Published in final edited form as:

Wiley Interdiscip Rev Syst Biol Med. 2014 March ; 6(2): 125–135. doi:10.1002/wsbm.1255.

Using Systems Approaches to Address Challenges for Clinical Implementation of Pharmacogenomics

Jason H Karnes,

Department of Medicine, Vanderbilt University, Nashville, TN

Sara Van Driest,

Department of Paediatrics, Vanderbilt University and the Monroe Carell Jr. Children's Hospital at Vanderbilt, Nashville, Tennessee, USA

Erica A Bowton,

Office of Personalised Medicine, Vanderbilt University, Nashville, Tennessee

Peter E Weeke,

Department of Medicine, Vanderbilt University, Nashville, TN

Jonathan D Mosley,

Department of Medicine, Vanderbilt University, Nashville, TN

Josh F Peterson,

Departments of Biomedical Informatics and Medicine, Vanderbilt University, Nashville, TN

Joshua C Denny, and

Departments of Biomedical Informatics and Medicine, Vanderbilt University, Nashville, TN

Dan M Roden

Departments of Medicine and Pharmacology, Vanderbilt University, Nashville, TN

Dan M Roden: dan.roden@vanderbilt.edu

Abstract

Many genetic variants have been shown to affect drug response through changes in drug efficacy and likelihood of adverse effects. Much of pharmacogenomic science has focused on discovering and clinically implementing single gene variants with large effect sizes. Given the increasing complexities of drug responses and their variability, a systems approach may be enabling for discovery of new biology in this area. Further, systems approaches may be useful in addressing challenges in moving these data to clinical implementation, including creation of predictive models of drug response phenotypes, improved clinical decision-making through complex biological models, improving strategies for integrating genomics into clinical practice, and evaluating the impact of implementation programs on public health.

For decades, genetic variation has been clearly implicated as an important determinant in drug disposition and effects.¹ One of the promises of the completion of the human genome project is personalised medicine, one aspect of which is pharmacogenomics, or tailoring drug therapy to an individual's genetic makeup.² To date, the field has focused largely on the effect of individual genetic variants with large effect sizes. Extending this paradigm to large numbers of drugs will likely require consideration of the complex interplay of genetic, metabolic, environmental, and developmental factors on drug responses.³ Enabling this type of analysis will be a framework that views drug response as a dynamic system and maps

important genes for each of these components using pharmacokinetic and pharmacodynamic relationships and biological data.⁴ Such a systems biology framework might be leveraged to determine relationships in specific cells, individuals, and populations, and predict responses as the systems are perturbed by medications, enabling more effective models of pharmacogenomics and improved approaches to disease management.

A handful of practice sites have developed initiatives to begin implementing pharmacogenomics in large, academic hospital settings.^{5–8} These programs are addressing multiple challenges for pharmacogenomics implementation, including uncertainty about clinical evidence in the absence of randomised clinical trials (RCTs), identification of variants modulating drug response across ancestries, translating genotype information into predicted drug response, optimal methods to deliver easily-understood information to busy practitioners, and assessment of clinical utility and cost-effectiveness (Table 1).⁹ These challenges underscore the need for continued development of implementation infrastructure, additional research into clinical validity, substantiation for benefits of pharmacogenomics in large patient populations, and the need for alternative study designs. The purpose of this review is to discuss potential applications of systems biology to pharmacogenomics and clinical implementation of pharmacogenomics.

SYSTEMS APPROACHES AND PHARMACOGENOMICS

Systems approaches that leverage a wealth of biological data (e.g. phenotypes, genotypes, and proteomic or transcriptomic data) have the potential to enable discovery in pharmacogenomics and contribute to the utility of known pharmacogenomic variants. Systems approaches seek to understand complex interactions, generate complex descriptive models, and predict phenotypic diversity based on static and dynamic factors and should thus be well-suited for pharmacogenomics. Important concepts in systems biology that apply in pharmacogenomic studies include 1) complex systems display emergent properties that are not displayed by individual parts; 2) phenotypic stability protects systems from fluctuations in environment; 3) modules are set up within a network that have strong interactions and common functions, and this modularity and overlap of function contributes to phenotypic stability.¹⁰ Data are visualised, modelled and refined iteratively, and phenotypic features are directly linked to other portions of the network, providing prediction of system behaviour with disturbances. As a system is perturbed by medications, key nodes within the system can be identified and phenotypic response predicted. Systems biology is especially fitting for pharmacogenomics as it involves hierarchical levels of different phenotypes and pharmacogenomics typically involves multiple phenotypes such as a disease of interest and a drug response.¹¹ With an approach utilizing vast amounts of biological data to predict a phenotype, there exists the opportunity for more effective translation of biological data into clinical practice.

