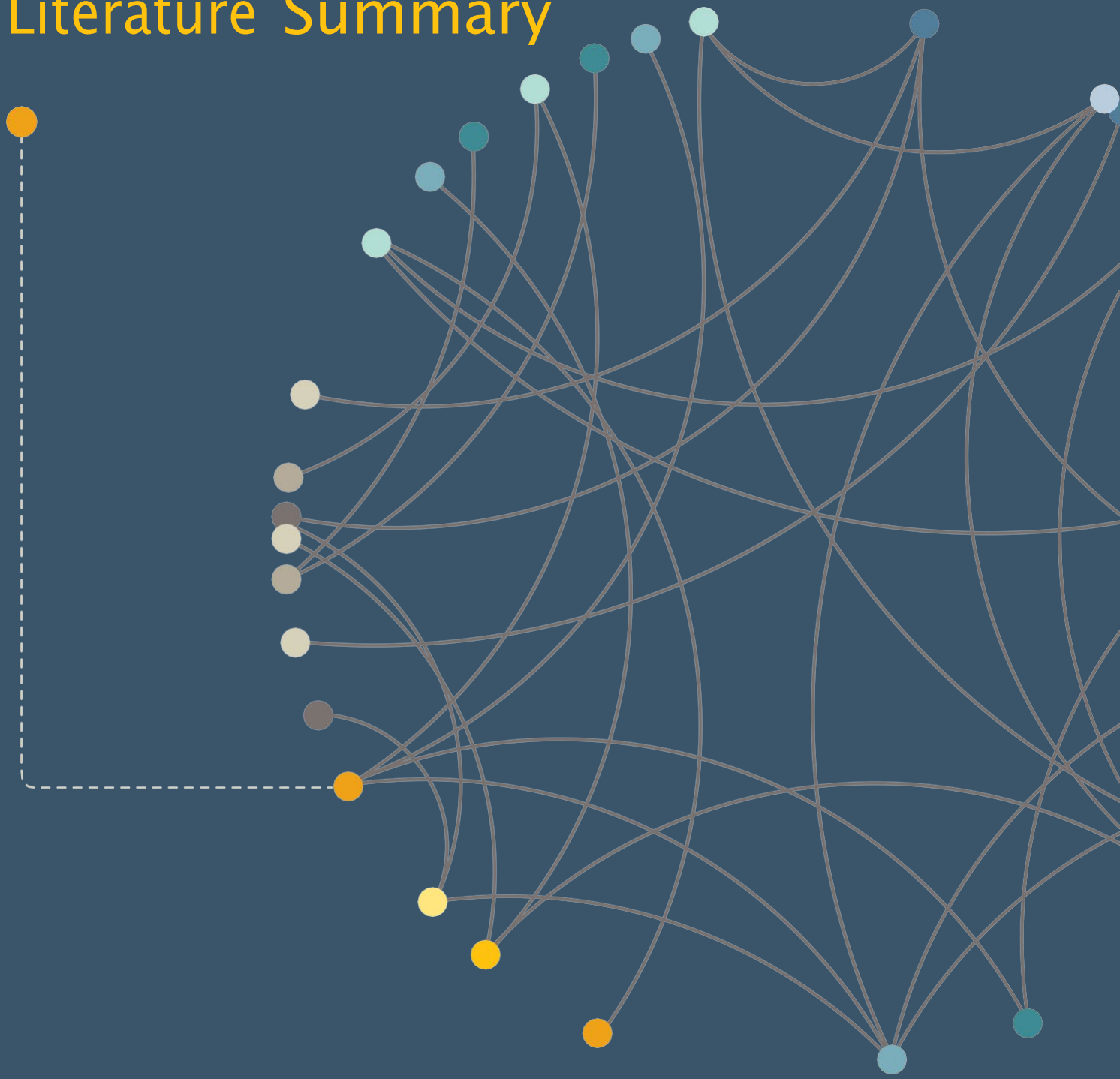
# Genomind Precision Health Platform: Literature Summary



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genomind
The Science Behind Better

## Summary of Literature and Clinical Impact

The following is a summary of the key published literature relevant to gene-drug associations on Genomind's Express and NeuroPsych pharmacogenetic reports. Prescribing health care professionals must use their independent medical judgment and are solely responsible for medication decisions. The clinician must consider other relevant clinical factors in determining which is the most appropriate medication for a patient. The understanding of the relationship between genetics, pharmacokinetics, and pharmacodynamics changes periodically. The information in this summary is current at the time of publication.

## Introduction

Genomind®, a unique personalized medicine platform that brings innovation to healthcare around the world, is pleased to present this summary of the genes behind our pharmacogenetic products. Our products are used to assist clinical decision-making when prescribing medication across multiple conditions. These products include:

1) The Genomind Pharmacogenetic Report:
    a. Genomind Express Report: A concise report of 6 pharmacodynamic and 11 pharmacokinetic genes that impact medications across multiple disease states and specialties including cardiology, psychiatry, gastroenterology, pain management, and genitourinary medicine.
    b. Genomind NeuroPsych PGx Report: A comprehensive report that includes 15 pharmacodynamic and 11 pharmacokinetic genes that impact dosing, sensitivity or response to many medications used in the practice of psychiatry.
2) GenMedPro™: an interactive clinical decision support software that identifies drug-drug interactions (DDI) and drug-gene interactions (DGI). The software provides published PGx treatment guidelines and an alternative medication feature.

For the sake of simplicity, we will refer to our products as the Genomind Pharmacogenetic Report throughout this document. Testing for our products is a simple, non-invasive buccal test (cheek swab) that can be administered quickly in a clinician's office or by the patient at home. A complimentary consultation with experts in the field of pharmacogenetics is available to the clinician with each patient report.

## Background on the Genomind pharmacogenetic report

It is well known that differences in patient response patterns may be partially explained by underlying genetic and biochemical disparities. Utilizing this information may provide an important tool in diminishing the trial-and-error process. The Genomind Pharmacogenetic Report is designed for this purpose. The Genomind Pharmacogenetic Report is a genetic test developed by Genomind to assess variations in deoxyribonucleic acid (DNA) that may alter gene function and response to pharmaceutical therapies. It is intended to help guide the clinician on informed and personalized therapeutic decisions.

Our pharmacogenetic report includes genes that fall into 2 categories: pharmacokinetic and pharmacodynamic. Pharmacokinetic genes can influence the absorption and metabolism of many medications and can provide guidance for common medications across multiple disease states, including cardiology, psychiatry, pain management, oncology, infectious disease and others. Our Pharmacogenetic Report and GenMedPro software account for these conditions and drugs and provide published PGx dosing recommendations when relevant. Pharmacodynamic genes are more related to drug sensitivity or response without providing any dosing guidance. The pharmacodynamic genes in our report are mostly utilized in the practice of psychiatry.

Psychiatric practice is uniquely challenging because of the variability in treatment response. Even with the application of treatment guidelines, many clinicians utilize a trial-and-error approach during treatment planning. Moreover, it is difficult to determine in advance whether a patient will respond positively to a medication or experience adverse effects that may force discontinuation. For this reason, we provide access to both pharmacokinetic and pharmacodynamic genes for psychiatric therapeutic decision making.

## Evidence supporting the Genomind pharmacogenetic report in clinical practice

**A naturalistic study of the effectiveness of pharmacogenetic testing to guide treatment in psychiatric patients with mood and anxiety disorders**

https://pubmed.ncbi.nlm.nih.gov/26445691/

This was a naturalistic, unblinded, prospective analysis of psychiatric patients and clinicians who utilized (Genomind PGx) between April and October of 2013. Data from 685 patients were collected. Approximately 70% and 29% of patients had primary diagnoses of either a mood or anxiety disorder, respectively. Clinician-reported data, as measured by the Clinical Global Impressions Improvement scale, indicated that 87% of patients showed clinically measurable improvement (rated as very much improved, much improved, or minimally improved), with 62% demonstrating clinically significant improvement. When analysis was restricted to the 69% of individuals with ≥ 2 prior treatment failures, 91% showed clinically measurable improvement. Patients also reported significant decreases in depression ($P < .001$), anxiety ($P < .001$), and medication side effects ($P < .001$) and increases in quality of life ($P<.001$). [1]

**Clinical utility of pharmacogenetics-guided treatment of depression and anxiety**

https://www.sciencedirect.com/science/article/pii/S2468171717300273

The use of Genecept testing was evaluated in an open-label trial of 468 patients. This study focused on the methylenetetrahydrofolate reductase (*MTHFR*) and serotonin transporter (*SLC6A4*) genes and evaluating their plausibility as putative predictors of MDD/GAD treatment outcome. After receiving genotyping, 50.6% of clinicians made assay-congruent changes to treatment. After 8 weeks of treatment, patients with a risk *MTHFR* genotype that were treated with assay-guided treatment regimens—as compared to those that were not—demonstrated a greater reduction in Quick Inventory of Depressive Symptoms (QIDS-SR) and Undersøgelser (UKU) scores, and an increased quality of life score (Q-LES-Q-SF). *SLC6A4* risk patients who adhered to assay-guided treatment achieved a greater reduction in QIDS-SR and UKU scores and a statistically significant increase in Q-LES-SF scores, *versus* those that did not.[2]

**Pharmacogenetic testing among patients with mood and anxiety disorders is associated with decreased utilization and cost: a propensity-score matched study**

https://pubmed.ncbi.nlm.nih.gov/29734486/

A propensity-score matched case-control analysis of longitudinal health claims data from a large US insurer was performed. Individuals with a mood or anxiety disorder diagnosis (N = 817) whose physician received Genomind PGx were matched to 2,745 individuals who did not receive such testing. Outcomes included number of outpatient visits, inpatient hospitalizations, emergency room visits, and prescriptions, as well as associated costs over 6 months. On average, individuals who underwent testing experienced 40% fewer all-cause emergency room visits (mean difference 0.13 visits; $P < 0.0001$) and 58% fewer inpatient all-cause hospitalizations (mean difference 0.10 visits; $P < 0.0001$) than individuals in the control group. The Genomind PGx users consumed an estimated $1948.00 less in health care resources than controls in the six-month period after testing. The two groups did not differ significantly in number of psychotropic medications prescribed or mood-disorder related hospitalizations. [3]

**Pharmacogenetic-guided psychiatric intervention associated with increased adherence and cost savings**

https://pubmed.ncbi.nlm.nih.gov/25326929/

Retrospective study utilizing medical claims databases of U.S. patients covered by commercial health insurance, Medicare, and Medicaid was performed. Patients with a psychiatric diagnosis, treatment, and use of the Genomind Genecept Assay were compared with age and disease severity-matched controls with no use of the assay. Individuals with assay-guided treatment were significantly more medication adherent ($P = 1.56\ 3\ 10^{-3}$; Cohen's $d = 0.511$) than patients with standard treatment and demonstrated a relative cost savings of 9.5% in outpatient costs over a 4-month follow-up period, or $562 in total savings. [4]

