



Pharmacogenomics and Precision Medicine

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LEARNING OBJECTIVES

1. Evaluate pharmacogenomic test results.
2. Distinguish between evidence-based resources for pharmacogenomics.
3. Assess somatic genetic test results to select appropriate targeted anticancer therapy.
4. Apply pharmacogenomic test results pertaining to drug metabolism to chemotherapy dosing.
5. Design an individualized supportive care regimen for patients with cancer using pharmacogenomic test results.

ABBREVIATIONS IN THIS CHAPTER

5-HT ₃	5-hydroxytryptamine type 3
ALK	Anaplastic lymphoma kinase
CML	Chronic myeloid leukemia
CPIC	Clinical Pharmacogenetics Implementation Consortium
DPD	Dihydropyrimidine dehydrogenase (enzyme)
DPYD	Dihydropyrimidine dehydrogenase (gene)
EGFR	Epidermal growth factor receptor
G6PD	Glucose-6-phosphate dehydrogenase
HER2	Human epidermal growth factor receptor 2
HLA	Human leukocyte antigen
NTRK	Neurotrophic receptor tyrosine kinase
NUDT15	Nudix hydrolase 15
PharmGKB	Pharmacogenomics Knowledgebase
TCA	Tricyclic antidepressant
TPMT	Thiopurine methyltransferase
UGT1A1	Uridine diphosphate glucuronosyltransferase 1A1

[Table of other common abbreviations](#)

INTRODUCTION

Pharmacogenomics is a key component of precision medicine that is increasingly used in clinical practice to optimize medication therapy, particularly in oncology. The term *pharmacogenomics* is used interchangeably with the term *pharmacogenetics*. *Precision medicine*, though often associated with genomics exclusively, is a broad term that includes the use of any clinical variable to individualize medication selection and dosing (Caudle 2019). With advances in genetic sequencing technologies and a growing body of literature to support gene-drug associations, clinicians can tailor therapy on the basis of genetic data.

As a disease that arises from genetic aberration, cancer has become one of the fastest-growing areas for the clinical application of pharmacogenomics. Indeed, in certain cancer centers and for certain types of cancer (e.g., lung cancer, breast cancer, melanoma, colorectal cancer), tumor profiling (genetic sequencing) has become standard of care. When considering pharmacogenomics in oncology, two distinct genomes are at play: the patient's genome and the tumor genome. Each offers valuable information for the individualization of pharmacotherapy. The patient's genome (inherited genetic variation) provides insights into the activity of important drug-metabolizing enzymes, which may place the patient at risk of severe toxicity or therapeutic failure with standard doses of certain chemotherapeutic agents. Understanding genetic variations in the patient's genome may also help optimize medication selection and dosing of various supportive care agents. The tumor genome (acquired genetic variation) provides insights into the mutation(s) causing uncontrolled cell growth, which, if targeted with the appropriate therapy, can mitigate cell growth. Genetic mutations within the tumor genome can also be linked to prognosis and may help dictate the optimal treatment

strategy. Targeted therapies (medications targeting a specific genetic mutation in the tumor genome) may be associated with fewer adverse effects than standard cytotoxic chemotherapy, which attacks healthy tissue as well as the cancer. For targeted therapies, genetic testing is required before use to ensure appropriateness of therapy and a potential therapeutic benefit.

Cost remains a barrier to widespread pharmacogenomic testing, and insurance companies are slow to adopt policies that cover such testing (unless required before prescribing a particular drug). However, interest in and access to testing are growing. The two main approaches to pharmacogenomic testing are reactive and preemptive. Reactive testing occurs when a drug therapy is being contemplated or after initiation, either to guide drug selection or dosing for a specific indication or to provide an explanation for therapeutic failure or adverse effects already experienced. Reactive testing typically involves testing for a single gene. In contrast, preemptive testing usually involves testing for a panel of genes up-front; it is independent of any specific medication the patient is, or will be, taking. The idea is to collect this information in advance so that it can be used immediately at the point of care to guide drug selection and dosing when needed. On a per-gene basis, it is much more cost-effective to conduct preemptive pharmacogenomic testing for a panel of genes than to conduct single gene tests at different points in time. Because pharmacogenomic tests have lifelong clinical usefulness, there is potential for a significant return on investment for preemptive testing over a patient's lifetime. Leveraging this return on investment requires integrating the results into the electronic health record with clinical decision support.

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- General knowledge of genetics, pharmacogenomics, and associated terminology
- General knowledge of cancer pathophysiology and associated pharmacotherapy, both for treatment and for supportive care

[*Table of common laboratory reference values*](#)

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- [Clinical Pharmacogenetics Implementation Consortium](#) (homepage on the Internet)
- [PharmGKB](#) (homepage on the Internet)

The potential benefit of preemptive clinical pharmacogenomic testing has been investigated in the oncology population. For example, a 2019 study enrolled a cohort of patients with advanced cancer to determine the prevalence of “pharmacogenetically actionable” medications among this population (i.e., those that were associated with recommendations from the Clinical Pharmacogenetics Implementation Consortium [CPIC]) (Nichols 2019). Among the 193 patients included in the study, 65% were taking at least one pharmacogenetically actionable medication (average of 11 total medications per patient). Using published genetic variation frequencies and adverse event risk, the study authors estimated that 7.1% of patients with cancer will both take a pharmacogenetically actionable medication and have a genotype requiring therapy modification, and 101 adverse events would be prevented per each 10,000 patients genotyped. Medications with the most preventable adverse events included ondansetron, capecitabine, and codeine.

To effectively apply pharmacogenomics to patient care, pharmacists must be familiar with the genetic basis for variability in drug response; pharmacogenomic terminology and nomenclature; pharmacogenomic test interpretation; and evidence-based resources for clinical pharmacogenomic information. These topics, together with specific clinical examples in oncology, are discussed in this chapter.

PRINCIPLES OF PHARMACOGENOMICS

Genetic Basis of Variability in Drug Response

Clinicians know that individual patients may respond differently to the same dose of a particular medication. This inter-individual variation in drug response can partly be explained by differences in genetics. Variation in the genes that encode for drug-metabolizing enzymes, drug transporters, drug targets, and drug receptors (“pharmacogenes”) may lead to differences in the structure, function, or expression of these proteins, which may in turn affect a drug's pharmacokinetic and/or pharmacodynamic parameters. Variations in genes that encode for human leukocyte antigens (HLAs) may lead to differences in predisposition to immune-related hypersensitivity reactions to medications, some of which are life-threatening. Genetics, therefore, is another clinical tool that can be used to personalize medication selection and dosing. Pharmacogenomic information should always be interpreted in the context of other clinical variables, given that genetic variation may not be the main driver of medication response; ultimately, genetics is predictive, not deterministic. Other factors, such as drug-drug interactions, may need to be accounted for in order to accurately interpret pharmacogenomic test results (e.g., a patient who is a CYP2D6 normal metabolizer by genotype may act like a CYP2D6 poor metabolizer if taking a medication that is a strong CYP2D6 inhibitor [e.g., fluoxetine, paroxetine, bupropion]).

Many clinically relevant germline pharmacogenomic examples involve genes that encode for drug-metabolizing enzymes (e.g., cytochrome P450 [CYP] enzymes). Genetic variations can lead to a spectrum of enzyme activity, from ultrarapid metabolizer to poor metabolizer, depending on the gene. If an active drug is converted by the enzyme into an inactive metabolite, increased enzyme activity can result in therapeutic failure, whereas decreased enzyme activity can lead to toxicity. In contrast, if the drug is a prodrug that requires metabolism to its active metabolite, the opposite is true. Whether these outcomes manifest in clinical practice depend on several factors, including the therapeutic index of the drug and the influence of other metabolic pathways on drug disposition and response.

Pharmacogenomic Terminology, Nomenclature, and Test Interpretation

An understanding of pharmacogenomics requires a familiarity with the associated terminology, including general genetic terms. Table 1 lists common genetic terms and their definitions.

