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Pharmacogenomics The previous chapter discussed mechanisms underlying variability in drug action, highlighting pharmacokinetic and pharmacodynamic pathways to beneficial and adverse drug events. Work in the past sev eral decades has defined how genetic variation can play a prominent role in modulating these pathways. Initial studies described unusual drug responses due to single genetic variants in individual subjects, defining the field of pharmacogenetics. A more recent view extends this idea to multiple genetic variants across populations, and the term “pharmacogenomics” is often used. Understanding the role of genetic variation in drug response could improve the use of current drugs, avoid drug use in those at increased risk for adverse drug reactions (ADRs), guide development of new drugs, and even be used as a lens through which to understand mechanisms of diseases themselves. This chapter will outline the principles of pharmacogenomics, cur rently available evidence that genetic factors play a role in variable drug actions, and areas of controversy and ongoing work. The chapter tables are available online. They can be viewed by opening the table of contents of Harrison’s 22nd edition at accessmedicine.com/harrisons. ■ ■PRINCIPLES OF GENETIC VARIATION AND DRUG RESPONSE (SEE ALSO CHAPS. 479 AND 480) A goal of traditional Mendelian genetics is to identify DNA variants associated with a distinct phenotype in multiple related family mem bers (Chap. 480). However, it is unusual for a drug response phenotype to be accurately measured in more than one family member, let alone across a kindred. Some clinical studies have examined drug disposition traits (such as urinary drug excretion after a fixed test dose) in twins and have, in some instances, shown greater concordance in mono zygotic compared to dizygotic pairs, supporting a genetic contribu tion to the trait under study. However, in general, non–family-based approaches are usually used to identify and validate DNA variants con tributing to variable drug actions. Both candidate gene and genomewide studies have been used, and as with any genomic study, results require replication before they should be accepted as valid. Types of Genetic Variants Influencing Drug Response (Table e72-1) The most common type of genetic variant is a single nucleotide polymorphism (SNP), and nonsynonymous SNPs (i.e., those that alter primary amino acid sequence encoded by a gene) are a common cause of variant function in genes regulating drug responses, often termed pharmacogenes. Small insertions and deletions can similarly alter protein function or

lead to functionally important splice variation. Examples of synonymous coding region variants altering pharmacogene function have also been described; postulated mechanisms include an altered rate of RNA translation and thus altered folding of the nascent protein, or altered splicing. Variation in phar macogene promoters or in copy number (gene deletion or multiple functional copies of the same gene) is also well described.

Table e72-1 lists examples of individual types of genomic variation and the impact they can have on function of pharmacogenes. Multiple genotyping approaches may be needed to detect important variants; for example, SNP assays may fail to detect large gene duplications, and highly polymorphic regions (such as the major histocompatibility locus on chromosome 6 that includes multiple genes of the human leukocyte antigen [HLA] family) are best evaluated by sequencing.

