Published in final edited form as:

Hum Genet. 2015 May ; 134(5): 459–465. doi:10.1007/s00439-014-1484-7.

Progress Towards the Integration of Pharmacogenomics in Practice

Sean D. Mooney¹

¹Buck Institute for Research on Aging, 8001 Redwood Blvd, Novato, CA 94945

Abstract

Understanding the role genes and genetic variants play in clinical treatment response continues to be an active area of research with the common goal of common clinical use. This goal has developed into today's industry of pharmacogenomics, where new drug-gene relationships are discovered and further characterized, published and then curated into national and international resources for use by researchers and clinicians. These efforts have given us insight into what a pharmacogenomic variant is, and how it differs from human disease variants and common polymorphisms. While publications continue to reveal pharmacogenomic relationships between genes and specific classes of drugs, many challenges remain toward the goal of widespread use clinically. First, the clinical guidelines for pharmacogenomic testing are still in their infancy. Second, sequencing technologies are changing rapidly making it somewhat unclear what genetic data will be available to the clinician at the time of care. Finally, what and when to return data to a patient is an area under constant debate. New innovations such as PheWAS approaches and whole genome sequencing studies are enabling a tsunami of new findings. In this review, pharmacogenomic variants, pharmacogenomic resources, interpretation clinical guidelines and challenges, such as WGS approaches, and the impact of pharmacogenomics on drug development and regulatory approval are reviewed.

Introduction

Pharmacogenetics and pharmacogenomics (PGx) are terms used to describe the relationship between drug responses and genetic variants. Many studies have now identified associated genes and/or drugs that are relevant to our understanding of PGx traits and integrating them into common clinical use remains an active challenge. Generally, PGx studies focus on both pharmacodynamics (PD) and pharmacokinetic (PK) effects. PD PGx effects are differences in patient response based upon genetic variants in drug target pathways or the drug targets themselves. Examples include the cancer drug irinotecan and the topoisomerase I gene (Hoskins, Marcuello et al. 2008) or drugs targeting the EGFR receptor. PK PGx effects are differences in patient response based upon genetic variants in pathways involved in metabolism or drug processing. For example, drug metabolic enzymes such as thiopurine methyltransferase (TPMT) or the cytochrome p450s are associated with PK effects. Drug transporters such as the ATP-binding cassette (ABC) transporters are also well known for their PK PGx effects (Ingelman-Sundberg 2005, Booth, Ansari et al. 2011).

Pharmacogenomics has a long rich history dating as far back as thousands of years, depending on the strictness of your definition (Nebert 1999). The past three or four decades

has seen research activity accelerate dramatically (Phillips, Veenstra et al. 2001, Evans and McLeod 2003, Eichelbaum, Ingelman-Sundberg et al. 2006, Eichelbaum 2013). Discovery of variants has proceeded through several paths, but many discovery studies have adopted one of three approaches: a candidate gene approach where a relatively small number of genes are tested (Wang and Weinshilboum 2008), a genome wide association approach where large numbers of markers are interrogated and tested (Crowley, Sullivan et al. 2009, Daly 2010, Motsinger-Reif, Jorgenson et al. 2013), and a hybrid approach where entire genome or exome sequences are interrogated for novel variants that may influence PGx (Price, Carson et al. 2012). More recently direct approaches employing medical records have been used as well (Neuraz, Chouchana et al. 2013).

Different countries have constructed their own research infrastructure for discovering and implementing PGx findings. In the US, the Pharmacogenomics Research Network (PGRN) has been active for more than a decade (Giacomini, Brett et al. 2007). Similarly, in Canada, the Canadian Pharmacogenomics Network for Drug Safety is identifying novel markers for adverse drug events (Ross, Visscher et al. 2010). There are also specific evolving drug or gene research communities, sometimes coordinating large studies to increase power to detect effects, such as the International Warfarin Consortium (Owen, Altman et al. 2008, Johnson, Gong et al. 2011). The Royal Dutch Association for the Advancement of Pharmacy has developed a Pharmacogenetics Working Group which has made recommendations on more than 53 drugs (Swen, Nijenhuis et al. 2011). Several US institutions have developed large efforts to provide pharmacogenomics clinical testing include the Indiana Institute for Personalized Medicine, the Personalized Medicine Program of the University of Florida Clinical and Translational Sciences Institute, and the Scripps Genomic Health Initiative, among others.

PGx effects are often described from either a drug or a genotype centric point of view. For example, the drug centric view of warfarin (Coumadin) has clinical dosing guidelines available for genotypes in the VKORC1 gene and the CYP2C9 gene (Johnson, Gong et al. 2011). Conversely, CYP2C19 genotypes influence the dosing of several drugs including amitriptyline, clomipramine, doxepin, imipramine, and trimipramine (and others without official dosing guidelines) (Li-Wan-Po, Girard et al. 2010). Clinical interpretation and dosing guidelines focus on the drug centric view, that is, how physicians will generally face PGx data in the clinic (Scott 2013).

