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Pharmacogenomics: Precision Medicine and Drug Response

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Abstract

Pharmacogenomics is the use of genomic and other “omic” information to individualize drug selection and drug use in order to avoid adverse drug reactions and to maximize drug efficacy. The science underlying pharmacogenomics has evolved rapidly over the 50 years since it was first suggested that genetics might influence drug response phenotypes. That process has occurred in parallel with advances in DNA sequencing and other molecular technologies, with striking increases in our understanding of the human genome. There are now many validated examples of the clinical utility of pharmacogenomics, and this type of clinical genomic information is increasingly being generated in clinical laboratories, incorporated into electronic health records (EHRs) and used to “tailor” or individualize drug therapy. This review will survey the origins and development of pharmacogenomics; it will address some of the challenges associated with the clinical implementation of pharmacogenomics; and it will attempt to foresee future advances in this important genomic discipline, one that almost certainly will be among the earliest and most widely adopted aspects of clinical genomics.

Keywords

Pharmacogenetics; Pharmacogenomics; Pharmaco-omics; Genomics; Adverse drug reactions; Drug efficacy; Precision medicine

INTRODUCTION

Pharmacogenomics is the study of the contribution of genomics and of other “omics” to individual variation in drug response phenotypes.^{1–3} That variation can range from inadequate therapeutic efficacy to serious, potentially life threatening adverse drug reactions. Pharmacogenomic information is increasingly being integrated into electronic health records (EHRs) and that information is rapidly becoming an important component of the

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DISCLOSURES

Drs. Wang and Weinshilboum are co-founders and stockholders in One

“therapeutic encounter”. As a result, pharmacogenomics is the aspect of clinical genomics that will almost certainly see the earliest and broadest clinical implementation—with the potential to eventually touch the care of every patient everywhere. In subsequent paragraphs, we will briefly review the origins and development of this important aspect of “rational therapeutics”, touch briefly on the science underlying pharmacogenomics, address challenges associated with the clinical implementation of this aspect of genomic science and, finally, describe a vision for a future in which “pharmacogenomics” will have evolved into “pharmaco-omics” and will be an integral component of every medical drug-related therapeutic decision.

PHARMACOGENOMICS: ORIGINS AND DEVELOPMENT

The concept of “pharmacogenetics” was first put forward by the famed American geneticist Arno Moltulsky over a half century ago⁴ at a time when it was already becoming clear that variation in drug response could be due, at least in part, to the effects of genetic inheritance. Subsequently, a steady stream of reports appeared that described the contribution of genetics to variation in drug effect. Those examples most often involved pharmacokinetics (PK), i.e., factors that influence the concentration of drug that will ultimately reach the therapeutic target. Of those PK factors, most important was genetic variation in the expression and function of drug metabolizing enzymes, enzymes that can influence plasma drug concentrations. Included among early pioneers in pharmacogenomic research were Werner Kalow at the University of Toronto with his studies of butyrylcholinesterase genetic variation and prolonged apnea after treatment with the muscle relaxant succinylcholine,^{5, 6} and David Price Evans at John’s Hopkins who pursued earlier reports⁷ of genetic variation in the N-acetylation of the anti-tuberculosis drug isoniazid.^{8, 9} Subsequently, genetic variation in the thiopurine S-methyltransferase (TPMT) enzyme that was associated with potentially life-threatening myelosuppression after treatment with the antineoplastic and immunosuppressant agents mercaptopurine and azathioprine, substrates for metabolism by TPMT,^{10, 11} was reported, as was genetic variation in another drug metabolizing enzyme, cytochrome P-450 (CYP) 2D6^{12, 13}, that was associated with variation in plasma concentrations and the therapeutic effects of a variety of drugs.^{14, 15} These early examples were discovered at a time before genes were being cloned and sequenced, and they were most often shown to be genetic on the basis of family studies—using techniques similar in principal to those applied by Mendel in the preceding century when he performed his famous breeding studies with peas. However, primitive though they may appear when viewed from the perspective of the present “Post-Human Genome Project” world, these early examples have stood the test of time and are now well understood mechanistically. They also served as a powerful stimulus that set the stage for a series of systematic attempts to identify, study, and determine the clinical implications for drug response of genetic variation within whole families of genes encoding drug metabolizing enzymes, drug transporters and drug targets. Initially, the majority of those studies continued to focus on PK. One reason for that focus was the fact that variation in PK genes was often associated with relatively easily measured phenotypes, blood drug and drug metabolite concentrations, phenotypes that were often associated with variation in clinical drug response. It should be emphasized that even these early examples served to illustrate that pharmacogenetic

variation could result in both serious adverse drug reactions and/or striking variation in drug efficacy. It should also be pointed out that drug metabolism may be required to “metabolically activate” a “prodrug”, a process that can also be significantly influenced by genetic variation in the biotransformation of the prodrug. We should also make it clear that metabolism is only one of many processes that can result in individual differences in drug response. For example, several severe adverse drug reactions can be predicted and prevented by knowledge of sequence variation involving HLA genes (<http://www.allelefrequencies.net/hla-adr/default.asp>).