Table e72-1 also highlights the fact that the frequency of important variation across pharmacogenes can vary strikingly by ancestry, with the result that certain ethnic groups may be at unusually high risk of displaying variant response to specific drugs. Candidate Gene Approaches Most studies to date have used an understanding of the molecular mechanisms modulating drug action to identify candidate genes in which variants could explain variable drug responses. One very common scenario is that variable drug actions can be attributed to variability in plasma drug concentrations. When plasma drug concentrations vary widely (e.g., more than an order of magnitude), especially if their distribution is non-unimodal as in Fig. 72-1, variants in single genes controlling drug concentra tions often contribute. In this case, the most obvious candidate genes are those responsible for drug metabolism and elimination. Other candidate genes are those encoding the target molecules with which drugs interact to produce their effects or molecules modulating that response, including those involved in disease pathogenesis. CHAPTER 72 Pharmacogenomics Genome-Wide Association Studies The field has also had some success with “unbiased” approaches such as genome-wide association (GWA) (Chap. 479), particularly in identifying single variants associ ated with high risk for certain forms of drug toxicity, and in validating the results of candidate gene studies. GWA studies have identified variants in the HLA locus that are associated with high risk for severe skin rashes during treatment with the anticonvulsant carbamazepine and hepatotoxicity with flucloxacillin, an antibiotic never marketed in the United States. A GWA study of simvastatin-associated myopathy identified a single noncoding SNP in SLCO1B1, encoding OATP1B1, a drug transporter known to modulate simvastatin uptake into the liver, which accounts for 60% of myopathy risk. African-American subjects are known to have higher dose requirements to achieve stable anticoagulation with warfarin, due in part to variations in CYP2C9 and VKORC1, discussed below; in GWA studies, variants in these two genes account for up to 50% of variable warfarin effects. ■ ■GENETIC VARIANTS AFFECTING PHARMACOKINETICS Clinically important genetic variants have been described in mul tiple molecular pathways of drug disposition (Table e72-2). A distinct multimodal distribution of drug disposition (as shown in Fig. 72-1) argues for a predominant effect of variants in a single gene in the metabolism of that substrate. Individuals with two alleles (variants) encoding for nonfunctional protein make up one group, often termed poor metabolizers (PM phenotype). For most genes, many variants can produce such a loss of function, and assessing whether they are on the same or different alleles (i.e., the diplotype) can complicate the use of genotyping in clinical practice. Furthermore, some variants produce only partial loss of function, and the presence of more than one variant may be required to define a specific allele. Individuals with one functional allele, or multiple reduction of function alleles, make up a second group (intermediate metabolizers) and

may or may not be distinguishable from those with two functional alleles (normal metabolizers, sometimes termed extensive metabolizers, EMs). Ultrarapid metabolizers (UMs) with especially high enzymatic activity (usually attributed to specific SNPs or to gene duplication; Table e72-1 and Fig. 72-1) have also been described for some traits. Many drugs in widespread use can inhibit specific drug disposition pathways (see Chap. 71, Table 71-1), and so EM individuals receiving such inhibi tors can respond like PM patients (phenocopying). Polymorphisms in genes encoding drug uptake or drug efflux transporters may be other contributors to variability in drug delivery to target sites and, hence, in

Enzymatic activity Greater Lesser Extensive metabolizers (EMs) Population frequency Poor metabolizers (PMs) 2 mutant alleles 1–2 wild-type alleles Duplication: >2 wild-type alleles A Single dose Chronic therapy PART 3 Pharmacology Concentration PM EM UM B FIGURE 72-1 A. Distribution of CYP2D6 metabolic activity across a population. The heavy arrow indicates an antimode, separating poor metabolizer subjects (PMs, black), with two loss-of-function CYP2D6 alleles (black), indicated by the intron-exon structures below the chart. Individuals with one or two functional alleles are grouped together as extensive metabolizers (EMs, blue). Also shown are ultra-rapid metabolizers (UMs, red), with 2–12 functional copies of the gene, displaying the greatest enzyme activity. (Adapted from M-L Dahl et al: J Pharmacol Exp Ther 274:516, 1995.) B. These simulations show the predicted effects of CYP2D6 genotype on disposition of a substrate drug. With a single dose (left), there is an inverse “gene-dose” relationship between the number of active alleles and the areas under the time-concentration curves (smallest in UM subjects; highest in PM subjects); this indicates that clearance is greatest in UM subjects. In addition, elimination half-life is longest in PM subjects. The right panel shows that these single-dose differences are exaggerated during chronic therapy: steady-state concentration is much higher in PM subjects (decreased clearance), as is the time required to achieve steady state (longer elimination half-life). drug effects. Examples of common pharmacogene polymorphisms are described here. CYP3A Members of the CYP3A family (CYP3A4, CYP3A5) metab olize the greatest number of drugs in therapeutic use. CYP3A4 activity is highly variable (up to an order of magnitude) among individuals, but nonsynonymous coding region polymorphisms (those that change the encoded amino acid) are unusual. Thus, the underlying mechanism likely reflects genetic variation in regulatory regions. Most subjects of European or Asian origin carry a polymorphism that disrupts splicing in the closely related CYP3A5 gene. As a result, these individuals display less CYP3A5 activity compared to subjects of African origin in whom splicing is not disrupted. Decreased efficacy of the antirejection agent tacrolimus in subjects of African origin has been attributed to more rapid CYP3A5-mediated elimination, and a lower risk of vincristine-associated neuropathy has been reported in CYP3A5 “expressers.” CYP2D6 CYP2D6 is second to CYP3A4 in the number of com monly used drugs that it metabolizes. CYP2D6 activity is polymor phically distributed, and 5–10% of European- and African-derived populations (but few Asians) display the PM phenotype (Fig. 72-1). Dozens of loss-of-function variants in CYP2D6 have been described; the PM phenotype arises in individuals with two such alleles. In addition, UMs with multiple functional copies of CYP2D6 have been identified especially in East Africa, the Middle East, and Oceania. PMs have slower elimination rates and lower clearance of substrate drugs; as a consequence (Fig. 72-1B), steady-state concentrations are higher and the time taken to achieve steady state is longer than in EMs (Chap. 71). Conversely, UMs display very low steady-state parent drug concentra tions and an abbreviated time to steady state.

