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Introduction

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Medical Genetics Summaries (MGS) is a collection of articles that feature conditions with a genetic component, for which information useful at the point of care is limited. Topics fall into two broad categories: diseases and drug responses.

The intended audience of *MGS* is clinicians who seek practical, evidence-based information to use in clinical care settings. The summaries are guideline-driven, drawn from authoritative sources, undergo a formal review process, and are regularly updated.

Genetic variants and disease

Pitt-Hopkins syndrome has a clear genetic component. A variant in the TCF4 gene results in the syndrome, and genetic testing of the *TCF4* gene confirms the diagnosis. However, for many other diseases, the underlying genetics is complex. For example, although schizophrenia is highly heritable, many genes have been implicated as contributing to the disease, and genetic testing is not currently available.

A person's blood group is determined by genetics—the four common blood groups (A, B, AB, and O) are encoded by *ABO* alleles. Serological testing is commonly used to determine an individual's blood type, e.g., before receiving a blood transfusion. However, in other settings, genetic testing may be used to determine an individual's ABO genotype, such as in the research setting, e.g., investigating the associations between ABO blood groups and the risk of diseases such as pancreatic cancer and thromboembolic disease.

Genetic variants and drug responses

There is often a wide variability in how different individuals respond to standard doses of the same drug. This is because a drug response can be influenced by age, gender, drug-drug interactions, drug-food interactions, comorbidity, liver and renal function, pregnancy, and genetic factors. For an increasing number of drugs, genetic testing (also known as pharmacogenetic testing) can be used to optimize drug therapy.

Currently, about 10% of drug labels approved by the U.S. Food and Drug Administration (FDA) contain pharmacogenetic information. However, actionable information on genetic variants can be hard to find, and sources often differ in their recommendations. *MGS* draws together information from different authoritative sources to one place, and includes a summary—thus providing accessible information at the point of care.

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To avoid confusion, only generic drug names are used. Nomenclature tables include both the official and commonly used terms for alleles, and phenotypes are termed "drug responses", e.g., omeprazole drug response. Finally, each summary links to the NIH's Genetic Testing Registry, which provides information about laboratories that offer genetic tests and details about the tests, including ordering information.

Genetic testing to ensure the drug has a therapeutic target

A small number of drugs are prescribed after genetic testing has been performed. One reason for this is that the drug is effective for specific genotypes. These drugs include trastuzumab—a chemotherapy agent only indicated for specific tumors that overexpress HER2, and maraviroc—an antiviral agent that is only indicated for a specific strain of the HIV virus (CCR-5 trophic HIV-1).

Genetic testing can help avoid idiosyncratic drug reactions

Another reason for genetic testing is to avoid severe, and potentially fatal, drug reactions. A category of drug reactions are idiosyncratic—they are unpredictable, severe, and not related to the dose and duration of the drug therapy.

The FDA recommends that all individuals be screened for the *HLA-B*57:01* allele before starting treatment with abacavir, a drug used in the treatment of HIV. This is because around 6% of Caucasians of European origin carry this variant allele, placing them at high risk of abacavir-induced hypersensitivity reaction. Symptoms include fever, rash, and acute respiratory symptoms.

An individual's ancestry may be important

For the epilepsy drug carbamazepine, the FDA states that patients with ancestry in "genetically at-risk populations" should be screened for the presence of *HLA-B*15:02* prior to initiating treatment. Carriers of this variant, which is most commonly found in individuals of Han Chinese descent, are at a high risk of developing Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)—both potentially fatal conditions—during carbamazepine therapy.

Also common in individuals with Han Chinese ancestry is the *HLA-B*58:01* allele, which is strongly associated with severe cutaneous adverse reactions (SCAR) triggered by allopurinol therapy, which is used to treat gout.