During the late 1980s and throughout the 1990s—prior to completion of the Human Genome Project—pharmacogenomic research often involved cloning and sequencing genes encoding proteins that might contribute to variation in drug response phenotypes. Those studies demonstrated that much of the genetic variation in drug response that had been reported previously resulted from common sequence variation within or near genes that encoded the enzymes that had originally been studied as phenotypes, i.e., “high” or “low” levels of enzyme activity. The fact that pharmacogenomic variation was often due to common genetic polymorphisms will come up again subsequently when we cite evidence that every member of our species carries many potentially clinically actionable pharmacogenomic variants. The studies performed during the decade of the 1990s often focused on isoforms of the cytochrome P-450s (CYPs) as an extremely important family of drug metabolizing enzymes^{14, 15}, but they also included other, so-called Phase II or conjugating drug metabolizing enzymes such as the sulfotransferases (SULTs),^{16, 17} methyltransferases (MTs) like TPMT^{18, 19} and UDP-glucuronosyltransferases (UGTs).^{20–22} Although research of that era predominately focused on gene cloning, gene sequencing and functional characterization of allozymes encoded by variant gene sequences, it was also during that time that we began to understand molecular mechanisms responsible for the functional effects of common genetic variation in those genes. For example, TPMT, as mentioned previously, catalyzes S-methylation, a reaction that inactivates thiopurine drugs such as azathioprine. The most common *TPMT* variant allele in European populations, *TPMT*3A*, with a minor allele frequency (MAF) of approximately 5%, resulting in one of every 300 European subjects being homozygous for this variant—is due to two nonsynonymous (ns) single nucleotide polymorphisms (SNPs) in the *TPMT* gene.^{23, 24} Those two changes in nucleotide sequence result in the alteration of two amino acids in the TPMT protein. The protein encoded by *TPMT*3A* is translated, but it misfolds and is rapidly degraded,^{25–27} with resultant lack of the enzyme and inability to metabolize thiopurines, leading to a ten-fold “overdose” of these cytotoxic agents when “standard” doses of thiopurines are administered to patients who are homozygous for *TPMT*3A*. Another example illustrating a different type of mechanism involved genetic variation in the TATA box in the promoter for the *UGT1A1* gene that encodes a protein that metabolizes bilirubin as well as drugs such as the antineoplastic agent irinotecan. Most people have six “TA” elements in this TATA box, but some subjects have seven rather than six, and they display decreased expression of both *UGT1A1* messenger RNA and protein—resulting in Gilbert’s Syndrome because of reduced bilirubin metabolism and, when they are exposed to irinotecan, an increased incidence of adverse drug reactions such as diarrhea and myelosuppression.^{21, 22} These examples and many others illustrate why, at the beginning of the 21st century, with completion of the Human Genome Project,

the stage had been set to move forward quickly with both pharmacogenomic discovery and pharmacogenomic clinical implementation. In a display of the potential power of public-private collaboration, those efforts were enabled by and greatly stimulated in the United States by National Institutes of Health (NIH) funded Pharmacogenomics Research Network (PGRN) grants from by the National Institute of General Medical Sciences (NIGMS) and eMERGE grants from the National Human Genome Research Institute (NHGRI)—public funding that not only served to drive discovery by providing access to new and very expensive techniques such as genome-wide association studies (GWAS) and Next Generation Sequencing (NGS) but which also acted as a strong stimulus for the clinical implementation of pharmacogenomics. This brief overview should make it clear that pharmacogenomics as a discipline progressed in parallel with the maturation of genomic science during the latter decades of the twentieth century and the opening decades of the twenty first century.

The progress that has been made in identifying, characterizing and determining the clinical utility of pharmacogenomic variants since Motulsky first suggested that genetics might influence drug response is illustrated in striking fashion by the information listed in Table 1 which represents a modified version of the US FDA Pharmacogenomics website (<https://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm>) that lists drugs for which there are pharmacogenomic biomarkers with demonstrated clinical utility. It should be noted that Table 1 does not include drugs that are used primarily in oncology, but that information can also be found on the FDA website. The information listed in Table 1 also serves to emphasize that virtually every medical discipline is touched by pharmacogenomics, which immediately raises the question of how we can make this information available to practitioners in an easily accessible and usable fashion, topics addressed in subsequent paragraphs.

PHARMACOGENOMICS: CLINICAL IMPLEMENTATION

The rapid growth of clinically relevant pharmacogenomic knowledge, as illustrated by the 127 drugs listed in Table 1, drugs used to treat patients in virtually every medical specialty, serves to highlight the challenges associated with pharmacogenomic implementation, one of which is that of making this information available to practitioners in a practical and easily understood fashion. To do that requires—among other important steps--objective, evidence-based guidelines and investment in the infrastructure required to make pharmacogenomic information accessible to physicians in a timely fashion. Physicians and other care-givers write prescriptions for drugs, not genes, so the approach that most institutions have taken is to focus on drug-gene pairs. Fortunately, the development of pharmacogenomics has occurred in parallel with the adoption of electronic health records (EHRs)—a development required for the storage of ever expanding genomic data as well as the tools required to instantly deliver that information to prescribers, preferably at the point of care, often while the prescription is being written. Of course, it always remains possible for a physician to order a specific pharmacogenomic test, either genotype-based—i.e., a test the queries only specific nucleotides that we currently know are of functional significance--or sequence-based, for a gene or genes known to be associated with variation in response to a specific drug or drugs. However, pharmacogenomic testing is moving increasingly to the use of