Ultrarapid metabolizers PM UM EM Time Codeine is biotransformed by CYP2D6 to the potent active metabo lite morphine, so its effects are blunted in PMs and exaggerated in UMs. Deaths due to respiratory depression in children given codeine after tonsillectomy have been attributed to the UM trait, and the U.S. Food and Drug Administration (FDA) has revised the package insert to include a prominent “black box” warning against its use in this set ting and, in fact, forbidding its use in children less than 12 years old. In the case of drugs with beta-blocking properties metabolized by CYP2D6, greater signs of beta blockade (e.g., bronchospasm, bradycar dia) have been reported in PM subjects than in EMs. This can be seen not only with orally administered beta blockers such as metoprolol and carvedilol, but also with ophthalmic timolol and with the sodium channel–blocking antiarrhythmic propafenone, a CYP2D6 substrate with beta-blocking properties. UMs may require very high dosages of nortriptyline and other tricyclic antidepressants to achieve a therapeu tic effect. Tamoxifen is a prodrug that undergoes CYP2D6-mediated biotransformation to active metabolites, so its efficacy may be in part related to this polymorphism. In addition, the widespread use of selec tive serotonin reuptake inhibitors (SSRIs) to treat tamoxifen-related hot flashes may also alter the drug’s effects because many SSRIs, notably fluoxetine and paroxetine, are also CYP2D6 inhibitors (see Table 71-2). CYP2C19 The PM phenotype for CYP2C19 is common (20%) among Asians and rarer (2–3%) in other populations; the frequency of the PM trait is especially high (>50%) in Oceania. The impact of polymorphic CYP2C19-mediated metabolism has been demonstrated with the proton pump inhibitor omeprazole, where ulcer cure rates with “standard” dosages were much lower in EM patients (29%) than in PMs (100%). CYP2C19 is responsible for bioactivation of the antiplatelet drug clopidogrel, and large retrospective and prospective

studies have documented decreased efficacy (e.g., increased myocar dial infarction after placement of coronary stents or increased stroke or transient ischemic attacks) among subjects with one or two reduction of function alleles. In addition, some studies suggest that omeprazole and possibly other proton pump inhibitors phenocopy this effect by inhibiting CYP2C19. CYP2C9 Relatively common loss-of-function alleles in CYP2C9 are associated with increased rates of neurologic complications with phenytoin, hypoglycemia with glipizide, and reduced warfarin dose required to maintain stable anticoagulation. Rare patients homozygous for loss-of-function alleles may require very low warfarin dosages. Up to 50% of the variability in steady-state warfarin dose requirement is attributable to polymorphisms in CYP2C9 and in the promoter of VKORC1, which encodes the warfarin target, with lesser contribu tions by genes such as CYP4F2 controlling vitamin K metabolism. The angiotensin receptor blocker losartan is a prodrug that is bioactivated by CYP2C9; as a result, PMs and those receiving inhibitor drugs may display little response to therapy. DPYD Individuals homozygous for loss-of-function alleles in dihy dropyrimidine dehydrogenase, encoded by DPYD, are at increased risk for severe toxicity when exposed to the substrate anticancer drug 5-fluorouracil (5-FU), as well as to capecitabine and tegafur, which are metabolized to 5-FU. Dose reductions have been recommended in intermediate metabolizers. Transferase Variants Thiopurine S-methyltransferase (TPMT) bioinactivates the antileukemic drug 6-mercaptopurine (6-MP), and 6-MP is itself an active metabolite of the immunosuppressive azathio prine. Homozygotes for alleles encoding inactive TPMT (1/300 indi viduals) predictably exhibit severe and potentially fatal pancytopenia on standard doses of azathioprine or 6-MP. On the other hand, homo zygotes for fully functional alleles may display less anti-inflammatory or antileukemic effect with standard doses of the drugs. GWA studies have also identified loss-of-function variants in NUDT15 that reduce degradation of thiopurine metabolites and, thereby, also increase risk of