How sequencing technologies evolve and get integrated into a clinical setting are playing an important role in the development of clinical tests for PGx. As described succinctly by Relling and Klein (Relling and Klein 2011), incorporating patient level pharmacogene data preemptively would increase the ease with which a physician could check PGx relationships with treatment options. Indeed, to address this challenge, Vanderbilt University Medical Center and St. Jude Children's Research Hospital have begun programs to genotype prospectively in patients under certain criteria (Relling and Klein 2011, Pulley, Denny et al. 2012). As whole genome and whole exome sequencing approaches begin to take root in clinical care, understanding the genetic effects on a prescription and treatment will become more readily available to the clinician. While initial results were promising (Ashley, Butte et al. 2010), much work, however, needs to be done to translate a genome to clinical utility as

many variants of clinical interest are not well covered in the sequence, particularly insertions and deletion variants (Dewey, Grove et al. 2014).

Approaches to discovering pharmacogenomic relationships

Like much of modern human genetics study design, PGx has had an explosion of genome wide association studies (GWAS) over the past decade, and now there is much interest in discoverable PGx effects from whole exome sequencing (WES) or whole genome sequencing (WGS) studies (Motsinger-Reif, Jorgenson et al. 2013). PGx variants do not necessarily occur within coding regions, or even within the genes themselves. While many amino acid substitutions are known to cause PGx effects, variants that affect transcript splicing, miRNA binding or regulation of transcription are also known. Further complicating our understanding of functional PGx variants are marker variants discovered through population based association studies that may not be causative, but perhaps are statistically associated with the causative marker or markers in the population it was discovered in (linkage disequilibrium) (Ardlie, Kruglyak et al. 2002). Some variants can be quite befuddling to the geneticist, such as the complicated landscape of CYP2D6 variants which are diverse, of variable functionality and highly polymorphic including whole gene duplications (Ingelman-Sundberg 2005). This emphasizes the need for detailed clinical guidelines that will evolve as new associations and adverse event risks are discovered.

Candidate gene approaches have been used for many years to discover PGx effects. Many genes in PGx, particularly PK pathways, are promiscuous for affecting different drugs or drug classes. CYP2D6, for example, has been associated with more than 50 drug substrates, and, since it is highly polymorphic, has many important PGx associations ((Ingelman-Sundberg 2005) and <http://en.wikipedia.org/wiki/CYP2D6>). Due to this promiscuity, genes such as the cytochromes, the ABC transporters, or other metabolic enzymes are commonly used as targets in studies where specific genotypes or sequencing is performed to confirm existing or to discover new associations with treatment outcomes, respectively. Advances in high throughput sequencing have led to the development of PGRNseq, a platform for sequencing VIP pharmacogenomic genes (Gordon, Smith et al. 2012).

More recently GWAS has become highly relevant to PGx research and many reviews have been written on GWAS approaches in pharmacogenomics (Daly 2010, Daly 2012, Ritchie 2012). In order to enable researchers to have access to patient level data for reanalysis and meta-analysis, several resources are available containing GWAS (and candidate gene) studies (see below). Now custom pharmacogenomic SNP assay chips are available for testing specific variants important for PGx (Johnson, Burkley et al. 2012).

Today PGx relationships can be discovered from the medical record directly if the patients are genotyped and matched with the record using the Phenome Wide Association Study (PheWAS). This is a recent innovative approach that shows much promise to discovering PGx variants and has been employed in several studies (Denny, Ritchie et al. 2010, Denny, Bastarache et al. 2013). A PheWAS study takes an approach that is reminiscent of model organism in silico association studies where strains of rodents or invertebrate models of known genotype are phenotyped and associated (Guo, Lu et al. 2007). One of the early

studies employing this approach re-identified the VKORC1 gene as associated with Warfarin dose in strains of mice where genotype was known and the strains individual dose was determined (Guo, Weller et al. 2006). In the PheWAS approach, electronic health record (EHR) data can be used to associate particular diagnoses, lab tests, or other phenotypic data with a population matched to genetics. As a proof of principle, PheWAS studies have been used by the eMERGE consortium to re-identify several GWAS phenotypes (McCarty, Chisholm et al. 2011).

Recently, the PheWAS approach was applied to TPMT enzyme activity, ICD-10 and biological test results to identify phenotypes associated with TPMT activity levels (Neuraz, Chouchana et al. 2013). A total of 442 patients were identified from an electronic medical record that had a TPMTa test performed, an ICD-10 code and a biological test result, along with evidence of thiopurine treatment. Many ICD codes were associated, including anemia which has been previously associated to thiopurines (Gisbert and Gomollon 2008).

Computer models of PGx variants

Many groups have developed computational approaches to predict and discover potential PGx genes or variants using a variety of datasets (Garten, Tatonetti et al. 2010). Concurrently, many tools have been constructed to predict missense (amino acid substitutions) likely to be disease causing such as PolyPhen-2 (Adzhubei, Jordan et al. 2013) and MutPred (Li, Krishnan et al. 2009). Fewer tools have been developed to predict regulatory variants (Zhao, Clark et al. 2011, Ritchie, Dunham et al. 2014) and variants associated with mRNA splicing sensitivity (Mort, Sterne-Weiler et al. 2014). Our group evaluated similar approaches on missense variants associated with PGx and found difficulties in developing accurately predictive algorithms (Li, et al. *in press*). The challenges were two fold, first, the database of known validated missense variants of high confidence was somewhat small (126) compared to other approaches such as MutPred (>10,000) and second, features used for classification of disease variants were not necessarily informative for PGx variants. We found that PK variants were easier to predict than PD variants, likely due to their lack of diversity compared to the diversity of target and target pathways, however features such as sequence conservation were not particularly informative (not shown).