System approaches have been used to analyse determinants of clinical responses to cardiovascular drugs, including QT prolonging drugs (see sidebar). Another example of system applications to cardiovascular pharmacogenomics is a recent study in which statin-induced changes in gene expression were assayed in lymphoblastoid cell lines from participants in a statin clinical trial.¹² This analysis identified expression quantitative trait loci (eQTLs) for statin exposure *in vitro*, and one of these, at glycine amidinotransferase (GATM), correlated with statin induced myopathy in clinical trials. This was further supported by RNA interference, and is biologically plausible since GATM encodes a key step in synthesis of creatinine. Thus a potential role of GATM was elucidated by analysing multiple large datasets each containing complementary information. Using systems approaches, including whole genome expression profiling of muscle and lipidomic analysis of plasma, effects of statins on non-hepatic tissues were demonstrated with potential

application to personalised drug and dose selection.¹³ Drug response transcriptome networks have also been used to increase our understanding of fenofibrate pharmacogenomics by identifying important drug response pathways and novel regulators of fenofibrate action in human endothelial cells.^{14, 15}

Diverse applications of a systems biology view: cardiac repolarisation

Cardiac repolarization is the process by which the heart recovers from excitation to allow repetitive stimulation. Abnormalities of repolarization commonly manifest on the electrocardiogram as prolongation of the QT interval. There is physiologic variability in this measurement, and when the QT interval is markedly prolonged, arrhythmias and even sudden death can ensue. Settings in which such prolongation is seen include the congenital long QT syndrome (LQTS) and a drug-induced form LQTS, a severe ADR.

A simple view is that cardiac repolarization at the cellular level represents a balance between inward depolarizing currents (notably L-type calcium current) and outward repolarizing potassium currents. These currents flow through channels, multiprotein complexes that open and close as a function of transmembrane voltage. Thus, even simple models of repolarization stress the interdependence of the individual components: as the function of one changes, this in turn affects voltage and thus the function of other components. Indeed, cardiac repolarization was one of the first physiologic processes to be the focus of *in silico* model building which resulted in a novel systems biology view of molecular processes. Mutations in multiple ion channel genes can all result in congenital LQTS. By contrast, many agents that cause the drug-related form of LQTS block one potassium current, I_{Kr} , encoded by *KCNH2*. Notably, loss of function mutations in this gene are also a common cause of the congenital syndrome.

A simple view would be that *KCNH2* mutations could also predispose to the drug-induced form of the syndrome. However, this is not the case, and *KCNH2* mutations have only rarely been associated with drug-induced LQTS. A fruitful approach to analysing risk has come from the development of increasingly complex *in silico* models of cardiac repolarization; these models now incorporate physiologic behaviours of dozens of individual electrogenic components (including ion channels and membrane transporters) and thus enable analyses of the way in which perturbations in function of these individual components affect the duration of repolarization and arrhythmia susceptibility. These models illustrate the way in which multiple physiologic mechanisms lead to tightly controlled repolarization and how, in many instances, multiple lesions are required to generate full-blown LQTS. For example, one relatively consistent finding in the drug-induced form has been that loss of function variants in genes encoding a second repolarizing potassium current, I_{Ks} , contribute to risk for the drug-induced syndrome. The concept has been advanced that such mutations remain undetected because I_{Kr} ordinarily can accomplish normal repolarization; however, when a patient harbouring such mutations is exposed to I_{Kr} blocking drugs, repolarization is severely impaired and drug-associated LQTS results. The term “reduced repolarization reserve” has been popularised to describe the situation of a “subclinical” I_{Ks} lesion that becomes apparent with I_{Kr} blocking drug administration.

This framework has been generalised to identify changes in multiple other components of physiologic repolarization as contributors to variable duration of cardiac repolarization and thus to risk for drug-induced LQTS. The framework allows interpretation of GWAS and other analyses of normal QT interval, including an unbiased examination of QT-prolonging drug responses in a set of mutagenised zebrafish lines.¹⁶ Further, the potassium channel proteins underlying I_{Kr} and I_{Ks} interact with other proteins. Analysis of the reported biology of individual components of repolarization has enabled the

generation of compendia of interacting proteins, and these in turn provide a framework for analysis of the role of other genomic variants identified by screening patients with drug-induced LQTS. Such system approaches have also been useful in prioritizing sequence variants to identify new disease genes in patients with the congenital syndrome. The complexities of cardiac repolarization highlight potential advantages not only of *in silico* modelling approaches to complex biology, but also the potential development of new clinical risk predictors through examination of cardiac repolarization in iPSC-derived cardiomyocytes from patients with the congenital or perhaps the drug-associated syndromes.^{17, 18}

Systems-based approaches have been applied in asthma pharmacogenomics.¹⁹ Bayesian networks were used to generate a predictive network for bronchodilator response using single nucleotide polymorphisms (SNPs) from candidate genes.²⁰ The Bayesian network model was then applied to existing pharmacogenomic data and was better at predicting bronchodilator response in comparison with single SNPs and regression models. Similarly, classification algorithms were used to search for genes influencing response to glucocorticoids in asthma.²¹ Using micro-array expression profiles from peripheral blood mononuclear cells, this analysis identified 923 genes that were significantly up- or down-regulated in response to cytokines *in vitro* and had reversed expression in glucocorticoid responders after glucocorticoid treatment. In addition, module networks analysis was used to identify responses to asthma treatment using publicly available expression data and the Ingenuity Knowledge Base.²²

Network modelling of pharmacogenomic data has also been applied to infectious disease pharmacology. Systems-based approaches have been used to identify Hepatitis C Virus polymorphic sites as predictors of treatment outcomes with interferon plus ribavirin therapy and to elucidate resistance-conferring human immunodeficiency virus (HIV) mutations during nucleoside and non-nucleoside reverse transcriptase inhibitor therapies.^{23, 24}

