Preemptive pharmacogenomics: investigating the relationship between genotype and drug response

In this white paper, we:

- Describe the importance of genotype in drug metabolism
- Provide examples of how an individual's genotype can affect their response to a pharmaceutical treatment
- Provide some examples of how pharmacogenomic testing can reduce costs of health care
- Describe some of the solutions offered by Thermo Fisher Scientific for pharmacogenomic research

Introduction

Modern pharmaceutical researchers and companies have been extremely effective at finding drugs that treat a wide variety of ailments. Our expectations are that for most of common diseases, a treatment can help alleviate at least some symptoms or speed recovery. Although modern medicines can be highly effective, they can also be expensive. In the US alone, spending on pharmaceutical treatments is around $350 billion annually (Rajkumar 2020). It is therefore important to find the drug that acts most efficiently and with minimal side effects such that health care costs can be minimized (Figure 1).

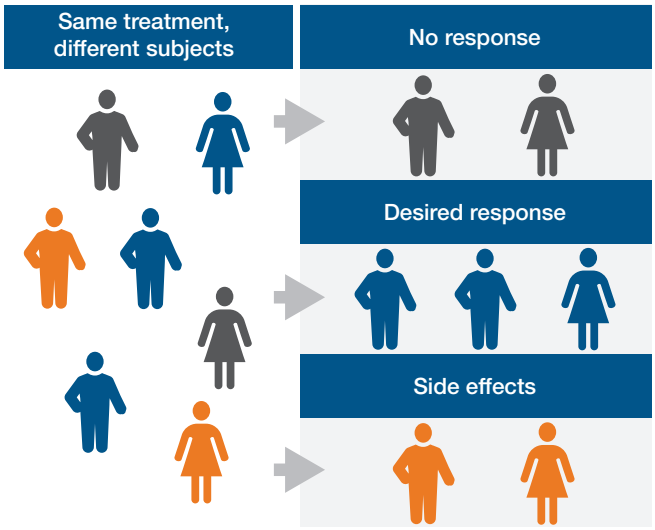

Figure 1. The same treatment can lead to a variety of responses.

A major downside of pharmaceutical treatments, one that has the highest impact on individuals and health care costs, is when a drug produces an unwanted effect or injury—also known as an adverse drug event (ADE). ADEs can range from unexpected side effects to life-threatening reactions. According to the U.S. Department of Health and Human Services (HHS) Office of Disease Prevention and Health Promotion (HHS 2021), annually, ADEs can:

- Account for an estimated 1 in 3 of all hospital adverse events
- Affect about 2 million hospital stays each year
- Prolong hospital stays by 1.7–4.6 days
- Account for over 3.5 million physician office visits
- Result in an estimated 1 million emergency department visits
- Drive approximately 125,000 hospital admissions

ADEs cause additional discomfort and stress for those affected. Additionally, ADEs are very expensive to manage, and therefore contribute to high health care costs.

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Importance of genotype in drug metabolism

Most modern drugs are acted on by drug metabolizing enzymes (DMEs). Many of the DMEs are heme-containing monooxygenases that oxidize a variety of different molecules, facilitating their clearance from the body. One class of DMEs includes cytochrome P450, cytochrome b5, and NADPH–cytochrome P450 reductase enzymes. The hepatic cytochrome P450s (CYPs) are a multigene family of enzymes that play a critical role in the metabolism of drugs and xenobiotics. Each cytochrome enzyme is induced or inhibited differently, depending on biological context. Although CYP enzymes have been best characterized in the liver, they are also expressed in other tissues, including the brain, where their actions and influences are less well defined (for example, see Taylor 2020). Another class of pharmacokinetically important molecules are the molecular transporters. These enzymes are responsible for transporting drugs across the cellular membrane to the interior of the cell and can be responsible for either the entrance or clearance of drugs from the cell.

The response of an individual to a drug often depends on the genotype of different DMEs and molecular transporters in the person's genome. As described above, these enzymes may be required to clear the drug from the system. DMEs might also be required to convert a precursor "prodrug" molecule into a biologically active molecule. However, not all individuals are equipped with the same set of DMEs. Some individuals may completely lack functional copies of the enzymes needed to convert a drug precursor into the biologically active molecule, rendering the treatment ineffective. Other individuals may have enzymes with lower functional activity, meaning the precursor molecule is converted to functional drug at a lower rate, effectively lowering the dose of the treatment.