**Open-label pilot study of psychiatric pharmacogenetic testing in an adult psychiatric inpatient population**
https://www.sciencedirect.com/science/article/abs/pii/S2468171720300065
An open-label pilot study examined the feasibility of Genomind PGx testing in an inpatient unit, examining clinical outcomes including the APA DSM-V Level 1 Cross Cutting Symptom Measure, APA DSM-V Level 2 Cross Cutting Symptom Specific Measure (8 specific symptoms), and the WHODAS 2.0 to assess quality of life, 3 months post-hospitalization in patients with anxiety and depression related diagnoses. Compared to a control group who did not have PGx testing, participants who received Genomind PGx testing reported significantly greater reductions in broad psychiatric symptomatology (p=0.028), quality of life impairment (p=0.004), and substance use (p=0.026). [5]

**Medication optimization using pharmacogenetic testing in a complex mental health population**
https://pubmed.ncbi.nlm.nih.gov/35075665/
12-week pilot study examined the clinical impact of provider access to PGx results and Genomind's gene-drug-drug interaction tool in Veterans prescribed polypharmacy, defined as 5 or more medications with at least 2 for a mental health indication. Psychiatric medication providers were given access to the information but were allowed to make their own decisions regarding medication management. Veteran outpatients (N=53) prescribed polypharmacy (Mean=13.15 medications) were enrolled into the study. In 92.4% of cases, providers changed medications at baseline, with 83% of providers indicating that they changed their original medication plan based on the PGx results. Clinical improvement over the 12-week treatment phase was seen in depression ($F(1.63, 45) = 5.45$, $P = .01$, $\eta 2 = .11$) and mental health quality of life ($F(2.00, 45) = 4.16$, $P < .05$, $\eta 2 = .16$). Adverse drug effects were unchanged or improved over time. Rates of polypharmacy remained unchanged. [6]

**Randomized, controlled, participant- and rater-blind trial of pharmacogenomic test-guided treatment versus treatment as usual for major depressive disorder**
https://pubmed.ncbi.nlm.nih.gov/32383277/
Eight-week multicenter RCT examined the impact of Genomind PGx testing (AGT; N=151) versus treatment-as-usual (TAU; N=153) among outpatients with major depressive disorder. Both participants and raters were blinded to treatment conditions for the primary outcome (Hamilton Depression Rating Scale; SIGH-D-17). For the primary outcome, no significant difference was detected between AGT and TAU at Week 8 ($p = .53$). Exploratory analyses suggested significantly fewer individuals experienced worsening of depressive symptoms following AGT, and that treatment concordant with assay results was associated with greater likelihood of remission (OR 2.23; 95% CI 1.17-2.83). [7]

**Use of a consultation service following pharmacogenetic testing in psychiatry**
https://pubmed.ncbi.nlm.nih.gov/35296147/
We established an expert PGx consultation service for psychiatric providers who utilize our commercial PGx assay. Consultants are pharmacists (PharmDs) or PhDs with extensive training on the assay as well as PGx guidelines and best practices. Consultations conducted from 15 October 2018 through 31 August 2020 are included in this evaluation. During this time, 94,910 tests were completed, of which 6,401 were accompanied by a consultation with extremely high levels of satisfaction; in an anonymous survey, 96% of respondents reported a rating of "very helpful" or "extremely helpful". [8]

**Predicting drug-drug and drug-gene interactions in a community pharmacy population**
https://pubmed.ncbi.nlm.nih.gov/36374614/
Drug-drug and drug-drug-gene interactions were assessed in a large community-based population utilizing the logic incorporated into GenMedPro, a commercially available digital gene-drug interaction software program that incorporates genetic variants to evaluate drug interactions (DDIs) and drug-gene interactions (DGIs). Based on prescription data only, the probability of a DDI of any impact (mild, moderate, or major) was 26% [95% CI: 0.248-0.272] in the population. This probability increased to 49.6% [95% CI: 0.484-0.507] when simulated genetic polymorphisms were additionally assessed. When assessing only major impact interactions, there was a 7.8% [95% CI: 0.070-0.085] probability of drug-drug interactions and 10.1% [95% CI: 0.095-0.108] probability with the addition of

genetic contributions. The probability of drug-drug-gene interactions of any impact was correlated with the number of prescribed medications, with an approximate probability of 77%, 85%, and 94% in patients prescribed 5, 6, or 7+ medications, respectively. When stratified by specific drug class, antidepressants (19.5%), antiemetics (21.4%), analgesics (16%), antipsychotics (15.6%), and antiparasitics (49.7%) had the highest probability of major drug-drug-gene interaction. [9]

**Pharmacogenomics and psychiatric clinical care**
https://pubmed.ncbi.nlm.nih.gov/28990639/
Approximately one in five individuals in the United States experiences mental health issues in any given year, and these disorders are consistently among the leading causes of years lived with disability. Unfortunately, many mental illnesses are lifelong conditions that require medication and therapy to improve quality of life, yet clinical trial data show that many patients fail to achieve remission or require several pharmacological interventions prior to remission. One approach that may help explain patient variability in response to medication is pharmacogenetic testing. The current review shows the clinical use of pharmacogenetic testing in a small subset of gene variants and how they pertain to psychiatric illness and treatment. Recent evidence suggests that genetic testing for psychiatric illness can improve patient outcomes in addition to decreasing health care costs. [10]

## Pharmacokinetic Genes

### ABCB1, ATP Binding Cassette Subfamily B Member 1

P-glycoprotein (P-gp), encoded by the ABCB1 gene, is an efflux pump responsible for transport of several drugs and exogenous compounds out of the cell. Depending on the tissue, these pumps can affect drug absorption (e.g., intestinal lining), distribution (e.g., blood-brain barrier), and excretion (e.g., proximal tubules of the kidney). Variants within this gene can increase intestinal absorption and brain permeability of a wide range of drugs that are biochemically unrelated. This gene has >120 polymorphisms, but only a handful have shown any predictive validity for response to pharmaceutical agents. A review paper authored by Brückl et al [11] identified two candidate SNPs (rs2032583 and rs1045642) that were more consistently associated with either clinical efficacy, drug exposure, or risk for side effects to some antidepressants, antipsychotics, and opioids. Some common antidepressants affected by the ABCB1 gene include citalopram, escitalopram, fluvoxamine, paroxetine, sertraline, venlafaxine, amitriptyline, nortriptyline, trimipramine. [12,13] Several opioids have also been shown to have increased brain permeability in the presence of variants in ABCB1 C3435T. [14–17] Furthermore, second generation antipsychotics like clozapine, olanzapine, aripiprazole, and risperidone have been shown to be sensitive to variants within ABCB1, resulting in higher rates of adverse events. [18–23] These data suggest that genetic variants of ABCB1, which impact drug absorption and brain penetration, may play a role in patient response to medications that are substrates of this protein. [10]

#### Literature Summary: ATP Bind Cassette Subfamily B Member 1 (ABCB1)

**PharmGKB: The Pharmacogenomics Knowledgebase**
https://www.pharmgkb.org/gene/PA267

**PharmGKB summary: very important pharmacogene summary: ABCB1 (MDR1, P-glycoprotein)**
https://pubmed.ncbi.nlm.nih.gov/20216335/
P-gp recognizes and effluxes a multitude of structurally and biochemically unrelated substrates (cyclic, linear, basic, uncharged, zwitterionic, negatively charged, hydrophobic, aromatic, nonaromatic, amphipathic) from 250 to 4000 molecular weight, sufficiently indeterminate to predict in drug design. Substrates include xenobiotics, endogenous compounds [e.g., peptides (including β-amyloids), steroid hormones, lipids, phospholipids, cholesterol, and cytokines], pharmaceuticals, nutraceuticals (e.g. St John's wort), dietary compounds (e.g. grapefruit juice, green tea), and other compounds, which may also modulate P-gp activity (Table 1). P-gp compounds can act as substrates, inhibitors, inducers, and repressors; and citations refer to P-gp compounds as being in more than one category, depending on the circumstance. Modulation of ABCB1 gene expression and/or P-gp activity by various mechanisms consequently influences P-gp-mediated drug. [24]

**ABCB1 gene variants and antidepressant treatment outcome: a meta-analysis**
https://pubmed.ncbi.nlm.nih.gov/25847751/
We investigated the association of treatment outcome and six ABCB1 single nucleotide polymorphisms (SNPs): rs2032583, rs2235015, rs2235040, rs1045642, rs2032582, rs1128503. We stratified for admission status, ethnicity, and prescription of concomitant medication. SNP rs2032583 showed a nominally significant association across all studies (P = 0.035, SNP was studied in a total of 2,037 patients) and a significant Bonferroni-corrected association among inpatients ($P = 1.5 \times 10^{-5}$, n = 485). [25]

### ABCG2, ATP Binding Cassette Subfamily G Member 2

ABC subfamily G, isoform 2 (ABCG2) is a gene encoding the Breast Cancer Resistance Protein (BCRP), an ATP-binding cassette (ABC) efflux transporter. While present in numerous areas of the body, BCRP is highly expressed in brain tissue, the cervix, the small intestine, kidneys, liver, uterus, and placenta. Within these areas of the body, BCRP is implicated in the absorption and disposition of its substrates. The functional 421C>A polymorphism in ABCG2 produces a change in amino acid sequence (Q141K substitution) of the transporter. This change leads to a decrease in protein expression and transporter activity that has been associated with increased systemic exposure to various medications, particularly certain statins. [26]

### Literature Summary: ATP Binding Cassette Subfamily G Member 2 (ABCG2)

**PharmGKB: The Pharmacogenomics Knowledgebase**
https://www.pharmgkb.org/gene/PA390

**PharmGKB summary: very important pharmacogene information for ABCG2**
https://pubmed.ncbi.nlm.nih.gov/28858993/
The c.421C>A variant has been found to affect pharmacokinetics of, response to, and toxicity of compounds that are BCRP substrates, including chemotherapeutics and endogenous compounds. This variant was identified by the International Transporter Consortium as a clinically important transporter pharmacogene based on three criteria: 1) genome wide significance of an association between the variant and one or more drugs from genome wide association studies, 2) significant association of the variant and drug outcome from candidate gene studies, and 3) functional changes resulting from the polymorphism found in in vitro studies. The in vivo intestinal BCRP transport activity in people homozygous for the A allele is reported to be approximately 23% of that in the c.421CC subjects. Furthermore, the AUC of sulfasalazine, a drug used as a BCRP probe in vivo, is reportedly 2.5 times greater in patients carrying the A allele compared to patients without it. [26]

**The Clinical Pharmacogenetics Implementation Consortium guideline for SLCO1B1, ABCG2, and CYP2C9 genotypes and statin-associated musculoskeletal symptoms**
https://pubmed.ncbi.nlm.nih.gov/35152405/
SLCO1B1 encodes a transporter (SLCO1B1; alternative names include OATP1B1 or OATP- C) that facilitates the hepatic uptake of all statins. ABCG2 encodes an efflux transporter (BCRP) that modulates the absorption and disposition of rosuvastatin. CYP2C9 encodes a phase I drug metabolizing enzyme responsible for the oxidation of some statins. Genetic variation in each of these genes alters systemic exposure to statins (i.e., simvastatin, rosuvastatin, pravastatin, pitavastatin, atorvastatin, fluvastatin, lovastatin), which can increase the risk for SAMS. We summarize the literature supporting these associations and provide therapeutic recommendations for statins based on SLCO1B1, ABCG2, and CYP2C9 genotype with the goal of improving the overall safety, adherence, and effectiveness of statin therapy. [27]