panels of “pharmacogenes” that simultaneously test most of the genes that contribute to variation in response to commonly prescribed drugs for which there is evidence of pharmacogenomic clinical utility. To assist care-givers, many institutions have created automatic computer-based alerts that “fire” whenever a drug is prescribed for which a pharmacogenomic test might provide helpful information. For example, at the Mayo Clinic 17 drug-gene pair alerts currently fire when a prescription is first written for a drug that is included among those 17 drug-gene pairs (see Table 2). As at many medical centers, review and approval of the implementation of these alerts is the responsibility of a subcommittee of the Formulary Committee. Decision making with regard to the implementation of an alert depends on evidence-based guidelines that come from sources such as CPIC, the Clinical Pharmacogenetics Implementation Consortium (<https://cpicpgx.org/guidelines/>), a collaboration between the PGRN and the PharmGKB database or a similar European consortium, the Dutch Pharmacogenetics Working Group. It should be emphasized that, even though this review has generally focused on North American pharmacogenomic discovery and implementation efforts, these efforts are truly international in scope—as illustrated, for example, by the European “Ubiquitous Pharmacogenomics Consortium.”²⁸ Current drug-gene pair alerts are primarily “reactive”, ie, they require that the physician—on the basis of his or her goals for the patient—order the genetic test in response to the alert. Although an important first step, reactive alerts represent only one step toward the eventual goal, which would involve having pharmacogenomic data for a specific patient “preemptively” available in the EHR so there will be no delay associated with waiting for a test result so the pharmacogenomic information can be incorporated into the clinical workflow seamlessly.

Some academic medical centers are already experimenting with “preemptive” pharmacogenomic alerts. For example, the PGRN Centers, as a group, supported a “Deep Sequencing” facility that developed an NGS reagent that initially included 84 pharmacogenes that were “captured” and sequenced across exons and splice junctions—thus making it possible to obtain information with regard to both known, functionally significant variants as well as many “variants of unknown significance” (VUS). One of the challenges facing pharmacogenomics will be the development of high throughput methods that will make it possible to functionally characterize the very large number of VUS identified when we apply NGS to DNA samples from a large number of patients. For example, if we just select two common and intensively studied cytochrome P-450 (CYP) genes, *CYP2C9* and *CYP2C19*, genes that encode enzymes that metabolize the anticoagulant agents warfarin and clopidogrel, respectively, we can compare what we currently know about these two highly studied genes with what we need to know. To determine what “we know”, we went to “The Human Cytochrome P450 Allele Nomenclature Database” at the Karolinska in Stockholm (<http://www.cypalleles.ki.se>). That canonical database for CYP genes and enzymes listed 165 missense variants for *CYP2C9* and 189 for *CYP2C19*. Of those variants, only 29 *CYP2C9* variants had been functionally validated—20 in a laboratory setting, and only 26 for *CYP2C19*—7 in a laboratory setting. Meanwhile in 60,000 DNA samples for which exome sequence data had been reported by the Broad Institute,³³ there were 235 missense variants in *CYP2C9* and 258 in *CYP2C19*. These numbers indicate that we need to develop methods to rapidly screen the function of these variant allozymes to determine what they

might mean clinically. To place this task in context, a decade ago it would have been possible to justify a multi-year PhD thesis project for only a dozen variants in a single gene. This example represents a microcosm of the task that we face as more and more DNA sequence information becomes available. This coming tidal wave of DNA sequence information also raises the issue of the most efficient and cost-effective way to establish the clinical utility of novel pharmacogenomic information. It is clear that it will not be practical to perform a randomized clinical trial for all of these genomic variants, but the most practical way in which to do that remains a subject of continuing debate.

The NIH PGRN and eMERGE Networks have already begun to perform “pilot” studies designed to set the stage for more widespread clinical use of preemptive pharmacogenomic information. For example, each of the NIH eMERGE grant sites used the original “PGRN-seq” NGS reagent to sequence DNA samples from their biobanks. The Mayo Clinic, as one example, used this reagent to sequence 1013 DNA samples from the Mayo Biobank for local patients who had consented for their DNA to be used for research purposes. Patients participating in that “RIGHT” study—RIGHT drug at the RIGHT dose at the RIGHT time—now have DNA sequence information in the EHR for the 17 drug-gene pairs for which “reactive alerts” are currently firing at Mayo, but, in their case, if an alert fires, it will not inform the prescriber that a genetic test is available.^{29, 30} For these patients, the alert will instantly tell the care-giver the patients gene sequence with a clinical interpretation. For example, among those original 1013 subjects, if only five “common” pharmacogenes out of the 84 sequenced were included, 99.1% of the subjects had at least one actionable variant in at least one of those five genes—with many subjects having clinically actionable variant sequences in several of the five genes.³¹ This observation explains why, at the beginning of this overview, we made the statement that “pharmacogenomics is the aspect of clinical genomics that will almost certainly see the earliest and broadest clinical implementation—with the potential to eventually touch the care of every patient everywhere”. To follow up on those initial RIGHT study results, the Mayo Clinic Center for Individualized Medicine, in collaboration with the Baylor Human Genome Sequencing Center, is currently moving beyond the original 1013 biobank samples to consent and sequence 10,000 additional Mayo Biobank participants for a “RIGHT 10K” study designed to test the hypothesis that having preemptive pharmacogenomic information in the EHR might result in cost-effective health benefits for the patients involved—helping them to avoid adverse drug reactions and obtain maximum efficacy from drug therapy.