These examples highlight the potential for systems approaches in pharmacogenomics and may ultimately provide pathways to improved patient-specific care. As illustrated in Figure 1, some diseases may manifest after a single molecular perturbation. In such a case, a targeted treatment (a “magic bullet”) may be curative. However, most common diseases are multifactorial or polygenic and a single molecule whose targeting would be curative cannot be identified. In this case, drugs are used to control manifestations or progression of disease. In such cases, drug response phenotypes may not depend exclusively on a drug-gene pair, but represent a complex interplay of disease mechanisms with factors such as adherence, disease severity, drug-drug interactions, and age. The future of personalised medicine will likely require incorporation of a variety of biological data in a systems-based approach. One appealing approach is the utilization of large electronic medical record (EMR) systems into pharmacogenomic discovery. These datasets have the advantage that they represent large numbers of “real world” patient drugs responses, and also represent platforms not only for discovery but also for implementing new pharmacogenomic knowledge into practice.²⁵

Statistical limitations make understanding contributions of rare variants as well as epistasis of variants specific to drug treatment difficult. Most well-described pharmacogenomic associations described to date demonstrate large effects sizes of relatively common variants.²⁶ As future determinants of pharmacogenomic importance are discovered, it will be important to consider additional variants with smaller allele frequencies and interactions of variants in complex biological systems. One approach to this issue is to integrate functional and statistical approaches. Systems approaches address are thus well-suited to address limitations of study designs, generate new evidence for pharmacogenomic

relationships, refine biological understanding of existing pharmacogenomics relationships, and ultimately to improve clinical genotype-tailored decision making.

SYSTEMS APPROACHES AND CLINICAL IMPLEMENTATION OF PHARMACOGENOMICS

Systems approaches may not only enable discovery of drug effects in the setting of complex biology, but could also be leveraged to understand the complex interplay of regulatory bodies, physician practices, educational information flow, and other important pieces of successful implementation.²⁷ Although systems biology is currently applied to biological data within a living system, systems approaches can also be used to predict outcomes in a complex health care system, exploiting financial data and performance measures, as well as social, cultural, economic, and policy factors.²⁸ Complex systems dynamic models have been used to study causes of obesity, including biological and behavioural factors and their interrelations to inform how specific policy interventions influence public health.²⁹ Simulations were used to determine the impact of investing in good food stores on body mass index (BMI) under different assumptions about the importance of friend networks on influencing diets. The results suggest that, for weak social network effects, the impact of policy is faster and stronger and the impact is more persistent with strong social network effects. Such a “systems epidemiology” approach may be applied to include environmental, educational, and policy interventions, constituting a bird’s eye view of complex clinical and regulatory system. Thus a systems approach may be applied to clinical implementation of pharmacogenomics directly and be used to identify key impediments in the implementation process.

Previously, decision analytic modelling and quantitative risk-benefit analysis have been used to prioritize genomic tests for development in the translational pathway, using warfarin pharmacogenomics as a proof of concept.³⁰ Although variants in the genes *CYP2C9* and *VKORC1* are clearly associated with changes in warfarin dose requirements, no study has definitively demonstrated that genetic information improves patient outcomes.³¹ Investigators developed a three-tiered framework included using decision-analytic modeling to synthesize data and project clinical event incidence, defining genomic test utility, and creating a risk-benefit policy matrix for implementation of pharmacogenomic data. The investigators concluded that such a framework might be used to accelerate utilization of genomic-based tests. This framework can be expanded to incorporate key processes in clinical implementation of pharmacogenomics. The framework also illustrates the availability of alternative strategies for generating evidence of clinical utility of pharmacogenomics. A systems perspective may be useful for understanding and identifying challenges in clinical implementation, including public and private financial investment, policy and legal frameworks, regulation, marketing, insurance coverage, education, and differential access to services.³² Such a perspective would leverage biological data (e.g. the metabolome, proteome, epigenome, bacteriome, transcriptome) against factors such as dietary intake, exercise, income, community factors, state and federal policies.

Systems biology and network analysis can also be applied to the pharmacogenomic implementation problem by leveraging techniques from other disciplines, such as implementation science, decision science, and social network analysis. Social network analysis offers a means of mapping and exposing channels of communication and information flow, as well as information disconnects, between people in strategically important groups within an organization.³³ Social network analysis of physician survey data supports that social network techniques can be used to identify physicians who affect the adoption and diffusion of medical technologies.³⁴ The results demonstrate importance of peer influences in communicating availability and efficacy of new practices and procedures.

Previously, social network analysis has been applied to factors that constitute challenges to pharmacogenomics implementation, including clinical decision making, social influence, process efficiencies, and diffusion of innovation.^{35–37} Most commonly used to help improve effectiveness and efficiency of decision making processes in commercial organizations, social network analysis could be applied to pharmacogenomics implementation.

CHALLENGES TO CLINICAL IMPLEMENTATION OF PHARMACOGENOMICS AND APPLICATIONS OF SYSTEMS APPROACHES

Defining clinically actionable pharmacogenomic variants

Systems approaches have the potential to increase clinical pharmacogenomic implementation by providing new evidence for existing pharmacogenomic relationships thus making new variants clinically actionable. Although multiple common variants with large pharmacogenomic effect sizes and clear underlying biology have been identified and replicated,²⁶ the challenge for implementation is whether such associations are “clinically actionable”; that is, whether a pharmacogenomic variant should be used to guide drug treatment. Genotyping for some germ line variants is strongly supported by professional guidelines.^{38–40} In other cases, there is no clear consensus on the utility of pharmacogenomic information^{41, 42} and guidelines recommend against routine pharmacogenetic testing citing a lack of sufficient evidence for routine pharmacogenomic testing.^{43, 44}

