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The Role of Pharmacogenetic and Pharmacogenomic Testing in Personalized Medicine

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Abstract

Genetic alterations between individuals contribute to variations in drug response and susceptibility to adverse drug reactions. Testing for these alterations is accomplished via pharmacogenetic and pharmacogenomic molecular methods, with PCR-based, microarray, and next-generation sequencing platforms available in many clinical laboratories. The integration of this information into clinical practice offers the prospect of tailoring drug therapy to individual genetic profiles, improving patient outcomes while minimizing adverse events. Despite the promise, many challenges persist in the implementation and rapid evolvement of these methodologies. We present an overview of pharmacogenetic and pharmacogenomics methods, highlight specific examples of well-established pharmacogenetic associations, and summarize available resources for clinical testing recommendations.

Keywords: *Pharmacogenetics; Pharmacogenomics; Personalized medicine; Genome; Genetic variant; Drug*

Introduction

In the era of personalized medicine, it is well-established that genetic variants amongst individuals result in differences in the metabolism and bioavailability of drugs, ultimately leading to variations in drug response and susceptibility to adverse drug reactions. In 1959, the term "pharmacogenetics" was first applied to describe this observation [1]. Since then, germline and somatic gene variants, as well as functional gene deficiencies, have been found to impact (i) drug pharmacokinetics (drug absorption, distribution, and metabolism), (ii) drug pharmacodynamics (interaction between drug and target), (iii) idiosyncratic reactions to drugs (e.g., a hypersensitivity reaction), and (iv) disease pathogenesis in response to specific drugs. Perhaps the most well-known pharmacogenetic association is Glucose 6-phosphate dehyrdrogenase (G6PD) deficiency. Inherited variants, almost entirely represented by missense mutations, lead to deficient enzyme activity, resulting in hemolytic anemia upon exposure to certain drugs [2]. By understanding how an individual's genetic code impacts drug metabolism, absorption, and efficacy, providers can select the most appropriate drug and dose for each patient, individualizing care by placing the patient at the center of pharmaceutical decisions.

Pharmacogenetic testing refers to the evaluation of gene variants and their association with a particular drug. Pharmacogenomic testing is the 'omics' version of this concept – a comprehensive assessment of an individual's genome to not only select the most appropriate drug(s), but to also maximize drug safety and efficacy. However, generating a strict divide between the definition of pharmacogenetics versus genomics is somewhat challenging, as these terms are often used interchangeably. In general, we have observed that testing exists on a spectrum, with the simplest end represented by PCR-based analysis of a single genetic variant, and the most complex end being complete genomic (and potentially transcriptomic, methylomic, etc.) sequencing. Most clinical tests lie in the middle of this spectrum, and even clinical laboratories with 'pharmacogenomic' platforms may not assay for novel variants or report variants of unknown significance. It thus becomes complicated to create a divide of where '-genetics' ends and '-genomics' begins. This article seeks to better define both pharmacogenetics and pharmacogenomics, highlight common examples of pharmacogenetic associations, and provide an overview of groups working to offer clinical testing recommendations.

Pharmacogenetics

In the United States, the Food and Drug Administration (FDA) has incorporated over 500 pharmacogenetic associations on the

labels for approximately 360 drugs [3], and in 2020, released a Table of Pharmacogenetic Associations with periodic updates [4]. These associations are categorized as (i) supporting therapeutic management recommendations, (ii) indicating a potential impact on patient safety or drug response, and (iii) demonstrating an effect on pharmacokinetic properties, offering providers a resource for pharmacogenetic associations and recommendations for testing and management [4]. In addition, the Clinical Pharmacogenetics Implementation Consortium (CPIC) is an international consortium that generates peer-reviewed, evidence-based clinical practice guidelines regarding the use of specific pharmacogenetic tests [5], and the Pharmacogenomics Knowledgebase (PharmGKB) grades levels of evidence for clinical actionability of gene-drug pairs [6]. Several commercially available and laboratory-developed tests are available to assay these gene-drug pairs by assessing single gene variants [7]. Gene panels have also been developed to assay a limited number of genes and their associated variants in a single assay, and largely represent targeted variant analysis with PCR-based methods or microarray technology [7]. These panels often assess pharmacogenetic interactions for a number of drug classes, including drugs used to treat psychiatric conditions, pain management, and cardiovascular conditions. While useful in the interrogation of established variants, an important limitation of targeted pharmacogenetic testing is that it is not designed to detect novel variants, which could have unpredictable effects on gene expression and protein production or function. The Association for Molecular Pathology has published recommendations for minimum sets of variants to be included in these clinical pharmacogenetic assays [8,9].