Alternatively, individuals might have lower activity of the enzymes that degrade a drug, resulting in higher circulating concentrations of the biologically active molecule. Some individuals may convert a drug into a toxic product as a result of their inborn metabolism, and others might be more sensitive to its side effects. In general, the combination of alleles carried by an individual can classify their metabolizing phenotype for a particular drug as poor (PM), intermediate (IM), normal (NM), rapid (RM), or ultrarapid (UM) metabolizers. Matching dosage to the metabolic genotype is therefore extremely important for the efficient delivery and action of drugs (Figure 2).

Pharmacogenomics is the field that analyzes the link between DME genotypes and drug metabolism. There is increasing interest among individuals, medical practitioners, governmental health services, and insurance providers to use pharmacogenomics to increase the effectiveness and safety of drug treatments. Finding the most effective, safe, and economical treatment options involves making sure the recipient's genotype can metabolize the drug as intended.

Here we provide examples of how an individual's genotype can affect their response to a pharmaceutical treatment. We provide some examples of how pharmacogenomic testing can reduce costs of health care. Finally, we describe some of the solutions offered by Thermo Fisher for pharmacogenomic research.

The interplay of genotype and drug response

Behavioral science

Psychiatric disorders encompass a wide range of defective brain functions. Some of these can be treated with certain drugs, but their efficacy is difficult to predict due to genetic heterogeneity and unrelated adverse events (reviewed in Stingl 2013).

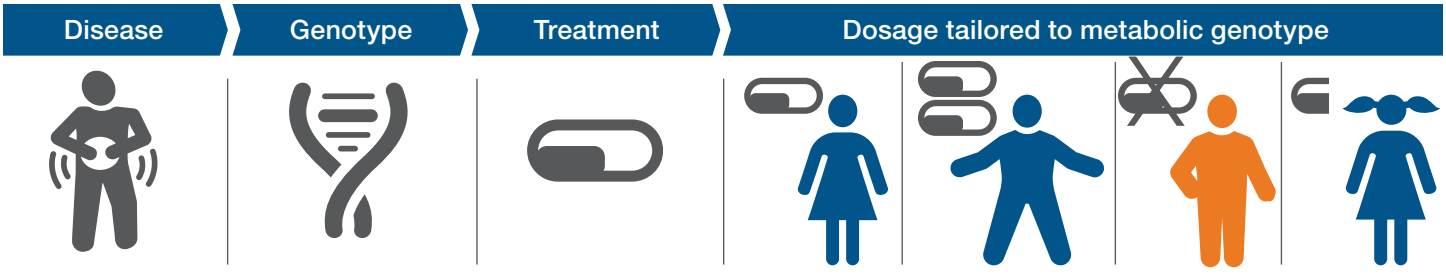

Figure 2. For a particular disease, genomic profile can influence treatment and dosage requirements.

Schizophrenia is a debilitating mental illness that can be treated with drugs such as olanzapine, aripiprazole, and risperidone. However, these drugs can produce various adverse drug reactions, including hyperprolactinemia, tremor, akathisia, dystonia, anxiety, and distress (reviewed in Soria-Chacartegui 2021). Since these drugs are metabolized by cytochrome P450 enzymes and other enzymes, the genotypes at these loci have been found to be important for the response. In their review, Soria-Chacartegui and her colleagues suggest that analyzing alleles present at these loci will reduce the appearance of adverse reactions and provide better outcomes.

Selective serotonin reuptake inhibitors (SSRIs) are commonly used to treat depression, anxiety, and other maladies. However, only about one-half of subjects respond to SSRI therapies, and several weeks of administration are often required before success or failure of the SSRI is seen (Trivedi 2006). Many studies have identified loci that are implicated in the responsiveness to SSRIs (for review, see Fabbri 2014). A result of these studies is that knowing which alleles in the genes *SLC6A4*, *HTR1A*, *HTR2A*, *BDNF*, and *ABCB1* are present in an individual before administering SSRI therapy may modulate the response to SSRIs and limit adverse events. To facilitate this, machine learning techniques are being developed that attempt to better predict the link between genotype, effectiveness, and adverse reactions (Athreya 2019).

Risperidone is used to control irritability and aggression in children with autism spectrum disorder (ASD). However, risperidone treatment can also result in hyperprolactinemia, producing numerous adverse effects, including amenorrhea and infertility in women and gynecomastia and impotence in men. Hongkaew et al. performed a study to identify DMEs and transport molecules associated with risperidone-induced hyperprolactinemia using the Applied Biosytems™ DMET Plus GeneChip™ microarray and verified the results using Applied Biosystems™ TaqMan® Assays (Hongkaew et al 2018). They found five different SNPs significantly associated with hyperprolactinemia, including three in the *UGT1A1* gene, which encodes a UDP-glucuronosyltransferase that transforms small lipophilic molecules into metabolites that can be excreted. Knowing the genotype at these loci before administering risperidone may identify individuals at risk for adverse effects on reproduction in these children.

