PHARMACOGENOMICS: THE FUTURE OF PRECISION MEDICINE

Abstract

Pharmacogenomics is the branch of precision medicine that studies how a person's genes affect their responses to drugs. It studies the different components of the genome that control the metabolism of drugs and how drug treatments can be adapted to a person's individual genetic make-up, while pharmacogenetics is the study of specific genetic variants that causes different drug responses in people. Although both terms overlap, pharmacogenomics takes a wider look at the overall genetic picture, rather than focusing on how single genes affect the action of pharmaceutical drugs.[1]

Background

Genetic variants influence drug therapy and play a fundamental role in the treatment outcome of diseases such as cancer, human immunodeficiency virus (HIV), heart disease, and hypertension. A genetic variant is a difference in genetic sequences among people. It has been estimated that 97% of individuals have high-risk variants that affect drug absorption, distribution, metabolism, and excretion. Data from the 1000 Genomes Project, which ran between 2008 and 2015, has contributed to the identification of several genomic variants that impact drug treatment.[2]

Variants can be influenced by heritability, epigenetic stimuli such as exercise, diet, smoking, air pollution, and a combination of these factors. Variants can also help to explain how responses to drugs can differ from person to person, adverse drug reactions (ADR), and differing therapeutic outcomes in diverse ethnic populations. Research has already found that between 40% and 70% of patients either do not respond adequately to drug treatment or they experience ADRs, and 30% of hospital admissions for ADRs are life-threatening. Understanding drug-gene interactions is allowing treatments to be personalized, which is resulting in better safety outcomes for the patient.[3]

If genomic information is routinely available in a person's health record, it could be used to make more beneficial and faster treatment decisions.[3]

Benefits of Pharmacogenomics

For variants that have been identified, therapies can be personalized using an individual's genetic profile to optimize treatment outcomes by selecting specific drug treatments or altering drug dosage levels.

The benefits of pharmacogenomic testing for a patient include reduced drug toxicity and hospital admissions, and improved treatment efficacy and general health. However, challenges remain, such as the current lack of guidelines and training around testing, and ongoing regulatory and ethical concerns. For many patients, there is significant concern as to who (or

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which entity) will have access to their test results and how that access might affect their insurability. Legislation often prohibits the use of genetic test results in insurance, but this means insurance applicants may miss out on certain benefits to them because of genetic testing.

The cost of testing differs across laboratories and by country, but a once-in-a-lifetime test for the genetic variants which affect commonly prescribed drugs may be less costly in the long run than carrying out regular blood tests to measure drug concentrations over a lifetime.

Pharmaceutical Labeling

The U.S. Food and Drug Administration (FDA) publishes a list of approved drugs (currently at 178) with pharmacogenomic labeling that contains information on indications for use, dosage recommendations, and warnings. The label information for abacavir, for example, a drug used to treat Human Immunodeficiency Virus (HIV), includes a warning for patients with the HLA-B*5701 allele, as a portion of these patients develop severe hypersensitivity reactions to the drug.[3]

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Demonstrating how important pharmacogenomics has become, the annual proportion of new FDA drug approvals with pharmacogenomic labeling has increased nearly threefold, from 10.3% in 2000 to 28.2% in 2020.[5]

Common Genetic Variants

Cytochrome P450 enzymes (CYPs) are primarily responsible for the metabolization of pharmaceutical drugs. Most CYP genes that encode for enzymes involved in drug metabolism have genetic variants. Importantly, there are three phenotype variants: ultra-rapid metabolizers, extensive (normal) metabolizers, and poor metabolizers. The most significant variants are observed in the CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5 genes. CYP3A4 and CYP3A5 contribute to the metabolism of approximately half of all drugs, while CYP2D6 acts on a quarter of all prescription drugs.[1]

Liver enzymes change the chemical make-up of drugs, sometimes making them more effective or less effective. Variants in the CYP2C19 gene, a liver enzyme involved in the processing or metabolizing of at least 10% of commonly prescribed drugs, is known to impact dosage levels for blood thinners such as warfarin and clopidogrel.[6] As warfarin has a narrow dosage range for treatment, genetic testing is available to assess if patients are especially sensitive to warfarin and therefore might require monitoring on a more frequent basis.[7]

The liver enzyme CYP2D6 plays a major role in human metabolization and in the elimination of commonly prescribed drug classes, including opioids, antiestrogens, antiarrhythmics, antipsychotics, antidepressants, β-blockers, antihypertensives, and antihistamines. People with extra copies of the CYP2D6 gene produce too much CYP2D6 enzyme, which means they process drugs of the listed classes extremely quickly. Meanwhile, some have copies of the CYP2D6 gene that do not work, which means they process these drugs very slowly.[6]

Evidence to date shows that the prevalence and frequency of variants in drug-related genes is highly diverse across different ethnic populations. Roughly half of all functional variants in these genes are unique to individuals of African, South Asian, East Asian, Finnish, non-Finnish European, and Latino ancestry.[2]

Effects on Disease Outcomes

Pharmacogenomics plays a significant role in cancer therapy, helping healthcare practitioners make appropriate drug choices and avoid drug toxicity. For example, 5-fluorouracil (5-FU) is widely used in the treatment of colorectal cancer, but resistance to it as well as the presence of toxicity remain a problem. Variants in the DPD gene have been identified in 3% to 5% of individuals, and those deficient in the DPD enzyme are

known to experience higher 5-FU toxicity.[8] In another example, variants in the GSTM1 and GSTT1 genes, which play a role in detoxifying cancer drugs, can reduce the efficacy of cisplatin, carboplatin, and oxaliplatin.[9]

Pharmacogenomic biomarkers have also emerged as an important tool in predicting recurrence of mood disorders. A recent meta-analysis showed that in 1,737 patients, pharmacogenetic-guided therapy achieved much better outcomes, with patients 1.7 times more likely to achieve symptom remission compared to patients who did not receive this guided therapy.[10]

Insurance Implications

Some health insurance policies already offer patients access to genetic tests, which may lead to more successful treatments and survival outcomes. Coverage of tests for KRAS, EGFR, HER2, and BRAF are common, but few policies cover tests for PMIRARA, CD25, or G6PD. The life insurance industry could benefit by exploring opportunities to apply pharmacogenomics to innovative product development. Pharmacogenomic benefits could, for example, be judiciously used to promote better disease control, improve the potential to avoid adverse drug reactions, and improve efficacy and survival. The principles of clinical validity and clinical utility should also be considered when recommending any type of genomic testing to ensure real benefit. Of course, insurers must keep in mind the legal, ethical, and cost barriers in using pharmacogenomic information.

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Conclusions

Personalized medicine and the use of pharmacogenomic biomarkers has been successful in improving patient outcomes through better drug efficacy and fewer adverse drug reactions. The evaluation of genetic markers to predict drug responses and health outcomes is opening new pathways in the prevention and treatment of diseases such as cancer, heart disease, and viral illnesses. The wider implementation of pharmacogenomics in clinical care could pave the way for life insurance companies to offer more favorable terms to insurance applicants and improved benefits to insurance policyholders. RGA

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