excessive myelosuppression. N-acetylation is accomplished by hepatic N-acetyl transferase (NAT), which represents the activity of two genes, NAT1 and NAT2. Both enzymes transfer an acetyl group from acetyl coenzyme A to the drug; polymorphisms in NAT2 are thought to underlie individual dif ferences in the rate at which drugs are acetylated and thus define “rapid acetylators” and “slow acetylators.” Slow acetylators make up ~50% of European and African populations but are less common among East Asians. Slow acetylators have an increased incidence of the druginduced lupus syndrome during procainamide and hydralazine therapy and of hepatitis with isoniazid. Individuals homozygous for a common promoter polymorphism that reduces transcription of uridine diphosphate glucuronosyltrans ferase (UGT1A1) have benign hyperbilirubinemia (Gilbert’s syndrome; Chap. 348). This variant has also been associated with diarrhea and increased bone marrow depression with the antineoplastic prodrug iri notecan, whose active metabolite is normally detoxified by UGT1A1mediated glucuronidation. The antiretroviral atazanavir is a UGT1A1 inhibitor and, thus, can increase bilirubin levels especially in individu als with the Gilbert’s variant. While this is benign, the hyperbilirubi nemia can complicate clinical care because it may raise the question of whether coexistent hepatic injury is present. Transporter Variants The risk for myotoxicity with simvastatin and possibly other statins appears increased with variants in SLCO1B1. Variants in MDR1, encoding the drug efflux transporter P-glycoprotein, may increase digoxin toxicity. Variants in the uptake transporters MATE1 and MATE2 have been reported to modulate metformin’s glucose-lowering activity. ■ ■GENETIC VARIANTS AFFECTING PHARMACODYNAMICS A variant in the VKORC1 promoter, especially common in Asian subjects (Table e72-1), reduces transcriptional activity generating less

protein and, thus, lowering warfarin dose requirement. Multiple poly morphisms identified in the β2-adrenergic receptor appear to be linked to specific drug responses in asthma and congestive heart failure, diseases in which β2-receptor function might be expected to determine drug response. Polymorphisms in the β2-receptor gene have also been associated with response to inhaled β2-receptor agonists, while those in the β1-adrenergic receptor gene have been associated with variability in heart rate slowing and blood pressure lowering.

Drugs may also interact with genetic pathways of disease to elicit or exacerbate symptoms of the underlying conditions. In the porphyrias, CYP inducers are thought to increase the activity of enzymes proximal to the deficient enzyme, exacerbating or triggering attacks (Chap. 428). Variants decreasing activity of glucose-6-phosphate dehydrogenase (G6PD), which occur most often in individuals of African, Mediterra nean, or South Asian descent, increase the risk of hemolytic anemia in response to the antimalarial primaquine (Chap. 105) and the uric acid–lowering agent rasburicase, which does not cause hemolysis in patients with normal amounts of the enzyme. Patients with mutations in RYR1 encoding the skeletal muscle intracellular release calcium (also termed type 1 ryanodine receptor) are asymptomatic until exposed to certain general anesthetics, which can trigger the rare syndrome of malignant hyperthermia. Certain antiarrhythmics and other drugs can produce marked QT prolongation and torsades de pointes (Chap. 253), and in a minority of affected patients, this adverse effect represents unmasking of previously subclinical congenital long QT syndrome. A variant in ACKR1 is common in African ancestry individuals and is associated with white cell counts lower than the conventional “normal range” but not associated with disease. While this has been termed “benign ethnic neutropenia,” these individuals not only undergo more diagnostic testing (including bone marrow biopsies that are almost always normal) but also have chemotherapy (associated with neutro penia) withdrawn at higher rates than noncarriers. CHAPTER