Opioid prodrugs, such as codeine, are metabolized into morphine and, among other things, are often used as analgesic agents. Codeine is metabolized into active morphine by *CYP2D6* (Thorn 2009) and is thus highly influenced by the alleles present in the *CYP2D6* locus. Individuals who are poor metabolizers can be expected to have poor analgesic effects when codeine is administered; conversely, ultrarapid metabolizers may demonstrate severe respiratory depression (Dean 2012, Racoosin 2013).

Oncology

Tamoxifen is an estrogen receptor antagonist in breast tissue and is commonly used to treat certain types of breast cancer. Tamoxifen is acted on by several DMEs (*CYP2D6, CYP3A4/5, CYP3A4*), and some of the metabolic products can have 100-fold greater antiestrogenic activity than tamoxifen (Goetz 2018). Individuals who have DME alleles that make them intermediate or poor metabolizers, and who therefore inefficiently convert tamoxifen to these other products, may demonstrate lower efficacy of the drug. As a result, several organizations recommend testing and suggest that other mechanisms be used in these individuals (Westergaard 2020).

Statins (HMG-CoA reductase inhibitors) are commonly used to reduce circulating levels of low-density lipoprotein cholesterol (LDL-C). However, it was noticed that in some cases statins were also linked to a reduced recurrence of breast cancer (for example, see Manthravadi 2016). To research this connection, Ahern et al. measured the impact of genetic variation in simvastatin-treated breast cancer. They found that certain alleles of drug transporters (*ABCB1* and *SLCO1B1*) and simvastatin-metabolizing enzymes (*CYP3A4* and *CYP3A5*) were significantly associated with a lower rate of recurrence of breast cancer.

Varnai et al. summarized studies of biomarkers that influenced the efficacy of docetaxel in prostate cancer (Varnai et al 2019). In this study, they analyzed research on germline genomic biomarkers and clinical trials that included a range of genetic signatures. From these research studies, they were able to conclude that certain genotypes of *CYP1B1, ABCG2, CHST3, PPARδ,* and *SULT1C* had improved response to docetaxel. They also identified polymorphisms that suggested reduced docetaxel toxicity; these could be identified by pharmacogenomic testing.

Irinotecan is a topoisomerase I inhibitor that is used alone or in combination with other medications to treat colon and rectal cancer. Irinotecan also has complex pharmacokinetics and pharmacodynamics that vary significantly between individuals and can lead to unpredictable toxicity (deMan 2018). In an effort to understand the basis of this variability, Michael et al. performed a study of irinotecan-treated subjects using the DMET Plus GeneChip microarray and hepatic imaging (Michael et al 2021). They found a number of loci that were correlated with differential response. Although this study could not explain all of the response variability to irinotecan, they suggested that the loci identified may help provide guidance to avoid the adverse toxicity associated with irinotecan treatment.

Cardiovascular diseases

Cardiovascular diseases are a major source of morbidity in the world. In the United States alone, each year approximately 690,000 individuals will have an ischemic stroke, and approximately 240,000 more will have a transient ischemic attack (Go 2014, Kleindorfer 2005). Although antiplatelet and anticoagulant therapies have reduced the risk of cardiovascular diseases, there is still variation in response to these agents that must be accounted for when considering dosage options (Duarte 2021).

Clopidogrel is a prodrug that is metabolized, mostly by *CYP2C19*, into an active drug that inhibits platelet activation and is therefore used to treat stroke and other cardiovascular ailments. Genetic variation at the *CYP2C19* locus can dictate how effective the drug dose will be. For example, it takes three times the dose of clopidogrel given to intermediate metabolizers to achieve the same platelet inhibition as normal metabolizers, whereas even four times is insufficient in poor metabolizers (Mega 2009). Conversely, gain-of-function mutations in *CYP2C19*, resulting in an overactive enzyme, can result in excessive bleeding (Sibbing 2010). Thus, knowing the allelic configuration of *CYP2C19* can guide dosage requirements.