Finally, it goes without saying that the implementation of pharmacogenomics across a large academic medical center requires significant effort and significant resources. It is for that reason that we emphasized that NIH support provided by the PGRN and eMERGE grants acted as a valuable “catalyst” to move this aspect of genomic science to the bedside, but that this process must be a partnership with hospitals and medical centers, beginning with committed institutional leadership, engagement across multiple medical staffs that include physicians, nurses, allied health personnel and pharmacists, with significant investments required for the education for all of these groups, including patients, as well as infrastructural investment in information technology and the EHR. This may seem ambitious but—as outlined subsequently—we are only at the beginning of this process of discovery and implementation of genomics and other “omics” techniques to enhance drug therapy.

PHARMACOGENOMICS: FUTURE PROSPECTS

In this overview, we have described, briefly, the origins and development of pharmacogenomics as well as ongoing efforts to bring pharmacogenomics into the clinic and to make it a standard component of routine patient care. It might be useful to point out that the *TPMT* and *CYP2D6* genetic polymorphisms that we are currently “implementing” clinically were discovered over 35 years ago^{10–13} and that both have been known to have clinical utility for over a quarter of a century. The association of statin-induced myopathy with a SNP in the *SLCO1B1* gene was one of the early success stories for pharmacogenomic GWAS—but that occurred a decade ago.³² Therefore, the information that we are currently implementing in the clinic has been known for decades—or at least for a decade. Included among the questions that we should be asking ourselves now are what are the scientific challenges that face pharmacogenomics as we increasingly apply NGS and increasingly move genome-wide in our perspective as we attempt to apply genomics to “inform” drug selection and use; what other types of “omics” information might help to better inform the “therapeutic encounter”; how we can merge other “omic” information with genomic data; and what other types of information might help make drug selection and use as “rational” and as highly “individualized” as possible. Finally, we should point out that the processes of biomedical “discovery”, “translation” and “implementation” are not separate and distinct activities, but rather they are tightly intertwined and they inform each other, as illustrated graphically in Figure 1. In subsequent paragraphs, we will briefly outline challenges and possible future directions as genomic science is applied to drug response. That discussion will be followed by a description of recent efforts to move beyond genomics alone to include data from other “omics” disciplines, ie transcriptomics, epigenomics, proteomics and metabolomics, in combination with genomics (see Figure 2), to determine whether that might better inform our attempts to optimize and individualize drug therapy by moving beyond pharmacogenomics to what might be called “Pharmaco-omics”.

As pointed out previously, many of the earliest clinically relevant examples of pharmacogenomics involved genes that encoded drug metabolizing enzymes, drug transporters and drug targets, proteins that might logically be expected to influence drug response. Furthermore, there was also an emphasis on ns SNPs, nucleotide sequence changes in the portion of the gene that encodes protein—resulting in altered protein amino acid sequence. However, it is becoming increasingly clear now that a large number of GWAS for drug response have been performed, with both drug efficacy and adverse drug reactions as phenotypes, that—even though SNPs within the open reading frame of a gene can have a striking effect on function—many of the “top hit” SNPs identified during GWA studies are outside of the coding portion of the gene. Those SNPs often alter transcription and, as a result, they alter gene expression. That can occur, for example, if the SNP either creates or disrupts a transcription factor binding site, a DNA sequence that the transcription factor “recognizes” and binds to in the promoter of the gene or in so-called “enhancer” elements, DNA sequence motifs that can be located hundreds of thousands of base pairs away from the gene. There are now databases that can be used predict whether a SNP might create or disrupt a transcription factor binding site and there is also the GTEx database (<https://www.gtexportal.org/home/>), which, in a tissue-specific fashion, provides information

with regard to whether a specific SNP might be an “expression quantitative trait locus” (eQTL), ie whether that SNP is associated with variation in the level of mRNA expression. To complicate the situation even further, there is recent evidence that SNPs located hundreds of base pairs away from sites of transcription factor binding can have a profound effect on the binding of the transcription factor and on subsequent gene expression.^{33, 34} Since exome sequencing only covers about 1.5% of the genome, in the future we will need to move beyond the portion of the gene that encodes protein if we want to understand the functional implications of genetic polymorphisms. There can be no doubt that we are currently missing a great deal of information that might be important for our understanding of variation in drug response. Therefore, new, high throughput approaches will be needed to help us understand and use that information because we are being inundated by a tidal wave of data with regard to genomic sequence variation.³⁵ The issue of the extremely large number of ns SNP variants within the coding regions of genes and how we can quickly and accurately predict their functional implications that was mentioned previously is just one example of the fact that we are still only at the beginning of our understanding of the relationship of genomic sequence variation with clinically relevant variation in drug response phenotypes. There is no doubt that we will soon be dealing not with hundreds of potentially functionally significant variants for each gene, but rather with thousands. Even if we develop high throughput methods to determine which gene sequence or structural variants have functional implications, there is no way that a human being could possibly remember all of them, so sophisticated computerized systems will be a necessity—as will systems to convey this information to the health care team caring for the patient in a form that can be easily and quickly understood and used. If that is true of only genomics alone, how will we approach the integration of other “omics” information with genomics, information with regard to the transcriptome, the epigenome, the proteome, the metabolome and the microbiome?