Pharmacogenomic alleles can be reported in a variety of ways, including star allele nomenclature (e.g., *TPMT*2*), nucleotide changes (e.g., rs1800462C>G [cytosine changed to guanine]), and amino acid changes (e.g., p.A80P [alanine changed to proline]). Note that italics (e.g., *CYP2D6*) are used when referring to the gene and that regular text (e.g., CYP2D6) is used when referring to the protein. Information about how particular pharmacogenomic alleles are defined can be found on the [Pharmacogene Variation Consortium](#) website. With star allele nomenclature, the “wild-type” (i.e., normal, reference)

sequence of an allele is assigned *1. All other alleles are called by other numbers (e.g., *2, *3, *4), which are assigned in the order each allele was discovered. For any given gene, an individual typically inherits two copies – one maternal allele and one paternal allele. Certain genes, such as *CYP2D6*, are susceptible to gene duplications, multiplications, and deletions, making it possible to have more or less than two copies of this gene. Therefore, copy number variation is an essential component in interpreting pharmacogenomic test results for *CYP2D6*. Without copy number variation, a phenotype cannot accurately be assigned.

The combination of alleles is what makes up a genotype (or diplotype) result (e.g., *TPMT*1/*2*). For many pharmacogenes, each allele is assigned a function (e.g., increased function, normal function, decreased function, no function). The combination of functions of the inherited alleles determines a patient’s phenotype (e.g., thiopurine methyltransferase [TPMT] intermediate metabolizer). Certain genes (e.g., *CYP2D6*, *CYP2C9*, and dihydropyrimidine dehydrogenase [*DPYD*]) use an activity score system to translate genotype to phenotype whereby particular alleles are assigned an activity value (e.g., 0 for no function alleles, 0.5 for decreased function alleles, and 1 for normal function alleles), and the sum of the activity values for a particular diplotype corresponds to a particular phenotype (e.g., an activity score of 2 for a *CYP2D6* result translates to a normal metabolizer). The Clinical Pharmacogenetics Implementation Consortium ([CPIC](#)) provides guidance on how to assign a phenotype from genotype for genes that are the subject of their clinical guidelines (see the Pharmacogenomic Resources section for more information).

Table 1. Genetic Terms and Their Definitions

Term	Definition
<i>Allele</i>	A version of a gene. An individual inherits two alleles for each gene, one from each parent
<i>Diplotype</i>	A haplotype pair (e.g., two alleles inherited for a particular gene)
<i>Gene</i>	Basic physical unit of inheritance
<i>Genotype</i>	An individual’s collection of genes. Can also refer to the two alleles inherited for a particular gene
<i>Haplotype</i>	A set of DNA variations that tend to be inherited together
<i>Heterozygous</i>	Two different alleles inherited for a given gene
<i>Homozygous</i>	Two identical alleles inherited for a given gene
<i>Nucleotide</i>	Basic building block of nucleic acids (RNA and DNA). Consists of a sugar molecule (ribose in RNA or deoxyribose in DNA) attached to a phosphate group and a nitrogen-containing base. The bases in DNA are adenine (A), cytosine (C), guanine (G), and thymine (T). In RNA, the base uracil (U) takes the place of thymine
<i>Phenotype</i>	An individual’s observable traits
<i>Polymorphism</i>	One of two or more variants of a particular DNA sequence. The most common type of polymorphism involves variation at a single base pair (i.e., single nucleotide polymorphism or SNP)

Information from: National Human Genome Research Institute. [Talking Glossary of Genetic Terms](#).

Table 2. Standardized Phenotype Terms for Drug-Metabolizing Enzymes, Drug Transporters, and HLA Molecules

Gene Category	Standardized Phenotype Terms
Drug-metabolizing enzymes (e.g., <i>CYP2C19</i> , <i>CYP2D6</i> , <i>CYP3A5</i> , <i>CYP2C9</i> , <i>TPMT</i> , <i>DPYD</i> , <i>UGT1A1</i>)	Ultrarapid metabolizer Rapid metabolizer Normal metabolizer Intermediate metabolizer Poor metabolizer
Drug transporters (e.g., <i>SLCO1B1</i>)	Increased function Normal function Decreased function Poor function
HLA molecules (e.g., <i>HLA-A</i> , <i>HLA-B</i>)	Positive Negative

DPYD = dihydropyrimidine dehydrogenase; *SLCO1B1* = solute carrier organic anion transporter family member 1B1; *TPMT* = thiopurine methyltransferase; *UGT1A1* = uridine diphosphate glucuronosyltransferase 1A1.

Information from: Caudle KE, Dunnenberger HM, Freimuth RR, et al. Standardizing terms for clinical pharmacogenetic test results: consensus terms from the Clinical Pharmacogenetics Implementation Consortium. *Genet Med* 2017;19:215-23.

Phenotype terms for drug-metabolizing enzymes, drug transporters, and HLA molecules have been standardized through expert consensus (Caudle 2017) (Table 2). The term *extensive metabolizer*, which can be found in the literature, indicates normal enzyme function and is equivalent to the new standardized term *normal metabolizer*.

The function of an allele cannot be determined on the basis of its star allele designation (e.g., *CYP2D6*2* has normal function, whereas *CYP2C19*2* has no function). Allele functionality tables and diplotype-to-phenotype translation tables accompany each CPIC guideline (see the Pharmacogenomic Resources section for more information on these resources). An important caveat with star allele nomenclature is that the *1 designation is not a guarantee of “normal” function; rather, the *1 implies that none of the interrogated variants (which may be a small subset of all known variants) were identified, leaving open the possibility that the patient could still harbor a genetic variant that affects medication response that was not interrogated by the testing technology.

PHARMACOGENOMIC RESOURCES

FDA Labeling

Over 250 medications have pharmacogenomic information in their FDA labeling, which can be found in the [Table of Pharmacogenomic Biomarkers in Drug Labeling](#) on the FDA

website. Ninety of these medications are tagged as relevant to oncology, some of which are associated with more than one biomarker (gene). The FDA has also published a [Table of Pharmacogenetic Associations](#), which has three sub-tables: (1) pharmacogenetic associations for which the data support therapeutic management recommendations, (2) pharmacogenetic associations for which the data indicate a potential impact on safety or response, and (3) pharmacogenetic associations for which the data show a potential impact on pharmacokinetic properties only. These tables are dynamic and subject to change, and the FDA welcomes the larger pharmacogenomic community to recommend edits on the basis of current evidence.

Pharmacogenomic information that is included in FDA drug labels can be found in many sections of the label, including Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, and Clinical Studies. In some cases (e.g., somatic variants), the FDA requires genetic testing before prescribing because the medication will only work in individuals with (or without) a particular genetic variant. The FDA includes information about both germline and somatic variants in drug labeling. Some of this information is actionable, meaning it provides clinicians with guidance regarding how to choose, dose, or monitor medication therapy on the basis of genetics. Sometimes, the genetic information is merely informative – the label may mention a gene-drug association but without corresponding prescribing recommendations. To address the need for updated information regarding pharmacogenomic information in clinical practice, experts in the field have come together to create evidence-based clinical pharmacogenomic guidelines (see the Clinical Practice Guidelines section).

Pharmacogenomics Knowledgebase

The [Pharmacogenomics Knowledgebase](#) (PharmGKB) was formed in 2000 to serve as a comprehensive online database that collects and curates pharmacogenomic information. This National Institutes of Health (NIH)-funded resource is maintained by a scientific team from Stanford University. The homepage contains a search bar through which users can search for genes, drugs, or a combination of both and retrieve expert-curated information, including available clinical practice guidelines (e.g., CPIC guidelines), drug label annotations, and clinical annotations summarizing the available literature. In addition, PharmGKB has a separate [Cancer Pharmacogenomics](#) webpage with links to information relevant to cancer drugs and their associated genes, as well as links to external resources. In addition, PharmGKB works closely with CPIC to maintain [gene-specific information tables](#), including allele definition tables, allele functionality tables, allele frequency tables, diplotype-phenotype translation tables, and gene resource mappings. Moreover, PharmGKB provides curated [pathway diagrams](#) that illustrate pharmacogenomic

pathways, more than 40 of which pertain to anticancer agents. Each pathway diagram is accompanied by a written summary of the pharmacokinetic or pharmacodynamic pathway together with other pharmacogenomic information and associated references.

Clinical Practice Guidelines

Clinical Pharmacogenetics Implementation Consortium

The Clinical Pharmacogenetics Implementation Consortium (CPIC) is a NIH-funded consortium that was formed in 2009 to facilitate the implementation of pharmacogenomics into clinical practice through disseminating evidence-based clinical practice guidelines (Relling 2011). CPIC has grown to over 350 members in 2019 from 245 institutions and 33 countries and has observers from both the FDA and the NIH. CPIC guidelines are drafted by an international, interprofessional team of pharmacogenomic experts who conduct a systematic review of the literature for a given gene-drug association to create evidence-based prescribing recommendations on the basis of pharmacogenomics. There are currently [24 published CPIC guidelines](#) covering 19 genes and 53 drugs. These guidelines are used worldwide by pharmacogenomic implementers. Several drugs that are the subject of CPIC guidelines are used to treat cancer (e.g., thiopurines, fluoropyrimidines, tamoxifen), and many more are used as supportive care for cancer therapy (e.g., ondansetron, selective serotonin reuptake inhibitors [SSRIs], rasburicase).