Warfarin is class of anticoagulants that works as a vitamin K antagonist. Warfarin metabolism depends on the activity of the *CYP2C9* gene (Lee 2002), and genetic variants are estimated to account for 30–40% of variability in response to warfarin treatment (Fung 2012). Because of this, a best-guess warfarin dosage is prescribed, monitored, and adjusted frequently for efficacy and adverse effects. However, efforts are underway in several clinical trials that research correlations of genotypes at various loci with optimal warfarin prescription dosage (IWPC 2009 and see reviews in Ross 2018).

Inflammatory bowel diseases

Crohn's disease and ulcerative colitis are chronic inflammatory gastrointestinal disorders commonly known as inflammatory bowel diseases (IBDs). Drugs used in the management of these disorders show pharmacogenomic relationships with effectiveness and side effects. For example, 5-aminosalicylates (5-ASA) are frequently recommended in mild to moderately active ulcerative colitis. In some subjects, nephrotoxicity is an adverse side effect that can lead to irreversible kidney damage and may ultimately lead to renal replacement. In a genome-wide association study (GWAS), an allele of *HLA-DRB1* was significantly associated with 5-ASA kidney damage (Heap 2016), suggesting that testing for this variant could help identify individuals who could be prone to treatment-induced nephrotoxicity.

Thiopurines are immunosuppressive drugs used to maintain steroid-free remission and prevent postoperative recurrence in IBD individuals. Although these drugs are inexpensive and effective, their use is limited due to commonly occurring adverse events (Chaparro 2013), including hepatic toxicity, myelosuppression, and pancreatitis. Genetic polymorphisms in the HLA region and in thiopurine-metabolizing genes have been implicated in determining adverse events (reviewed in Voskuil 2019). Although the at-risk allele frequencies in a population should be considered, these results suggest that testing may help alleviate adverse events in response to these drugs.

The examples described are just a sampling of the current research being performed on the link between genotype, drug responsiveness, and adverse drug effects. As more data are collected, the importance of knowing the genotype of an individual when considering a pharmaceutical regimen will make the health care industry more cost efficient and produce less discomfort to the treated.

The economic case for preemptive pharmacogenomics

As mentioned previously, SSRI dosing is subject to the genotype of the individual. The serotonin transporter *5-HTTLPR* polymorphism moderates response to SSRIs and their side-effect burden. Serretti et al. conducted a study in which they modeled cost-effectiveness of antidepressant treatment guided by *5-HTTLPR* genotype. They found that by incorporating into the model the genotype of *5-HTTLPR* on antidepressant response and tolerability, cost-effectiveness acceptability showed a >80% probability of being under the commonly accepted costing threshold (three times gross domestic product (GDP) according to the WHO) (Serretti 2011). These results were confirmed by a further simulation using data from 27 European states stratified by GDP. This study demonstrated that cost-effectiveness was favorable in >90% of evaluated high-income countries (Olgiati 2012).

Mitropoulou et al. performed a retrospective analysis of subjects who received a percutaneous coronary intervention (PCI) for myocardial infarction and received clopidogrel. Subjects were divided into groups that experienced in-hospital bleeding and those that did not. Genotyping of *CYP2C19* revealed that intermediate metabolizers and poor metabolizers were generally less prone to bleeding but had an increased risk of recurring infarction. They also averaged a higher cost compared to normal metabolizers (€2,799 vs. €2,547). They developed a model that involved health resource utilization and the cost of alternative medication. Results from the model demonstrated a cost savings of €80, which did not include the cost of testing. Another PCI study by Deiman et al. analyzed 3,260 PCI subjects who were genotyped for *CYP2C19* (Deiman et al 2016). The study concluded that unguided treatment aimed at avoiding potential *CYP2C19* genetic implications using prasugrel in all would have resulted in a quality-adjusted life year cost of €38,611. This number was brought down to €5,972–€9,792 when various genotype-guided strategies were employed.

Similar results in cost savings have been seen in multiple retrospective analyses of psychiatric pharmacogenomic studies. Chou et al. noted that individuals with a *CYP2D6* mutation are poor metabolizers and averaged seven more in-hospital days per year than normal metabolizers (24 vs. 17) (Chou et al 2000). They also showed that individuals with a *CYP2D6* mutation who are ultrarapid metabolizers or poor metabolizers had increased care costs of $4,000–$6,000 per year compared to normal or intermediate metabolizers. Finally, they reported an increase in adverse drug events in poor metabolizers. Another study (Winner 2013) looked at health resource utilization by 96 subjects receiving psychiatric care who were tested with a multi-gene panel that included *CYP2D6*, *CYP2C19*, *CYP1A2*, *SLC6A4*, and *HTR2A*. It found that subjects on genetically suboptimal medications had twice as many health care visits, three times as many medical absence days, and four times as many disability claims, amounting to an estimated $5,188 in additional health care utilization.