72 Pharmacogenomics Immunologically Mediated Drug Reactions Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) is a potentially fatal skin and systemic reaction now increasingly recognized to be linked to specific HLA alleles (Table e72-2), as have cases of drug-induced hepa totoxicity and of the drug rash with eosinophilia and systemic symp toms (DRESS) syndrome. The frequency of risk alleles often varies by ancestry (Table e72-1). The HLA risk alleles appear to be necessary but not sufficient to elicit these reactions. For example, HLA-B∗57:01 is a risk allele for abacavir-related SJS/TEN and flucloxacillin-related hepatotoxicity. However, while 55% of abacavir-exposed subjects will develop a reaction, only 1/10,000 subjects exposed to flucloxacillin develop hepatotoxicity. Thus, a third factor, the nature of which has not yet been established, seems necessary. Tumor and Infectious Agent Genomes The actions of drugs used to treat infectious or neoplastic disease may be modulated by variants in these nonhuman germline genomes. Genotyping tumors to target therapies to underlying mechanisms and to avoid potentially toxic therapy in patients who would derive no benefit is now stan dard in many cancers (Chap. 76). Trastuzumab, which potentiates anthracycline-related cardiotoxicity, is ineffective in breast cancers that do not express the Herceptin receptor. Imatinib targets a specific tyrosine kinase, BCR-Abl1, that is generated by the translocation that creates the Philadelphia chromosome typical of chronic myelogenous leukemia (CML). Imatinib is also an inhibitor of another kinase, c-kit, and the drug is remarkably effective in c-kit–driven cancer, such as gastrointestinal stromal tumors (Chap. 76). Vemurafenib does not inhibit wild-type BRAF but is active against the V600E mutant form of the kinase. Crizotinib is highly effective in non-small-cell lung cancers harboring anaplastic lymphoma kinase (ALK) mutations. ■ ■INCORPORATING PHARMACOGENETIC INFORMATION INTO CLINICAL PRACTICE The discovery of common variant alleles with relatively large effects on drug response raises the prospect that these variants could be used to guide therapy. Desired outcomes could be better ways of choosing likely effective drugs and dosages, or avoiding drugs that are likely

to produce severe adverse drug events or be ineffective in individual subjects. Indeed, the FDA now incorporates pharmacogenetic data into package inserts meant to guide prescribing. A decision to adopt pharmacogenetically guided dosing for a given drug depends on multiple factors. The most important are the magnitude and clinical importance of the genetic effect and the strength of evidence linking genetic variation to variable drug effects (e.g., anecdote vs post hoc analysis of clinical trial data vs randomized clinical trial [RCT]). The evidence can be strengthened if statistical arguments from clinical trial data are complemented by an understanding of underlying physiologic mechanisms. Cost versus expected benefit may also be a factor.

Point of Care Versus Preemptive Approaches Two approaches to pharmacogenetic implementation have been put in place at “early adopter” institutions and are currently being evaluated. In the first, variant-specific assays are ordered at the time of drug prescription and delivered rapidly (often within an hour or two), and the results are then used to guide therapy with that specific drug. The alternative to this “point-of-care” approach is a “preemptive” approach in which pharmacogenetic testing for large numbers of potential variants across many drugs is undertaken prior to prescription of any drug. The data are then available in electronic health record (EHR) systems and coupled to real-time clinical decision support (CDS). When a drug whose effects are known to be influenced by pharmacogenetic variants is prescribed, the EHR system looks up whether variants likely to affect response are present; if so, CDS will alert health care providers that an alternate drug or a different dose may be required. Challenges There are multiple