CPIC guidelines adhere to the National Academies of Medicine Standards for Developing Trustworthy Clinical Practice Guidelines and maintain a strict conflict of interest policy to avoid bias in guideline recommendations. The underlying assumption for all CPIC guidelines is that the pharmacogenomic test result is available at the point of prescribing. Rather than advising on when to order pharmacogenomic testing, CPIC provides guidance on how best to use pharmacogenomic test results to optimize medication selection and dosing when a result is available. In addition, CPIC only creates guidelines for germline genetic variants, not somatic genetic variants, so tumor-specific targeted therapies are not included.

Dutch Pharmacogenetics Working Group

The Dutch Pharmacogenetics Working Group (DPWG) was established in 2005 by the Royal Dutch Association for the Advancement of Pharmacy. Like CPIC, the DPWG provides evidence-based clinical pharmacogenomic guidelines for gene-drug pairs focusing on germline genetic variants and does not weigh in on whether pharmacogenomic testing should be ordered. The DPWG provides guidelines for certain cancer drugs and for cancer-related supportive therapy. The most up-to-date DPWG guidelines can be found on the [PharmGKB](#) website.

Canadian Pharmacogenomics Network for Drug Safety Consortium

The [Canadian Pharmacogenomics Network for Drug Safety](#) is a national program whose mission is to reduce serious adverse drug reactions, particularly in children. In addition to its research mission, the network creates evidence-based clinical practice guidelines. Unlike CPIC and DPWG, its guidelines provide recommendations on whether pharmacogenomic testing should be ordered for particular groups of patients. To date, this group has published six guidelines, three of which pertain to cancer drugs. These guidelines, together with the CPIC and DPWG guidelines, are annotated in PharmGKB.

French National Network of Pharmacogenetics

The French National Network of Pharmacogenetics has published pharmacogenomic recommendations, including recommendations for cancer drugs. Depending on the level of evidence, one of three recommendations is issued for pharmacogenomic testing: essential, advisable, and potentially useful. To date, this group has published five guidelines that pertain to multiple gene-drug pairs, and two of these guidelines pertain to cancer drugs. These guidelines are also annotated in PharmGKB.

CHEMOTHERAPY PHARMACOGENOMICS: SOMATIC GENETIC VARIATION

There are many examples of how somatic genetic variation is used to provide targeted therapy to patients with cancer. Some cancer drugs have companion diagnostic tests, and specific genetic testing is required before use (Table 3). This section reviews some of these examples in greater detail.

HER2 and Trastuzumab

Trastuzumab first received FDA approval in 1998 for use in women with metastatic breast cancer. Trastuzumab is a monoclonal antibody that exerts its anticancer effect by binding to the extracellular domain of the human epidermal growth factor receptor 2 (HER2) protein, thereby inhibiting the proliferation of cells that overexpress the HER2 protein. The official gene name of HER2 is ERBB2 (Erb-B2 receptor tyrosine kinase 2); these terms are used interchangeably. Trastuzumab has since been approved for the treatment of HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma as part of a combination regimen in patients who have not received prior treatment for metastatic disease. HER2 gene amplification must be assessed before prescribing trastuzumab. A similar agent, pertuzumab, also has this requirement.

BCR-ABL and Imatinib

When imatinib was approved in 2001, it was revolutionary for patients with chronic myeloid leukemia (CML); it improved

Table 3. Cancer Drugs with Companion Diagnostic Tests

Drug	Gene
Ado-trastuzumab	<i>HER2</i>
Afatinib	<i>EGFR</i>
Alectinib	<i>ALK</i>
Alpelisib	<i>PIK3CA, HER2</i>
Atezolizumab	<i>PD-L1</i>
Ceritinib	<i>ALK</i>
Cetuximab	<i>EGFR, KRAS</i>
Cobimetinib	<i>BRAF^a</i>
Crizotinib	<i>ALK</i>
Dabrafenib	<i>BRAF</i>
Dacomitinib	<i>EGFR</i>
Enasidenib	<i>IDH2</i>
Encorafenib	<i>BRAF</i>
Erdafitinib	<i>FGFR</i>
Erlotinib	<i>EGFR</i>
Gefitinib	<i>EGFR</i>
Gilteritinib	<i>FLT3</i>
Imatinib	<i>BCR-ABL, KIT, PDGFRB^b</i>
Ivosidenib	<i>IDH1</i>
Midostaurin	<i>FLT3</i>
Nilotinib	<i>BCR-ABL</i>
Niraparib	<i>BRCA</i>
Olaparib	<i>BRCA</i>
Osimertinib	<i>EGFR</i>
Panitumumab	<i>EGFR, KRAS</i>
Pembrolizumab	<i>PD-L1</i>
Pertuzumab	<i>HER2</i>
Rucaparib	<i>BRCA</i>
Talazoparib	<i>BRCA</i>
Trametinib	<i>BRAF^c</i>
Trastuzumab	<i>HER2</i>
Vemurafenib	<i>BRAF</i>
Venetoclax	<i>BCL-2</i>

^aIn combination with vemurafenib.

^bDepending on the disease.

^cIn combination with dabrafenib.

Information from: FDA. [List of Cleared or Approved Companion Diagnostic Devices \(In Vitro and Imaging Tools\)](#).

the survival rate for patients with CML from under 30% to over 80%. Imatinib is a tyrosine kinase inhibitor indicated for patients with CML who are Philadelphia chromosome (*BCR-ABL*) positive, which accounts for over 90% of the CML population. The Philadelphia chromosome is characterized by a translocation of the *ABL* gene onto the *BCR* gene, which in turn encodes for a mutant tyrosine kinase signaling protein that is always “on,” causing uncontrollable cell growth. Testing for the presence of the Philadelphia chromosome is required before imatinib can be initiated for CML and acute lymphoblastic leukemia. Additional tyrosine kinase inhibitors have been developed that target BCR-ABL and the acquired resistance to imatinib, including dasatinib, nilotinib, and bosutinib. One mutation that can occur de novo or be acquired is the T315I mutation, which does not respond to any of these therapies. Ponatinib was developed specifically to overcome this mutation.

EGFR and Erlotinib

Erlotinib is approved for the treatment of metastatic non-small cell lung cancer. Erlotinib specifically targets epidermal growth factor receptor (EGFR) tyrosine kinase activity. Once activated, EGFR sets off a cascade of intracellular signaling that ultimately affects gene transcription, which in turn results in cancer cell proliferation, reduced apoptosis, invasion, and metastasis and stimulates tumor-induced angiogenesis. Therefore, erlotinib inhibition of EGFR prevents this downstream signaling and results in cell death. Erlotinib is indicated if an *EGFR*-activating mutation is present (e.g., *EGFR* exon 19 deletion or exon 21 L858R), and genetic testing is required before use. Other agents that target EGFR mutations include gefitinib, afatinib, and dacomitinib. If the T790M EGFR mutation is present, erlotinib and many other EGFR inhibitors are not effective. However, osimertinib specifically targets this mutation and is approved for use in non-small cell lung cancer.

EGFR, RAS, and Cetuximab

Cetuximab, an EGFR inhibitor, is indicated for the treatment of *RAS* wild-type, EGFR-positive (i.e., EGFR-expressing) metastatic colorectal cancer. The EGFR signaling pathway normally controls the activation of KRAS and NRAS, which are downstream signaling proteins that promote cell growth. However, *RAS* activating mutations cause KRAS and NRAS to be perpetually “on,” causing uncontrollable cell growth irrespective of EGFR involvement; therefore, blockade of the upstream EGFR will not arrest cell growth, rendering EGFR inhibitors in this setting ineffective. Genetic testing for *RAS* mutations and testing for EGFR expression are required before use. This applies to the EGFR inhibitor panitumumab as well.