Prospective trials have largely confirmed the conclusions from retrospective data. Herbild et al. found that *CYP2D6* and *CYP2C19* genotyping reduced treatment costs among poor metabolizers and ultrarapid metabolizers by 28% when compared to subjects treated without genotyping (Herbild et al 2013). They also found that treatment costs for these individuals rose to 239% of the average, but when pharmacogenomics testing was employed, this could be reduced by 69% (from $67,064 to $20,532). Another recent study linked pharmacogenomic testing with a 50% reduction in adverse drug reactions—and an 84% reduction in health care costs—leading to a total cost savings of $1,100 per individual (Maciel 2018). Winner et al. analyzed prescription data from 2,168 pharmacogenomics panel–tested individuals along with 10,880 propensity-matched controls. They found that over the course of 12 months, the genotyped group accrued $1,035 less medication expenditures compared to the group receiving no pharmacogenomic testing (Winner 2015).

Together, these studies demonstrated an average savings of $1,800 in health care and $500 in medication, representing total cost savings of $2,300 per year. These results are a small subset of studies performed, and the results strongly support the use of pharmacogenomics as a cost-saving measure when prescribing medications for which pharmacogenetic links are known.

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References

Ahern TP et al. (2020) Predictive pharmacogenomic biomarkers for breast cancer recurrence by simvastatin. *Acta Oncologica* 59(9):1009–1015.

Athreya AP et al. (2019) Pharmacogenomics-driven prediction of antidepressant treatment outcomes: a machine-learning approach with multi-trial replication. *Clin Pharm Therap* 106(4):855–865.

Chaparro M et al. (2013) Safety of thiopurine therapy in inflammatory bowel disease: long term follow-up study of 3931 patients. *Inflamm Bowel Dis* 19:1404–1410.

Chou WH et al. (2000) Extension of a pilot study: Impact from the cytochrome P450 2D6 polymorphism on outcome and costs associated with severe mental illness. *J Clin Psychopharmacol* 20:246–251.

Dean L (2012) Codeine therapy and *CYP2D6* genotype. In: *Medical Genetics Summaries*. Bethesda, MD: NCBI. pp 1–9.

Deiman B et al. (2016) Reduced number of cardiovascular events and increased cost-effectiveness by genotype-guided antiplatelet therapy in patients undergoing percutaneous coronary interventions in the Netherlands. *Neth Heart J* 24:589–599.

deMan FM et al. (2018) Individualization of irinotecan treatment: a review of pharmacokinetics, pharmacodynamics and pharmacogenetics. *Clin Pharmacokinet* 57(10):1229–1254.

Duarte DD and Cavallari LH (2021) Pharmacogenomics to guide cardiovascular drug therapy. *Nat Rev Cardiol* 18:649–665.

Fabbri C et al. (2014) Understanding the pharmacogenetics of selective serotonin reuptake inhibitors. *Expert Opin Drug Metab Toxicol* 10(8):1093–1118.

Fung MB et al. (2012) Effect of genetic variants, especially *CYP2C9* and *VKORC1*, on the pharmacology of warfarin. *Semin Thromb Hemost* 38(8):893–904.

Go AS et al. (2014) Heart disease and stroke statistics—2014 update: a report from the American Heart Association. *Circulation* 129:e28–e292.

Goetz MP et al. (2018) Clinical Pharmacogenomics Implementation Consortium (CPIC) guideline for *CYP2D6* and tamoxifen therapy. *Clin Pharmacol Ther* 2103(5):770–777.

Heap GA et al. (2016) Clinical features and HLA association of 5-aminosalicylate (5-ASA)-induced nephrotoxicity in inflammatory bowel disease. *J Crohns Colitis* 10:149–158.

Herbild L et al. (2013) Does pharmacogenetic testing for CYP450 2D6 and 2C19 among patients with diagnoses within the schizophrenic spectrum reduce treatment costs? *Basic Clin Pharmacol Toxicol* 113:266–272.

Hongkaew Y et al. (2018) *UGT1A1* polymorphisms associated with prolactin response in risperidone-treated children and adolescents with autism spectrum disorder. *Pharmacogenomics J* 18:740–748.

International Warfarin Pharmacogenomics Consortium (IWPC) (2009) Estimation of the warfarin dose with clinical and pharmacogenomic data. *N Engl J Med* 360:753–764.