The process of joining multiple “omics” datasets to us help make better informed therapeutic decisions represents a significant challenge. However, it is now commonplace to use both exome and RNA-seq data, ie to join genomics and transcriptomics, for a tumor to gain greater insight into underlying—potentially “druggable”—therapeutic targets. That process is also “pharmacogenomics”. Psychiatry represents another clinical discipline in which multiple “omics” have been joined. It is probably fair to say that the application of genomics alone has been somewhat disappointing in psychiatry—perhaps, at least in part, because the phenotypes in psychiatry have not yet been closely related to the underlying biology in same way that they have been in many other medical specialities. In an attempt to overcome that limitation, there have been recent attempts to “inform” genomic analyses by beginning with metabolomics data, determine which metabolite is most highly associated with the psychiatric phenotype (eg., Hamilton D Scores for patients with Major Depressive Disorder), perform a GWAS to identify genes associated with the concentration of the metabolite and then functionally validate the genes/SNPs that were identified during the GWAS.³⁶ These examples have begun to show us that, in the future, biomarkers for drug response might well be composed jointly of genomic data, transcriptomic data and metabolomic data, ie that we will be using “pharmaco-omics” to help us individualize and optimize drug therapy.

CONCLUSIONS

Pharmacogenomics is the application of genomic—and other “omic” information—to help guide, inform and individualize drug therapy. In the decades since Arno Motulsky first put forward the concept of pharmacogenetics, striking progress has been made and there can no longer be any doubt that drug efficacy and the occurrence of adverse drug reactions can both be influenced by genomics or that genomic information can be used to help maximize efficacy and minimize the occurrence of adverse drug reactions. That progress has occurred in parallel with the striking advances that have occurred in human genomics during the past half century. As outlined in preceding paragraphs, pharmacogenomics and pharmaco-omics are still young disciplines, but they are already moving into the clinic and are already being used to help physicians and other healthcare team members to make better and more highly individualized therapeutic decisions. A great remains to be done, and we are only at the beginning of the process of bringing this aspect of genomics to the bedside, but we will end this overview as we began. Pharmacogenomics is the aspect of clinical genomics that will almost certainly see the earliest and broadest clinical implementation—with the potential to eventually touch the care of every patient everywhere.

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ABBREVIATIONS

PK	Pharmacokinetics
NAT	N-Acetyltransferase
TPMT	Thiopurine S-methyltransferase
CYP	Cytochrome P-450
SULT	Sulfotransferase
MT	Methyltransferase
UGT	UDP-Glucuronosyltransferase
MAF	Minor allele frequency
ns	Nonsynonymous
NIH	National Institutes of Health
FDA	Food and Drug Administration
EHR	Electronic Health Record
VUS	Variants of Unknown Significance

NGS	Next Generation Sequencing
SNP	Single Nucleotide Polymorphism
GWAS	Genome-wide Association Study

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Pharmacogenetics-Pharmacogenomics