Resources to collect and curate pharmacogenomic variants

Many resources now exist to curate pathogenicity or clinical effects of disease or other phenotype associated variants. These include the Human Gene Mutation Database (HGMD) (Stenson, Ball et al. 2012), OMIM and ClinVar for disease variants (Landrum, Lee et al. 2014), dbSNP for unannotated variants in the human population and others (Glubb, Paugh et al. 2013). Seeing the future wealth of genetic associations to outcomes of drug and clinical treatments, the National Institutes of Health funded the laboratory of Prof. Russ Altman and Teri Klein at Stanford University School of Medicine to create the Pharmacogenomics Knowledgebase (PharmGKB) to act as a data coordination center for the growing network of pharmacogenomics researchers and to synthesize their findings into a useful resource for clinical interpretation and for researchers characterizing pharmacogenes (Thorn, Klein et al.

2013). PharmGKB curates both variants and so-called *VIP genes* that are highly studied and have significant reproduced associations. In order to disentangle the complexities of gene-drug associations, PharmGKB has developed a list of, as of this writing, 51 ‘*VIP*’ genes, that have curated a list of clinically useful associations, variant annotations, dosing guidelines, and drug label information. The overall *VIP* text is similar in style to OMIM disease genes and is actively curated by submitters and curators.

Today, in the US, there are many resources containing PGx data. Both the genetic study resource dbGAP and PharmGKB store PGx study GWAS data (Glubb, Paugh et al. 2013). A new consortium of NIH funded investigators, ClinGen, aim to collect clinically relevant variants including PGx variants (Ramos, Din-Lovinescu et al. 2014). This consortium collaborates both with PharmGKB and ClinVar, the clinically important variant database at the NIH. Elsewhere, the European Bioinformatics Institute (EBI) has recently increased genetic variant curation activities that may include PGx variants (Brooksbank, Bergman et al. 2014). Further, the Human Variome Project (HVP) is continuing to develop country data collection nodes and develop standards for data collection and practical interpretation (Oetting, Robinson et al. 2013). Recently, BioBase introduced a new product, the Pharmacogenomic Mutation Database (PGMD) that is available by license (<http://www.biobase-international.com/product/pgmd>). Obviously, the early stages of this effort are very complicated, as many resources exist, however PharmGKB remains central to all efforts.

Clinical Pharmacogenomics Implementation Consortium development process and guidelines

The pharmacogenomics community has recognized the need for clinical guidelines on the use of pharmacogenomic tests. To that end, the community of PGx and clinical interests coalesced to develop implementation guidelines for genetics, thus the Clinical Pharmacogenomics Implementation Consortium (CPIC) was formed (Relling and Klein 2011). As of this writing, 26 CPIC Dosing guidelines for drugs have been published and are available from PharmGKB (<http://www.pharmgkb.org/page/cpic>). Each guideline is published as a reviewed manuscript. In addition to characterizing *VIP* genes and disseminating clinical guidelines, PharmGKB has developed Clinical Annotation Levels of Evidence (<https://www.pharmgkb.org/page/clinAnnLevels>). The levels of evidence include preliminary (Level 4), low (Level 3), moderate (Levels 2a and 2b) and high (Level 1a and 1b). Level 2a are combinations that are present in known *VIP* genes, and Level 1a is a combination with an existing CPIC or other clinical implementation guideline.

Now tools such as the Coriell Pharmacogenomics Appraisal, Evidence Scoring and Interpretation System (PhAESIS) are enabling PGx practice (Gharani, Keller et al. 2013, Huang and Gamazon 2013). Further, experiences implementing a practicing PGx program in a medical center that are described from the perspective of genetics professionals argue for a collaborative approach between geneticists, pharmacologists, informaticians and medical practitioners (Sturm, Sweet et al. 2013).

Whole genome sequencing and interpretation of pharmacogenomic data

Through cost reduction in sequencing technologies and the expansion of whole genome sequencing, whole genome sequencing application is close to becoming clinically viable. If entire genomes could be matched to a patient's medical record, prospective genetic testing becomes possible and will not burden the physician or other clinician with ordering (and waiting for) genetic tests. A first step toward interpretation of pharmacogenetic variants in a whole genome sequence was published in 2010 (Ashley, Butte et al. 2010). In that work, pharmacogenomic whole genome profiling results were initially classified into three groups, a) Pharmacogenomic effects that increase likelihood of positive effects, few side effects or predictable dosing, b) Pharmacogenomic effects that increase likelihood of adverse events, lack of efficacy or uncertain dosing, and c) Pharmacogenomic effects that are mixed and hard to integrate (Ashley, Butte et al. 2010). In a recent more extensive study, patients with whole genome sequences were compared to the Clinical Pharmacogenomic Implementation Guidelines to identify variants present in 12 individuals of PGx relevance, identifying variants and haplotypes in several genes including CYP2C19, CYP2D6, TMPT, CYP2C9, and VKORC1 (Ormond, Wheeler et al. 2010).