challenges in putting in place either system. Assay validity and reproducibility have been issues in the past but are less likely now. While common variants in genes such as those listed in Table e72-1 have been clearly associated with variable drug responses, the effect of rare variants, now readily discoverable by large-scale sequencing, remains largely unexplored. The Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Dutch Pharmacogenetics Working Group have developed and published guidelines for multiple drug-gene pairs focusing on the question of what might be an appropriate drug dose adjustment given the availabil ity of genetic data. These resources do not directly address the question of when or how such genetic testing should be undertaken. Developing Evidence That Pharmacogenetic Testing Alters Drug Outcomes A major issue is whether pharmacogenetic test ing affects important drug response outcomes. When the evidence is compelling, alternate therapies are not available, and there are clear recommendations for dosage adjustment in subjects with variants, there is a strong argument for deploying genetic testing as a guide to prescribing; HLA-B∗57:01 testing for abacavir is an example described below. In other situations, the arguments are less compelling: the mag nitude of the genetic effect may be smaller, the consequences may be less serious, alternate therapies may be available, or the drug effect may be amenable to monitoring by other approaches. PART 3 Pharmacology One school argues that the physiology and pharmacology are known and that RCTs are, therefore, unnecessary (and conceivably unethical). The analogy is sometimes drawn to well-recognized dose adjustment of renally excreted drugs in the presence of renal dysfunction. RCTs have not been conducted and the idea of such dose adjustment is well accepted in the medical community and recommended in FDA-approved drug labels. Others have argued that the effect of genetic variants is generally modest and variability in drug actions has many nongenetic sources, so genetic testing might provide marginal benefit at best. Efforts to demonstrate the value of pharmacogenetic testing have met with mixed results. An RCT clearly showed that HLA-B∗57:01 testing eliminates SJS/TEN due to abacavir. Similarly, regulatory authorities in some countries in Southeast Asia mandated HLA-B∗15:02 testing prior to initiation of carbamazepine; however, in this case, an unfortunate out come in some jurisdictions was that prescribers stopped using carbam azepine, often substituting phenytoin (another drug associated with SJS/ TEN), so the incidence of the severe ADR was unchanged. RCTs evaluating the effect of using pharmacogenetically guided therapy to optimize warfarin treatment have shown either no effect or a

modest benefit of incorporating genetic information into prescribing the drug. New effective alternate therapies to clopidogrel that appear to lack important pharmacogenetic variants have emerged. One approach to therapy, therefore, is to use pharmacogenetic testing to identify subjects in whom variants are absent and, therefore, a standard dose of clopidogrel is likely to be effective and to reserve alternate more expensive therapies for subjects likely to have variant responses to warfarin or clopidogrel. Two large trials have randomized patients with acute coronary syndromes to newer antiplatelet therapies (ticagrelor or prasugrel) or clopidogrel if CYP2C19 variants were absent; in one, clopidogrel was superior, and in the second, there was a trend in the same direc tion. A meta-analysis including these trials and others suggested that therapy guided by platelet function testing and genotyping resulted in improved efficacy and decreased minor bleeding with clopidogrel. A 6944-patient trial conducted in seven European countries reported in 2023 that genotyping for 50 pharmacogene variants in 12 genes reduced serious ADRs (associated with 42 drugs) by 30% compared to standard prescribing pharmacogenetically guided treatment. Although there was heterogeneity in the effect across countries, the result of this large trial further