**The association between ABCG2 421C>A (rs2231142) polymorphism and rosuvastatin pharmacokinetics: a systematic review and meta-analysis**
https://pubmed.ncbi.nlm.nih.gov/35335877/

Among the 318 identified studies, a total of 8 studies involving 423 patients is included in this meta-analysis. The A allele carriers of ABCG2 421C>A showed 1.5 times higher in both AUC0-∞ (lnGM = 0.43; 95% CI = 0.35-0.50; p < 0.00001) and Cmax (lnGM = 0.42; 95% CI = 0.33-0.51; p < 0.00001) than non-carriers, while there was no significant difference in Tmax and half-life. There was no significance in the pharmacokinetic parameters of the subgroups using either ethnicity or mean values. This meta-analysis demonstrates that subjects carrying the A allele of ABCG2 421C>A show significantly increased AUC0-∞ and Cmax values compared to subjects with the CC genotype. Therefore, information about ABCG2 genotypes might be useful for individualized rosuvastatin therapy. [28]

### SLCO1B1, Solute Carrier Organic Anion Transporter Family Member 1B1

The solute carrier organic anion transporter family member 1B1 (SLCO1B1) gene encodes for a membrane-bound, sodium-independent organic anion transporter protein (OATP1B1). This transporter protein is expressed predominantly on the basolateral membrane of hepatocytes, where it works to moderate the uptake and hepatic transport of various drugs and compounds, including the HMG-CoA reductase inhibitors (statins). [29]

Previous data have shown that the minor allele of SLCO1B1 T521C may lead to increased circulating concentrations of statins [29]. This may be a result of intracellular protein sequestration and reduced surface expression. [30]

### Literature Summary: Solute Carrier Organic Anion Transporter Family Member 1B1 (SLCO1B1)

**PharmGKB: The Pharmacogenomics Knowledgebase**
**https://www.pharmgkb.org/gene/PA134865839**

**PharmGKB very important pharmacogene: SLCO1B1**
**https://pubmed.ncbi.nlm.nih.gov/19952871/**
OATP1B1-dependent transport is an important step in mediating hepatic clearance of statins. The minor allele of SLCO1B1 T521C (present in *5, *15, *16, *17 haplotypes) has been consistently associated with elevated circulating concentrations of statins.

Associations have also been observed between SLCO1B1 T521C and pharmacokinetic handling and drug efficacy for other classes of drugs. Repaglinide is an antidiabetic agent and OATP1B1 substrate. Repaglinide plasma AUC was increased in SLCO1B1:T521C carriers in several studies across a range of dosages.

*SLCO1B1*: T521C, as observed in the *5 and *15 haplotypes, has also been associated with increased irinotecan plasma AUC, an anticancer agent, and, in two studies, was predictive of irinotecan-induced neutropenia. This variant has also been associated with altered steady state concentrations of the antihypertensive agent, torsemide. [29]

**The Clinical Pharmacogenetics Implementation Consortium guideline for SLCO1B1, ABCG2, and CYP2C9 genotypes and statin-associated musculoskeletal symptoms**
**https://pubmed.ncbi.nlm.nih.gov/35152405/**
SLCO1B1 encodes a transporter (SLCO1B1; alternative names include OATP1B1 or OATP- C) that facilitates the hepatic uptake of all statins. ABCG2 encodes an efflux transporter (BCRP) that modulates the absorption and disposition of rosuvastatin. CYP2C9 encodes a phase I drug metabolizing enzyme responsible for the oxidation of some statins. Genetic variation in each of these genes alters systemic exposure to statins (i.e., simvastatin, rosuvastatin, pravastatin, pitavastatin, atorvastatin, fluvastatin, lovastatin), which can increase the risk for SAMS. We summarize the literature supporting these associations and provide therapeutic recommendations for statins based on SLCO1B1, ABCG2, and CYP2C9 genotype with the goal of improving the overall safety, adherence, and effectiveness of statin therapy. [27]

**Role of genetics in the prediction of statin-associated muscle symptoms and optimization of statin use and adherence**
**https://pubmed.ncbi.nlm.nih.gov/29878063/**

The SLCO1B1 rs4149056 variant is by far the most robustly associated variant with SAMS [Statin-associated muscle symptoms], suggesting that testing for this variant may be used to identify or prevent SAMS. However, despite its highly statistical significant association with SAMS, data to support the clinical validity of testing for rs4149056 remain limited. Based on published data, the sensitivity and specificity of one copy of the rs4149056 risk allele is estimated to be 70.4% and 73.7%, respectively. The corresponding positive and negative predictive values are 4.1% and 99.4%, respectively. The low positive predictive value relates to the fact that while rs4149056 is common (12.9%), statin myopathy is rare (typically <1 in 10 000 individuals). These observations suggest that SLCO1B1 genotype, in isolation, lacks sufficient sensitivity and specificity to be used as an accurate diagnostic test for SAMS. The relatively high negative predictive value may be helpful to rule out true statin-induced myopathy, particularly in response to simvastatin. [31]

### UGT1A4 & UGT2B15: UDP Glucuronosyltransferase Genes

Uridine 5'-diphospho-glucuronosyltransferase (UGT) is an enzyme responsible for transferring the glucuronic acid component of UDP-glucuronic acid to a drug, to increase water solubility and aid in drug excretion.[32] It is an important part of phase II drug metabolism, and mutations in the UGT genes, similar to mutations in CYP450 enzymes, can produce changes in drug exposure. Two UGT enzymes have been shown to have a clinically significant impact on drug exposure for anxiolytics, mood stabilizers, and antipsychotics. UGT1A4*3 is a variant of UGT1A4 in which a single SNP substitution may result in ultra-rapid metabolizer (UM) status and decreased serum levels of lamotrigine. [33–35] UGT2B15*2, a variant of another family of UGT enzymes, may result in intermediate metabolizer (IM) status and subsequent increased serum levels of some benzodiazepines. Both in vitro and in vivo studies observed an impact of this polymorphism on oxazepam and lorazepam drug exposure. [36–39] As oxazepam is an active metabolite of several other benzodiazepines (e.g., chlordiazepoxide, clorazepate, diazepam, and temazepam), drug exposure of these compounds may be affected as well.

#### Literature Summary: UGT1A4

**PharmGKB: The Pharmacogenomics Knowledgebase**
**https://www.pharmgkb.org/gene/PA37179**

**Relevance of UDP-glucuronosyltransferase polymorphisms for drug dosing: a quantitative systematic review**
**https://pubmed.ncbi.nlm.nih.gov/24076267/**
"… compared to other drug metabolizing enzymes much less systematic research has been conducted on the polymorphisms of UGT enzymes. However, there is evidence of the existence of large monogenetic functional polymorphisms affecting pharmacokinetics and suggesting a potential use of UGT polymorphisms for the individualization of drug therapy." [36]

#### Literature Summary: UGT2B15

**PharmGKB: The Pharmacogenomics Knowledgebase**
**https://www.pharmgkb.org/gene/PA37188**

**The functionality of UDP-glucuronosyltransferase genetic variants and their association with drug responses and human diseases**
**https://pubmed.ncbi.nlm.nih.gov/34198586/**
The *UGT1A* and *2B* genes are highly polymorphic, and their genetic variants may affect the pharmacokinetics and hence the responses of many drugs and fatty acids. This study collected data and updated the current view of the molecular functionality of genetic variants on *UGT* genes that impact drug responses and the susceptibility to human diseases. The functional information of *UGT* genetic variants with clinical associations are essential to understand the inter-individual variation in drug responses and susceptibility to toxicity. [40]

### Cytochrome P450 (CYP450) Genes

Literature Summary: (CYP1A2) Cytochrome P450 1A2

**PharmGKB: The Pharmacogenomics Knowledgebase**
https://www.pharmgkb.org/gene/PA27093

**PharmGKB summary: very important pharmacogene information for CYP1A2**
https://pubmed.ncbi.nlm.nih.gov/21989077/
CYP1A2 is an important metabolizing enzyme in the liver, comprising approximately 13% of all CYP protein (compared with CYP2D6 at 2%). There are over 100 substrates reported for CYP1A2, including many clinically important drugs (e.g., clozapine, tacrine), procarcinogens (e.g. benzopyrene and aflatoxin b1), and endogenous substrates (e.g. steroids and arachidonic acid). [41]

**The impact of genetic polymorphisms on CYP1A2 activity in humans: a systematic review and meta-analysis**
https://pubmed.ncbi.nlm.nih.gov/29282363/
This systematic review and meta-analysis assessed the effects of genetic polymorphisms on CYP1A2 activity, as measured by caffeine metabolism, in a total of 3570 individual subjects. Higher enzyme activity was observed among those who were homozygous or heterozygous for the -163C>A polymorphism (rs762551), when compared to the wild-type individuals (SMD = 0.40, 95%CI = 0.12-0.68, p = 0.005; SMD = 0.32, 95%CI = 0.11-0.54, p = 0.003, respectively) and this was more pronounced among smokers (SMD = 0.92, 95%CI = 0.27-1.57, p = 0.005; SMD = 0.56, 95%CI = 0.22-0.90, p = 0.001, respectively). [42]

**Impact of CYP1A2 genetic polymorphisms on pharmacokinetics of antipsychotic drugs: a systematic review and meta-analysis**
https://pubmed.ncbi.nlm.nih.gov/30112761/
Ten studies involving 872 clozapine users, seven studies involving 712 olanzapine users, and two studies involving 141 haloperidol users were included. All but one study reported no associations between any CYP1A2 genetic polymorphisms and the pharmacokinetics of CYP1A2-metabolized antipsychotic drugs. The pooled-effect estimates through meta-analyses of seven studies demonstrated no significant associations between the -163C>A or -2467delT polymorphism and clozapine or olanzapine concentrations in the blood. [43]

**Insights into the substrate specificity, inhibitors, regulation, and polymorphisms and the clinical impact of human cytochrome P450 1A2**
https://pubmed.ncbi.nlm.nih.gov/19590965/
A large interindividual variability in the expression and activity of CYP1A2 and elimination of drugs that are mainly metabolized by CYP1A2 has been observed, which is largely caused by genetic (e.g., SNPs) and epigenetic (e.g., DNA methylation) and environmental factors (e.g., smoking and comedication) … To date, more than 15 variant alleles and a series of subvariants of the CYP1A2 gene have been identified and some of they have been associated with altered drug clearance and response to drug therapy. For example, lack of response to clozapine therapy due to low plasma drug levels has been reported in smokers harboring the -163A/A genotype; there is an association between CYP1A2*1F (-163C>A) allele and the risk for leflunomide-induced host toxicity. The *1F allele is associated with increased enzyme inducibility whereas *1C causes reduced inducibility. [44]

**Variation in CYP1A2 activity and its clinical implications: influence of environmental factors and genetic polymorphisms**
https://pubmed.ncbi.nlm.nih.gov/18466106/
The reasons for the discrepancies in distribution patterns between different studies and populations could be related to the influence of environmental factors on the activity of CYP1A2 via induction and/or inhibition, which may mask possible genetic variation in enzyme activity… The G to A mutation in the 5′ flanking region at position -3860 of the gene, was reported to cause decreased inducibility of the enzyme in Japanese smokers, most probably owing to decreased expression of the enzyme. Likewise, the -163C>A, in intron 1, was reported to influence the inducibility of the enzyme, leading to a higher enzyme activity in the presence of an inducer, such as smoking or omeprazole

treatment. Smokers with the -163C/C genotype have been shown to have 40% lower plasma 17X:137X ratios compared with those with the -163A/A genotype, while no influence of this polymorphism has been detected among nonsmokers. However, the influence of this polymorphism on the activity of the enzyme in smokers was not always repeated. [45]