Much of the challenges of whole genome sequencing lie in the costs of sequencing technologies and regulation surrounding using sequencers as a medical device. The recent FDA authorization of a genetic sequencer, the Illumina MiSeqDx, raises expectations that this will increase the impact of PGx tests in the clinic (Sheridan 2014). Concurrently the personal genomics industry has exploded to meet the needs of whole genome interpretation, although many barriers still remain (Allison 2010), and regulatory challenges are playing an evolving role in application of genetic testing of PGx markers.

Warfarin

Few therapies have been discussed for pharmacogenomic effects as much as Warfarin (Coumadin). Warfarin dose is associated with variants in the CYP2C9 and VKORC1 genes, and an abundance of other clinical factors. Warfarin is notoriously tricky to dose because individual response is variable over a narrow therapeutic range (Lee and Klein 2013). In 2013, The Warfarin Dose Refinement (DR) Collaboration has developed a website to aid in Warfarin dosing at <http://warfarindosing.org/>. Clinical studies have shown mixed results. Studies in 2013 have shown improvement (Pirmohamed, Burnside et al. 2013) and a lack of improvement of using genetics as part of a dosing algorithm (Kimmel, French et al. 2013, Verhoef, Ragia et al. 2013). While this story has not concluded, a recent meta-analysis has suggested that a genotype-guided dosing strategy does not reduce major adverse events associated with Warfarin (Stergiopoulos and Brown 2014).

Cancer Pharmacogenomics

Targeted therapies in cancer require knowledge of the patterns of somatic mutations within a specific tumor, and further, specific inherited variants may lead to lower adverse events and side effects (McLeod 2013). A recent review highlights the challenges that are important in this area (Wheeler, Maitland et al. 2013). Much effort has been spent studying tamoxifen response and CYP2D6 a well known functionally polymorphic metabolic enzyme (Klein,

Thorn et al. 2013). Whether variants in CYP2D6 associated with outcomes in breast cancer patients with ER-positive tumors continues to be debated (Brauch and Schwab 2014).

The role of pharmacogenetics in drug development

As research continues and knowledge grows surrounding PGx, there is increasing interest in use of PGx in the drug discovery and approval process. This role involves both premarket drug development and in the development of labeling for available drugs. The US Food and Drug Administration (FDA) has been supporting these efforts for a decade (Zineh and Pacanowski 2011) and recently, the FDA released nonbinding clinical guidelines on these topics in January 2013 ((FDA) 2013). Among the areas addressed include use of PGx approaches in Phase 1 and 2 studies, use in design of phase 3, and considerations for clinical study design. Labeling should be considered if it is relevant to PGx, including informing of an impact or no impact, whether testing is available and under what circumstances it should be recommended.

Future

Overall steady progress is being made toward pervasive application of PGx testing. This is being enabled by substantial research efforts of geneticists and informaticians to describe and validate variants associated with a clinical effect. However, there have been many successes in pharmacogenomics so far. First, data resources and clinical guidelines are continuing to grow and be developed. Second, the growth in pharmacogenomics is being fueled by new approaches for discovery such as whole genome sequencing and integration of sequence data with electronic health records (PheWAS). Third, the algorithmic toolbox for characterizing and applying previously discovered variants to human genomes continue to be evaluated and improved in terms of coverage of sequencing of PGx variants, methods for interpretation and clinical assessment. Many challenges remain, including keeping up with the complex regulatory landscape, new sequencing technologies and approved devices, translating research successes to clinical successes and discovering new markers.

Acknowledgements

SDM is funded by NIH R01 LM009722 (PI:Mooney) and the Buck Trust.

References Cited

- T. F. a. D. A. (FDA). Clinical Pharmacogenomics: Premarket Evaluation in Early-Phase Clinical Studies and Recommendations for Labeling. 2013. from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM337169.pdf>.
- Adzhubei I, Jordan DM, Sunyaev SR. Predicting functional effect of human missense mutations using PolyPhen-2. *Curr Protoc Hum Genet*. 2013 **Chapter 7**: Unit7 20.
- Allison M. Genetic testing clamp down. *Nat Biotechnol*. 2010; 28(7):633. [PubMed: 20622812]
- Ardlie KG, Kruglyak L, Seielstad M. Patterns of linkage disequilibrium in the human genome. *Nat Rev Genet*. 2002; 3(4):299–309. [PubMed: 11967554]
- Ashley EA, Butte AJ, Wheeler MT, Chen R, Klein TE, Dewey FE, Dudley JT, Ormond KE, Pavlovic A, Morgan AA, Pushkarev D, Neff NF, Hudgins L, Gong L, Hodges LM, Berlin DS, Thorn CF, Sangkuhl K, Hebert JM, Woon M, Sagreiya H, Whaley R, Knowles JW, Chou MF, Thakuria JV, Rosenbaum AM, Zaranek AW, Church GM, Greely HT, Quake SR, Altman RB. Clinical