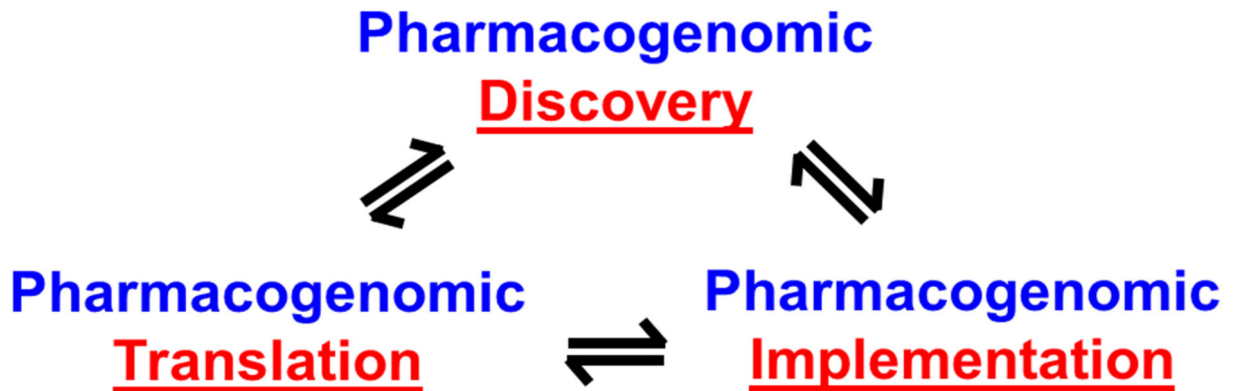


Figure 1.
Pharmacogenomic Discovery, Translation, Implementation

Pharmacogenomics to Pharmaco-Omics

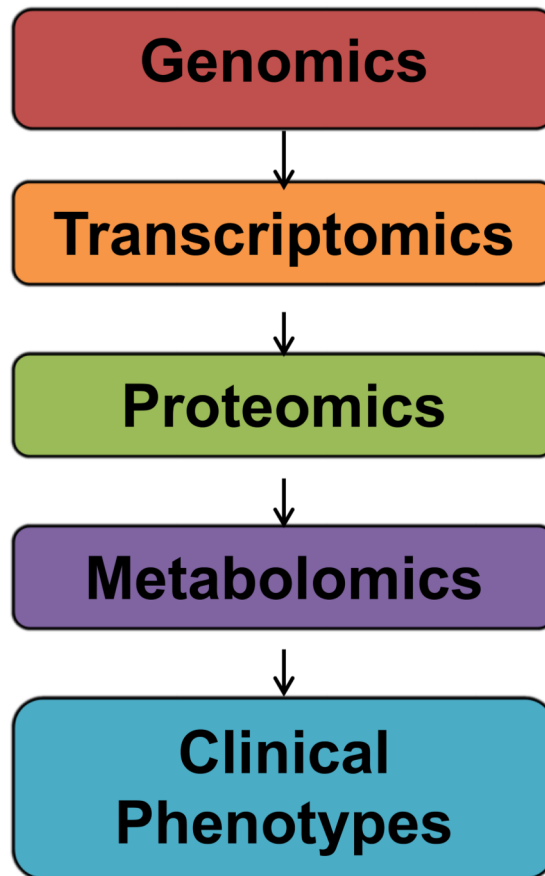


Figure 2.
Pharmacogenomics to Pharmaco-Omics

Pharmaco-omics The Future

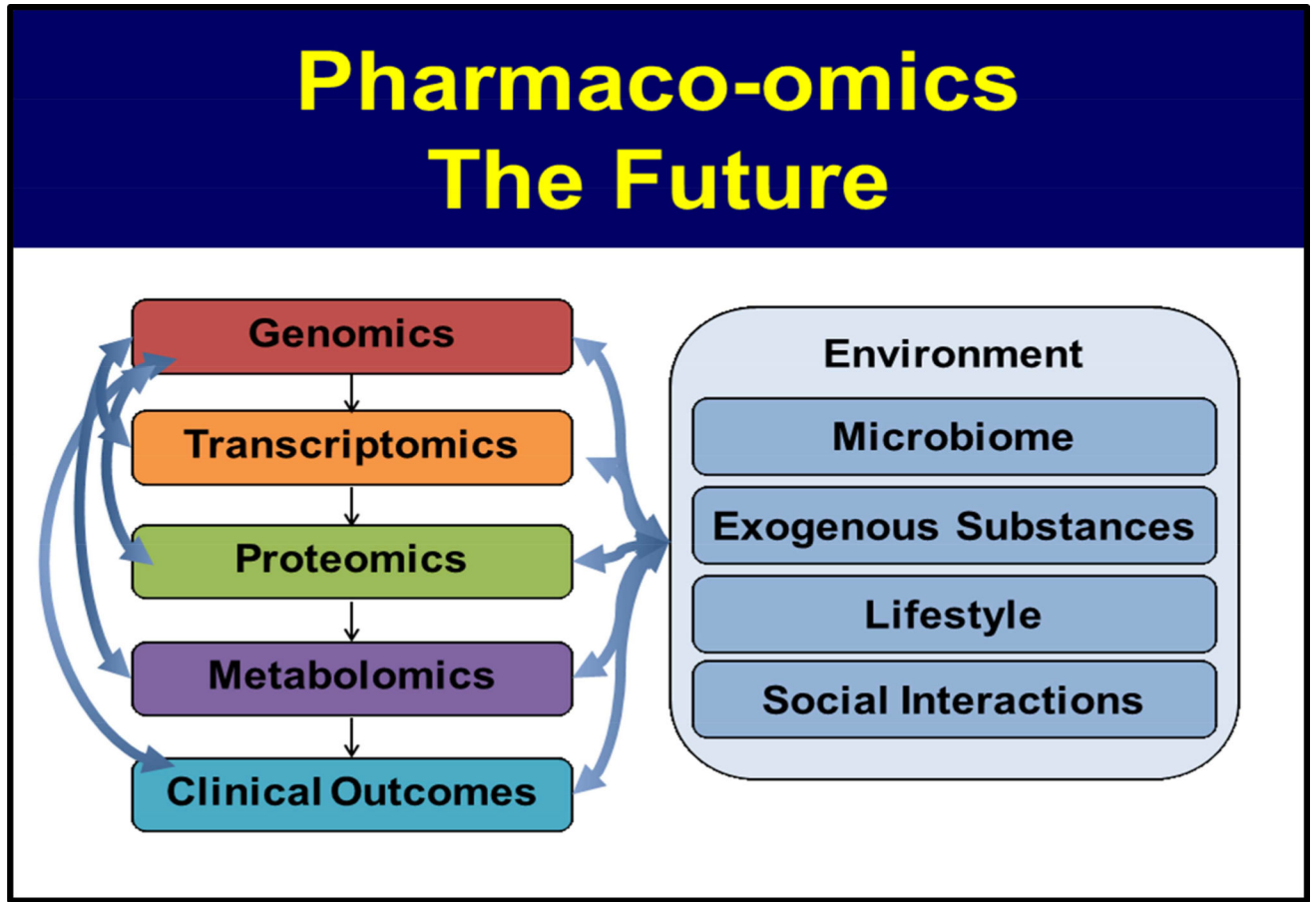


Figure 3.
Pharmaco-Omics, The Future

Table 1

FDA Pharmacogenomic Biomarkers for Non-Cancer Therapeutics. (Modified from the FDA Website to remove antineoplastic agents).