**Influence of genetic polymorphisms, smoking, gender, and age on CYP1A2 activity in a Turkish population**
https://pubmed.ncbi.nlm.nih.gov/19450128/
CYP1A2 activity was determined by plasma paraxanthine:caffeine ratio (17X:137X) 4 h after the intake of a standardized cup of coffee in 146 Turkish healthy volunteers. Seven CYP1A2 polymorphisms (-3860G>A, -3113G>A, -2467del/T, -739T>G, -729C>T, -163C>A and 5347T>C) were analyzed…. Multiple regression analyses including smoking, gender, -163C>A genotype and age revealed a significant influence of smoking ($p < 0.0001$) and gender ($p = 0.002$) in the overall study population. However, in nonsmokers only the influence of gender remained significant ($p = 0.021$), while in smokers the influence of the -163C>A genotype held the statistical significance ($p = 0.019$) ...The influence of the -163C>A polymorphism on CYP1A2 activity in smokers suggests an effect on the inducibility of the enzyme. [46]

**Induction of CYP1A2 by heavy coffee consumption is associated with the CYP1A2 – 163C>A polymorphism**
https://pubmed.ncbi.nlm.nih.gov/20390257/
Significant association of heavy coffee consumption with high CYP1A2 enzyme activity was observed only in carriers of -163 A/A. Increasing effect of -163C>A on CYP1A2 inducibility was found in both Serbian (P=0.022) and Swedish (P=0.016) nonsmoking heavy coffee consumers….CYP1A2 polymorphism -163C>A has an important increasing effect on CYP1A2 inducibility by heavy coffee consumption and may possibly be a contributing factor for interindividual variations in CYP1A2 enzyme activity. [47]

### Literature Summary: (CYP2B6) Cytochrome P450 2B6

**PharmGKB: The Pharmacogenomics Knowledgebase**
https://www.pharmgkb.org/gene/PA123

**PharmGKB summary: very important pharmacogene information for CYP2B6**
https://pubmed.ncbi.nlm.nih.gov/20648701/
*CYP2B6* is a member of the cytochrome P450 family of important pharmacogenes and makes up approximately 2–10% of the total hepatic CYP content. *CYP2B6* is also expressed in the brain and may be an important factor in the metabolism of drugs acting on the central nervous system (CNS) and neurological side effects of drug treatments. CYP2B6 is responsible for the metabolism of 4% of the top 200 drugs and is highly inducible by several drugs and other xenobiotics. [48]

**Serum concentrations of hydroxybupropion for dose optimization of depressed patients treated with bupropion**
https://www.ncbi.nlm.nih.gov/pubmed/24452068
Bupropion is a dopamine and norepinephrine reuptake inhibitor approved for the treatment of depression and smoking cessation. According to the recently published reviews, it is a candidate for therapeutic drug monitoring (TDM) to improve therapeutic outcomes and reduce risks of intolerability or intoxication. In practice, however, the use of TDM is limited due to the chemical instability of bupropion. This investigation sought to determine if the major, active, and chemically stable metabolite 4- hydroxybupropion is a suitable measure to guide antidepressant drug therapy with bupropion…Despite multiple limitations of this naturalistic study, evidence could be given that the measurement of 4- hydroxybupropion in serum is suitable to perform TDM for bupropion. Blood levels should be above 860 ng/mL to attain therapeutic improvement. Potential sex differences in bupropion pharmacokinetics, probably due to differential activities of CYP2B6, should be taken into account when the drug is prescribed. [49]

**Association of CYP2B6 genetic polymorphisms with bupropion and hydroxybupropion exposure: A systematic review and meta-analysis**
https://pubmed.ncbi.nlm.nih.gov/34752647/

Eleven studies were included in the systemic review, and a total of 413 individuals from 10 studies were analyzed in the meta-analysis to determine the effects of CYP2B6*6 variant allele on bupropion pharmacokinetics. Furthermore, 276 individuals were also included in the analysis of CYP2B6 phenotypes to evaluate the relationship between CYP2B6 genotype-derived phenotypes and bupropion exposure….our meta-analysis showed a 33% and 20% decrease of HB AUC in CYP2B6 PMs and IMs, respectively, compared to NMs…A previous study examining steady-state levels of bupropion and HB and CYP2B6 in patients receiving 300 mg/day of bupropion also suggested that CYP2B6 PMs need a bupropion dose of 420 mg/day (40% dose increase) to reach a 700 ng/mL HB concentration. Those authors used 700 ng/mL as a desired HB concentration. A HB serum level of at least 850 ng/mL is currently recommended to attain therapeutic improvement. Therefore, CYP2B6 PMs appear to need >40% increase in bupropion dose. Collectively, the clinically applicable translations of these findings are that an approximately 25% and approximately 50% dose increase may be required in CYP2B6 IMs and PMs, respectively. We emphasize that these are estimates requiring confirmation prior to formally adopting as part of clinical practice. [50]

**Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2D6, CYP2C19, CYP2B6, SLC6A4, and HTR2A genotypes and serotonin reuptake inhibitor antidepressants**
**https://pubmed.ncbi.nlm.nih.gov/37032427/**
This guideline updates and expands the 2015 Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2D6 and CYP2C19 genotypes and SSRI dosing and summarizes the impact of CYP2D6, CYP2C19, CYP2B6, SLC6A4, and HTR2A genotypes on antidepressant dosing, efficacy, and tolerability…Based on the current literature, CYP2D6-guided recommendations are made for paroxetine, fluvoxamine, venlafaxine, and vortioxetine; CYP2C19-guided recommendations are made for citalopram, escitalopram, and sertraline; and CYP2B6-guided recommendations are made for sertraline.[51]

## Literature Summary: (CYP2C9) Cytochrome P450 2C9

**PharmGKB: The Pharmacogenomics Knowledgebase**
**https://www.pharmgkb.org/gene/PA126**

**Cytochrome P450 2C9-CYP2C9**
**https://pubmed.ncbi.nlm.nih.gov/20150829/**
CYP2C9 is a phase I drug-metabolizing cytochrome P450 (CYP450) enzyme isoform that plays a major role in the oxidation of both xenobiotic and endogenous compounds. Gray et al. identified *CYP2C9* as one of several *CYP2C* genes clustered in a 500 kb region on chromosome 10q24. The cluster comprises four genes arranged in the order *CYP2C8-CYP2C9-CYP2C19-CYP2C18*. Several studies identified a single nucleotide polymorphism (SNP) linkage between the CYP2C8 and CYP2C9 genes. CYP2C9 is primarily expressed in the liver, and the expression level is reported to be the second highest among CYP isoforms. Only the CYP enzyme CYP3A4 is quantitatively more highly expressed in the human liver. It has been estimated that CYP2C9 is responsible for the metabolic clearance of up to 15-20% of all drugs undergoing phase I metabolism. [52]

**Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2C9 and HLA-B genotypes and phenytoin dosing: 2020 update**
**https://pubmed.ncbi.nlm.nih.gov/32779747/**
Phenytoin is an antiepileptic drug with a narrow therapeutic index and large interpatient pharmacokinetic variability, partly due to genetic variation in CYP2C9. Furthermore, the variant allele HLA-B*15:02 is associated with an increased risk of Stevens- Johnson syndrome and toxic epidermal necrolysis in response to phenytoin treatment. We summarize evidence from the published literature supporting these associations and provide therapeutic recommendations for the use of phenytoin based on CYP2C9 and/or HLA-B genotypes (updates on cpicpgx.org). [53]

**Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2C9 and nonsteroidal anti-inflammatory drugs**
**https://pubmed.ncbi.nlm.nih.gov/32189324/**

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used analgesics due to their lack of addictive potential. However, NSAIDs have the potential to cause serious gastrointestinal, renal, and cardiovascular adverse events. CYP2C9 polymorphisms influence metabolism and clearance of several drugs in this class, thereby affecting drug exposure and potentially safety. We summarize evidence from the published literature supporting these associations and provide therapeutic recommendations for NSAIDs based on CYP2C9 genotype (updates at www.cpicpgx.org). [54]

**Annotation of FDA label for warfarin and CYP2C9, PROC, PROS1, VKORC1**
https://www.pharmgkb.org/labelAnnotation/PA166104776
Increased bleeding risk and lower initial warfarin dose requirements have been associated with the CYP2C9*2 and CYP2C9*3 alleles. Approximately 30% of the variance in warfarin dose could be attributed to genetic variation in VKORC1, and about 40% of dose variance could be explained taking into consideration both VKORC1 and CYP2C9 genetic polymorphisms. Accounting for genetic variation in both VKORC1 and CYP2C9, age, height, body weight, interacting drugs, and indication for warfarin therapy explained about 55% of the variability in warfarin dose. For the complete drug label text with sections containing pharmacogenetic information highlighted, see the warfarin drug label. Pharmacogenomics-related dosing information is found in Table 5 on page 27. [55]

## Literature Summary: (CYP2C19) Cytochrome P450 2C19

**PharmGKB: The Pharmacogenomics Knowledgebase**
**https://www.pharmgkb.org/gene/PA124**

**PharmGKB summary: very important pharmacogene information for cytochrome P450, family 2, subfamily C, polypeptide 19**
**https://pubmed.ncbi.nlm.nih.gov/22027650/**
The cytochrome P450, family 2, subfamily C, polypeptide 19 (*CYP2C19*) gene is located within a cluster of cytochrome P450 genes (centromere-*CYP2C18*-*CYP2C19*-*CYP2C9*-*CYP2C8*-telomere) on chromosome 10q23.33.The CYP2C19 enzyme contributes to the metabolism of a large number of clinically relevant drugs and drug classes such as antidepressants, benzodiazepines, mephenytoin, proton pump inhibitors (PPIs), and the antiplatelet prodrug clopidogrel. Similar to other CYP450 genes, inherited genetic variation in *CYP2C19* and its variable hepatic expression contributes to the interindividual phenotypic variability in *CYP2C19* substrate metabolism. The *CYP2C19* 'poor-metabolism' phenotype was initially discovered by studies on impaired mephenytoin metabolism and the major molecular defect responsible for the trait is the *CYP2C19*2* (c.681G > A; rs4244285) loss-of-function allele. *CYP2C19* genotype has since been shown to affect the metabolism of several drugs and clinical *CYP2C19* genetic testing is currently available. [56]

**Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for *CYP2D6*, *CYP2C19*, *CYP2B6*, *SLC6A4,* and *HTR2A* genotypes and serotonin reuptake inhibitor antidepressants**
**https://pubmed.ncbi.nlm.nih.gov/37032427**
This guideline updates and expands the 2015 Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for *CYP2D6* and *CYP2C19* genotypes and SSRI dosing and summarizes the impact of *CYP2D6, CYP2C19, CYP2B6, SLC6A4,* and *HTR2A* genotypes on antidepressant dosing, efficacy, and tolerability…Based on the current literature, *CYP2D6*-guided recommendations are made for paroxetine, fluvoxamine, venlafaxine, and vortioxetine; *CYP2C19*-guided recommendations are made for citalopram, escitalopram, and sertraline; and *CYP2B6*-guided recommendations are made for sertraline.[51]

**Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for *CYP2D6* and *CYP2C19* genotypes and dosing of tricyclic antidepressants: 2016 update**
https://pubmed.ncbi.nlm.nih.gov/27997040/

*CYP2D6* and *CYP2C19* polymorphisms affect the exposure, efficacy and safety of tricyclic antidepressants (TCAs), with some drugs being affected by CYP2D6 only (e.g., nortriptyline and desipramine) and others by both polymorphic

enzymes (e.g., amitriptyline, clomipramine, doxepin, imipramine, and trimipramine). Evidence is presented for *CYP2D6* and *CYP2C19* genotype-directed dosing of TCAs. This document is an update to the 2012 Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for *CYP2D6* and *CYP2C19* Genotypes and Dosing of Tricyclic Antidepressants. [57]

**Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2C19 and proton pump inhibitor dosing**
**https://pubmed.ncbi.nlm.nih.gov/32770672/**
Proton pump inhibitors (PPIs) are widely used for acid suppression in the treatment and prevention of many conditions, including gastroesophageal reflux disease, gastric and duodenal ulcers, erosive esophagitis, Helicobacter pylori infection, and pathological hypersecretory conditions. Most PPIs are metabolized primarily by cytochrome P450 2C19 (CYP2C19) into inactive metabolites, and CYP2C19 genotype has been linked to PPI exposure, efficacy, and adverse effects. We summarize the evidence from the literature and provide therapeutic recommendations for PPI prescribing based on CYP2C19 genotype (updates at www.cpicpgx.org). The potential benefits of using CYP2C19 genotype data to guide PPI therapy include (i) identifying patients with genotypes predictive of lower plasma exposure and prescribing them a higher dose that will increase the likelihood of efficacy, and (ii) identifying patients on chronic therapy with genotypes predictive of higher plasma exposure and prescribing them a decreased dose to minimize the risk of toxicity that is associated with long-term PPI use, particularly at higher plasma concentrations. [58]

**Clinical Pharmacogenetics Implementation Consortium guideline for CYP2C19 genotype and clopidogrel therapy: 2022 update**
**https://pubmed.ncbi.nlm.nih.gov/35034351/**
CYP2C19 catalyzes the bioactivation of the antiplatelet prodrug clopidogrel, and CYP2C19 genotype impacts clopidogrel active metabolite formation. CYP2C19 intermediate and poor metabolizers who receive clopidogrel experience reduced platelet inhibition and increased risk for major adverse cardiovascular and cerebrovascular events. This guideline is an update to the 2013 Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for the use of clopidogrel based on CYP2C19 genotype and includes expanded indications for CYP2C19 genotype-guided antiplatelet therapy, increased strength of recommendation for CYP2C19 intermediate metabolizers, updated CYP2C19 genotype to phenotype translation, and evidence from an expanded literature review (updates at www.cpicpgx.org). [59]

### Literature Summary: (CYP2D6) Cytochrome P450 2D6

**PharmGKB: The Pharmacogenomics Knowledgebase**
**https://www.pharmgkb.org/gene/PA128**

**Very important pharmacogene: CYP2D6**
**https://www.pharmgkb.org/vip/PA166170264**
The cytochrome P450 2D6 (CYP2D6) is an enzyme of great historical importance for pharmacogenetics and is now thought to be involved in the metabolism of up to 25% of the drugs that are in common use in the clinic…
*CYP2D6* polymorphisms have implications across many different therapeutic areas, as a diverse array of clinically used drugs are metabolized by CYP2D6…The impact that a *CYP2D6* polymorphism has on therapy with any of the aforementioned drugs is related to the resulting metabolizer status that the polymorphism(s) cause in the individual receiving therapy, as well as whether the parent drug is active or if it requires CYP2D6 to metabolize it into an active metabolite. If the parent drug is active, then UMs may suffer from a lack of efficacy whereas IMs and PMs may suffer from complications resulting from higher than desired plasma concentrations of the drug. If the parent drug must be converted to an active metabolite in order to relieve symptoms, then IMs and PMs may be deficient in the formation of the metabolite, and therefore not receive symptomatic relief. [60]

**Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for *CYP2D6*, *CYP2C19*, *CYP2B6*, *SLC6A4,* and *HTR2A* genotypes and serotonin reuptake inhibitor antidepressants**
**https://pubmed.ncbi.nlm.nih.gov/37032427**

This guideline updates and expands the 2015 Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for *CYP2D6* and *CYP2C19* genotypes and SSRI dosing and summarizes the impact of *CYP2D6, CYP2C19, CYP2B6, SLC6A4,* and *HTR2A* genotypes on antidepressant dosing, efficacy, and tolerability…Based on the current literature, *CYP2D6*-guided recommendations are made for paroxetine, fluvoxamine, venlafaxine, and vortioxetine; *CYP2C19*-guided recommendations are made for citalopram, escitalopram, and sertraline; and *CYP2B6*-guided recommendations are made for sertraline. [51]

**Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for *CYP2D6* and *CYP2C19* genotypes and dosing of tricyclic antidepressants: 2016 update**
**https://pubmed.ncbi.nlm.nih.gov/27997040/**
*CYP2D6* and *CYP2C19* polymorphisms affect the exposure, efficacy and safety of tricyclic antidepressants (TCAs), with some drugs being affected by CYP2D6 only (e.g., nortriptyline and desipramine) and others by both polymorphic enzymes (e.g., amitriptyline, clomipramine, doxepin, imipramine, and trimipramine). Evidence is presented for *CYP2D6* and *CYP2C19* genotype-directed dosing of TCAs. This document is an update to the 2012 Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for *CYP2D6* and *CYP2C19* Genotypes and Dosing of Tricyclic Antidepressants. [57]

**Dutch Pharmacogenetics Working Group (DPWG) guideline for the gene-drug interaction between CYP2D6, CYP3A4, and CYP1A2 and antipsychotics**
**https://pubmed.ncbi.nlm.nih.gov/37002327/**
The DPWG identified gene-drug interactions that require therapy adjustments when respective genotype is known for CYP2D6 with aripiprazole, brexpiprazole, haloperidol, pimozide, risperidone and zuclopenthixol, and for CYP3A4 with quetiapine. Evidence-based dose recommendations were obtained based on a systematic review of published literature. Reduction of the normal dose is recommended for aripiprazole, brexpiprazole, haloperidol, pimozide, risperidone and zuclopenthixol for CYP2D6-predicted PMs, and for pimozide and zuclopenthixol also for CYP2D6 IMs. For CYP2D6 UMs, a dose increase or an alternative drug is recommended for haloperidol and an alternative drug or titration of the dose for risperidone. In addition, in case of no or limited clinical effect, a dose increase is recommended for zuclopenthixol for CYP2D6 UMs. Even though evidence is limited, the DPWG recommends choosing an alternative drug to treat symptoms of depression or a dose reduction for other indications for quetiapine and CYP3A4 PMs.[61]

**Clinical Pharmacogenetics Implementation Consortium guideline for CYP2D6, OPRM1, and COMT genotypes and select opioid therapy**
**https://pubmed.ncbi.nlm.nih.gov/33387367/**
Opioids are mainly used to treat both acute and chronic pain. Several opioids are metabolized to some extent by CYP2D6 (codeine, tramadol, hydrocodone, oxycodone, and methadone). Polymorphisms in CYP2D6 have been studied for an association with the clinical effect and safety of these drugs. Other genes that have been studied for their association with opioid clinical effect or adverse events include OPRM1 (mu receptor) and COMT (catechol-O-methyltransferase). This guideline updates and expands the 2014 Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2D6 genotype and codeine therapy and includes a summation of the evidence describing the impact of CYP2D6, OPRM1, and COMT on opioid analgesia and adverse events. We provide therapeutic recommendations for the use of CYP2D6 genotype results for prescribing codeine and tramadol and describe the limited and/or weak data for CYP2D6 and hydrocodone, oxycodone, and methadone, and for OPRM1 and COMT for clinical use. [62]

**Clinical Pharmacogenetics Implementation Consortium guideline for cytochrome P450 (CYP)2D6 genotype and atomoxetine therapy**
**https://pubmed.ncbi.nlm.nih.gov/30801677/**

Atomoxetine is a nonstimulant medication used to treat attention-deficit/hyperactivity disorder (ADHD). Cytochrome P450 (CYP)2D6 polymorphisms influence the metabolism of atomoxetine thereby affecting drug efficacy and safety.

We summarize evidence from the published literature supporting these associations and provide therapeutic recommendations for atomoxetine based on CYP2D6 genotype (updates at www.cpicpgx.org). [63]

**Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for *CYP2D6* genotype and use of ondansetron and tropisetron**
**https://pubmed.ncbi.nlm.nih.gov/28002639/**
5-hydroxytryptamine type 3 (5-$HT_3$) receptor antagonists are used in the prevention of chemotherapy- induced, radiation-induced and postoperative nausea and vomiting. *CYP2D6* polymorphisms can influence the metabolism of some of these drugs (i.e., ondansetron and tropisetron) thereby affecting drug efficacy. We summarize evidence from the published literature supporting these associations and provide therapeutic recommendations for ondansetron and tropisetron based on *CYP2D6* genotype (updates at www.pharmgkb.org). [64]

**Dutch Pharmacogenetics Working Group (DPWG) guideline for the gene-drug interaction between CYP2D6, CYP3A4 and CYP1A2 and antipsychotics**
**https://pubmed.ncbi.nlm.nih.gov/37002327/**
The DPWG identified gene-drug interactions that require therapy adjustments when respective genotype is known for CYP2D6 with aripiprazole, brexpiprazole, haloperidol, pimozide, risperidone and zuclopenthixol, and for CYP3A4 with quetiapine. Evidence-based dose recommendations were obtained based on a systematic review of published literature. Reduction of the normal dose is recommended for aripiprazole, brexpiprazole, haloperidol, pimozide, risperidone and zuclopenthixol for CYP2D6-predicted PMs, and for pimozide and zuclopenthixol also for CYP2D6 IMs. For CYP2D6 UMs, a dose increase or an alternative drug is recommended for haloperidol and an alternative drug or titration of the dose for risperidone. In addition, in case of no or limited clinical effect, a dose increase is recommended for zuclopenthixol for CYP2D6 UMs. Even though evidence is limited, the DPWG recommends choosing an alternative drug to treat symptoms of depression or a dose reduction for other indications for quetiapine and CYP3A4.[61]

### Literature Summary: (CYP3A4/5) Cytochrome P450 3A4/5

**PharmGKB: The Pharmacogenomics Knowledgebase**
**https://www.pharmgkb.org/gene/PA130**
**https://www.pharmgkb.org/gene/PA131**