- assessment incorporating a personal genome. *Lancet*. 2010; 375(9725):1525–1535. [PubMed: 20435227]
- Booth RA, Ansari MT, Loit E, Tricco AC, Weeks L, Doucette S, Skidmore B, Sears M, Sy R, Karsh J. Assessment of thiopurine S-methyltransferase activity in patients prescribed thiopurines: a systematic review. *Ann Intern Med*. 2011; 154(12):814–823. W-295-818. [PubMed: 21690596]
- Brauch H, Schwab M. Prediction of tamoxifen outcome by genetic variation of CYP2D6 in post-menopausal women with early breast cancer. *Br J Clin Pharmacol*. 2014; 77(4):695–703. [PubMed: 24033728]
- Brooksbank C, Bergman MT, Apweiler R, Birney E, Thornton J. The European Bioinformatics Institute's data resources 2014. *Nucleic Acids Res*. 2014; 42:D18–D25. (Database issue). [PubMed: 24271396]
- Crowley JJ, Sullivan PF, McLeod HL. Pharmacogenomic genome-wide association studies: lessons learned thus far. *Pharmacogenomics*. 2009; 10(2):161–163. [PubMed: 19207016]
- Daly AK. Genome-wide association studies in pharmacogenomics. *Nat Rev Genet*. 2010; 11(4):241–246. [PubMed: 20300088]
- Daly AK. Using genome-wide association studies to identify genes important in serious adverse drug reactions. *Annu Rev Pharmacol Toxicol*. 2012; 52:21–35. [PubMed: 21819236]
- Denny JC, Bastarache L, Ritchie MD, Carroll RJ, Zink R, Mosley JD, Field JR, Pulley JM, Ramirez AH, Bowton E, Basford MA, Carrell DS, Peissig PL, Kho AN, Pacheco JA, Rasmussen LV, Crosslin DR, Crane PK, Pathak J, Bielinski SJ, Pendergrass SA, Xu H, Hindorff LA, Li R, Manolio TA, Chute CG, Chisholm RL, Larson EB, Jarvik GP, Brilliant MH, McCarty CA, Kullo IJ, Haines JL, Crawford DC, Masys DR, Roden DM. Systematic comparison of phenome-wide association study of electronic medical record data and genome-wide association study data. *Nat Biotechnol*. 2013; 31(12):1102–1110. [PubMed: 24270849]
- Denny JC, Ritchie MD, Basford MA, Pulley JM, Bastarache L, Brown-Gentry K, Wang D, Masys DR, Roden DM, Crawford DC. PheWAS: demonstrating the feasibility of a phenome-wide scan to discover gene-disease associations. *Bioinformatics*. 2010; 26(9):1205–1210. [PubMed: 20335276]
- Dewey FE, Grove ME, Pan C, Goldstein BA, Bernstein JA, Chaib H, Merker JD, Goldfeder RL, Enns GM, David SP, Pakdaman N, Ormond KE, Caleshu C, Kingham K, Klein TE, Whirl-Carrillo M, Sakamoto K, Wheeler MT, Butte AJ, Ford JM, Boxer L, Ioannidis JP, Yeung AC, Altman RB, Assimes TL, Snyder M, Ashley EA, Quertermous T. Clinical interpretation and implications of whole-genome sequencing. *JAMA*. 2014; 311(10):1035–1045. [PubMed: 24618965]
- Eichelbaum M. [Pharmacogenetics: current state after 30 years of research]. *Dtsch Med Wochenschr*. 2013; 138(13):659–661. [PubMed: 23512369]
- Eichelbaum M, Ingelman-Sundberg M, Evans WE. Pharmacogenomics and individualized drug therapy. *Annu Rev Med*. 2006; 57:119–137. [PubMed: 16409140]
- Evans WE, McLeod HL. Pharmacogenomics--drug disposition, drug targets, and side effects. *N Engl J Med*. 2003; 348(6):538–549. [PubMed: 12571262]
- Garten Y, Tatonetti NP, Altman RB. Improving the prediction of pharmacogenes using text-derived drug-gene relationships. *Pac Symp Biocomput*. 2010:305–314. [PubMed: 19908383]
- Gharani N, Keller MA, Stack CB, Hodges LM, Schmidlen TJ, Lynch DE, Gordon ES, Christman MF. The Coriell personalized medicine collaborative pharmacogenomics appraisal, evidence scoring and interpretation system. *Genome Med*. 2013; 5(10):93. [PubMed: 24134832]
- Giacomini KM, Brett CM, Altman RB, Benowitz NL, Dolan ME, Flockhart DA, Johnson JA, Hayes DF, Klein T, Krauss RM, Kroetz DL, McLeod HL, Nguyen AT, Ratain MJ, Relling MV, Reus V, Roden DM, Schaefer CA, Shuldiner AR, Skaar T, Tantisira K, Tyndale RF, Wang L, Weinshilboum RM, Weiss ST, Zineh I. N. Pharmacogenetics Research. The pharmacogenetics research network: from SNP discovery to clinical drug response. *Clin Pharmacol Ther*. 2007; 81(3):328–345. [PubMed: 17339863]
- Gisbert JP, Gomollon F. Common misconceptions in the diagnosis and management of anemia in inflammatory bowel disease. *Am J Gastroenterol*. 2008; 103(5):1299–1307. [PubMed: 18477354]
- Glubb DM, Paugh SW, van Schaik RH, Innocenti F. A guide to the current Web-based resources in pharmacogenomics. *Methods Mol Biol*. 2013; 1015:293–310. [PubMed: 23824864]