ALK, ROS1, and Crizotinib

Crizotinib is an inhibitor of receptor tyrosine kinases, including anaplastic lymphoma kinase (ALK), hepatocyte growth

factor receptor, ROS proto-oncogene 1 (ROS1), and *recepteur d'origine nantais* indicated for the treatment of patients with metastatic non–small cell lung cancer whose tumors contain an *ALK* or *ROS1* gene alteration. Inhibition of the *ALK* tyrosine kinase reduces the cell proliferation of cancer cells that express a genetic alteration in *ALK*. Anaplastic lymphoma kinase genetic abnormalities may result in the expression of oncogenic fusion proteins that alter cell signaling and result in increased cell proliferation and survival in tumors. As with *ALK*, *ROS1* genetic alternations are also chromosomal rearrangements and fusions of the gene to other genes, and pathways downstream become activated. Testing for these genetic abnormalities is required before use. Other *ALK* inhibitors for which testing is required before use include alectinib, ceritinib, brigatinib, and lorlatinib.

BRAF and Vemurafenib

Vemurafenib is a reversible and highly selective BRAF serine/threonine kinase inhibitor approved for the treatment of unresectable or metastatic melanoma in patients with the BRAF V600E mutation. The V600E is the most common BRAF mutation in cancers and results in an amino acid change at position 600 in the BRAF protein from a valine (V) to a glutamic acid (E). The BRAF is an activating mutation, which results in constitutive activation of downstream signaling through the MAPK (mitogen-activated protein kinase) pathway, leading to cell proliferation and survival. BRAF mutations are found in about 50% of melanoma cases. Vemurafenib inhibits the signaling of mutant BRAF, leading to G1 cell cycle arrest. Vemurafenib is ineffective against melanoma cells with wild-type BRAF. Vemurafenib is also used off-label for patients with metastatic melanoma who have the BRAF V600K mutation, which is another known activating mutation. Data analyses from a phase III, randomized study that included a subset of patients with the BRAF V600K mutation showed that 40% of these patients responded favorably to vemurafenib (Chapman 2011). Testing for *BRAF* mutations is required before prescribing vemurafenib and other drugs in the same class (e.g., dabrafenib, encorafenib).

Tissue-Agnostic Targeted Therapies

Approval of tissue-agnostic targeted therapies represents a new paradigm in cancer treatment: rather than treating cancers on the basis of where the tumor originated (e.g., breast, colon, lung), cancers are treated on the basis of distinguishing genetic features that are targeted by a given therapeutic agent. The era of tissue-agnostic targeted therapies began in 2017 with the approval of pembrolizumab for cancers of a particular genetic subtype, with approval of larotrectinib and entrectinib following in 2018 and 2019, respectively.

Pembrolizumab

Pembrolizumab, a highly selective anti-programmed cell death-1 (PD-1) humanized monoclonal antibody, was initially

approved in 2014 for patients with unresectable or metastatic melanoma after treatment failure. By blocking the interaction between PD-1 and its ligands, pembrolizumab enables an anti-tumor immune response. Pembrolizumab has since received approval for the treatment of several other types of cancer, including cervical cancer, endometrial carcinoma, esophageal cancer, gastric cancer, head and neck cancer, and hepatocellular carcinoma. In 2017, the FDA granted accelerated approval to pembrolizumab for the treatment of unresectable or metastatic, microsatellite instability-high or mismatch repair deficient solid tumors in adult and pediatric patients, regardless of tumor site or histology. This was the FDA's first tissue/site-agnostic approval. Microsatellite instability-high cancer is characterized by genetic mutations within microsatellites, which are short, repeated sequences of DNA. Mismatch repair deficient cancer is characterized by genetic mutations that are involved in correcting mistakes when DNA is copied in a cell. Combined data analyses from disease-specific pembrolizumab clinical trials show that patients with microsatellite instability-high or mismatch repair deficient cancer had improved outcomes (e.g., improved objective response rate and response duration).

Larotrectinib

The second tissue-agnostic FDA approval for cancer was for larotrectinib in 2018. Larotrectinib is a tyrosine kinase inhibitor that is approved for the treatment of adult and pediatric patients with solid tumors that have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation. Specifically, larotrectinib therapy is indicated in the setting of metastatic disease or when surgical resection is likely to result in severe morbidity in patients with no satisfactory alternative treatments or whose cancer has progressed after treatment. This is the only labeled indication for larotrectinib use. Approval was based on data from three multicenter, open-label, single-arm clinical trials, which showed improved outcomes (e.g., overall response rate and response duration) in patients who were positive for the NTRK gene fusion. The most common cancers represented in these studies included salivary gland tumors, soft tissue sarcoma, infantile fibrosarcoma, and thyroid cancer.

Entrectinib

In 2019, the FDA granted accelerated approval to entrectinib, the third tissue-agnostic cancer therapy. Like larotrectinib, entrectinib is a tyrosine kinase inhibitor that is approved for the treatment of adult and pediatric patients with solid tumors that have an NTRK gene fusion without a known acquired resistance mutation. Also like larotrectinib, entrectinib is indicated in the setting of metastatic disease or when surgical resection is likely to result in severe morbidity when no satisfactory alternative treatments are available or in patients whose cancer has progressed after treatment. Approval was based on data from three multicenter,

single-arm clinical trials, which showed improved outcomes (e.g., overall response rate and response duration) in patients who were positive for the NTRK gene fusion. The most common cancers represented in these studies included sarcoma, non-small cell lung cancer, mammary analog secretory carcinoma, breast, thyroid, and colorectal cancer.

CHEMOTHERAPY PHARMACOGENOMICS: GERMLINE GENETIC VARIATION

The most clinically useful examples of germline genetic variation to inform chemotherapy prescribing involve drug-metabolizing enzymes. Specifically, increased or decreased activity of these enzymes because of genetic variation may place patients at risk of toxicity or therapeutic failure. Knowledge of enzyme activity through pharmacogenomic tests can inform initial medication selection decisions or dose adjustments that could improve clinical outcomes. This section reviews some of these examples in greater detail.

***TPMT*, *NUDT15*, and Thiopurines**

The thiopurines mercaptopurine and thioguanine are most commonly used to treat lymphoid malignancies and myeloid leukemias, respectively. Thiopurine methyltransferase catalyzes the S-methylation of thiopurines, which is their principal mechanism of inactivation. This pathway reduces the amount of parent drug that is metabolized to the active thioguanine nucleotides. Thioguanine nucleotides are responsible for thiopurine efficacy and, when in excess, thiopurine toxicity (e.g., myelosuppression). Genetic variants in the gene *TPMT* (e.g., *2, *3A, *3C) have been linked to impaired *TPMT* activity, high levels of thioguanine nucleotides, and life-threatening myelosuppression with standard thiopurine dosages. The relationship between *TPMT* genetic variation and thiopurine response has been known since the 1980s. About 90% of individuals inherit two normal function *TPMT* alleles (e.g., *1/*1) and are characterized as *TPMT* normal metabolizers; about 10% of individuals inherit one normal function and one no function variant allele and are characterized as *TPMT* intermediate metabolizers (e.g., *1/*3A); and about 1 in 300 individuals inherit two no function alleles and are characterized as *TPMT* poor metabolizers (e.g., *3A/*3A). Preemptive dose reductions in patients who are *TPMT* intermediate or poor metabolizers decrease the incidence of toxicity while maintaining efficacy.

Recent genome-wide association studies have identified an additional gene, nudix hydrolase 15 (*NUDT15*), which is predictive of thiopurine toxicity (Yang 2015; Yang 2014). The gene *NUDT15* encodes for the *NUDT15* enzyme, which catalyzes the conversion of cytotoxic thioguanine nucleotides (i.e., thioguanine triphosphate metabolites) to the less-toxic thioguanine monophosphate metabolites. Genetic variants *NUDT15* (e.g., rs116855232; c.415C>T) have been linked to impaired *NUDT15* activity, and carriers of these variants are

at high risk of life-threatening myelosuppression with standard thiopurine dosages because of excessive thioguanine nucleotide-mediated cytotoxicity. Individuals carrying two normal function alleles are characterized as *NUDT15* normal metabolizers; those carrying one normal function allele plus one no function allele are characterized as *NUDT15* intermediate metabolizers; and those carrying two no function alleles are characterized as *NUDT15* poor metabolizers. Whereas inactivating *TPMT* variants explain most of the thiopurine intolerance for individuals of European and African descent, inactivating *NUDT15* variants explain most of the thiopurine intolerance for individuals of Asian and Hispanic descent.