**Very important pharmacogene: CYP3A4**
**https://www.pharmgkb.org/vip/PA166169915**
*CYP3A4* (cytochrome P450 3A4) encodes a member of the cytochrome P450 superfamily of enzymes. CYP3A4 and CYP3A5 are believed to be the predominant cytochrome P450s expressed in adult human liver, with CYP3A4 thought to dominate in Whites and CYP3A5 in Blacks/African Americans. The two have overlapping substrate specificities. CYP3A4 is responsible for the metabolism of approximately 50-60% of clinical drugs used today, including acetaminophen, codeine, cyclosporine A, diazepam, and erythromycin. It is important for the metabolism of steroid hormones [Articles: 9667077, 9054608, 9187528, 3259858].[65]

**PharmGKB summary: very important pharmacogene information for CYP3A5**
**https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3738061/**
The human CYP3A subfamily, CYP3A4, CYP3A5, CYP3A7, and CYP3A43, is one of the most versatile of the biotransformation systems that facilitate the elimination of drugs (37% of the 200 most frequently prescribed drugs in the US). Together, CYP3A4 and CYP3A5 account for ~30% of hepatic cytochrome P450, and approximately half of the medications that are oxidatively metabolized by P450 are CYP3A substrates. Both CYP3A4 and CYP3A5 are expressed in the liver and intestine, with *CYP3A5* being the predominant form expressed in extrahepatic tissues. [66]

**Dutch Pharmacogenetics Working Group (DPWG) guideline for the gene-drug interaction between CYP2D6, CYP3A4, and CYP1A2 and antipsychotics**

https://pubmed.ncbi.nlm.nih.gov/37002327/
The DPWG identified gene-drug interactions that require therapy adjustments when respective genotype is known for CYP2D6 with aripiprazole, brexpiprazole, haloperidol, pimozide, risperidone and zuclopenthixol, and for CYP3A4 with quetiapine. Evidence-based dose recommendations were obtained based on a systematic review of published literature. Reduction of the normal dose is recommended for aripiprazole, brexpiprazole, haloperidol, pimozide, risperidone and zuclopenthixol for CYP2D6-predicted PMs, and for pimozide and zuclopenthixol also for CYP2D6 IMs. For CYP2D6 UMs, a dose increase or an alternative drug is recommended for haloperidol and an alternative drug or titration of the dose for risperidone. In addition, in case of no or limited clinical effect, a dose increase is recommended for zuclopenthixol for CYP2D6 UMs. Even though evidence is limited, the DPWG recommends choosing an alternative drug to treat symptoms of depression or a dose reduction for other indications for quetiapine and CYP3A4 PMs.[61]

**Pharmacogenomics of drug metabolizing enzymes and transporters: relevance to precision medicine**
https://pubmed.ncbi.nlm.nih.gov/27729266/
More than 50% of clinically administered drugs are metabolized by CYP3A4, which is the most abundant CYP enzyme in the liver. Therefore, polymorphisms in *CYP3A4* are of great concern in the study of interindividual altered drug metabolisms and related ADRs. More than 26 *CYP3A4* variants have been identified (https://www.pharmvar.org/gene/CYP3A4) and most of these variants are responsible for varied enzyme activities ranging from modest to highly reduced catalytic efficiencies among the affected individuals. Comparatively, high frequencies of allelic variants of the *CYP3A4* gene (*CYP3A4*2* and *CYP3A4*3*) were observed in Caucasian whereas high frequencies of allelic variant *CYP3A4*18* were observed in Chinese people. The clinical consequences of different allelic variants of *CYP3A4* are still undefined for many substrates of CYP3A4. Considering the relatively low frequencies, only small changes in the enzyme activity have been caused by *CYP3A4*16* and *CYP3A4*18* variants. CYP3A5 is one of the factors that contribute to the complexity of CYP3A4. With few exceptions, CYP3A5 can metabolize most drugs that are substrates of and metabolized by CYP3A4. Although slower in most cases, the metabolic activity of CYP3A5 is equal to or even faster than that of CYP3A4 in some cases. *In vivo* studies revealed that the metabolic rates for the drug that are metabolized by both CYP3A4 and CYP3A5 are the sum of the activities of both enzymes. Functionally active variants of *CYP3A5* are expressed in half of the African population and one-fourth of Caucasians. This may partially explain why human studies of the *CYP3A4* allelic variants do not agree with its clinical effect. [67]

**A new functional CYP3A4 intron 6 polymorphism significantly affects tacrolimus pharmacokinetics in kidney transplant recipients**
https://pubmed.ncbi.nlm.nih.gov/21903774/
The overall mean daily-dose requirement to reach the same predose Tac blood concentration was 33% lower for carriers of the T variant allele (CYP3A4*22) than for rs35599367CC patients (95% CI, -46% to -20%; P = 0.018). When combined with the *3 genotype of the CYP3A5 (cytochrome P450, family 3, subfamily A, polypeptide 5) gene, the rs35599367C>T SNP was also associated with a risk of supratherapeutic Tac concentrations (>15 µg/L) during the first 3 days after surgery, with an odds ratio of 8.7 for carriers of the CYP3A4 T allele plus CYP3A5*3/*3 (P = 0.027) and 4.2 for the CYP3A4 CC homozygotes plus CYP3A5*3/*3 (P = 0.002), compared with CYP3A4 CC homozygotes having 1 or 2 CYP3A5*1 alleles. The overall increase in the Tac dose-adjusted trough blood concentration was +179% for carriers of the CYP3A4 T allele with CYP3A5*3/*3 (P < 0.001), +101% for CYP3A4 CC homozygotes with CYP3A5*3/*3 (P < 0.001), and +64% for CYP3A4 T allele carriers with CYP3A5*1 (P = 0.020),compared with CYP3A4 CC homozygotes with CYP3A5*1... Analysis of this CYP3A4*22 SNP may help in identifying patients at risk of Tac overexposure. [68]

## Pharmacodynamic Genes

### ADRA2A, Alpha-2A Adrenergic Receptor

ADRA2A encodes a subtype of alpha 2 adrenergic receptors. Norepinephrine (NE) is the main catecholamine which signals via adrenergic receptors, and ADRA2A is the major receptor subtype found in the brain, particularly the prefrontal cortex (PFC). NE and the PFC are both critical for working memory and executive function measures, such

as regulating attention, controlling impulses and inhibiting inappropriate behavior. [69] Methylphenidate enhances PFC function by facilitating endogenous NE stimulation of ADRA2A. [70,71]

Children and adolescents have been shown to have an increased response to methylphenidate for inattentive symptoms of ADHD if they are carriers of the G allele variant in ADRA2A. [72–74]

### Literature Summary: Alpha-2A Adrenergic Receptor (ADRA2A)

**Pharmacogenetics predictors of methylphenidate efficacy in childhood ADHD**
**https://pubmed.ncbi.nlm.nih.gov/29230023/**
Using meta-analysis, researchers sought to identify predictors of pharmacotherapy to further the clinical implementation of personalized medicine. 36 studies were identified (3647 children) linking the effectiveness of methylphenidate treatment with DNA variants. Pooled data revealed a statistically significant association between rs1800544 ADRA2A (odds ratio: 1.69; confidence interval: 1.12-2.55), and response rate. [72]

**Noradrenergic genes polymorphisms and response to methylphenidate in children with ADHD: a systematic review and meta-analysis**
**https://pubmed.ncbi.nlm.nih.gov/34797323/**
This meta-analysis includes 15 studies and 1382 patients. Four polymorphisms of the NET gene (rs5569, rs28386840, rs2242446, rs3785143) and 2 polymorphisms of the α2A-adrenergic receptor gene (ADRA2A) gene (MspI and DraI) were selected for the analysis. None of the ADRA2A polymorphisms correlated significantly with MPH response as a whole. However, G allele carriers of the MspI polymorphism showed a relationship with significantly inattention symptoms improvement (P < .001, mean difference:0.31, 95% CI: 0.15, 0.47). [73]

**Review and meta-analysis on the Impact of the *ADRA2A* Variant rs1800544 on methylphenidate outcomes in attention-deficit/hyperactivity disorder**
**https://pubmed.ncbi.nlm.nih.gov/36325160/**
This meta-analysis included 9 studies that compared methylphenidate outcomes in patients with ADHD categorized by rs1800544 genotype. G-allele carriers experienced significantly greater improvements in ADHD symptom scores (Swanson, Nolan, and Pelham Version-IV Scale or ADHD Rating Scale-IV) relative to noncarriers (odds ratio 3.08, 95% confidence interval 1.71–5.56, $p$ = .0002) and greater response rates as measured by a ≥50% improvement in symptom scores (odds ratio 2.68, 95% confidence interval 1.23–5.82, $p$ = .01); no significant difference in response rate as measured by Clinical Global Impressions score ≤2 was found. Stouffer's $z$-score method showed significant improvement across all methylphenidate outcomes in G-allele carriers relative to noncarriers ($z$ = 3.03, $p$ = .002). [74]

### ANK3, Sodium Channel Component, Ankyrin 3

ANK3 belongs to a family of scaffolding proteins known as the ankyrins and plays a role in the maintenance of sodium ion channels. A variation in this gene, the T allele, can potentially lead to abnormal clusters of sodium channels and dysfunction in action potential firing. [75–77]

Genome-wide association studies (GWAS) have shown a correlation between this variant and disorders characterized by mood instability and lability, but the contribution to disease risk is very small. [77–81] Many studies indicate that this variant is associated with changes in anatomical connections that may be related to cognitive and affective symptoms. More specifically, this variation has been associated with anhedonia, altered novelty seeking, impaired threat/stress signal processing, poorer cognition and reduced integrity of white matter tracts. These traits have been observed in healthy populations and not those exclusively diagnosed with a mood disorder. [82–87]

Currently, therapeutic implications of this variation are not yet fully understood and are mostly preclinical in nature. Where clinically appropriate, traditional mood stabilizers or omega-3 fatty acids may be considered to reduce excess excitatory signaling by sodium channels. [88,89] The WFSBP and CANMAT guidelines for the treatment of psychiatric disorders with nutraceuticals and phytoceuticals recommend omega-3 fatty acids at doses of 1 g to 2 g of eicosapentoaenoic acid (EPA) for adjunctive use in major depressive disorder. They also weakly recommend the same

dose for adjunctive use in bipolar depression. [90] While the antidepressant efficacy of omega-3 fatty acids is not fully elucidated, it may be related to stabilization of calcium and/or sodium channels. [91–93]

### Literature Summary: Ankyrin 3 (ANK3)

**Collaborative genome-wide association analysis supports a role for *ANK3* and *CACNA1C* in bipolar disorder**
https://pubmed.ncbi.nlm.nih.gov/18711365/
We present evidence that variation in *ANK3* confers risk of bipolar disorder in three independent datasets. ANK3 is an adaptor protein found at axon initial segments that has been shown to regulate the assembly of voltage-gated sodium channels…In addition, we have recently shown that both *ANK3* and subunits of the calcium channel are downregulated in the mouse brain in response to lithium, one the most effective bipolar pharmacotherapies. Taken together, these results point to the possibility that bipolar disorder is in part an ion channelopathy. [79]

### BDNF, Brain-Derived Neurotrophic Factor

BDNF is implicated in regulating the growth, development, and survival of neurons, as well as the modulation of neurotransmitters. Furthermore, BDNF plays a crucial role in neuronal plasticity, an essential function in learning and memory. [94] A variation in this gene, the Val66Met polymorphism, has been associated with a reduction in neuronal-activity dependent secretion of BDNF. [95] Studies have shown an ethnicity dependent association to antidepressant response in depression, with Met carriers of Caucasian ancestry displaying a poorer response to SSRIs and an improved likelihood of response to SNRIs or TCAs, whereas Met carriers of East Asian ancestry have exhibited a higher likelihood of response to SSRIs. [96–99] Additionally, several studies indicate that physical activity may improve cognition and working memory skills, as well as modulate stress response and mood, in Met carriers. [95,100–102]