Kleindorfer D et al. (2005) Incidence and short-term prognosis of transient ischemic attack in a population-based study. *Stroke* 36:720–723.

Lee CR et al. (2002) Cytochrome P450 2C9 polymorphisms: a comprehensive review of the *in vitro* and human data. *Pharmacogenomics* 12:251–263.

Maciel A et al. (2018) Estimating cost savings of pharmacogenetic testing for depression in real-world clinical settings. *Neuropsychiatr Dis Treat* 14:225–230.

Manolopoulos VG et al. (2010) Pharmacogenetics of coumarinic oral anticoagulants. *Pharmacogenomics* 11:493.

Manthravadi S et al. (2016) Impact of statin use on cancer recurrence and mortality in breast cancer: a systematic review and meta-analysis. *Int J Cancer* 139(6):1281–1288.

Mega JL et al. (2009) Cytochrome P450 genetic polymorphisms and the response to prasugrel: relationship to pharmacokinetic, pharmacodynamic and clinical outcomes. *Circulation* 119:2553–2560.

Michael M et al. (2021) Pharmacogenomics and functional imaging to predict irinotecan pharmacogenetics and pharmacodynamics: the predict IR study. *Cancer Chemother Pharm* 88:39–52.

Mitropoulou C et al. (2016) Economic analysis of pharmacogenomic-guided clopidogrel treatment in Serbian patients with myocardial infarction undergoing primary percutaneous coronary intervention. *Pharmacogenomics* 17(16):1775–1784.

Olgiati P et al. (2012) Should pharmacogenetics be incorporated in major depression treatment? Economic evaluation in high- and middle-income European countries. *Prog Neuropsychopharmacol Biol Psychiatry* 36:147–54.

Racoosin JA et al. (2013) New evidence about an old drug—risk with codeine after adenotonsillectomy. *N Engl J Med* 368:2155–2157.

Rajkumar SV (2020) The high cost of prescription drugs: causes and solutions. *Blood Cancer J* 10(6):71.

Ross S and Paré G (2018) Pharmacogenomics of stroke. *Stroke* 49:2541–2548.

Serretti A et al. (2011) A model to incorporate genetic testing (5-HTTLPR) in pharmacological treatment of major depressive disorders. *World J Biol Psychiatry* 12:501–15.

Sibbing D et al. (2010) Cytochrome 2C19*17 allelic variant, platelet aggravation, bleeding events, and stent thrombosis in clopidogrel-treated patients with coronary stent replacement. *Circulation* 121:512–518.

Soria-Chacartegui P et al. (2021) Genetic polymorphisms associated with the pharmacokinetics, pharmacodynamics and adverse effects of olanzapine, aripiprazole and risperidone. *Front Pharmacol* 12:711940.

Stingl JC et al. (2013) Genetic variability of drug-metabolizing enzymes: the dual impact on psychiatric therapy and regulation of brain function. *Mol Psych* 18:273–287.

Taylor C et al. (2020) A review of the important role of *CYP2D6* in pharmacogenomics. *Genes* 11:1295.

Thorn CF et al. (2009) Codeine and morphine pathway. *Pharmacogenet Genomics* 19(7):556–8.

Trivedi MH et al. (2006) Medication augmentation after the failure of SSRIs for depression. *N Engl J Med* 354:1243–1252.

U.S. Department of Health and Human Services (HHS) Office of Disease Prevention and Health Promotion (2021) Adverse Drug Events. https://health.gov/our-work/health-care-quality/adverse-drug-events

Varnai R et al. (2019) Pharmacogenomic biomarkers in docetaxel treatment of prostate cancer: from discovery to implementation. *Genes* 10:599.

Voskuil MD et al. (2019) Predicting (side) effects for patients with inflammatory bowel disease: the promise of pharmacogenomics. *World J Gastroenterol* 25(21):2539–2548.

Westergaard N et al. (2020) Drug use in Denmark for drugs having pharmacogenomics (PGx)-based dosing guidelines from CPIC for *CYP2D6* and *CYP2C19* drug-gene pairs: Perspectives for introducing PGx test to polypharmacy patients. *J Pers Med* 10(1):3.

Winner J et al. (2013) Psychiatric pharmacogenomics predicts health resource utilization of outpatients with anxiety and depression. *Transl Psychiatry* 3:e242.

Winner JG et al. (2015) Combinatorial pharmacogenomic guidance for psychiatric medications reduces overall pharmacy costs in a 1 year prospective evaluation. *Curr Med Res Opin* 31:1633–1643.

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