The FDA labeling for thiopurines acknowledges the importance of *TPMT* and *NUDT15* in determining the optimal dosage with these agents. The FDA labeling also provides recommendations for testing in patients who have severe or repeated episodes of myelosuppression and a warning stating that patients who are heterozygous or homozygous for either *TPMT* or *NUDT15* inactivating variants may require substantial thiopurine dose reductions. CPIC provides more detailed dosing guidelines, accounting for patients who may have a *TPMT* genotype, a *NUDT15* genotype, or both (Relling 2019). In general, *TPMT* or *NUDT15* intermediate metabolizers require around 30%–80% of the standard starting dose, and *TPMT* or *NUDT15* poor metabolizers require around 10% of the standard dose given three times weekly instead of daily. Individuals who are both *TPMT* and *NUDT15* intermediate metabolizers may require a lower dose than individuals who are only intermediate metabolizers with respect to one gene.

***DPYD* and Fluoropyrimidines**

The fluoropyrimidine fluorouracil and its oral prodrug, capecitabine, are used to treat several solid tumor types, including colorectal, gastric, and head and neck cancers. Around 10%–40% of patients experience severe toxicity with these agents, including neutropenia, nausea, vomiting, severe diarrhea, stomatitis, and hand-foot syndrome. These toxicities are sometimes associated with a deficiency in the enzyme dihydropyrimidine dehydrogenase (DPD), which catalyzes the rate-limiting step in fluoropyrimidine catabolism. DPD is encoded by the gene *DPYD*. Genetic variants in *DPYD* that cause decreased DPD activity result in impaired clearance and increased half-life of fluoropyrimidines at normal doses, which may lead to profound dose-related toxicities. Preemptive *DPYD* genotyping for common inactivating variants and a dose reduction in patients with lower-than-normal predicted DPD activity decrease the incidence of fluoropyrimidine toxicities and may be a cost-effective medication safety strategy (Henricks 2019, 2018).

Predicted DPD phenotype can be assigned on the basis of genotype. Determination of DPD phenotype uses an activity score system that assigns activity values to allele functions. Normal function alleles are assigned an activity value of 1, decreased function alleles an activity value of 0.5, and

Table 4. Assignment of DPYD Phenotype on the Basis of Activity Score

Phenotype	Activity Score	Genotype
DPYD normal metabolizer	2	2 normal function alleles
DPYD intermediate metabolizer	1.5 1	1 normal function allele + 1 decreased function allele 1 normal function allele + 1 no function allele OR 2 decreased function alleles
DPYD poor metabolizer	0.5 0	1 decreased function allele + 1 no function allele 2 no function alleles

Information from: Amstutz U, Henricks LM, Offer SM, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for dihydropyrimidine dehydrogenase genotype and fluoropyrimidine dosing: 2017 update. *Clin Pharmacol Ther* 2018;103:210-6.

no function alleles an activity value of 0. The sum of the activity values for each allele in a given diplotype comprises the activity score, which is used to translate genotype into phenotype (Table 4). Four of the most clinically relevant *DPYD* variants are the decreased-function alleles c.2846A>T (i.e., rs67376798) and c.1129-5923C>G (i.e., rs75017182, HapB3) and the no-function alleles c.190511G>A (i.e., rs3918290, *DPYD*2A*) and c.1679T>G (rs55886062, *DPYD*13*).

CPIC provides dosing recommendations for fluoropyrimidines on the basis of DPYD phenotype (Amstutz 2018). Patients known to be DPYD normal metabolizers are at “normal” risk of developing fluoropyrimidine toxicity and should receive protocol-recommended doses of fluoropyrimidines. Intermediate metabolizers of DPYD should receive a dose reduction of 50%, followed by dose titration on the basis of toxicity or therapeutic drug monitoring, if available. Poor metabolizers of DPYD should avoid use of fluoropyrimidines because of the risk of severe or even fatal drug toxicity. In certain cases, use of a fluoropyrimidine may be warranted, in which case a significantly reduced dose (less than 25% of the normal starting dose) is recommended with early therapeutic drug monitoring. The FDA labeling for fluoropyrimidines warns of severe or fatal adverse reactions in patients with DPD deficiency, but there is no recommendation for genetic testing. In clinical practice, testing is rarely performed before treating a patient with fluoropyrimidines, but deficiency should be considered in patients who develop early myelosuppression or other severe toxicities.

***UGT1A1* and Irinotecan**

Irinotecan is a topoisomerase I inhibitor indicated for the treatment of metastatic carcinoma of the colon or rectum, either as first-line therapy or for recurrent disease after fluorouracil-based treatment. Irinotecan is a prodrug, and its active metabolite, SN-38, has a 100-fold higher antitumor activity than the parent compound. SN-38 undergoes conjugation by uridine diphosphate glucuronosyltransferase 1A1 (*UGT1A1*) to form an inactive glucuronide metabolite that is ultimately excreted in the bile and urine. The *UGT1A1*28*

allele is characterized by seven (instead of the usual six) thymine-adenine repeats in the promoter region of the gene. This genetic variation results in decreased gene expression, to about 30% of normal. Individuals who are homozygous for *UGT1A1*28* (*UGT1A1* poor metabolizers) are typically given a diagnosis of Gilbert syndrome (benign inherited unconjugated hyperbilirubinemia). These patients are predisposed to increased SN-38 plasma concentrations, leading to more irinotecan-associated dose-limiting toxicities (i.e., neutropenia and diarrhea).

The FDA-approved drug label for irinotecan states that a reduction in the starting dose by at least one level should be considered for patients who are known to be homozygous for *UGT1A1*28*. Similarly, the FDA-approved drug label for liposomal irinotecan recommends a dose reduction on the basis of *UGT1A1* genotype and states that the recommended starting dose in patients who are known to be homozygous for *UGT1A1*28* is 50 mg/m² every 2 weeks, whereas the normal starting dose is 70 mg/m² every 2 weeks. CPIC does not currently have a guideline for irinotecan and *UGT1A1*; however, the DPWG and the French National Network of Pharmacogenetics do have guidelines for this. The DPWG recommends starting with 70% of the standard irinotecan dose in patients who are known to be homozygous for *UGT1A1*28*, with subsequent dose titration depending on tolerability of that initial dose and guided by neutrophil count. No action is recommended for patients who are heterozygous for *UGT1A1*28* (*UGT1A1* intermediate metabolizers). The French National Network of Pharmacogenetics stratifies its recommendations according to the indicated dose (Quaranta 2017). For low doses (less than 180 mg/m²/week), genotype-guided dosing is not recommended. For intermediate doses (180–230 mg/m² spaced by 2- to 3-week intervals), a 25%–30% dose reduction is recommended for patients who are homozygous for *UGT1A1*28*, with dose adjustment for subsequent cycles depending on tolerance. High doses (240 mg/m² or greater spaced by 2- to 3-week intervals) are only recommended for patients with the *UGT1A1*1/*1* and **1/*28* genotypes (*UGT1A1* normal and intermediate metabolizers, respectively). The dosing

recommendations were developed when higher doses of irinotecan were consistently used and may not be as helpful clinically now, given that irinotecan is now most commonly administered at lower doses every 2 weeks or in daily or weekly doses.

UGT1A1 and Belinostat

Belinostat is a histone deacetylase inhibitor indicated for the treatment of relapsed or refractory peripheral T-cell lymphoma. Belinostat is primarily (80%–90%) metabolized by UGT1A1 into inactive metabolites. Therefore, alleles associated with decreased UGT1A1 function (e.g., *UGT1A1*28*) may have significantly impaired clearance and be at increased risk of toxicity (e.g., neutropenia, thrombocytopenia). The standard recommended dose of belinostat is 1000 mg/m², and the FDA-approved drug label for belinostat states that patients who are known to be homozygous for the *UGT1A1*28* allele should receive a reduced starting dose of 750 mg/m² in order to minimize dose-limiting toxicities. The FDA does not require *UGT1A1* genotyping before use.