A wide range of gene variants are associated with idiosyncratic drug reactions

Idiosyncratic drug reactions are not just limited to variant *HLA-B* alleles. For the antibiotic gentamicin, genetically predisposed individuals who carry a variant in a mitochondrial gene (*MT-RNR1*) may suffer from irreversible hearing loss after just a single dose of gentamicin. And for individuals who require treatment with thiopurines (e.g., azathioprine), the FDA recommends *TPMT* genotyping or phenotyping prior to treatment. This is because patients who carry two non-functional *TPMT* alleles universally experience life-threatening myelosuppression when treated with thiopurines.

Genetic testing can help optimize the drug dose

Drug labels always provide standard dosing information. But a growing number of labels also include recommendations for adjusting the dose, or selecting an alternative drug, based on a patient's genotype (if known). Generally, dose adjustment is recommended for variants in genes that are known to influence drug metabolism, leading to altered plasma levels of active drugs and metabolites.

Cytochrome P450 (CYP) genes influence drug levels

The "CYP" gene family encodes enzymes that metabolize over a quarter of commonly prescribed drugs. One of these genes, *CYP2D6*, is particularly complex. Over 100 variants are known, many of which encode enzymes with different levels of activity. Depending on the level of CYP2D6 activity, individuals may respond poorly to

the analgesics codeine and tramadol. A standard dose of codeine may provide inadequate pain relief in some, and severe toxicity, such as respiratory depression, in others.

In addition, standard doses of a wide range of drugs (e.g., atomoxetine—used in ADHD, venlafaxine—an antidepressant, clozapine—an antipsychotic, and tamoxifen—used to treat breast cancer) will lead to higher than expected active drug plasma levels in individuals who have low or absent CYP2D6 activity. This can increase the risk of side effects, and may contribute to non-compliance and treatment failure.

Barriers to genetic testing

Ordering a genetic test to help determine whether a particular drug will be effective or safe is a relatively new area for doctors and genetic counselors. The field is rapidly evolving, evidenced by an increasing panorama of genetic tests becoming available. And there are potential legal concerns, such as a cause for liability in cases where the optimal dose of a drug was not given. Education and training are needed.

More prospective randomized trials are needed to investigate the clinical outcomes when drug therapy or a specific dose is selected on the basis of genotype. The effectiveness data can be used for cost-effectiveness analysis, and be summarized into actionable clinical guidelines with prescribing recommendations.

Sometimes, genetic testing has not been possible because of the acute nature of the clinical scenario (e.g., gentamicin and neonatal sepsis). However, as technology improves and turn-around time is reduced, the use of genetic testing can be expected to increase.

For example, clopidogrel is an antiplatelet agent that is used in patients presenting with acute coronary syndrome, and patients who may need to undergo percutaneous intervention. Because clopidogrel is a pro-drug, it must first be metabolized by CYP2C19 before it becomes effective. However, in the 3% of Caucasians and 15 to 20% of Asians who have low or absent CYP2C19 activity, clopidogrel will have a smaller or no effect on platelet function. Fortunately, the advent of "bedside testing" and a faster turn-around of results means that more of these patients can be identified and offered alternative antiplatelet agents.

The use of genetic testing is often not clear-cut

In the case of warfarin, the FDA-approved drug label provides a dosing table, allowing for the adjustment of initial doses of warfarin based on *CYP2C9* and *VKORC1* genotypes. Warfarin is an anticoagulant, given to prevent the formation of blood clots. If the dose of warfarin is too low, the risk of thrombosis remains, but if the dose is too high, there is an increased risk of bleeding. And both outcomes can be a cause of a stroke.

Despite the drug label's dosing table, it is thought that less than 1% of patients commence warfarin therapy with their *CYP2C9* and *VKORC1* genotypes known. Interestingly, however, the most recent evidence suggests that *CYP2C9* and *VKORC1* variants may have less of an effect on warfarin levels than previously thought, with many other clinical factors having more of an impact.

The future

Genetic testing is important—it can help avoid drug toxicity and help optimize drug efficacy. As the number of genetic tests grows, *Medical Genetics Summaries* will expand to help ensure that healthcare providers have the information they need to provide evidence-based care.

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