The vast majority of pharmacogenetic associations discovered to date deal with pharmacokinetics, primarily in the arena of drug-metabolizing enzymes. The cytochrome P450 superfamily of mixed function oxidases (CYPs), in particular, are the major system for oxidative metabolism of drugs. Sequencing of the human genome has revealed 57 CYP genes, which encode various CYP isoenzymes [10]. Importantly, the CYP genes are highly polymorphic, and variants that affect drug metabolism are seen in a significant portion of the population [11] with prevalence varying according to ancestry [12].

One such pharmacogenetic association is CYP2C19 and clopidogrel [13]. Clopidogrel is a drug used to reduce the risk of myocardial infarction (MI) in patients with acute coronary syndrome (ACS) or who have recently undergone a percutaneous coronary intervention (PCI). Once converted to its active metabolite, clopidogrel inhibits the $P2Y_{12}$ receptor, irreversibly inhibiting platelet aggregation. Conversion to the active metabolite requires multiple oxidative steps, with CYP2C19 serving as a major contributor in this process [14,15]. Meta-analyses have demonstrated that "intermediate" and "poor" metabolizers of CYP2C19 have decreased serum active metabolite concentrations, and patients are at increased risk for major adverse cardiovascular events and stent thrombosis, compared to "normal" metabolizers [13,16,17]. Thus, alternative drug options are often recommended for these patients. Variants of CYP2C19 have also been associated with differences in the metabolism and effectiveness of proton pump inhibitors [18], used commonly to treat gastroesophageal reflux [19], and a number of platforms have been developed to assay the CYP2C19 gene.

An example of a genetic alteration affecting pharmacodynamics is vitamin K epoxide reductase complex 1 (*VKORC1*) and the anticoagulant drug warfarin. Warfarin therapy is clinically challenging due to its narrow therapeutic index and large variability in drug response between patients. Through the identification of common single nucleotide polymorphisms (SNPs), patients can be stratified into haplotypes that correlate with mRNA levels, and have been shown to account for 25% of the phenotypic availability in warfarin dosing [20,21]. In this case, the CPIC recommends an algorithm for warfarin dosing based on *VKORC1* and *CYP2C9* genotyping for both pediatric and adult populations [21]. Finally, there are a number of genetic associations with idiosyncratic reactions that have prompted CPIC recommendations for testing to prevent said adverse drug reactions, including hypersensitivity to abacavir with HLA-B*57:01 [22], severe cutaneous adverse reactions to allopurinol with HLA-B*58:01 [23], and hypersensitivity to carbamazepine with HLA-B*15:02 [24].

Pharmacogenomics

As previously mentioned, an important limitation of pharmacogenetic testing is the inability to detect novel variants that may affect function. Only annotated, established variants being tested for will ultimately be detected. Another limitation is that multiple interacting genes, epigenetic changes, or alterations in gene expression may affect various stages of drug metabolism or efficacy. Pharmacogenomics takes a broader view, examining a number of genomic components and their role in drug response. Like pharmacogenetics, this can include genetic sequence variants, but can also include structural changes in chromosomes (e.g., translocations), epigenetic variants (e.g., methylation, acetylation), and changes in gene expression via alterations in coding and non-coding RNAs. High-throughput techniques have allowed for interrogation of the entire genome (or comprehensive sections of the genome) and an assessment of interacting gene networks affecting drug activity.

