilitate translation of genetic test results into prescribing actions.

Genes	Drugs	Link to guidelines
HLA-B	Abacavir	https://cpicpgx.org/guidelines/guideline-for-abacavir-and-hla-b/
HLA-B	Allopurinol	https://cpicpgx.org/guidelines/guideline-for-allopurinol-and-hla-b/
CYP2C19 CYP2D6	Amitriptyline	https://cpicpgx.org/guidelines/guideline-for-tricyclic-antidepressants-and-cyp2d6-and-cyp2c19/
UGT1A1	Atazanavir	https://cpicpgx.org/guidelines/guideline-for-atazanavir-and-ugt1a1/
TPMT	Azathioprine	https://cpicpgx.org/guidelines/guideline-for-thiopurines-and-tpmt/
DPYD	Capecitabine	https://cpicpgx.org/guidelines/guideline-for-fluoropyrimidines-and-dpyd/
HLA-B	Carbamazepine	https://cpicpgx.org/guidelines/guideline-for-carbamazepine-and-hla-b/
CYP2C19	Citalopram, Escitalopram	https://cpicpgx.org/guidelines/guideline-for-selective-serotonin-reuptake-inhibitors-and-cyp2d6-and-cyp2c19/
CYP2C19 CYP2D6	Clomipramine	http://cpicpgx.org/guidelines/guideline-for-tricyclic-antidepressants-and-cyp2d6-and-cyp2c19/
CYP2C19	Clopidogrel	https://cpicpgx.org/guidelines/guideline-for-clopidogrel-and-cyp2c19/
CYP2D6	Codeine	https://cpicpgx.org/guidelines/guideline-for-codeine-and-cyp2d6/
CYP2D6	Desipramine	http://cpicpgx.org/guidelines/guideline-for-tricyclic-antidepressants-and-cyp2d6-and-cyp2c19/
CYP2C19 CYP2D6	Doxepin	https://cpicpgx.org/guidelines/guideline-for-selective-serotonin-reuptake-inhibitors-and-cyp2d6-and-cyp2c19/
DPYD	Fluorouracil	https://cpicpgx.org/guidelines/guideline-for-fluoropyrimidines-and-dpyd/
CYP2D6	Fluvoxamine	https://cpicpgx.org/guidelines/guideline-for-selective-serotonin-reuptake-inhibitors-and-cyp2d6-and-cyp2c19/
CYP2C19 CYP2D6	Imipramine	http://cpicpgx.org/guidelines/guideline-for-tricyclic-antidepressants-and-cyp2d6-and-cyp2c19/
CFTR	Ivacaftor	https://cpicpgx.org/guidelines/guideline-for-ivacaftor-and-cftr/
TPMT	Mercaptopurine	https://cpicpgx.org/guidelines/guideline-for-thiopurines-and-tpmt/
CYP2D6	Nortriptyline	https://cpicpgx.org/guidelines/guideline-for-tricyclic-antidepressants-and-cyp2d6-and-cyp2c19/
CYP2D6	Ondansetron	https://cpicpgx.org/guidelines/guideline-for-ondansetron-and-tropisetron-and-cyp2d6-genotype/
CYP2D6	Paroxetine	https://cpicpgx.org/guidelines/guideline-for-selective-serotonin-reuptake-inhibitors-and-cyp2d6-and-cyp2c19/
IFNL3	Peginterferon alfa- 2a, Peginterferon alfa-2b, Ribavirin	https://cpicpgx.org/guidelines/guideline-for-peg-interferon-alpha-based-regimens-and-ifnl3/
CYP2C9 HLA-B	Phenytoin	https://cpicpgx.org/guidelines/guideline-for-phenytoin-and-cyp2c9-and-hla-b/
G6PD	Rasburicase	https://cpicpgx.org/guidelines/guideline-for-rasburicase-and-g6pd/
CYP2C19	Sertraline	https://cpicpgx.org/guidelines/guideline-for-selective-serotonin-reuptake-inhibitors-and-cyp2d6-and-cyp2c19/
SLCO1B1	Simvastatin	https://cpicpgx.org/guidelines/guideline-for-simvastatin-and-slco1b1/
CYP3A5	Tacrolimus	https://cpicpgx.org/guidelines/guideline-for-tacrolimus-and-cyp3a5/
DPYD	Tegafur	https://cpicpgx.org/guidelines/guideline-for-fluoropyrimidines-and-dpyd/
TPMT	Thioguanine	https://cpicpgx.org/guidelines/guideline-for-thiopurines-and-tpmt/

Genes	Drugs	Link to guidelines
CYP2C19	Trimipramine	http://cpicpgx.org/guidelines/guideline-for-tricyclic-antidepressants-and-cyp2d6-and-cyp2c19/
CYP2D6		
CYP2D6	Tropisetron	https://cpicpgx.org/guidelines/guideline-for-ondansetron-and-tropisetron-and-cyp2d6-genotype/
CYP2C19	Voriconazole	https://cpicpgx.org/guideline-for-voriconazole-and-cyp2c19/
CYP2C9	Warfarin	https://cpicpgx.org/guidelines/guideline-for-warfarin-and-cyp2c9-and-vkorc1/
CYP4F2		
VKORC1		

This table includes 33 guidelines with at least one moderate or strong action recommended. These entries are obtained from the CPIC webpage, https://cpicpgx.org/guidelines/