The lack of sufficient evidence for clinical implementation of pharmacogenomic variants is often related to limitations in currently available study designs to evaluate pharmacogenomic variants. For instance, randomised controlled trials (RCTs) are viewed as the “gold standard” methodological design to establish new treatments,⁴⁵ but logistical, ethical and statistical barriers exist. These barriers are particularly difficult for pharmacogenomic research considering sample size requirements to prove clinical benefits among genotype groups, the necessity of assessing interactions, and requirements for replication, especially when complex traits are studied. Indeed, an RCT for personalised medicine may be a contradiction in terms, in so much as employing a randomised treatment structure to a treatment that is meant to be tailored to an individual. Systems approaches may provide effective alternative strategies to address such limitations. In the warfarin study discussed above, a three-tiered framework of decision analytic modelling and quantitative risk-benefit analysis was used to prioritize genomic tests for development in the translational pathway.³⁰ Such a framework could be used to accelerate utilization of genomic-based tests in the absence of RCT evidence.

Although currently available study designs have gleaned invaluable insights, limitations in these methods underscore the need for development of additional study designs to facilitate incorporation of pharmacogenomic information into clinical care.¹⁰ Table 2 summarizes examples of pharmacogenomic variants for which potentially clinically actionable pharmacogenomic variants exist. Common variants identified thus far likely leave a substantial portion of variability and heritability of drug effects unexplained, affirming the need for a more comprehensive approach to generating pharmacogenomic evidence. As drug therapy is refined to the individual, a paradigm shift occurs from using drugs based on average response, adverse drug reaction (ADR) prevalence, and trial and error drug administration to prescribing the drug and dose as accurately as possible before the drug is first administered.

Systems approaches provide alternative strategies to generating clinical evidence for pharmacogenomic relationships and establishing new ones. For instance, a recent study investigated novel genetic predictors for aspirin resistance using pathway analysis of

metabolomics signatures before and after treatment with aspirin and used this information to determine genomic variants associated with aspirin resistance.⁴⁶ This “pharmacometabolomics-informed pharmacogenomics” approach provides another illustration of the potential power of combining systems analysis and biological data to facilitate pharmacogenomic discovery and could be accomplished with relatively small patient sample sizes. Systems approaches and network analyses address several issues inherent in traditional evidentiary standards since they allow application of increasingly robust and inexpensive technologies, analysis of the role of rare variation, and interrogation of drug-gene and gene-environment interactions.

Operational issues in pharmacogenomic testing

As personalised clinical care is implemented, we will be required to coordinate vast amounts of biological data, use it to predict drug response phenotypes, and make manageable recommendations for clinicians. Comprehensive data from an EMR can be leveraged in a systems-based approach to model the complex interplay of biological data, output from laboratory tests and exams, and drug information. Systems approaches should enable researchers to leverage a wealth of biological data to understand more complex biological relationships and create more effective approaches to disease management. In addition, systems approaches can be combined with multiple disciplines to identify major impediments to clinical implementation of pharmacogenomics. Comparative effectiveness research (CER), social network analysis, and implementation sciences have the potential to identify key processes and barriers to implementation. Network structure and communication principles can be applied to maximize process efficiencies within a hospital setting.³³

In general, knowledge of genotype is most valuable at the start of pharmacotherapy. However, most genotyping results currently require days or weeks, by which time the patient encounter is over or the drug has already been administered⁴⁷ and even the fastest point of care tests take a minimum of sixty minutes.⁴⁸ In order to acquire a genotype for a patient, a clinician can order a genotype directly, an electronic environment might trigger genomic testing, or a pre-emptive genotyping approach can be used. (Figure 2) The logical extension for the concept of pre-emptive genotyping is a vision in which whole genome sequences are acquired at birth and then used over a lifetime for disease prevention and drug prescribing. At this point, however, the vast majority of sequence variation in the human genome is of uncertain clinical significance, and assay procedures and data storage and retrieval do not yet meet clinical standards for whole genome sequencing. Systems approaches can be integrated into clinical decision making by weighing the complex interplay of patient characteristics and the growing amount of dense biological data. Such biological data can be combined with patient characteristics including drug exposure, duration of exposure, genetic polymorphisms, results of laboratory tests, environmental factors, race/ethnicity, adherence, disease severity, age, and even pharmacoeconomic or psychosocial considerations, providing a more comprehensive model of a patient to provide personalised medicine. These systems could then be applied hierarchically to different cell types, organisms, populations, or other systems in which multiple perturbations affect phenotypic expression, and continuously inform new decision making and adapt to emerging data.

Professional education

Systems approaches also have the potential to improve targeted professional education by establishing important influences on clinical practice and information dissemination. In a survey of United States (US) physicians, 98 percent of respondents agreed that genetic variation may influence drug response, but only 10 percent felt adequately informed about

pharmacogenomic testing.⁴⁹ The results of this and a similar survey highlight a willingness to accept pharmacogenomics in practice but also insufficient education and lack of comfort among clinicians.⁵⁰ In light of expanding and increasingly complex pharmacogenomic information, practitioners will require additional education regarding fundamentals of pharmacogenomic medicine, interpretation of genetic test results, recognition of important pharmacogenomic variants, and clinical recommendations. Manual integration of an extensive and ever-changing pharmacogenomic knowledge base into the point of care is unreasonable for most clinicians.⁵¹ Provision of electronic decision support will mitigate the amount of specific knowledge required to make a prescribing decision, and to enable implementation of complex treatment algorithms.⁶ Social network analysis offers a means of mapping and exposing channels of communication and information flow, as well as information disconnects, between people in strategically important groups within an organization.³³ Social network analysis has provided valuable insight into what influences clinical patterns of providers and the roles of providers in disseminating and influencing clinical practice.³⁴ This approach would allow better understanding of diffusion of information and social influences in clinical settings and facilitate clinical implementation of pharmacogenomics by helping researchers to overcome important issues such as education, awareness, and social influence of opinion leaders.

