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Implementing pharmacogenetics in private clinical settings

Abstract

Pharmacogenetics is a rapidly advancing field of genetic medicine that offers promise for improved patient outcomes. Prescription drugs dominate the medical system, which makes it imperative to utilize technology which identifies gene-drug compatibility. Clinicians in a private clinical setting must understand the definitions and science behind pharmacogenetics (PGx). There are at least five good reasons for clinicians to implement PGx into their practice. There is emerging research demonstrating that PGx can decrease hospital admissions as well as adverse drug events in large specialties such as cardiology, oncology, and psychiatry. In some situations PGx has been demonstrated to be cost-effective. Drugs that have compelling gene-drug research included in this review include warfarin, clopidogrel, cholesterol-lowering statins, abacavir, antidepressants, and irinotecan. There are also limitations to evidence-based gene-drug interactions that clinicians should be familiar with. Lastly, there are several considerations that clinicians should be aware of in regards to legal and ethical concerns.

Keywords: pharmacogenetics, pharmacogenomics, drug-gene, clinical genetics, drug response, PGx, adverse drug event

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Abbreviations: PGx, pharmacogenetics; SNPs, single nucleotide polymorphisms; FDA, food and drug administration; CPIC, clinical pharmacogenetics implementation consortium; ADRs, adverse drug reactions; GINA, genetic information nondiscrimination act

Introduction

Pharmacogenetics is a rapidly advancing field of genetic medicine that offers promise for improved patient outcomes and drug development. Since pharmacogenetics (PGx) is a relatively new field, there are challenges for the clinician in terms of interpreting and implementing PGx test results into the clinical practice. This paper will provide a review of PGx and how to implement it in a private clinical setting based on a variety of parameters.

Definitions

The terms pharmacogenetics and pharmacogenomics are often used interchangeably. However, there are slight differences in the definitions. The Stanford managed website PharmGKB summarizes the essence of these two definitions by stating that pharmacogenetics generally refers to how variation in a single gene influences drug response, while pharmacogenomics studies how the genome influences drug response.[1,2] In addition, in an article in the Mayo Clinic Proceedings, it is stated that pharmacogenomics also has a broader-based definition: "the study of the contribution of genomics and of other "omics" to individual variation in drug response phenotypes".[3] Additional definitions pertinent to PGx include polymorphism and mutation. In the context of PGx, polymorphisms are defined as" sequence variations in a gene that occur at a frequency of at least 1%" and mutations as variations that occur less frequently, at less than 1%.[4]

The focus of pharmacogenetics

Most genetic variations are composed of single nucleotide polymorphisms (SNPs), insertions, deletions, or duplications of DNA sequences. The most common sequence variations in the human genome are SNPs, which account for approximately 90% of all known sequence variations. SNPs involve a change in a single nucleotide in the genomic sequence. They occur on average every 100 to 300 base pairs.[5] The identification and correlation of these variations with drug efficacy and toxicity are the main focus of PGx researchers.

Five reasons to implement pharmacogenetics in the private practice

There are at least five good reasons for clinicians to implement PGx in a private practice. These are:

First, that research has demonstrated that this type of knowledge can be used for a highly diverse number of medical specialties and has "the potential to eventually touch the care of every patient everywhere".[3]

Secondly, that it is a recognized branch of medicine. For example, the Food and Drug Administration (FDA) has a subdivision of its Office of Clinical Pharmacology, which is The Genomics and Targeted Therapy Group.[6] The FDA oversees and regulates information on genomic biomarkers used with drug labeling. These biomarkers include "genotype-specific dosing" and "polymorphic drug target and disposition genes".[7] The FDA maintains a table that lists therapeutic products with pharmacogenomic information pertaining to drug labeling. They note that these biomarkers may include germline or somatic gene variants, functional deficiencies related to genetic etiology, differences in gene expression, chromosome abnormalities, and selected protein biomarkers that are useful in selecting patient treatments.[7]

Thirdly, there is an emerging body of published research supporting the validity of PGx. For example, an international group of pharmacists, scientists, and various health care professions are known as the Clinical Pharmacogenetics Implementation Consortium (CPIC). This group has developed clinical guidelines for several gene-

drug pairs.[8] The CPIC publishes their ongoing actionable findings regularly in partnership with the journal Clinical Pharmacology and Therapeutics, as well as posting these findings to their website.[9]

Fourthly, there is recent research demonstrating that PGx decreases hospital admissions and visits, as well as adverse drug events in common specialties such as cardiology, oncology, and psychiatry.[8] There is also intensive research by the world's largest pharmaceutical companies, including GlaxoSmithKline, Janssen Research, and Pfizer with regards to PGx.[10–12] Their primary focus is applying pharmacogenetics to guide dosing and drug selection.[13] Determining the correct drug and dose based on PGx not only facilitates finding the right therapy for each patient but also reduces the occurrence of adverse drug reactions (ADRs). This type of research is highly welcomed by the medical, insurance, and patient communities since ADRs are a leading cause of morbidity and mortality, account for 30% of hospital admissions, and have costs of about $170 billion annually.[14]