### Literature Summary: Brain-Derived Neurotrophic Factor (BDNF)

**Brain-derived neurotrophic factor Val66Met polymorphism and 6-month antidepressant remission in depressed Caucasian patients**
https://pubmed.ncbi.nlm.nih.gov/25658497/
In a 6-month, prospective, real-world setting, treatment study of 345 Caucasian patients with depression, investigators found with SSRI, Val/Val patients had a higher response rate 3 months post-treatment than Met patients (68.1% versus 44%; adjusted-OR: 3.04, IC95% [1.05; 9.37], p=0.04). With SNRI/TCA, Val/Val patients had a lower remission rate 6 months post-treatment than Met patients (33.3% versus 60.9%, adjusted-OR: 0.27, IC95% [0.09; 0.76], p=0.02). This study argues for a personalized prescription of antidepressants in Caucasian patients with major depressive disorder, based on the BDNF Val66Met polymorphism: SSRI should be preferred for Val/Val patients and SNRI/TCA for Met patients. Further studies are required to confirm these data. [96]

**Pharmacogenetics in major depression: a comprehensive meta-analysis**
https://pubmed.ncbi.nlm.nih.gov/23733030/
This meta-analysis of studies assessing pharmacogenetic factors on antidepressant response in major depression included an investigation of 15 polymorphisms in 11 genes. Authors conclude that the BDNF rs6265 (Val66Met) heterozygous genotype was associated with better SSRIs response compared to the homozygous genotypes, particularly in Asians (OR = 1.53, 95%CI 1.12–2.07, p =0.007)….In conclusion, our findings suggested the BDNF Val66Met as the best single candidate involved in AD response, with a selective effect on SSRI treatment. [97]

**Meta-analysis of BDNF Val66Met polymorphism association with treatment response in patients with major depressive disorder**
https://pubmed.ncbi.nlm.nih.gov/20167454/
This meta-analysis of 8 studies, inclusive of 1115 subjects, aimed to assess the association between BDNF Val66Met polymorphism and treatment response in patients with MDD…Meta-analysis was performed for genotypes Met/Met versus Val/Val, Val/Met versus Val/Val, Met/Met versus Val/Met, Val/Met + Met/Met versus Val/Val, Met/Met versus Val/Val + Val/Met, and Met allele versus Val allele. When all groups were pooled, a significant association of Val/Met genotype and increased response rate was found in comparison to Val/Val in overall population (OR=1.66, 95%CI=1.07-2.57, P=0.02). In the subgroup analysis, similar result was shown in Asian population (OR=1.83,

95%CI=1.03-3.26, P=0.04), but not in Caucasian population…This meta-analysis demonstrates the association between BDNF Val66Met polymorphism and treatment response in patients with MDD, and Val66Met heterozygous patients have a better response rate in comparison to Val/Val homozygote patients, especially in Asian population. [98]

**Brain-derived neurotrophic factor Val66Met polymorphism association with antidepressant efficacy: a systematic review and meta-analysis**
https://pubmed.ncbi.nlm.nih.gov/25231750/
A meta-analysis of 16 studies compared antidepressant response and remission rates amongst three BDNF genotypes in Caucasians and Asian patients. In Asians, the Met carrier was positively associated with response rate (odds ratio; 95% confidence interval: 1.48; 1.02-2.14) in the SSRI group (1.81; 1.10-2.97) and with treatments ≥6 weeks. Met/Val showed a positive association with the response rate versus homozygotes (1.60; 1.20-2.13) and for ≥6 weeks (mixed antidepressant, 1.36; 1.04-1.77; SSRI, 1.55; 1.11-2.17). There was a weak effect of Met/Val versus Val/Val in response to SSRIs (mixed time, 2.07; 1.48-2.89; ≥6 weeks, 2.25; 1.53-3.32). For remission, Met/Val was better than the homozygotes (1.71; 1.09-2.68, Asians, SSRIs only). Our meta-analysis confirms the effects of the BDNF polymorphism on SSRI response in Asians. [99]

**The brain-derived neurotrophic factor Val66Met polymorphism moderates an effect of physical activity on working memory performance**
https://pubmed.ncbi.nlm.nih.gov/23907543/
To determine whether the BDNF polymorphism moderated an association of physical activity with cognitive functioning among 1,032 midlife volunteers (mean age = 44.59 years), we evaluated participants' performance on a battery of tests assessing memory, learning, and executive processes, and evaluated their physical activity with the Paffenbarger Physical Activity Questionnaire. BDNF genotype interacted robustly with physical activity to affect working memory, but not other areas of cognitive functioning. In particular, greater levels of physical activity offset a deleterious effect of the Met allele on working memory performance. These findings suggest that physical activity can modulate domain-specific genetic (BDNF) effects on cognition. [100]

**Depression and cognitive dysfunction in older U.S. military veterans: moderating effects of BDNF Val66Met polymorphism and physical exercise**
https://pubmed.ncbi.nlm.nih.gov/32122804/
A study in 1,386 European-American U.S miliary veterans (mean age = 63) aimed to assess the effects of depression, BDNF Val66Met genotype, and exercise on cognition. Engagement in physical exercise moderated the association between depression and cognitive function, with depressed exercisers scoring better than depressed nonexercisers on a subjective measure of reasoning, and objective measures of processing speed, attention, and visual learning (d = 0.58-0.99): further, in depressed Met allele carriers, exercisers scored better than nonexercisers on subjective cognitive (d's = 0.80-1.92), and objective measures of visual learning (d = 0.8-1.31) and working memory (d = 0.67). Depression is associated with moderate decrements in cognitive functioning in older U.S. military veterans, and this association is moderated by BDNF Val66Met genotype and physical exercise. [103]

**BDNF Val66Met polymorphism and posttraumatic stress symptoms in U.S. miliary veterans: protective effect of physical exercise**
https://pubmed.ncbi.nlm.nih.gov/30388593/
In this study, we examined the relationship between the BDNF Val66Met polymorphism and PTSD symptoms in two nationally representative samples of European American U.S. military veterans (main sample, n = 1386; replication sample, n = 509)… Specifically, among veterans with high lifetime trauma burden, Met allele carriers who exercised had significantly lower severity of PTSD symptoms compared to those who did not exercise. These findings suggest that interventions designed to bolster engagement in physical exercise may help mitigate PTSD symptoms in veterans who are Met allele carriers and highly exposed to trauma. [95]

**Exploration of the moderating effects of physical activity and early life stress on the relation between brain-derived neurotrophic factor (BDNF) rs6265 variants and depressive symptoms among adolescents**

https://pubmed.ncbi.nlm.nih.gov/35886019/
In this study, we explored the relation between *BDNF* rs6265 polymorphism and childhood stress, as well as the moderating effect of physical activity in relation to depressive symptoms… Physical activity and childhood stress have been shown to exert moderating effects on the relation between *BDNF* rs6265 polymorphism and depressive symptoms among adolescent carriers of GA and AA, respectively. These carriers have a reduced number of depressive symptoms when physical activity increases and childhood stress levels are low, but symptom numbers increase when childhood stress levels are high. Moreover, physical activity moderates the effect of childhood stress on the presence of depressive symptoms in carriers of the *BDNF* rs6265 AA polymorphism. This implies that mild increased physical activity exerts a preventive action for the occurrence of depressive symptoms in individuals with this genetic susceptibility who have experienced high levels of childhood stress. [102]

### CACNA1C, Calcium Channel, L-type Voltage-gated, Alpha 1C Subunit

CACNA1C is a gene that encodes for the subunit of L-type, voltage-gated calcium channels, which are involved in excitatory signaling in the brain. Variations in this gene may lead to ion channel dysfunction, resulting in a prolongation of the period during which the pore remains open, leading to increased excitatory signaling. Several large-scale studies (genome-wide association studies (GWAS), meta-analyses) have identified that a variant in this gene is associated with conditions of mood instability and lability as well as increased startle response, anxiety measures, and attention deficits, though the contribution to disease risk is very small. [86,104–108]

This variant has also been hypothesized to be related to glutamate signaling. [109] Like ANK3, the implications for treatment are not fully understood; however, if clinically appropriate, traditional mood stabilizers or omega-3 fatty acids may be considered to reduce excess excitatory signaling by calcium channels. [91,92]

### Literature Summary: Calcium Channel, L-type Voltage gated, Alpha 1C Subunit (CACNA1C)

**Collaborative genome-wide association analysis supports a role for *ANK3* and *CACNA1C* in bipolar disorder**
https://pubmed.ncbi.nlm.nih.gov/18711365/
"…here we present the results of combining two previously published and one new GWAS of bipolar disorder… The second strongest region of association was located in the third intron of CACNA1C on chromosome 12p13 (rs1006737, P = 7.0 × 10-8). We also provide independent support that CACNA1C is associated with bipolar disorder. In addition, we have recently shown that both ANK3 and subunits of the calcium channel are downregulated in the mouse brain in response to lithium14, one the most effective bipolar pharmacotherapies. Taken together, these results point to the possibility that bipolar disorder is in part an ion channelopathy." [79]

**Phenotypes, mechanisms and therapeutics: insights from bipolar disorder GWAS findings**
https://pubmed.ncbi.nlm.nih.gov/35351989/
Although the genes encoding ion channels (e.g. CACNA1C, CACNA1B, CACNB2) were not validated targets of existing medications for bipolar disorder, they are targets of antiepileptic drugs such as Gabapentin (CACNA1B), Topiramate (CACNA1C, CACNB2), and Phenytoin (CACNA1C, CACNB2, as well as SCN2A). It should be mentioned that mood stabilizers for treatment of bipolar disorder (e.g., Lamotrigine, Carbamazepine and Valproic acid) were originally used as anticonvulsants for treating epilepsy, and it is therefore of great value to examine whether compounds targeting ion channel-related proteins have mood-stabilizing effects…In addition to the clinical drug information, additional intensive clinical and biological evidence also supported the involvement of ion channel and dynamics in bipolar disorder. For instance, calcium imbalance has long been implicated in bipolar disorder, as earlier studies using cells from patients with bipolar disorder and healthy subjects showed that intracellular calcium signaling is elevated in bipolar disorder…Intriguingly, lithium normalized the hyper-activated calcium signaling, whereas long-term lithium treatment lead to altered calcium metabolism, suggesting that lithium might exert therapeutic functions through blocking calcium channels. So far, there are several calcium channel blockers (e.g., verapamil) that could block L-type calcium channels have been used in the cure of hypertension and angina, facilitating the hypothesis whether they could be repurposed for treatment of BD. The L-type voltage-gated calcium channel antagonists thus have been deployed in BD for many years, and their therapeutic outcomes have been tested in different clinical trials. Although

no evidence that they are effective in clinic has been found yet, researchers call for future and further pharmacological investigations of these calcium channels. [105]