Conclusion

Despite the potential utility of pharmacogenomics to improve patient care, clinical implementation of pharmacogenomics has been slow due to challenges such as setting evidentiary standards and addressing operational issues. Traditional study designs have limitations for evaluation of pharmacogenomic tests and new techniques are required to understand complex biological interactions. As future determinants of pharmacogenomic importance are elucidated, it will be important to consider them within a broader biological context, determine interactions of variants in complex systems, and evaluate clinical implementation strategies. By leveraging increasingly available biological, social, and financial data, systems approaches can be used to address limitations in currently available methods to both discover new pharmacogenomic variants and determine their clinical utility. If pharmacogenomics is to be instituted clinically on a larger scale, it is likely that new techniques will be necessary for evaluating both pharmacogenomic relationships and clinical pharmacogenomics implementation. Systems approaches have the potential to inform clinical decision-making by facilitating discovery and enabling translation of pharmacogenomics into clinical care.

References

1. Kalow W, Tang BK, Endrenyi L. Hypothesis: comparisons of inter- and intra-individual variations can substitute for twin studies in drug research. *Pharmacogenetics*. 1998; 8:283–289. [PubMed: 9731714]
2. Collins FS, McKusick VA. Implications of the Human Genome Project for medical science. *JAMA*. 2001; 285:540–544. [PubMed: 11176855]
3. Clayton TA, Lindon JC, Cloarec O, Antti H, Charuel C, Hanton G, Provost JP, Le Net JL, Baker D, Walley RJ, et al. Pharmacometabonomic phenotyping and personalized drug treatment. *Nature*. 2006; 440:1073–1077. [PubMed: 16625200]
4. Ahn K, Luo J, Berg A, Keefe D, Wu R. Functional mapping of drug response with pharmacodynamic-pharmacokinetic principles. *Trends Pharmacol Sci*. 2010; 31:306–311. [PubMed: 20488563]
5. Johnson JA, Elsey AR, Clare-Salzler MJ, Nessler D, Conlon M, Nelson DR. Institutional Profile: University of Florida and Shands Hospital Personalized Medicine Program: clinical implementation of pharmacogenetics. *Pharmacogenomics*. 2013; 14:723–726. [PubMed: 23651020]

6. Pulley JM, Denny JC, Peterson JF, Bernard GR, Vnencak-Jones CL, Ramirez AH, Delaney JT, Bowton E, Brothers K, Johnson K, et al. Operational implementation of prospective genotyping for personalized medicine: the design of the Vanderbilt PREDICT project. *Clin Pharmacol Ther.* 2012; 92:87–95. [PubMed: 22588608]
7. Crews KR, Cross SJ, McCormick JN, Baker DK, Molinelli AR, Mullins R, Relling MV, Hoffman JM. Development and implementation of a pharmacist-managed clinical pharmacogenetics service. *Am J Health Syst Pharm.* 2011; 68:143–150. [PubMed: 21200062]
8. O'Donnell PH, Bush A, Spitz J, Danahey K, Saner D, Das S, Cox NJ, Ratain MJ. The 1200 patients project: creating a new medical model system for clinical implementation of pharmacogenomics. *Clin Pharmacol Ther.* 2012; 92:446–449. [PubMed: 22929923]
9. Shuldiner AR, Relling MV, Peterson JF, Hicks K, Freimuth RR, Sadee W, Pereira NL, Roden DM, Johnson JA, Klein TE. The Pharmacogenomics Research Network Translational Pharmacogenetics Program: Overcoming Challenges of Real-World Implementation. *Clin Pharmacol Ther.* 2013
10. Koster ES, Rodin AS, Raaijmakers JA, Maitland-van der Zee AH. Systems biology in pharmacogenomic research: the way to personalized prescribing? *Pharmacogenomics.* 2009; 10:971–981. [PubMed: 19530964]
11. Rodin AS, Gogoshin G, Boerwinkle E. Systems biology data analysis methodology in pharmacogenomics. *Pharmacogenomics.* 2011; 12:1349–1360. [PubMed: 21919609]
12. Mangravite LM, Engelhardt BE, Medina MW, Smith JD, Brown CD, Chasman DI, Mecham BH, Howie B, Shim H, Naidoo D, et al. A statin-dependent QTL for GATM expression is associated with statin-induced myopathy. *Nature.* 2013
13. Laaksonen R, Katajamaa M, Paiva H, Sysi-Aho M, Saarinen L, Junni P, Lutjohann D, Smet J, Van Coster R, Seppanen-Laakso T, et al. A systems biology strategy reveals biological pathways and plasma biomarker candidates for potentially toxic statin-induced changes in muscle. *PLoS One.* 2006; 1:e97. [PubMed: 17183729]
14. Tamada Y, Araki H, Imoto S, Nagasaki M, Doi A, Nakanishi Y, Tomiyasu Y, Yasuda K, Dunmore B, Sanders D, et al. Unraveling dynamic activities of autocrine pathways that control drug-response transcriptome networks. *Pac Symp Biocomput.* 2009:251–263. [PubMed: 19209706]
15. Araki H, Tamada Y, Imoto S, Dunmore B, Sanders D, Humphrey S, Nagasaki M, Doi A, Nakanishi Y, Yasuda K, et al. Analysis of PPARalpha-dependent and PPARalpha-independent transcript regulation following fenofibrate treatment of human endothelial cells. *Angiogenesis.* 2009; 12:221–229. [PubMed: 19357976]
16. Milan DJ, Kim AM, Winterfield JR, Jones IL, Pfeufer A, Sanna S, Arking DE, Amsterdam AH, Sabeh KM, Mably JD, et al. Drug-sensitized zebrafish screen identifies multiple genes, including GINS3, as regulators of myocardial repolarization. *Circulation.* 2009; 120:553–559. [PubMed: 19652097]
17. Jonsson MKB, Vos MA, Mirams GR, Duker G, Sartipy P, de Boer TP, van Veen TAB. Application of human stem cell-derived cardiomyocytes in safety pharmacology requires caution beyond hERG. *Journal of Molecular and Cellular Cardiology.* 2012; 52:998–1008. [PubMed: 22353256]
18. Liang P, Lan F, Lee AS, Gong T, Sanchez-Freire V, Wang Y, Diecke S, Sallam K, Knowles JW, Wang PJ, et al. Drug Screening Using a Library of Human Induced Pluripotent Stem Cell-Derived Cardiomyocytes Reveals Disease-Specific Patterns of Cardiotoxicity. *Circulation.* 2013; 127:1677–1691. [PubMed: 23519760]
19. Dahlin A, Tantisira KG. Integrative systems biology approaches in asthma pharmacogenomics. *Pharmacogenomics.* 2012; 13:1387–1404. [PubMed: 22966888]
20. Himes BE, Wu AC, Duan QL, Klanderma B, Litonjua AA, Tantisira K, Ramoni MF, Weiss ST. Predicting response to short-acting bronchodilator medication using Bayesian networks. *Pharmacogenomics.* 2009; 10:1393–1412. [PubMed: 19761364]
21. Hakonarson H, Bjornsdottir US, Halapi E, Bradfield J, Zink F, Mouy M, Helgadottir H, Gudmundsdottir AS, Andrasen H, Adalsteinsdottir AE, et al. Profiling of genes expressed in peripheral blood mononuclear cells predicts glucocorticoid sensitivity in asthma patients. *Proc Natl Acad Sci U S A.* 2005; 102:14789–14794. [PubMed: 16203992]