Finally, there is emerging evidence that many types of PGx are cost-effective. Kennedy notes that it is hard to compare the cost-effectiveness of PGx due to differences in study design and analysis, yet concludes "the majority of evidence to date indicates that pharmacogenetic test-guided treatment is cost-effective."[8] Also, Verbelen et al. studied the cost-effectiveness of pharmacogenetic-guided treatment with 44 economic evaluations relating to ten drugs. They determined that "over half of the reviewed studies concluded that the PGx-informed treatment strategy is more cost-effective than the alternatives considered under present-day economics".[15] However, they note that PGx guided treatment is currently not cost-effective in all situations. There is, however, an increasing number of laboratories offering PGx and the costs are decreasing.[8] Ultimately, the decision about PGx and its use in personalized medicine is between the patient and the clinician. However, factors such as insurance verse cash payment must be discussed with the patient before an informed decision can be made for ordering PGx.

Education requirements

Approximately 80% of first visits to a clinic involve a drug prescription.[16] Therefore, clinicians must be educated in PGx to improve medication selection. Since the completion of the Human Genome Project in 2003, the clinical implementation of PGx has been slower than predicted.[8] However, a recent survey of 69 schools of medicine, pharmacy, nursing, and health professions around the world found that 87% included pharmacogenomics education in their curriculum.[17] Pharmacogenetic competency requires education in these four areas: basic genetic concepts, genetics and disease, pharmacogenetics/pharmacogenomics, and ethical, legal and social implications.[8] It is recommended that clinicians take accredited coursework or continuing education seminars from knowledgeable professionals in the field of PGx. It is expected that pharmacogenetic training will continue to be expanded for medical doctors and pharmacists in their respective school programs. The American Board of Colleges of Pharmacy already stated PGx education as a requirement in their 2015 Accreditation Council for Pharmacy Education.[18] Other health organizations have proposed recommendations on PGx education and implementation in the classroom and clinic as well.[18]

Evidence-based testing

The number of drug-gene combinations that have substantial evidence based on PGx is still limited but steadily increasing.[19] Clinicians should focus on PGx recommendations that have good evidence for its reliability. This requires the clinician to keep up to date with the published literature regarding the evidence of analytic validity, clinical validity, clinical utility, and other factors for prescribing medications.[19] Literature reviews can be done in part through publications of the Clinical Pharmacogenetics Implementation Consortium and FDA-approved labeling. Below are examples of drug-gene categories with good evidence for PGx.

Warfarin is the most commonly prescribed anticoagulant in the world and is associated with frequent adverse events.[20] Testing for variants such as those present in the genes *CYP2C9*, *VKORC1*, and *CYP4F2* helps predict "steady-state-dosage" as opposed to the international normalized ratio (INR) of biomarker variability.[20] A 2017 article notes that testing for variants in those genes early in the course of warfarin therapy helps with a shortened time to stable INR, an increased time within the therapeutic INR range, reduced underdosing or overdosing during the initial treatment, and potentially a reduced risk of bleeding and thromboembolic events.[21] Patients with loss of function alleles and slower clearance such as *VKORC1*: AA and *CYP2C9*: *1/*2 should start on a lower dose of 3 to 4 mg.[22]

Clopidogrel is a commonly prescribed drug for those with ischemic heart disease or acute coronary syndromes. Carriers of *CYP2C19* reduced function alleles are known to be at increased risk of myocardial infarction, stent thrombosis, and death compared to non-carriers of these alleles.[23] The FDA instituted a "black box" warning for clopidogrel for those who are poor metabolizers with genotypes *CYP2C19**2 or *CYP2C19**3.[24] Clinicians are to consider other anti-platelet mediations for these genotypes since they do not convert clopidogrel to its active form.[24]

Cholesterol-lowering statin drugs have the risk of causing myopathy. Variants in *SLCO1B1* are known to increase myopathy risk and affect the efficacy of statins.[25] The main *SLCO1B1* variant that increases myopathy risk is *SLCO1B1**5.[26] The Clinical Pharmacogenetics Implementation Consortium recommends that for those who are *5 carriers high dose simvastatin should be avoided and instead low-dose simvastatin or an alternative statin should be prescribed.[27]

Abacavir is a drug used in combination with other antiretroviral agents to treat HIV patients. The *HLA-B**5701 allele is a good predictor of hypersensitivity to Abacavir while patients without the allele are unlikely to develop a hypersensitivity reaction to Abacavir.[28]