- Gordon, AS.; Smith, JD.; Xiang, Q.; Metzker, ML.; Gibbs, RA.; Mardis, ER.; Nickerson, DA.; Fulton, RS.; Scherer, SE. PGRNseq: a new sequencing-based platform for high-throughput pharmacogenomic implementation and discovery. Boston, USA: American Society of Human Genetics (ASHG) Annual Meeting, Session 46. Pharmacogenetics: From Discovery to Implementation; 2012.
- Guo Y, Lu P, Farrell E, Zhang X, Weller P, Monshouwer M, Wang J, Liao G, Zhang Z, Hu S, Allard J, Shafer S, Usuka J, Peltz G. In silico and in vitro pharmacogenetic analysis in mice. *Proc Natl Acad Sci U S A*. 2007; 104(45):17735–17740. [PubMed: 17978195]
- Guo Y, Weller P, Farrell E, Cheung P, Fitch B, Clark D, Wu SY, Wang J, Liao G, Zhang Z, Allard J, Cheng J, Nguyen A, Jiang S, Shafer S, Usuka J, Masjedizadeh M, Peltz G. In silico pharmacogenetics of warfarin metabolism. *Nat Biotechnol*. 2006; 24(5):531–536. [PubMed: 16680137]
- Hoskins JM, Marcuello E, Altes A, Marsh S, Maxwell T, Van Booven DJ, Paré L, Culverhouse R, McLeod HL, Baiget M. Irinotecan Pharmacogenetics: Influence of Pharmacodynamic Genes. *Clinical Cancer Research*. 2008; 14(6):1788–1796. [PubMed: 18347181]
- Huang RS, Gamazon ER. Translating pharmacogenomics discoveries into the clinic: an implementation framework. *Genome Med*. 2013; 5(10):94. [PubMed: 24134796]
- Ingelman-Sundberg M. Genetic polymorphisms of cytochrome P450 2D6 (CYP2D6): clinical consequences, evolutionary aspects and functional diversity. *Pharmacogenomics J*. 2005; 5(1):6–13. [PubMed: 15492763]
- Johnson JA, Burkley BM, Langae TY, Clare-Salzler MJ, Klein TE, Altman RB. Implementing personalized medicine: development of a cost-effective customized pharmacogenetics genotyping array. *Clin Pharmacol Ther*. 2012; 92(4):437–439. [PubMed: 22910441]
- Johnson JA, Gong L, Whirl-Carrillo M, Gage BF, Scott SA, Stein CM, Anderson JL, Kimmel SE, Lee MT, Pirmohamed M, Wadelius M, Klein TE, Altman RB. C. Clinical Pharmacogenetics Implementation. Clinical Pharmacogenetics Implementation Consortium Guidelines for CYP2C9 and VKORC1 genotypes and warfarin dosing. *Clin Pharmacol Ther*. 2011; 90(4):625–629. [PubMed: 21900891]
- Kimmel SE, French B, Kasner SE, Johnson JA, Anderson JL, Gage BF, Rosenberg YD, Eby CS, Madigan RA, McBane RB, Abdel-Rahman SZ, Stevens SM, Yale S, Mohler ER 3rd, Fang MC, Shah V, Horenstein RB, Limdi NA, Muldowney JA 3rd, Gujral J, Delafontaine P, Desnick RJ, Ortel TL, Billett HH, Pendleton RC, Geller NL, Halperin JL, Goldhaber SZ, Caldwell MD, Califf RM, Ellenberg JH. C. Investigators. A pharmacogenetic versus a clinical algorithm for warfarin dosing. *N Engl J Med*. 2013; 369(24):2283–2293. [PubMed: 24251361]
- Klein DJ, Thorn CF, Desta Z, Flockhart DA, Altman RB, Klein TE. PharmGKB summary: tamoxifen pathway, pharmacokinetics. *Pharmacogenet Genomics*. 2013; 23(11):643–647. [PubMed: 23962908]
- Landrum MJ, Lee JM, Riley GR, Jang W, Rubinstein WS, Church DM, Maglott DR. ClinVar: public archive of relationships among sequence variation and human phenotype. *Nucleic Acids Res*. 2014; 42:D980–D985. (Database issue). [PubMed: 24234437]
- Lee MT, Klein TE. Pharmacogenetics of warfarin: challenges and opportunities. *J Hum Genet*. 2013; 58(6):334–338. [PubMed: 23657428]
- Li B, Krishnan VG, Mort ME, Xin F, Kamati KK, Cooper DN, Mooney SD, Radivojac P. Automated inference of molecular mechanisms of disease from amino acid substitutions. *Bioinformatics*. 2009; 25(21):2744–2750. [PubMed: 19734154]
- Li-Wan-Po A, Girard T, Farndon P, Cooley C, Lithgow J. Pharmacogenetics of CYP2C19: functional and clinical implications of a new variant CYP2C19*17. *Br J Clin Pharmacol*. 2010; 69(3):222–230. [PubMed: 20233192]
- McCarty CA, Chisholm RL, Chute CG, Kullo IJ, Jarvik GP, Larson EB, Li R, Masys DR, Ritchie MD, Roden DM, Struwing JP, Wolf WA, e MT. The eMERGE Network: a consortium of biorepositories linked to electronic medical records data for conducting genomic studies. *BMC Med Genomics*. 2011; 4:13. [PubMed: 21269473]
- McLeod HL. Cancer pharmacogenomics: early promise, but concerted effort needed. *Science*. 2013; 339(6127):1563–1566. [PubMed: 23539596]