22. Novershtern N, Itzhaki Z, Manor O, Friedman N, Kaminski N. A functional and regulatory map of asthma. *Am J Respir Cell Mol Biol*. 2008; 38:324–336. [PubMed: 17921359]
23. Lara J, Xia G, Purdy M, Khudyakov Y. Coevolution of the hepatitis C virus polyprotein sites in patients on combined pegylated interferon and ribavirin therapy. *J Virol*. 2011; 85:3649–3663. [PubMed: 21248044]
24. Deforche K, Camacho RJ, Grossman Z, Soares MA, Van Laethem K, Katzenstein DA, Harrigan PR, Kantor R, Shafer R, Vandamme AM. Bayesian network analyses of resistance pathways against efavirenz and nevirapine. *AIDS*. 2008; 22:2107–2115. [PubMed: 18832874]
25. Kohane IS. Using electronic health records to drive discovery in disease genomics. *Nat Rev Genet*. 2011; 12:417–428. [PubMed: 21587298]
26. Daly AK. Genome-wide association studies in pharmacogenomics. *Nat Rev Genet*. 2010; 11:241–246. [PubMed: 20300088]
27. Khoury MJ, Gwinn ML, Glasgow RE, Kramer BS. A population approach to precision medicine. *Am J Prev Med*. 2012; 42:639–645. [PubMed: 22608383]
28. Hamburg MA, Collins FS. The path to personalized medicine. *N Engl J Med*. 2010; 363:301–304. [PubMed: 20551152]
29. Galea S, Riddle M, Kaplan GA. Causal thinking and complex system approaches in epidemiology. *Int J Epidemiol*. 2010; 39:97–106. [PubMed: 19820105]
30. Veenstra DL, Roth JA, Garrison LP Jr, Ramsey SD, Burke W. A formal risk-benefit framework for genomic tests: facilitating the appropriate translation of genomics into clinical practice. *Genet Med*. 2010; 12:686–693. [PubMed: 20808229]
31. Kangelaris KN, Bent S, Nussbaum RL, Garcia DA, Tice JA. Genetic testing before anticoagulation? A systematic review of pharmacogenetic dosing of warfarin. *J Gen Intern Med*. 2009; 24:656–664. [PubMed: 19306050]
32. Khoury MJ, Gwinn M, Bowen MS, Dotson WD. Beyond base pairs to bedside: a population perspective on how genomics can improve health. *Am J Public Health*. 2012; 102:34–37. [PubMed: 22095352]
33. Chambers D, Wilson P, Thompson C, Harden M. Social network analysis in healthcare settings: a systematic scoping review. *PLoS One*. 2012; 7:e41911. [PubMed: 22870261]
34. Anderson JG. Evaluation in health informatics: social network analysis. *Comput Biol Med*. 2002; 32:179–193. [PubMed: 11922934]
35. Samarth CN, Gloor PA. Process efficiency. Redesigning social networks to improve surgery patient flow. *J Healthc Inf Manag*. 2009; 23:20–26. [PubMed: 19181197]
36. Benham-Hutchins MM, Effken JA. Multi-professional patterns and methods of communication during patient handoffs. *Int J Med Inform*. 2010; 79:252–267. [PubMed: 20079686]
37. Sykes TA, Venkatesh V, Rai A. Explaining physicians' use of EMR systems and performance in the shakedown phase. *J Am Med Inform Assoc*. 2011; 18:125–130. [PubMed: 21292704]
38. Aberg JA, Kaplan JE, Libman H, Emmanuel P, Anderson JR, Stone VE, Oleske JM, Currier JS, Gallant JE. Primary care guidelines for the management of persons infected with human immunodeficiency virus: 2009 update by the HIV medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis*. 2009; 49:651–681. [PubMed: 19640227]
39. Gazzard BG, Anderson J, Babiker A, Boffito M, Brook G, Brough G, Churchill D, Cromarty B, Das S, Fisher M, et al. British HIV Association Guidelines for the treatment of HIV-1-infected adults with antiretroviral therapy 2008. *HIV Med*. 2008; 9:563–608. [PubMed: 18826546]
40. Martin MA, Klein TE, Dong BJ, Pirmohamed M, Haas DW, Kroetz DL. Clinical pharmacogenetics implementation consortium guidelines for HLA-B genotype and abacavir dosing. *Clin Pharmacol Ther*. 2012; 91:734–738. [PubMed: 22378157]
41. Johnson JA, Gong L, Whirl-Carrillo M, Gage BF, Scott SA, Stein CM, Anderson JL, Kimmel SE, Lee MT, Pirmohamed M, et al. Clinical Pharmacogenetics Implementation Consortium Guidelines for CYP2C9 and VKORC1 genotypes and warfarin dosing. *Clin Pharmacol Ther*. 2011; 90:625–629. [PubMed: 21900891]
42. Scott SA, Sangkuhl K, Gardner EE, Stein CM, Hulot JS, Johnson JA, Roden DM, Klein TE, Shuldiner AR. Clinical Pharmacogenetics Implementation Consortium guidelines for cytochrome