supports the idea of preemptive pharmacogenetic screening. ■ ■GENETICS AND DRUG DEVELOPMENT Genetic tools are now being increasingly used to identify or validate new drug targets. Available data suggest that a new drug development program is more likely to succeed if evidence from human genetics supports the role of a possible drug target in disease pathogenesis and suggests that the risk of toxicity due to high-risk pharmacokinetics or other mechanisms is small. Furthermore, studies of the relationships between variants in genes encoding drug target molecules and a range of phenotypes (e.g., those in EHRs) are being used for drug “repurpos ing,” identifying new indications for existing drugs. Finding Protective Alleles Can Identify Drug Targets One example of using genetics to identify a new drug target started with the discovery that very rare gain-of-function variants in PCSK9 are a rare cause of familial hypercholesterolemia. Subsequently, popula tion studies showed that carriers of loss-of-function SNPs (2.5% of African Americans) had decreased low-density lipoprotein cholesterol, decreased incidence of coronary artery disease, and no deleterious conse quences in other organ systems. These data triggered the development of PCSK9 monoclonal antibodies, which were marketed <10 years after the initial population studies. Other targets implicated by similar popula tion genetic studies include HSD17B13 for prevention of chronic liver disease and ANGPTL3 for hyperlipidemia. Discovering rare protec tive alleles may require very large data sets (>100,000), such as EHR systems coupled to DNA biobanks as in the U.S. All of Us cohort or epidemiologic cohorts like the UK Biobank. Cancer In cancer, tumor sequencing has identified new targets for drug development, often constitutively active kinases. A problem in this area has been the rapid emergence of drug resistance, often after extraordinary initial responses. For example, 40% of melano mas appear to be driven by the V600E mutant form of BRAF, and the specific inhibitor vemurafenib can produce clinically spectacular remission. However, durable responses are rare, and it is now apparent that combination therapy, often with inhibitors of the MEK pathway, can provide improved therapy. Another approach that is rapidly gain ing wide use in cancer involves drugs that reverse immune system inhibition (Chap. 78). In some patients, the release of this “brake” can provide durable remissions, whereas in others, severe adverse events, including colitis, pneumonitis, and myocarditis, have been reported. Understanding the mechanisms underlying variability to these thera pies is a major emerging challenge in the field. Using Multiple Data Types The development of methods to understand associations across multiple large data sets is another approach that is being explored in drug development. For example, a GWA study of risk of rheumatoid arthritis identified multiple risk loci, many encoding proteins that are known targets for intervention in the disease. Interestingly, others encode proteins that are targets for drugs

used in other conditions, such as certain cancers, raising the question of whether such drugs could be “repurposed” for rheumatoid arthritis. While the field has, to date, focused on individual high effect size variants (that are often common in a population), newer approaches combining many (dozens to millions) common variants into polygenic risk scores to predict drug responses are also being explored. An exten sion of this approach is the broader issue of systems pharmacology (see Chap. 71), in which multiple sources of data are used to identify potential molecules or pathways that would be amenable to treatment, by new drugs or by existing agents, using analysis of genomic, tran scriptomic, proteomic, and other large data sets. SUMMARY The science of pharmacogenomics has evolved from isolated examples of rare adverse drug actions to a more comprehensive view of the role of genetic variation in mediating the effects of most drugs. Current principles include: • Genetic variants with an important effect on drug actions can be common, and their frequencies often vary by ancestry. • One common mechanism is modulation of drug

concentrations.

• No practitioner can be expected to remember all variants impor

tant for all drugs. Electronic data systems can now be accessed to describe this information. Ultimately, this information will be used by linking individual pharmacogenetic data to smart EHR systems. • Incorporating genetic approaches into drug development projects holds the promise of more rapid development of targeted, safe, and effective therapies. ■ ■FURTHER READING Diogo D et al: Phenome-wide association studies across large population cohorts support drug target validation. Nat Commun 9:4285, 2018. Galli M et al: Comparative effects of guided vs. potent P2Y12 inhibi tor therapy in acute coronary syndrome: A network meta-analysis of 61 898 patients from 15 randomized trials. Eur Heart J 43:959, 2022. Osanlou O et al: Pharmacogenetics of adverse drug reactions. Adv Pharmacol 83:155, 2018. Roden DM et al: Pharmacogenomics. Lancet 394:521, 2019. Swen JJ et al: A 12-gene pharmacogenetic panel to prevent adverse drug CHAPTER 72 reactions: An open-label, multicentre, controlled, cluster-randomised crossover implementation study. Lancet 401:10374, 2023. Pharmacogenomics

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