- Mort M, Sterne-Weiler T, Li B, Ball EV, Cooper DN, Radivojac P, Sanford JR, Mooney SD. MutPred Splice: machine learning-based prediction of exonic variants that disrupt splicing. *Genome Biol.* 2014; 15(1):R19. [PubMed: 24451234]
- Motsinger-Reif AA, Jorgenson E, Relling MV, Kroetz DL, Weinshilboum R, Cox NJ, Roden DM. Genome-wide association studies in pharmacogenomics: successes and lessons. *Pharmacogenet Genomics.* 2013; 23(8):383–394. [PubMed: 20639796]
- Nebert DW. Pharmacogenetics and pharmacogenomics: why is this relevant to the clinical geneticist? *Clinical Genetics.* 1999; 56(4):247–258. [PubMed: 10636440]
- Neuraz A, Chouchana L, Malamut G, Le Beller C, Roche D, Beaune P, Degoulet P, Burgun A, Lorient MA, Avillach P. Phenome-wide association studies on a quantitative trait: application to TPMT enzyme activity and thiopurine therapy in pharmacogenomics. *PLoS Comput Biol.* 2013; 9(12):e1003405. [PubMed: 24385893]
- Oetting WS, Robinson PN, Greenblatt MS, Cotton RG, Beck T, Carey JC, Doelken SC, Girdea M, Groza T, Hamilton CM, Hamosh A, Kerner B, MacArthur JA, Maglott DR, Mons B, Rehm HL, Schofield PN, Searle BA, Smedley D, Smith CL, Bernstein IT, Zankl A, Zhao EY. Getting ready for the Human Phenome Project: the 2012 forum of the Human Variome Project. *Hum Mutat.* 2013; 34(4):661–666. [PubMed: 23401191]
- Ormond KE, Wheeler MT, Hudgins L, Klein TE, Butte AJ, Altman RB, Ashley EA, Greely HT. Challenges in the clinical application of whole-genome sequencing. *Lancet.* 2010; 375(9727):1749–1751. [PubMed: 20434765]
- Owen RP, Altman RB, Klein TE. PharmGKB and the International Warfarin Pharmacogenetics Consortium: the changing role for pharmacogenomic databases and single-drug pharmacogenetics. *Hum Mutat.* 2008; 29(4):456–460. [PubMed: 18330919]
- Phillips KA, Veenstra DL, Oren E, Lee JK, Sadee W. Potential role of pharmacogenomics in reducing adverse drug reactions: a systematic review. *JAMA.* 2001; 286(18):2270–2279. [PubMed: 11710893]
- Pirmohamed M, Burnside G, Eriksson N, Jorgensen AL, Toh CH, Nicholson T, Kesteven P, Christersson C, Wahlstrom B, Stafberg C, Zhang JE, Leathart JB, Kohnke H, Maitland-van der Zee AH, Williamson PR, Daly AK, Avery P, Kamali F, Wadelius M. E.-P. Group. A randomized trial of genotype-guided dosing of warfarin. *N Engl J Med.* 2013; 369(24):2294–2303. [PubMed: 24251363]
- Price MJ, Carson AR, Murray SS, Phillips T, Janel L, Tisch R, Topol E, Levy S. FIRST PHARMACOGENOMIC ANALYSIS USING WHOLE EXOME SEQUENCING TO IDENTIFY NOVEL GENETIC DETERMINANTS OF CLOPIDOGREL RESPONSE VARIABILITY: RESULTS OF THE GENOTYPE INFORMATION AND FUNCTIONAL TESTING (GIFT) EXOME STUDY. *Journal of the American College of Cardiology.* 2012; 59(13s1):E9–E9. [PubMed: 22281261]
- Pulley JM, Denny JC, Peterson JF, Bernard GR, Vnencak-Jones CL, Ramirez AH, Delaney JT, Bowton E, Brothers K, Johnson K, Crawford DC, Schildcrout J, Masys DR, Dilks HH, Wilke RA, Clayton EW, Shultz E, Laposata M, McPherson J, Jirjis JN, Roden DM. Operational implementation of prospective genotyping for personalized medicine: the design of the Vanderbilt PREDICT project. *Clin Pharmacol Ther.* 2012; 92(1):87–95. [PubMed: 22588608]
- Ramos EM, Din-Lovinescu C, Berg JS, Brooks LD, Duncanson A, Dunn M, Good P, Hubbard TJ, Jarvik GP, O'Donnell C, Sherry ST, Aronson N, Biesecker LG, Blumberg B, Calonge N, Colhoun HM, Epstein RS, Flicek P, Gordon ES, Green ED, Green RC, Hurles M, Kawamoto K, Knaus W, Ledbetter DH, Levy HP, Lyon E, Maglott D, McLeod HL, Rahman N, Randhawa G, Wicklund C, Manolio TA, Chisholm RL, Williams MS. Characterizing genetic variants for clinical action. *Am J Med Genet C Semin Med Genet.* 2014; 166(1):93–104. [PubMed: 24634402]
- Relling MV, Klein TE. CPIC: Clinical Pharmacogenetics Implementation Consortium of the Pharmacogenomics Research Network. *Clin Pharmacol Ther.* 2011; 89(3):464–467. [PubMed: 21270786]
- Ritchie GR, Dunham I, Zeggini E, Flicek P. Functional annotation of noncoding sequence variants. *Nat Methods.* 2014; 11(3):294–296. [PubMed: 24487584]