- P450-2C19 (CYP2C19) genotype and clopidogrel therapy. *Clin Pharmacol Ther.* 2011; 90:328–332. [PubMed: 21716271]
43. Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE Jr, Chavey WE 2nd, Fesmire FM, Hochman JS, Levin TN, et al. 2012 ACCF/AHA Focused Update Incorporated Into the ACCF/AHA 2007 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2013
 44. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, Chambers CE, Ellis SG, Guyton RA, Hollenberg SM, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *Catheter Cardiovasc Interv.* 2012; 79:453–495. [PubMed: 22328235]
 45. Mrazek DA, Lerman C. Facilitating clinical implementation of pharmacogenomics. *JAMA.* 2011; 306:304–305. [PubMed: 21771991]
 46. Yerges-Armstrong LM, Ellero-Simatos S, Georgiades A, Zhu H, Lewis JP, Horenstein RB, Beitelshes AL, Dane A, Reijmers T, Hankemeier T, et al. Purine pathway implicated in mechanism of resistance to aspirin therapy: pharmacometabolomics-informed pharmacogenomics. *Clin Pharmacol Ther.* 2013; 94:525–532. [PubMed: 23839601]
 47. Scott SA. Clinical pharmacogenomics: opportunities and challenges at point of care. *Clin Pharmacol Ther.* 2013; 93:33–35. [PubMed: 23212102]
 48. Roberts JD, Wells GA, Le May MR, Labinaz M, Glover C, Froeschl M, Dick A, Marquis JF, O'Brien E, Goncalves S, et al. Point-of-care genetic testing for personalisation of antiplatelet treatment (RAPID GENE): a prospective, randomised, proof-of-concept trial. *Lancet.* 2012; 379:1705–1711. [PubMed: 22464343]
 49. Stanek EJ, Sanders CL, Taber KA, Khalid M, Patel A, Verbrugge RR, Agatep BC, Aubert RE, Epstein RS, Frueh FW. Adoption of pharmacogenomic testing by US physicians: results of a nationwide survey. *Clin Pharmacol Ther.* 2012; 91:450–458. [PubMed: 22278335]
 50. Haga SB, Burke W, Ginsburg GS, Mills R, Agans R. Primary care physicians' knowledge of and experience with pharmacogenetic testing. *Clin Genet.* 2012; 82:388–394. [PubMed: 22698141]
 51. Stead WW, Searle JR, Fessler HE, Smith JW, Shortliffe EH. Biomedical informatics: changing what physicians need to know and how they learn. *Acad Med.* 2011; 86:429–434. [PubMed: 20711055]
 52. Mallal S, Phillips E, Carosi G, Molina JM, Workman C, Tomazic J, Jagel-Guedes E, Rugina S, Kozyrev O, Cid JF, et al. HLA-B*5701 screening for hypersensitivity to abacavir. *N Engl J Med.* 2008; 358:568–579. [PubMed: 18256392]
 53. Link E, Parish S, Armitage J, Bowman L, Heath S, Matsuda F, Gut I, Lathrop M, Collins R. SLCO1B1 variants and statin-induced myopathy--a genomewide study. *N Engl J Med.* 2008; 359:789–799. [PubMed: 18650507]
 54. Anstey AV, Wakelin S, Reynolds NJ. Guidelines for prescribing azathioprine in dermatology. *Br J Dermatol.* 2004; 151:1123–1132. [PubMed: 15606506]

Figure 1.