The *CYP2D6* gene affects the metabolism of approximately 25% of commonly prescribed medications, which includes opioids, anti-psychotics, and tricyclic antidepressants.[29] Also, the *CYP2C19* gene plays a central role in the metabolism of common antidepressants such as citalopram, escitalopram, imipramine, and amitriptyline.[30] For example, a 2019 study demonstrated significantly higher rates of *CYP2C19* poor metabolizer variants in patients with bipolar disorder than in those with major depressive disorder among patients with a history of multiple drug failures and treatment resistance.[31] Also, another 2019 study found a benefit of pharmacogenetic testing in patients with major depressive disorder who had an inadequate response to at least one antidepressant. These patients were randomized to receive treatment as usual or have pharmacogenetic testing of 59 variants in eight genes (a.o. *CYP2C19*) to guide medication selection. Researchers found patients' responses and remission were significantly improved in these difficult to treat depression patients.[32]

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There are several chemotherapy agents for which pharmacogenetics can identify those at risk for adverse events. For example, those with the genetic variations of *UGT1A1**28 are at increased risk of toxicity from the chemotherapy drug irinotecan, which can result in febrile neutropenia and diarrhea.[33] The FDA states that patients who are homozygous for the *28 variant should start therapy with a lower dosage.[33]

Pharmacogenetic implementation in a private clinical setting

To implement PGx into a private clinical setting requires several steps. First, the clinician must have a foundation of education in pharmacogenetics. The next step is to identify reputable labs that will perform pharmacogenetic testing. These tests typically involve a mouth swab or blood sample to collect the genomic DNA.[4] The clinician must also understand the insurance requirements and proper diagnosis codes for the labs they choose. Also, for patients who cannot use insurance, the clinician and their staff must provide a listing of direct pay cash prices for patients who are willing to pay out-of-pocket. A patient consent form for testing should be provided and reviewed with the patient before testing is ordered. Also, the clinician must be able to understand and interpret the test results as provided by the PGx lab. These results should be explained clearly to the patient with the proper recommendations. It should also be noted that there are two strategies for PGx as outlined by Weitzel as follows. The first is preemptive testing, where the results are obtained for future use. The second and currently more common strategy is reactive testing, which is a point of care for a current health situation to guide the clinician in drug selection.

Limitations of pharmacogenetics

There are a number of limitations of PGx testing that the clinician should be familiar with. One of the main considerations is the fact that PGx does not measure the influence of environmental factors on drug metabolism, particularly on the CYP enzymes.[34] There are also intrinsic, non-genetic factors that affect drug metabolism.[35] Non-genetic factors that affect drug metabolism include age (especially the pediatric population), pregnancy, disease states (e.g., liver and kidney disease, cancer), diet (meal volume, food composition, and food preparation techniques), smoking, and other medications.[35] Apart from non-genetic factors, there is also an increasing amount of research showing substantial ethnic differences in polymorphisms that affect drug metabolism up to three-fold.[4] Baskys states that one of the difficulties for the clinician with PGx is "a relatively large number of data points for a prescriber to consider". The same author also notes that PGx companies provide detailed genotyping reports, but it can be very time consuming for the clinician to review these reports. Baskys proposes the solution to be user-friendly bioinformatics tools that will provide "genetic and drug interaction data to clinicians at the point of service".[34] Another potential problem is insurance reimbursement as PGx is often viewed by insurance companies as preventive medicine and thus non-reimbursable.[19] As a result, many patients are required to pay costs for PGx out-of-pocket, which reduces the number of potential tests performed.[36]

Ethical and legal considerations

The clinician should also be aware of ethical and legal considerations with PGx. For example, the Genetic Information Nondiscrimination Act (GINA) protects Americans from genetic discrimination except for life, disability, long-term care insurance, or care provided by the military, Veterans Administration, or Indian Health Service.[37] Furthermore, if the patients PGx results end up in a database that they did not consent to, it may negatively affect their status with life insurance or one of the groups aforementioned. There are also legal issues about the ownership and intellectual property rights of DNA samples. Genetic specimens are often archived in biobanks and may be used for future research. Also, approximately 20% of all human genes are under US patents. For example, the company Myriad Genetics owns a minimum of seven patents for *BRCA1* and *BRCA2* mutations.[38]

Conclusion

In conclusion, the use of PGx to identify and predict drug response and adverse event likelihood offers benefits to the patient in a medical system dominated by prescription drugs. There are many parameters a clinician must consider when implementing PGx into a private clinical setting. The use of personalized medicine to better serve patients will inevitably involve PGx at an increased rate as research clarifies drug-gene relationships.

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Conflicts of interest

The author declares there is no conflict of interest.

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