CYP2D6 and Tamoxifen

Tamoxifen is a selective estrogen receptor modulator indicated for the prevention and treatment of breast cancer. Tamoxifen is a prodrug; it is metabolized by CYP2D6 to 4-hydroxy-tamoxifen and through CYP3A4/5 to *N*-desmethyl-tamoxifen. Each metabolite is further metabolized into endoxifen (4-hydroxy-tamoxifen through CYP3A4/5 and *N*-desmethyl-tamoxifen through CYP2D6). 4-Hydroxy-tamoxifen and endoxifen are 30- to 100-fold more potent than tamoxifen. Studies have reported decreased endoxifen plasma concentrations and decreased efficacy of tamoxifen (i.e., increased risk of breast cancer recurrence, death) in the presence of moderate (e.g., sertraline) and strong (e.g., paroxetine, fluoxetine) CYP2D6 inhibitors. Similarly, studies have shown that CYP2D6 poor metabolizers by genotype have lower plasma concentrations of endoxifen, which may be associated with worse outcomes; however, outcomes data are conflicting. Postulated reasons for the conflicting data include nonadherence to tamoxifen, interacting medications (e.g., CYP2D6 inhibitors), and use of tumor tissue for *CYP2D6* genotyping. Other CYP enzymes also influence endoxifen concentrations. Current oncology guidelines, including those of the National Comprehensive Cancer Network and the American Society of Clinical Oncology, do not recommend routine *CYP2D6* genotyping before tamoxifen use. The FDA-approved drug label for tamoxifen states that the impact of *CYP2D6* polymorphisms on the efficacy of tamoxifen is not well established but that CYP2D6 poor metabolizers have lower endoxifen concentrations than those carrying one or more fully functional *CYP2D6* alleles.

CPIC provides evidence-based guidelines for tamoxifen use when the *CYP2D6* genotype is known before therapy (Goetz 2018). For CYP2D6 poor metabolizers, CPIC strongly

recommends the use of alternative hormonal therapy such as an aromatase inhibitor for postmenopausal women or an aromatase inhibitor together with ovarian function suppression in premenopausal women, given that these approaches are superior to tamoxifen regardless of *CYP2D6* genotype. If there are contraindications to aromatase therapy, a higher dose of tamoxifen (i.e., 40 mg/day) may increase (but does not normalize) endoxifen concentrations and can be considered. This recommendation applies to CYP2D6 intermediate metabolizers as well, but is graded with a “moderate” strength of recommendation and with the added recommendation to avoid strong, moderate, and weak CYP2D6 inhibitors. For CYP2D6 normal and ultrarapid metabolizers, normal tamoxifen dosing (i.e., 20 mg/day) applies, with the recommendation to avoid moderate and strong CYP2D6 inhibitors.

SUPPORTIVE CARE PHARMACOGENOMICS

In addition to providing insights for optimal chemotherapy selection and dosing, pharmacogenomic testing can help guide supportive care therapy as it pertains to nausea/vomiting, pain, depression, fungal infections, tumor lysis syndrome, and immunosuppression.

Antiemetic Therapy

5-hydroxytryptamine type 3 (5-HT₃) receptor antagonists are the cornerstone of antiemetic therapy for chemotherapy- and radiation-induced nausea and vomiting. 5-HT₃ receptor antagonists are metabolized to inactive metabolites by several CYP enzymes, including CYP2D6, CYP3A4, and CYP1A2. Studies have shown that CYP2D6 ultrarapid metabolizers experience increased metabolism of ondansetron to inactive metabolites compared with CYP2D6 normal metabolizers and have decreased antiemetic efficacy (i.e., vomiting) (Bell 2017). CPIC recommends selecting an alternative drug not predominantly metabolized by CYP2D6 (i.e., granisetron, which is metabolized primarily by CYP3A4 and CYP1A1) in known CYP2D6 ultrarapid metabolizers. Other 5-HT₃ receptor antagonists, including dolasetron and palonosetron, are also metabolized by CYP2D6, but evidence is limited regarding the appropriate use of *CYP2D6* genotype results to inform the use of these agents.

Pain Management

Patients with cancer often have nociceptive pain requiring opioid therapy or neuropathic pain requiring tricyclic antidepressant (TCA) therapy. Pharmacogenomic testing may help determine an optimal pain management strategy in both of these settings. Several opioids, including codeine, tramadol, hydrocodone, and oxycodone, are bioactivated by CYP2D6. For the prodrugs codeine and tramadol, CYP2D6 activation into morphine and *O*-desmethyltramadol, respectively, is essential for efficacy with these agents. CYP2D6 ultrarapid metabolizers are at risk of toxicity (e.g., severe respiratory

depression) because of supratherapeutic plasma concentrations of the active metabolite, and CYP2D6 poor metabolizers are at risk of therapeutic failure because of subtherapeutic plasma concentrations of the active metabolite. CPIC recommends avoiding codeine and tramadol in CYP2D6 ultrarapid and poor metabolizers (Crews 2014). In contrast to codeine and tramadol, hydrocodone and oxycodone are sufficiently active at the mu-opioid receptor to provide analgesia on their own, but not as much as their metabolites, hydromorphone and oxymorphone, respectively. Because of limited data, the significance of *CYP2D6* genetic variation on clinical outcomes associated with hydrocodone and oxycodone is less clear. When implemented into practice, *CYP2D6*-guided opioid therapy improves pain control in CYP2D6 intermediate and poor metabolizers (Smith 2019).

An adverse effect of many chemotherapeutic agents is neuropathic pain, which can be treated with TCAs. The tertiary amine TCAs (e.g., amitriptyline) are metabolized into secondary amine TCAs (e.g., nortriptyline) through CYP2C19. Both tertiary and secondary amine TCAs are inactivated by CYP2D6. CPIC provides dosing guidelines for TCAs according to the *CYP2C19* and *CYP2D6* genotypes (Hicks 2017). The CPIC recommendations primarily apply to the higher doses of TCAs used to treat depression. At the lower doses of TCAs typically used for neuropathic pain (e.g., 25 mg/day in adults), it is unlikely that CYP2D6 or CYP2C19 poor or intermediate metabolizers will have adverse effects because of supratherapeutic plasma concentrations. However, CPIC recommends that TCAs be avoided in patients known to be CYP2D6 ultrarapid metabolizers because of the increased risk of subtherapeutic plasma concentrations and treatment failure. Tricyclic antidepressants can be prescribed at normal doses for neuropathic pain for all other CYP2D6 and CYP2C19 phenotypes, but caution should be used when patients have a combination of poor metabolizer or ultrarapid metabolizer phenotypes (e.g., a patient is both a CYP2D6 poor metabolizer and a CYP2C19 ultrarapid metabolizer).

Antidepressant Therapy

Given the life-altering changes and uncertainties that a cancer diagnosis and cancer treatment bring, these patients may have concomitant depression. Several pharmacokinetic (e.g., *CYP2D6*, *CYP2C19*) and pharmacodynamic (e.g., *HTR2A*, *HTR2C*, *SLC6A4*) genes are offered by commercial testing laboratories to guide antidepressant therapy selection and dosing. The *CYP2D6* and *CYP2C19* genes have the most clinical usefulness at this time, given that they significantly affect the pharmacokinetics of certain SSRIs. Specifically, CYP2D6 serves as an inactivating metabolic pathway for paroxetine and fluvoxamine, and CYP2C19 serves as an inactivating metabolic pathway for citalopram, escitalopram, and sertraline. In general, ultrarapid metabolizers for these genes may be at risk of subtherapeutic plasma concentrations of their associated SSRIs and therapeutic failure; therefore,

they may benefit from an alternative drug that is not significantly affected by the relevant gene. Poor metabolizers may be at risk of supratherapeutic plasma concentrations of their associated SSRIs and dose-related toxicities; therefore, they may benefit from alternative drug therapy that is not significantly affected by the relevant gene or from a decreased initial dose. Specific dosing recommendations, together with the strength of recommendations assigned according to level of evidence, are provided in the CPIC guideline for SSRIs (Hicks 2015). Although not first line, TCAs can be used to treat depression, and as mentioned earlier, CPIC also provides dosing guidelines for TCAs according to *CYP2D6* and *CYP2C19* genotypes (Hicks 2017).

Antifungal Therapy

In an immunocompromised patient, such as a patient with cancer undergoing chemotherapy treatment, fungal infections may occur. Pharmacogenomic data may help guide clinicians to the appropriate antifungal therapy and dosage. Specifically, voriconazole is primarily inactivated by CYP2C19, and *CYP2C19* genetic variations have been associated with varying voriconazole exposure and response. In adults, CYP2C19 ultrarapid and rapid metabolizers have a decreased chance of attaining therapeutic voriconazole plasma concentrations with standard dosing; for these patients, the CPIC guideline recommends choosing an alternative agent that is not dependent on CYP2C19 metabolism (e.g., isavuconazole, liposomal amphotericin B, or posaconazole) (Moriyama 2017). CYP2C19 poor metabolizers have an increased chance of higher dose-adjusted trough concentrations, which can lead to adverse events such as hepatotoxicity, visual disturbances, visual hallucinations, and other neurologic disorders; for these patients, the CPIC recommends choosing an alternative agent that is not dependent on CYP2C19 metabolism. If the clinical situation supports voriconazole as the most appropriate agent, CYP2C19 poor metabolizers should receive a lower dose than normal with careful therapeutic drug monitoring to guide dose adjustments.