Two views of drug action. In the top row (panels 1A & 2A), the healthy individual is modelled as a system of interacting nodes, each of represents a molecular entity or set of molecules. In panel 1B, disease is represented by over-activity (dark green) of a single molecule. In panel 1C, a targeted drug returns activity to normal and restores health. However, disease may also result from changes in interactions (shown in red/blue) that may result in increased (γ_2) or decreased (light green, α_1) molecular abundance or activity (panel 2B). Administration of a drug corrects some of these perturbations, returning the system towards health (panel 2C). However, the system as a whole still manifests abnormal activity. Thus, in situations in which a single molecular lesion causes a disease, drug may be curative. In situations of complex disease or coexisting pathophysiology, this outcome is less likely.

Figure 2.

Operational aspects of genotyping for pharmacogenomic variants from point of drug prescription to genotype-guided drug or dose

Table 1**Major Challenges and Potential Solutions for Clinical Implementation of Pharmacogenomics**

Major Challenges	Potential Solutions
Defining variants as clinically actionable	
clinically actionable variant identification	new research strategies including systems biology and statistical techniques
Designate best clinical use of genetic data	further research into pharmacogenomic effects; guidelines development
Setting a standard of evidence	
characterization of true pharmacogenomic effects	targeted research strategies; conduct RCTs when feasible
genetic exceptionalism and a lack of RCTs	change standard of evidence; new research strategies; conduct RCTs when feasible
determining effects of rare variants or variants with low effect sizes	new research strategies including systems biology and statistical techniques; whole genome sequencing studies; implementation of a “learning healthcare system”
Operational issues in pharmacogenomic testing	
test initiation	pre-emptive testing; automatic testing at prescription
test availability and cost	custom pharmacogenomic arrays; CLIA approval; establish and improve genotyping infrastructure
delay in test results	pre-emptive testing; develop point of care testing techniques
selection of patients to receive test	development of patient selection and phenotypic risk models
Professional knowledge and education	
practitioner knowledge, training, and comfort	develop guidelines; provide decision support and expert consultations; incorporate into training
standardized reporting of results	develop guidelines; develop standardized/intuitive mutation nomenclature
test result interpretation	develop guidelines; create standardized genotype- phenotype conversions; P&T committee guidance
Bioinformatic challenges	
decision support and standardized EMR incorporation	bioinformatics infrastructure and decision support development
storage/security of genetic data	legislation for genetic information protection; bioinformatics infrastructure; digital safeguards
dissemination of implementation tools	develop universal EMR; establish best practices/guidelines for clinical implementation
Ethical, legal, and social issues	
patient attitudes/acceptance	legislation for genetic information protection; patient and provider education
access to genetic information	digital safeguards; legislation for genetic information protection
disclosure of genetic information and incidental findings	rules for genetic data access and reporting to patients and family members

CLIA indicates Clinical Laboratory Improvement Amendments, EMR electronic medical record, RCT randomised controlled trial, P&T pharmacy and therapeutics

Table 2
Examples of clinically actionable variants in pharmacogenomics and evidence supporting use in practice

Drug/drug class	Gene/mutation	Clinical recommendation (approved indication, CPIC, FDA label)	Clinical endorsement(s)	Major supporting evidence
abacavir	<i>HLA-B*5701</i>	test all abacavir-naïve patients and avoid drug to prevent ADR (standard of care)	clinical guidelines, ^{38, 39} CPIC, FDA label	RCT, ⁵² retrospective and prospective associations, replication in multiple populations/ethnicities
allopurinol	<i>HLA-B*5801</i>	alternative drug recommendation	CPIC	retrospective associations, replication in multiple populations/ethnicities
carbamazepine	<i>HLA-B*1502</i>	alternative drug recommendation	FDA label, CPIC	retrospective associations, replication in multiple populations/single ethnic group
clopidogrel	<i>CYP2C19*2*3</i>	alternative drug recommendation	FDA label and Boxed Warning, CPIC	retrospective and prospective associations, replication in multiple populations/ethnicities ^a
codeine	<i>CYP2D6^b</i>	alternative drug/dose recommendation	FDA label, CPIC	retrospective and prospective associations, replication in multiple populations/ethnicities
simvastatin	<i>SLCO1B1*5</i>	alternative drug/dose recommendation	CPIC	Retrospective study, ⁵³ replication
tacrolimus	<i>CYP3A^{5b}</i>	dose modification	-	retrospective and prospective associations, replication in multiple populations/ethnicities
thiopurines ^c	TPMT ^b	modify dose based on genotype	clinical guidelines, ⁵⁴ CPIC, FDA label	retrospective and prospective associations, replication in multiple populations/ethnicities
tricyclic antidepressants ^d	<i>CYP2D6^b</i> <i>CYP2C19^b</i>	dose modification or use avoidance	FDA label, CPIC	retrospective and prospective associations, replication in multiple populations/ethnicities
warfarin	<i>CYP2C9 *2/*3</i> <i>VKORC1 -1639G>A</i>	Dose modification based on pharmacogenomic algorithm	FDA label, CPIC	retrospective and prospective associations, replication in multiple populations/ethnicities ^a

CLIA indicates Clinical Laboratory Improvement Amendments, CPIC Clinical Pharmacogenomics Implementation Consortium, FDA Food and Drug Administration, TPMT thiopurine methyltransferase.

^aRCT currently in progress

^bmultiple variants within gene are potentially clinically actionable for relevant drug(s)

^cinclude azathioprine, mercaptopurine, and thioguanine

^dapply primarily to amitriptyline and nortriptyline, but may be extrapolated to other tricyclic antidepressants