	Drug	Therapeutic Area	Biomarker
1	Abacavir	Infectious Diseases	HLA-B*57:01
2	Amitriptyline	Psychiatry	CYP2D6
3	Arformoterol	Pulmonary	UGT1A1, CYP2D6
4	Aripiprazole	Psychiatry	CYP2D6
5	Aripiprazole Lauroxil	Psychiatry	CYP2D6
6	Atomoxetine	Psychiatry	CYP2D6
7	Azathioprine	Rheumatology	TPMT
8	Boceprevir	Infectious Diseases	IFNL3 (IL28B)
9	Brexipiprazole	Psychiatry	CYP2D6
10	Brivaracetam	Neurology	CYP2C19
11	Carbamazepine	Neurology	HLA-B*15:02, HLA-A*31:01
12	Carglumic Acid	Inborn Errors of Metabolism	NAGS
13	Carisoprodol	Rheumatology	CYP2C19
14	Carvedilol	Cardiology	CYP2D6
15	Celecoxib	Rheumatology	CYP2C9
16	Cevimeline	Dental	CYP2D6
17	Chloroquine	Infectious Diseases	G6PD
18	Chlorpropamide	Endocrinology	G6PD
19	Citalopram	Psychiatry	CYP2C19, CYP2D6
20	Clobazam	Neurology	CYP2C19
21	Clomipramine	Psychiatry	CYP2D6
22	Clopidogrel	Cardiology	CYP2C19
23	Clozapine	Psychiatry	CYP2D6
24	Codeine	Anesthesiology	CYP2D6
25	Daclatasvir	Infectious Diseases	IFNL3 (IL28B)
26	Dapsone	Dermatology, Infectious Diseases	G6PD
27	Darifenacin	Urology	CYP2D6
28	Dasabuvir, Ombitasvir, Paritaprevir, and Ritonavir	Infectious Diseases	IFNL3 (IL28B)
29	Desipramine	Psychiatry	CYP2D6
30	Dexlansoprazole	Gastroenterology	CYP2C19
31	Dextromethorphan and Quinidine	Neurology	CYP2D6
32	Diazepam	Neurology	CYP2C19
33	Dolutegravir	Infectious Diseases	UGT1A1
34	Doxepin	Psychiatry	CYP2D6, CYP2C19
35	Dronabinol	Gastroenterology	CYP2C9

	Drug	Therapeutic Area	Biomarker
36	Drospirenone and Ethinyl Estradiol	Gynecology	CYP2C19
37	Duloxetine	Psychiatry	CYP2D6
38	Efavirenz	Infectious Diseases	CYP2B6
39	Elbasvir and Grazoprevir	Infectious Diseases	IFNL3 (IL28B)
40	Eliglustat	Inborn Errors of Metabolism	CYP2D6
41	Elosulfase	Inborn Errors of Metabolism	GALNS
42	Eltrombopag	Hematology	F5 (Factor V Leiden), SERPINC1 (Antithrombin III)
43	Erythromycin and Sulfisoxazole	Infectious Diseases	G6PD
44	Escitalopram	Psychiatry	CYP2D6, CYP2C19
45	Esomeprazole	Gastroenterology	CYP2C19
46	Eteplirsen	Neurology	DMD
47	Fesoterodine	Urology	CYP2D6
48	Flibanserin	Gynecology	CYP2C9, CYP2C19, CYP2D6
49	Fluorouracil	Dermatology	DPYD
50	Fluoxetine	Psychiatry	CYP2D6
51	Flurbiprofen	Rheumatology	CYP2C9
52	Fluvoxamine	Psychiatry	CYP2D6
53	Galantamine	Neurology	CYP2D6
54	Glimepiride	Endocrinology	G6PD
55	Glipizide	Endocrinology	G6PD
56	Glyburide	Endocrinology	G6PD
57	Hydralazine	Cardiology	NAT1, NAT2
58	Iloperidone	Psychiatry	CYP2D6
59	Imipramine	Psychiatry	CYP2D6
60	Indacaterol	Pulmonary	UGT1A1
61	Isoniazid, Pyrazinamide, and Rifampin	Infectious Diseases	NAT1, NAT2
62	Isosorbide Dinitrate	Cardiology	CYB5R1, CYB5R2, CYB5R3, CYB5R4
63	Isosorbide Mononitrate	Cardiology	CYB5R1, CYB5R2, CYB5R3, CYB5R4
64	Ivacaftor	Pulmonary	CFTR
65	Ivacaftor and Lumacaftor	Pulmonary	CFTR
66	Lacosamide	Neurology	CYP2C19
67	Lansoprazole	Gastroenterology	CYP2C19
68	Ledipasvir and Sofosbuvir	Infectious Diseases	IFNL3 (IL28B)
69	Lenalidomide	Hematology	del (5q)
70	Lesinurad	Rheumatology	CYP2C9
71	Lidocaine and Prilocaine	Anesthesiology	G6PD
72	Mafenide	Infectious Diseases	G6PD
73	Methylene Blue	Hematology	G6PD
74	Metoclopramide	Gastroenterology	CYB5R1, CYB5R2, CYB5R3, CYB5R4, G6PD