A paramount example is in the field of psychiatry, in which many genes are involved with processing and modulating the effects of psychotropic drugs. Serotonin reuptake inhibitor drugs are used to treat depression and anxiety disorders. Genetic variants in *CYP2D6*, *CYP2C19*, and *CYP2B6* result in changes to drug metabolism, with more than 170, 35, and 45 variant alleles

reported, respectively [25]. In addition, two other genes – *SLC6A4* and *HTR2A* – have known pharmacogenetic associations. *SLC6A4* encodes the presynaptic serotonin transporter (5-HTT), which recycles serotonin to terminate synaptic action. Reuptake inhibitor drugs bind to this receptor to block reuptake and enhance the synaptic effect of serotonin. Variants in the promoter region of *SLC6A4* have been shown to differ in transport activity [26], and epigenetic alterations lead to changes in gene expression and activity [27]. HTR2A encodes the postsynaptic serotonin-2A receptor (5-HT_{2A}), and promoter variants have also been associated with changes in gene expression [28].

Opioids are used to treat acute and chronic pain, and many of these drugs are metabolized by *CYP2D6*. Well over 100 alleles of *CYP2D6* have been identified, including single nucleotide variants (SNVs), deletions, and copy number variants (CNVs) [29]. Commonly reported alleles are categorized into groups based on enzyme function and include normal function alleles (e.g., *CYP2D6*1, *2, and *35*), decreased function alleles (e.g., *CYP2D6*9, *10, *17, *29, and *41*), and no function alleles (e.g., *CYP2D6*3, *4, *5, and *6*). Increased copies of *CYP2D6* lead to increased function. An activity score can be calculated based on the predicted function of each allele, and allows for the classification of "ultrarapid", "intermediate", or "poor" metabolizers [30,31]. Clinical laboratories may not always perform complete sequencing of the entire *CYP2D6* gene in order to analyze each known variant position, and instead test for common variants and copy number alterations. Because of this, rare or novel variants (with altered function) may be reported as a normal allele. Yet, until additional genomics-based studies are carried out to better define both rare and novel variants, their function may remain uncertain. In addition, the clinical impact and safety of opioids have been explored in relation to two additional genes – *OPRM1* (mu receptor) and *COMT* (catechol-O-methyltransferase) [29]. Therapeutic recommendations for the use of genotyping prior to prescribing two opioids – codeine and tramadol – have been described by CPIC [29].

Studies have suggested that approximately 90-99% of the population may contain an actionable variant for a gene with an established drug association, and argue for preemptive pharmacogenomic testing [32,33]. In addition, the discovery-enabled capacity of pharmacogenomic testing with next-generation sequencing (NGS) methods may provide further benefit over traditional genotyping methods developed to evaluate variants, particularly for patients of genetic ancestries not widely represented in benchmark studies. Of course, a significant limitation of broader genomics methodologies is the identification of novel or rare variants with uncertain significance. Without thorough analysis and research, actionable clinical recommendations cannot be made. Medical specialties with the most relevance to, and thus those likely to see the largest benefit from, pharmacogenetic and pharmacogenomic testing include oncology, pain management, psychiatry, and populations at high risk for polypharmacy (e.g., geriatric patients). In oncology, chemotherapeutic drugs are often prescribed at very high concentrations, making toxicities and adverse drug events more likely, and the addictive nature of certain pain medications makes it important to establish upfront if a drug is likely to be useful before initiating treatment. Interactions between drugs, and genetic predispositions for increased or decreased drug metabolism, in the setting of polypharmacy is also of utmost importance. However, multiple barriers exist that affect the pace of pharmacogenomic testing implementation. These include the laboratory resources and staffing needs to establish NGS and data storage platforms, as well as the cost of those platforms, the complexity of test interpretation and reporting, the uncertainty of rare and novel variant function, gene nomenclature and reporting, clinician engagement, and concerns regarding reimbursement. Nonetheless, the progress towards pharmacogenomic testing methods represents an intriguing and evolving area within the field of personalized medicine.

Conclusion

Despite the challenges discussed herein, the integration of information gleaned from pharmacogenetic and pharmacogenomic testing into clinical practice holds immense promise for optimizing drug therapy, reducing adverse events, and ultimately improving patient outcomes. Moving forward, sustained collaboration between researchers, healthcare providers, and policymakers will be essential to the advancement and further implementation of these testing platforms. The journey towards precision pharmacotherapy is ongoing, and we anticipate a future where each patient is prescribed drugs tailored to their unique genetic makeup, ushering in a new era of personalized medicine.

Conflict of Interest

The authors declare that they have no conflict of interest.

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