Tumor Lysis Syndrome Management

Tumor lysis syndrome, which occurs in some patients with a diagnosis of cancer, leads to hyperuricemia. Tumor lysis syndrome is treated by administering uric acid-lowering medications such as rasburicase or allopurinol. Rasburicase is a recombinant urate oxidase enzyme that breaks down uric acid to a water-soluble metabolite, allantoin, and hydrogen peroxide. Hydrogen peroxide is a source of oxidative stress, which cells can normally manage with reducing agents such as reduced nicotinamide adenine dinucleotide phosphate (NADPH). In erythrocytes, a primary source of NADPH is glucose-6-phosphate dehydrogenase (G6PD), an enzyme that produces NADPH through the pentose phosphate pathway. In the setting of G6PD deficiency, patients are unable to effectively handle oxidative stress and are thus more susceptible

Patient Care Scenario

A 50-year-old woman with stage II, HER2-positive breast cancer is about to begin adjuvant therapy with doxorubicin and cyclophosphamide followed by paclitaxel and trastuzumab. Her pharmacogenomic test results include *CYP2D6**1/*2 (duplication) and *CYP2C19**2/*2. If, during

ANSWER

The first step is to interpret the patient's pharmacogenomic test results. The patient has inherited the *1 and *2 alleles for *CYP2D6*, and one of those alleles is duplicated. The *CYP2D6* allele functionality table available through the PharmGKB and CPIC websites may be referenced to determine allele function. Because both *CYP2D6**1 and *2 alleles are assigned normal function, it does not matter which allele is duplicated; the patient is a *CYP2D6* ultrarapid metabolizer because she has inherited more than two copies of normal function *CYP2D6* alleles. For *CYP2C19*, the patient has inherited two copies of the *2 allele. Note that *CYP2C19**2, unlike *CYP2D6**2, is a no function allele. Because the patient inherited two copies of a *CYP2C19* no function allele, she is a *CYP2C19* poor metabolizer.

CPIC provides guidelines for the use and dosing of ondansetron, SSRIs, and voriconazole on the basis of genetics. The CPIC guideline for ondansetron states that *CYP2D6* ultrarapid metabolizers may have increased metabolism of ondansetron to less-active compounds than normal metabolizers and therefore may experience decreased efficacy when treated with ondansetron. Therefore, the recommendation is to select an alternative drug not predominantly metabolized by *CYP2D6*, such as granisetron. Dolasetron, palonosetron, and ramosetron are also metabolized by *CYP2D6*, but data are limited regarding the use of *CYP2D6* genetic variation to guide the use of these drugs.

The CPIC guideline for SSRIs includes gene-based dosing information for *CYP2D6* and paroxetine and fluvoxamine as well as *CYP2C19* and citalopram, escitalopram,

and sertraline. The guideline states that *CYP2D6* ultrarapid metabolizers treated with paroxetine may experience increased metabolism to less-active compounds than normal metabolizers and that lower/undetectable plasma concentrations may increase the probability of treatment failure. Therefore, paroxetine should be avoided in these patients. Although fluvoxamine is also metabolized into inactive metabolites through *CYP2D6*, data are insufficient for CPIC to provide a clinical recommendation for *CYP2D6* ultrarapid metabolizers. In addition, the CPIC guideline states that *CYP2C19* poor metabolizers treated with citalopram, escitalopram, and sertraline have greatly reduced metabolism compared with normal metabolizers and that the higher plasma concentrations may increase the probability of adverse effects. The recommendation is to consider a 50% reduction of the standard starting dose and to titrate to response or to select an alternative drug not predominantly metabolized by *CYP2C19*.

The CPIC guideline for voriconazole states that *CYP2C19* poor metabolizers treated with voriconazole may have higher dose-adjusted trough concentrations and increased probability of adverse events. The recommendation is to avoid voriconazole in these patients and to instead choose an alternative antifungal agent that does not depend on *CYP2C19* metabolism (e.g., isavuconazole, liposomal amphotericin B, or posaconazole). If voriconazole must be used, it should be administered at a lower-than-standard dosage with careful therapeutic drug monitoring.

The CPIC guideline for voriconazole states that *CYP2C19* poor metabolizers treated with voriconazole may have higher dose-adjusted trough concentrations and increased probability of adverse events. The recommendation is to avoid voriconazole in these patients and to instead choose an alternative antifungal agent that does not depend on *CYP2C19* metabolism (e.g., isavuconazole, liposomal amphotericin B, or posaconazole). If voriconazole must be used, it should be administered at a lower-than-standard dosage with careful therapeutic drug monitoring.

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to hemolytic anemia. The FDA has a boxed warning on rasburicase, contraindicating its use in patients who are G6PD deficient, and recommends screening patients at higher risk of G6PD deficiency (e.g., patients of African or Mediterranean ancestry) before initiating therapy. CPIC also recommends against the use of rasburicase in G6PD-deficient patients (Relling 2014).

There are some unique considerations with the *G6PD* gene terminology and test interpretation. The *G6PD* gene is located on the X chromosome; therefore, the term *hemizygous* may be used for males to refer to the fact that they have inherited only one copy of the gene. Alleles may be described using the WHO nomenclature, classes I, II, III, and IV. Class I, II, and III

alleles are considered "deficient," and class IV alleles are considered "non-deficient." Females who carry one non-deficient allele and one deficient allele may have a normal or a deficient G6PD phenotype because of X-linked mosaicism. Therefore, in these patients, the phenotype is described as "variable" and is more accurately predicted through an enzyme activity test. Another consideration is that a *G6PD* genotype result may lead to secondary findings of sex chromosomal abnormalities such as Klinefelter syndrome when a self-declared male patient is found to have two copies of the *G6PD* gene (Haidar 2019).

An alternative to rasburicase for tumor lysis syndrome management is allopurinol. Allopurinol, a hypoxanthine

analog, inhibits the conversion of hypoxanthine and xanthine to uric acid by xanthine oxidase. Allopurinol has been associated with severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome and toxic epidermal necrolysis. Presence of the *HLA-B*58:01* allele has strongly been linked with allopurinol-induced SCARs. CPIC recommends that patients who are positive for *HLA-B*58:01* (i.e., carry one or two copies of the risk allele) avoid allopurinol (Saito 2016). This allele is most common in patients of East Asian ancestry.

Immunosuppression

Tacrolimus is a commonly used immunosuppressant after a hematopoietic stem cell transplant. Tacrolimus pharmacokinetics are influenced by *CYP3A5* genotype. Tacrolimus dosing is standardized for patients of European ancestry who are *CYP3A5* poor metabolizers (“*CYP3A5* non-expressers”). However, patients of African ancestry who are *CYP3A5* intermediate and normal metabolizers (“*CYP3A5* expressers”) have lower dose-adjusted trough concentrations of tacrolimus and a decreased chance of achieving target tacrolimus therapeutic concentrations with standard doses. Therefore, CPIC recommends increasing the starting dose of tacrolimus by 1.5–2 times the recommended starting dose, not to exceed a total starting dose of 0.3 mg/kg/day, in known *CYP3A5* intermediate and normal metabolizers. Therapeutic drug monitoring should subsequently be used to guide tacrolimus dose adjustments (Birdwell 2015).

ROLE OF THE PHARMACIST ON MOLECULAR TUMOR BOARDS

An emerging role for clinical pharmacists specializing in oncology is to participate in – or lead – interprofessional molecular tumor boards through which patients’ tumor mutations are analyzed and discussed to guide individualized therapy decisions (Walko 2016). Many of the anticancer agents that target specific somatic mutations still have cancer-specific approvals. However, as our understanding and knowledge grows, we recognize that these mutations are not always associated with just that particular cancer. Treating a target mutation regardless of the type of tumor is becoming more common. For example, this is common with non-melanoma BRAF V600E mutation–positive tumors and with *ALK* mutations that occur in cancers other than non–small cell lung cancer. The newer tissue-agnostic therapies, such as the NTRK inhibitors, are receiving approvals on the basis of genetic mutations alone. This is expected to become more common with future drug approvals.