	Drug	Therapeutic Area	Biomarker
75	Metoprolol	Cardiology	CYP2D6
76	Modafinil	Psychiatry	CYP2D6
77	Mycophenolic Acid	Transplantation	HPRT1
78	Nalidixic Acid	Infectious Diseases	G6PD
79	Nebivolol	Cardiology	CYP2D6
80	Nefazodone	Psychiatry	CYP2D6
81	Nitrofurantoin	Infectious Diseases	G6PD
82	Nortriptyline	Psychiatry	CYP2D6
83	Ombitasvir, Paritaprevir, and Ritonavir	Infectious Diseases	IFNL3 (IL28B)
84	Omeprazole	Gastroenterology	CYP2C19
85	Ondansetron	Gastroenterology	CYP2D6
86	Oxcarbazepine	Neurology	HLA-B*15:02
87	Palonosetron	Gastroenterology	CYP2D6
88	Pantoprazole	Gastroenterology	CYP2C19
89	Parathyroid Hormone	Inborn Errors of Metabolism	CASR
90	Paroxetine	Psychiatry	CYP2D6
91	Peginterferon Alfa-2b	Infectious Diseases	IFNL3 (IL28B)
92	Pegloticase	Rheumatology	G6PD
93	Perphenazine	Psychiatry	CYP2D6
94	Phenytoin	Neurology	CYP2C9, CYP2C19, HLA-B*15:02
95	Pimozide	Psychiatry	CYP2D6
96	Piroxicam	Rheumatology	CYP2C9
97	Prasugrel	Cardiology	CYP2C19, CYP2C9, CYP3A4, CYP2B6
98	Primaquine	Infectious Diseases	G6PD, CYB5R1, CYB5R2, CYB5R3, CYB5R4
99	Propafenone	Cardiology	CYP2D6
100	Propranolol	Cardiology	CYP2D6
101	Protriptyline	Psychiatry	CYP2D6
102	Quinidine	Cardiology	CYP2D6
103	Quinine Sulfate	Infectious Diseases	G6PD, CYP2D6
104	Rabeprazole	Gastroenterology	CYP2C19
105	Risperidone	Psychiatry	CYP2D6
106	Rosuvastatin	Endocrinology	SLCO1B1
107	Sevoflurane	Anesthesiology	RYR1
108	Simeprevir	Infectious Diseases	IFNL3 (IL28B)
109	Sodium Nitrite	Toxicology	G6PD
110	Sofosbuvir	Infectious Diseases	IFNL3 (IL28B)
111	Sofosbuvir and Velpatasvir	Infectious Diseases	IFNL3 (IL28B)
112	Succimer	Hematology	G6PD
113	Sulfamethoxazole and Trimethoprim	Infectious Diseases	G6PD

Drug	Therapeutic Area	Biomarker
114 Sulfasalazine	Gastroenterology	G6PD
115 Telaprevir	Infectious Diseases	IFNL3 (IL28B)
116 Tetrabenazine	Neurology	CYP2D6
117 Thioridazine	Psychiatry	CYP2D6
118 Ticagrelor	Cardiology	CYP2C19
119 Tolterodine	Urology	CYP2D6
120 Tramadol	Anesthesiology	CYP2D6
121 Trimipramine	Psychiatry	CYP2D6
122 Ustekinumab	Dermatology and Gastroenterology	IL12A, IL12B, IL23A
123 Valproic Acid	Neurology	POLG, ABL2, ASL, ASS1, CPS1, NAGS, OTC
124 Venlafaxine	Psychiatry	CYP2D6
125 Voriconazole	Infectious Diseases	CYP2C19
126 Vortioxetine	Psychiatry	CYP2D6
127 Warfarin	Hematology	CYP2C9, VKORC1, PROS1, PROC

Table 2

“Drug-Gene Pairs” included in Mayo Clinic Pharmacogenomic Electronic Alerts

	Drug	Gene(s)
1.	Abacavir	HLA-B*57:01
2.	Allopurinol	HLA-B*58:01
3.	Carbamazepine	HLA-B*15:02 and HLA-A*31:01
4.	Citalopram	CYP2C19
5.	Clopidogrel	CYP2C19
6.	Codeine	CYP2D6
7.	Escitalopram	CYP2C19
8.	Fluoxetine	CYP2D6
9.	Fluvoxamine	CYP2D6
10.	Paroxetine	CYP2D6
11.	Simvastatin	SLCO1B1
12.	Tacrolimus	CYP3A5
13.	Tamoxifen	CYP2D6
14.	Thiopurines	TPMT
15.	Tramadol	CYP2D6
16.	Venlafaxine	CYP2D6
17.	Warfarin	CYP2C9 and VKORC1

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