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Introduction

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Medical Genetics Summaries (MGS) is a collection of articles featuring phenotypes with a genetic component, for which information useful at the point of care is limited. The main focus of *MGS* is pharmacogenomics, but there are also chapters about diseases.

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 Drug Responses

There can be 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. To provide actionable information at the point of care, *MGS* draws together information from different authoritative sources to one place and includes a summary.

Chapters in *MGS* use generic drug names. Nomenclature tables include both the official and commonly used terms for alleles with links to molecular resources, including ClinVar and dbSNP. Phenotypes that encompass how an individual responds to a drug are termed "drug responses", such as omeprazole drug response. Finally, each summary links to the NIH 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 only for specific genotypes. These drugs include trastuzumab, a chemotherapy agent only indicated for specific tumors that overexpress HER2, and maraviroc, an antiviral agent indicated only for a specific strain of the HIV virus (CCR-5 trophic HIV-1). Additionally, specific variants or conditions that indicate a lack of efficacy are discussed, such as dabrafenib and *BRAF* variant colorectal cancer or *BRAF* wild-type malignancies.

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Genetic Testing to Avoid Idiosyncratic Drug Reactions

Another reason for genetic testing is to avoid severe and potentially fatal drug reactions. Some drug reactions are idiosyncratic—they are unpredictable, severe, and not related to the dose or 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. Around 6% of Caucasians of European origin carry this variant allele, placing them at high risk of abacavir-induced hypersensitivity reaction, with symptoms including fever, rash, and acute respiratory symptoms. Similarly, individuals with dihydropyrimidine dehydrogenase deficiency are at risk of fatal reactions with fluoropyrimidines like capecitabine and fluorouracil.

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, most commonly found in individuals of Han Chinese descent, are at a high risk of developing Stevens-Johnson syndrome and toxic epidermal necrolysis—both potentially fatal conditions—during carbamazepine therapy.

The *HLA-B*58:01* allele, also common in individuals with Han Chinese ancestry, is strongly associated with severe cutaneous adverse reactions 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 limited to variant *HLA-B* alleles. For the antibiotic gentamicin, genetically predisposed individuals carrying a variant in a mitochondrial gene (*MT-RNR1*) may suffer irreversible hearing loss after just a single dose of gentamicin. For individuals requiring treatment with thiopurines (for example, azathioprine), the FDA recommends thiopurine S-methyltransferase (*TPMT)* genotyping or phenotyping prior to treatment because patients with 2 non-functional *TPMT* alleles experience life-threatening myelosuppression when treated with thiopurines.

Genetic Testing to Optimize 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 known to influence drug metabolism, leading to altered plasma levels of active drugs and metabolites. Decreased activity of the liver enzyme SLCO1B1 (a drug transporter) can lead to increased exposure and adverse muscle symptoms with statins like simvastatin, prompting experts to recommend lower doses or alternative medications.

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, with over 100 known variants, many encoding enzymes with different activity levels. Depending on the level of CYP2D6 activity, individuals may respond poorly to analgesics like codeine and tramadol. A standard dose of codeine may provide inadequate pain relief in some, and severe toxicity, such as respiratory depression, in others.

Additionally, standard doses of a wide range of drugs (for example, atomoxetine for Attention-Deficit/Hyperactivity Disorder, venlafaxine as an antidepressant, clozapine as an antipsychotic, and tamoxifen for breast cancer) can lead to higher than expected active drug plasma levels in individuals with low or absent CYP2D6 activity, increase the risk of side effects and potentially lead to non-compliance and treatment failure.

Barriers to Genetic Testing

At this time, there is a lack of recommendations from authoritative professional societies for indication for pharmacogenetic testing. The field is rapidly evolving, as evidenced by an increasing number of available pharmacogenetic tests. There are potential legal concerns, such as 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 specific doses are selected based on genotype. Effectiveness data can be used for cost-effectiveness analysis and summarized into actionable clinical guidelines with prescribing recommendations. Similarly, the breadth of evidence for various ancestral groups may be limited, and guidelines may not exist for variants that are rare.

Sometimes, genetic testing is not possible due to the acute nature of the clinical scenario (such as gentamicin and neonatal sepsis). However, as technology improves and turnaround time is reduced, the use of genetic testing is expected to increase.

For example, clopidogrel, an antiplatelet agent used in patients with acute coronary syndrome who may undergo percutaneous intervention, must be metabolized by CYP2C19 before becoming effective. In 3% of Caucasians and 15–20% of Asians with low or absent CYP2C19 activity, clopidogrel will have a smaller or no effect on platelet function. The advent of "bedside testing" and faster turnaround times means that more 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 for adjusting initial doses based on *CYP2C9* and *VKORC1* genotypes. Warfarin is an anticoagulant given to prevent the formation of blood clots. If the dose is too low, the risk of thrombosis remains; if too high, there is an increased risk of bleeding, both of which can cause strokes.

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. Recent evidence suggests that *CYP2C9* and *VKORC1* variants may have less effect on warfarin levels than previously thought, with many other clinical factors having a more significant impact.

The Future

Genetic testing is important—it can help avoid drug toxicity and 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.

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. For many other diseases, the underlying genetics is complex. For example, although schizophrenia is highly heritable, many genes contribute 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 before receiving a blood transfusion. However, in other settings, genetic testing may determine an individual's ABO genotype, such as in research investigating associations between ABO blood groups and the risk of diseases like pancreatic cancer and thromboembolic disease.

These chapters focusing on genetic diseases are maintained for legacy use and reference but are no longer the primary focus of MGS. Readers are encouraged to check other sources for information on specific genetic

disorders including MedGen which provides links to search PubMed for recent review articles, professional practice guidelines, and links to the Bookshelf at NCBI for additional resources.

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