CONCLUSION

Pharmacogenomics and precision medicine play a critical role in the selection and dosing of anticancer agents and supportive care therapies to maximize the likelihood of drug

Practice Points

Pharmacogenomics is a key component of precision medicine that is increasingly used in clinical practice to optimize medication therapy, particularly in oncology. Pharmacists play a critical role in interpreting and applying pharmacogenomic test results. Regarding pharmacogenomics in oncology, pharmacists should remember the following:

- Evidence-based resources, such as FDA labeling, clinical practice guidelines (e.g., CPIC guidelines), and PharmGKB, are available to help interpret and apply pharmacogenomic test results to patient care.
- Somatic (tumor) genetic testing may be required before prescribing certain anticancer agents.
- Germline genetic testing of genes that encode drug-metabolizing enzymes may provide insight into the optimal dosing of anticancer agents and supportive care therapies.
- Recent approvals of tissue-agnostic targeted therapies with indications based on the presence of specific genetic mutations, rather than cancer type, represent a paradigm shift in cancer treatment.
- Pharmacists can play a key role on interdisciplinary molecular tumor boards through which patients’ tumor mutations are analyzed and discussed to guide individualized therapy decisions.

efficacy and minimize the likelihood of adverse events. Evidence-based resources are available to help pharmacists interpret clinical genetic data and apply these results to the care of patients with cancer.

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Self-Assessment Questions

1. A 56-year-old postmenopausal woman with a history of estrogen receptor–positive breast cancer, hypothyroidism, and depression, is being evaluated for tamoxifen therapy after surgery. She currently takes levothyroxine 100 mcg and fluoxetine 40 mg. Her *CYP2D6* genotype is **1/*2*. The test used to determine *CYP2D6* genotype can determine copy number variation; no gene duplications were detected. Taking into consideration both genetics and concomitant medications, which one of the following is best to recommend for this patient after surgery to minimize breast cancer recurrence?
 - A. Administer tamoxifen 20 mg daily.
 - B. Administer tamoxifen 40 mg twice daily.
 - C. Avoid tamoxifen; use anastrozole 1 mg daily.
 - D. Avoid tamoxifen; use anastrozole 2 mg daily.

Questions 2 and 3 pertain to the following case.

L.T., a 70-year-old woman with metastatic melanoma, is being evaluated for targeted therapy with encorafenib.

2. Which one of the following pharmacogenomic resources is best to find information about the somatic variant to test before prescribing encorafenib for L.T.?
 - A. CPIC guidelines
 - B. DPWG guidelines
 - C. Canadian Pharmacogenomics Network for Drug Safety Consortium guidelines
 - D. PharmGKB
3. Which one of the following pharmacogenomic resources provides the best information about whether a pharmacogenomic test should be ordered before prescribing encorafenib for L.T.?
 - A. CPIC guidelines
 - B. DPWG guidelines
 - C. FDA labeling
 - D. Genetic Testing Registry
4. A 65-year-old man with Philadelphia chromosome–positive chronic myeloid leukemia undergoes genetic analysis of his tumor, which shows the T315I *BCR-ABL* mutation. Which one of the following tyrosine kinase inhibitors is best to recommend initiating in this patient?
 - A. Imatinib
 - B. Dasatinib
 - C. Nilotinib
 - D. Ponatinib
5. A 47-year-old woman with non–small cell lung cancer had disease progression while taking erlotinib 150 mg daily. Genetic analysis shows the T790M *EGFR* mutation.

Which one of the following is best to recommend for this patient?

- A. Increase the erlotinib dose to 150 mg twice daily.
 - B. Discontinue erlotinib and initiate osimertinib 80 mg daily.
 - C. Discontinue erlotinib and initiate gefitinib 250 mg daily.
 - D. Use supportive care only.
6. For which one of the following patients with metastatic colorectal cancer would cetuximab be the best choice?
 - A. Patient with *KRAS* wild-type, EGFR-expressing cancer
 - B. Patient with *KRAS* wild-type, EGFR non-expressing cancer
 - C. Patient with *KRAS* mutation, EGFR-expressing cancer
 - D. Patient with *KRAS* mutation, EGFR non-expressing cancer
 7. Which one of the following patients is most likely to benefit from pembrolizumab?
 - A. 42-year-old woman with newly diagnosed metastatic melanoma with the V600E mutation
 - B. 56-year-old man with unresectable microsatellite instability-high metastatic esophageal cancer
 - C. 67-year-old woman with metastatic thyroid cancer that has a neurotropic receptor tyrosine kinase gene fusion without a known acquired resistance mutation
 - D. 78-year-old man with metastatic non–small cell lung cancer with an *ALK* gene alteration

Questions 8 and 9 pertain to the following case.

C.D. is an 11-year-old girl (body surface area 1 m²) with newly diagnosed acute lymphoblastic leukemia. Part of her initial therapy includes mercaptopurine (standard dosing: 75 mg/m²/day). Pharmacogenomic testing shows *TPMT*1/*3A* and *NUDT15*1/*1*.

8. Which one of the following is the best interpretation of C.D.'s pharmacogenomic test results?
 - A. TPMT normal metabolizer and NUDT15 normal metabolizer
 - B. TPMT intermediate metabolizer and NUDT15 normal metabolizer
 - C. TPMT intermediate metabolizer and NUDT15 poor metabolizer
 - D. TPMT poor metabolizer and NUDT15 poor metabolizer

9. Which one of the following is the best starting dose of mercaptopurine to recommend for C.D.?
- 75 mg daily
 - 75 mg three times weekly
 - 60 mg daily
 - 60 mg three times weekly

Questions 10–13 pertain to the following case.

E.F. is a 60-year-old man with metastatic colorectal cancer who will begin a FOLFIRINOX regimen (2-week cycles): leucovorin, fluorouracil, irinotecan, and oxaliplatin. Pharmacogenomic testing shows *CYP2D6**1/*1 (duplication), *CYP2C19**1/*1, *DPYD**1/*2A, and *UGT1A1**28/*28.

10. Which one of the following is the best interpretation of E.F.'s *DPYD* pharmacogenomic test results?
- Activity score: 2; *DPYD* normal metabolizer
 - Activity score: 1.5; *DPYD* normal metabolizer
 - Activity score: 1; *DPYD* intermediate metabolizer
 - Activity score: 0; *DPYD* poor metabolizer
11. If the total fluorouracil dose per cycle is normally 2800 mg/m², which one of the following is best to recommend for E.F.?
- Administer 2800 mg/m² of fluorouracil per cycle and titrate on the basis of tolerability.
 - Administer 2100 mg/m² of fluorouracil per cycle and titrate on the basis of tolerability.
 - Administer 1400 mg/m² of fluorouracil per cycle and titrate on the basis of tolerability.
 - Avoid fluorouracil; use an alternative agent.
12. Which one of the following best evaluates E.F.'s *UGT1A1* pharmacogenomic test results?
- UGT1A1* normal metabolizer/no Gilbert syndrome
 - UGT1A1* intermediate metabolizer/Gilbert syndrome
 - UGT1A1* poor metabolizer/no Gilbert syndrome
 - UGT1A1* poor metabolizer/Gilbert syndrome
13. If the total irinotecan dose per cycle is normally 180 mg/m², which one of the following is best to recommend for E.F.?
- Administer 180 mg/m² of irinotecan per cycle and titrate on the basis of tolerability.
 - Administer 125 mg/m² of irinotecan per cycle and titrate on the basis of tolerability.
 - Administer 90 mg/m² of irinotecan per cycle and titrate on the basis of tolerability.
 - Avoid irinotecan; use an alternative agent.
14. A 25-year-old Asian American man with B-cell lymphoma is receiving day 3 of his first cycle of chemotherapy. Today's laboratory tests have the following abnormal results: uric acid 15 mg/dL, potassium 6 mmol/L, phosphorus 7 mg/dL, and calcium 6 mg/dL. He carries a *G6PD* class IV allele and is *HLA-B*58:01* positive. Which one of the following best assesses the optimal uric acid-lowering therapy for this patient?
- Rasburicase should be avoided. Use allopurinol instead.
 - Allopurinol should be avoided. Use rasburicase instead.
 - Rasburicase and allopurinol are equally appropriate.
 - Avoid both rasburicase and allopurinol.
15. A 16-year-old African American female adolescent with chronic myeloid leukemia undergoes a hematopoietic stem cell transplant. Her immunosuppressive regimen includes tacrolimus. Pharmacogenomic testing shows that her *CYP3A5* genotype is *1/*1. Which one of the following best describes this patient's *CYP3A5* phenotype and recommended tacrolimus starting dose?
- Normal metabolizer/normal starting dose
 - Normal metabolizer/double the normal starting dose
 - Poor metabolizer/normal starting dose
 - Poor metabolizer/double the normal starting dose