- Ritchie MD. The success of pharmacogenomics in moving genetic association studies from bench to bedside: study design and implementation of precision medicine in the post-GWAS era. *Hum Genet.* 2012; 131(10):1615–1626. [PubMed: 22923055]
- Ross CJ, Visscher H, Sistonen J, Brunham LR, Pussegoda K, Loo TT, Rieder MJ, Koren G, Carleton BC, Hayden MR, Consortium C. The Canadian Pharmacogenomics Network for Drug Safety: a model for safety pharmacology. *Thyroid.* 2010; 20(7):681–687. [PubMed: 20578893]
- Scott SA. Clinical pharmacogenomics: opportunities and challenges at point of care. *Clin Pharmacol Ther.* 2013; 93(1):33–35. [PubMed: 23212102]
- Sheridan C. Milestone approval lifts Illumina's NGS from research into clinic. *Nat Biotechnol.* 2014; 32(2):111–112. [PubMed: 24509734]
- Stenson PD, Ball EV, Mort M, Phillips AD, Shaw K, Cooper DN. The Human Gene Mutation Database (HGMD) and its exploitation in the fields of personalized genomics and molecular evolution. *Curr Protoc Bioinformatics.* 2012 **Chapter 1**: Unit1 13.
- Stergiopoulos K, Brown DL. Genotype-Guided vs Clinical Dosing of Warfarin and Its Analogues: Meta-analysis of Randomized Clinical Trials. *JAMA Intern Med.* 2014; 174(8):1330–1338. [PubMed: 24935087]
- Sturm AC, Sweet K, Manickam K. Implementation of a clinical research pharmacogenomics program at an academic medical center: role of the genetics healthcare professional. *Pharmacogenomics.* 2013; 14(7):703–706. [PubMed: 23651015]
- Swen JJ, Nijenhuis M, de Boer A, Grandia L, Maitland-van der Zee AH, Mulder H, Rongen GA, van Schaik RH, Schalekamp T, Touw DJ, van der Weide J, Wilffert B, Deneer VH, Guchelaar HJ. Pharmacogenetics: from bench to byte--an update of guidelines. *Clin Pharmacol Ther.* 2011; 89(5):662–673. [PubMed: 21412232]
- Thorn CF, Klein TE, Altman RB. PharmGKB: the Pharmacogenomics Knowledge Base. *Methods Mol Biol.* 2013; 1015:311–320. [PubMed: 23824865]
- Verhoef TI, Ragia G, de Boer A, Barallon R, Kolovou G, Kolovou V, Konstantinides S, Le Cessie S, Maltezos E, van der Meer FJ, Redekop WK, Remkes M, Rosendaal FR, van Schie RM, Tavridou A, Tziakas D, Wadelius M, Manolopoulos VG, Maitland-van der Zee AH. E.-P. Group. A randomized trial of genotype-guided dosing of acenocoumarol and phenprocoumon. *N Engl J Med.* 2013; 369(24):2304–2312. [PubMed: 24251360]
- Wang L, Weinshilboum RM. Pharmacogenomics: candidate gene identification, functional validation and mechanisms. *Hum Mol Genet.* 2008; 17(R2):R174–179. [PubMed: 18852207]
- Wheeler HE, Maitland ML, Dolan ME, Cox NJ, Ratain MJ. Cancer pharmacogenomics: strategies and challenges. *Nat Rev Genet.* 2013; 14(1):23–34. [PubMed: 23183705]
- Zhao Y, Clark WT, Mort M, Cooper DN, Radivojac P, Mooney SD. Prediction of functional regulatory SNPs in monogenic and complex disease. *Hum Mutat.* 2011; 32(10):1183–1190. [PubMed: 21796725]
- Zineh I, Pacanowski MA. Pharmacogenomics in the assessment of therapeutic risks versus benefits: inside the United States Food and Drug Administration. *Pharmacotherapy.* 2011; 31(8):729–735. [PubMed: 21923598]