### COMT, Catechol-O-Methyltransferase

COMT is an enzyme responsible for the breakdown of dopamine in the frontal lobes of the brain. Dopamine levels here are critical for memory, attention, judgment and other executive functions. [110,111] A valine (Val) to methionine (Met) variation results in reduced capacity of the enzyme to degrade dopamine, which results in increased dopamine activity. [112] Individuals with normal levels of dopamine degradation possess one increased and one decreased function allele (Val/Met). Individuals with the Val/Val genotype have elevated enzyme activity and increased dopamine degradation; conversely, patients who are Met/Met have reduced enzyme function activity and reduced dopamine degradation. [112–115] Clinical studies have shown that the Val/Val genotype may have behavioral consequences regarding cognitive function, memory, attention, motivation, and judgement. [115,116]

In Val/Val (high-activity) individuals, dopaminergic agents have been shown to improve executive function and working memory, particularly in individuals with ADHD. However, these agents may produce a deleterious effect on cognition in Met/Met (low-activity) individuals. [72,117–120]

Recent clinical studies investigating the clinical response of antipsychotic medications in schizophrenia and schizoaffective disorder found that patients with the Met/Met genotype who were treated with atypical antipsychotics had improved scores on measures of executive function and positive symptoms of schizophrenia when compared with their Val/Met and Val/Val counterparts. [121–127]

Alternative antidepressant therapeutic strategies include electroconvulsive therapy (ECT), transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS), which may be modulated by COMT genotype. Studies have shown an association with COMT Val/Val genotype with greater sensitivity to ECT and improvements in depressive scores. [128] There is also evidence COMT genotype may differentially impact executive function in tDCS therapy. [129–131] TMS, similar to other neurostimulation techniques, has been shown to increase dopamine in the prefrontal cortex [132–137], but data evaluating the effect of COMT on TMS response has been limited.

### Literature Summary: Catechol-O-Methyltransferase (COMT)

**Pharmacogenetics predictors of methylphenidate efficacy in childhood ADHD**
https://pubmed.ncbi.nlm.nih.gov/29230023/
Using meta-analysis, researchers sought to identify predictors of pharmacotherapy to further the clinical implementation of personalized medicine. 36 studies were identified (3647 children) linking the effectiveness of methylphenidate treatment with DNA variants. Pooled-data revealed a statistically significant association with rs4680 COMT (odds ratio (OR): 1.40) and response rate. [72]

**Catechol-O-methyltransferase Val158Met polymorphism and clinical response to antipsychotic treatment in schizophrenia and schizo-affective disorder patients: a meta-analysis**
https://pubmed.ncbi.nlm.nih.gov/26745992/
Ten studies met inclusion criteria for the meta-analysis. Five additional antipsychotic-treated samples were analyzed for Val158Met and response and included in the meta-analysis (n total=1416). Met/Met individuals were significantly more likely to respond than Val-carriers (P=.039, OR Met/Met=1.37, 95% CI: 1.02-1.85). Met/Met patients also experienced significantly greater improvement in positive symptoms relative to Val-carriers (P=.030, SMD=0.24, 95% CI: 0.024-0.46). Post hoc analyses on patients treated with atypical antipsychotics (n=1207) showed that Met/Met patients were significantly more likely to respond relative to Val-carriers (P=.0098, OR Met/Met=1.54, 95% CI: 1.11-2.14), while no difference was observed for typical-antipsychotic-treated patients (n=155) (P=.65). [122]

**Association between the COMT Val158Met polymorphism and antipsychotic efficacy in schizophrenia: an updated meta-analysis**
https://pubmed.ncbi.nlm.nih.gov/33100205/

Searches of PubMed, Web of Science, EMBASE, OVID, Google Scholar, and Baidu Scholar databases yielded 30 peer-reviewed studies published before January 2020 with a pooled total of 6291 participants. Pooled results indicated a highly significant association between COMT Val158Met and antipsychotic response (Z = 6.709, P = 9.8 × 10-12). Further, this relationship remained significant in subgroup analyses of Caucasian patients (Z = 3.180, P = 7.4 × 10-4) and Asian patients (Z = 4.487, P = 3.6 × 10-6). [121]

**Association between COMT gene Val108/158Met and antidepressive treatment response: a meta-analysis**
**https://pubmed.ncbi.nlm.nih.gov/31972309/**
A total of 11 studies involving 2845 individuals were included in this meta-analysis. The results of the subgroup analysis indicated that patients who carried the G allele had remission or a better response to electroconvulsive therapy (ECT) in four genetic models. Excluding the studies that might lead to heterogeneity, overall ORs were recalculated, and no obvious association between rs4680 polymorphism and therapeutic reaction was detected in the allelic, recessive and additive models. In the dominant model, COMT rs4680 variants showed significant associations with antidepressive treatment, but the result was highly dependent on the individual study. In addition, the patients with the GG or AG + GG genotype in comparison to AA were associated with a better response to ECT treatment. [128]

### DRD2, Dopamine 2 Receptor

Most antipsychotics act through antagonism of the D2 receptor to inhibit dopamine signaling. The deletion (DEL) variant reduces gene expression in vitro, resulting in altered D2 receptor density. [138,139] Individuals with this variant have been shown to have increased risk for poor and/or delayed response and adverse events (predominately weight gain) with various antipsychotic medications.[140–142]

### Literature Summary: Dopamine 2 Receptor (DRD2)

**DRD2 promoter region variation predicts antipsychotic-induced weight gain in first episode schizophrenia**
**https://pubmed.ncbi.nlm.nih.gov/20664489/**
Authors examined the relationship between -141C Ins/Del (rs1799732), a functional promoter region polymorphism in DRD2, and antipsychotic-induced weight gain in 58 first episode schizophrenia patients enrolled in a randomized trial of risperidone versus olanzapine. Carriers of the deletion allele (n=29) were compared with Ins/Ins homozygotes (noncarriers, n=29) in a mixed model encompassing 10 weight measurements over 16 weeks. Deletion allele carriers showed significantly more weight gain after 6 weeks of treatment regardless of assigned medication. [140]

**DRD2 promoter region variation as a predictor of sustained response to antipsychotic medication in first-episode schizophrenia patients**
**https://pubmed.ncbi.nlm.nih.gov/16513877/**
Patients experiencing their first episode of schizophrenia (N=61) were genotyped for two DRD2 promoter region polymorphisms (A-241G and -141C Ins/Del) and were randomly assigned to receive 16 weeks of treatment with either risperidone or olanzapine…. Relative to wild type homozygotes, G carriers (A-241G) exhibited a significantly faster time until response, whereas -141C Del carriers took a significantly longer time to respond. Diplotype analysis revealed similar results. [141]

**D2 receptor genetic variation and clinical response to antipsychotic drug treatment: a meta-analysis**
**https://pubmed.ncbi.nlm.nih.gov/20194480/**
A total of six studies reported results for the -141C Ins/Del polymorphism. There was a significant difference in response rate between the Del carrier vs. Ins/Ins genotypes (pooled OR = 0.65, 95% CI = 0.43 ~ 0.97, p = 0.03), indicating that Del carriers tend to have less favorable antipsychotic drug responses than patients with the Ins/Ins genotype. Medications in this analysis included chlorpromazine, risperidone, olanzapine, clozapine, and aripiprazole.[142] However, studies with this DRD2 polymorphism and clozapine have produced contradictory results. [143]

### GRIK1, Glutamate Receptor Kainate 1

GRIK encodes for the kainite GluK1 receptor subunit of glutamate receptors. Topiramate, an anticonvulsant also utilized in the treatment of alcohol use disorder, blocks highly selective glutamate receptors, with its effects being

most notable for receptors containing the GluK1 subunit. [144] Polymorphisms in this gene have been shown to predict response to topiramate in alcohol use disorder, though the exact mechanism by which this effect is moderated remains undetermined. [144–146]

Specifically, an initial study showed C/C homozygosity at GRIK1 was associated with an increased likelihood of response to topiramate for alcohol use disorder in individuals of European descent; however, recent studies show contradictory results. Other genetic and clinical factors may also influence response. [144–150]

### Literature Summary: Glutamate Receptor Kainate 1 (GRIK1)

**Topiramate treatment of heavy drinkers: moderation by a GRIK1 polymorphism**
https://pubmed.ncbi.nlm.nih.gov/24525690/
Topiramate has been shown to reduce drinking and heavy drinking in individuals with alcohol dependence whose goal was to stop drinking. The authors evaluated the efficacy and tolerability of topiramate in heavy drinkers whose treatment goal was to reduce drinking to safe levels... Topiramate treatment significantly reduced heavy drinking days and increased abstinent days relative to placebo. In a European American subsample (N=122), topiramate's effect on heavy drinking days was significantly greater than that for placebo only in rs2832407 C-allele homozygotes. [144]

**Prospective randomized pharmacogenetic study of topiramate for treating alcohol use disorder**
https://pubmed.ncbi.nlm.nih.gov/33568796/
The present study sought to replicate prospectively the effect of topiramate and rs2832407 in patients with DSM-5 alcohol use disorder (AUD) who sought to reduce or stop their drinking. We stratified the randomization on genotype (rs2832407*C-allele homozygotes vs. A-allele carriers) and assigned 170 European-American participants (71.2% male) to receive 12 weeks of treatment with topiramate (N = 85), at a maximal daily dosage of 200 mg, or matching placebo (N = 85). There was no significant difference in topiramate's effect on heavy drinking days (HDDs) between genotype groups. Although consistent with other studies showing a reduction in heavy drinking with topiramate treatment, the prior finding of a moderating effect of rs2832407 genotype was not replicated in this prospective trial. [147]

**Post-treatment effects of topiramate on alcohol-related outcomes: a combined analysis of two placebo-controlled trials**
https://pubmed.ncbi.nlm.nih.gov/35229945/
In a randomized controlled trial (RCT) of topiramate, rs2832407, a single nucleotide polymorphism (SNP) in the GRIK1 gene moderated topiramate's effects (Study 1). However, a second RCT (Study 2) did not replicate the SNP's moderating effect during treatment. The current analysis combines data from these two studies to examine topiramate's effects on alcohol-related outcomes and on its pharmacogenetic moderation during a 6-month post-treatment period… Despite robust effects of topiramate on drinking during treatment, the overall multivariate medication effects on outcomes during 3- and 6-month follow-up were not significant ($p = 0.08$ and $p = 0.26$, respectively). The moderating effect of the SNP on primary treatment outcomes was also not significant during either follow-up period ($p = 0.13$ and $p = 0.16$, respectively). However, during the 3-month post-treatment period, drinks per day was significantly lower in the topiramate group than the placebo group in the rs2832407*CC-genotype group. [149]

**An intensive longitudinal examination of topiramate treatment for alcohol use disorder: a secondary analysis of data from a randomized controlled trial**
Participants were 164 individuals (70% male, mean age=51.5, 36% rs2832407*C-allele homozygotes) who sought to reduce or stop drinking. Participants were assigned to medication (topiramate or placebo), with stratification by genotype group (CC vs. AA/AC) and treatment goal (reduce versus abstain). On any given day during treatment, participants who received topiramate had lower odds of IVR-reported heavy drinking (odds ratio [OR]=0.257, b (standard error [SE])=-1.351 (0.334), $p<0.001$) and lower levels of desire to drink (b (SE)=-0.323 (0.122), $p=0.001$) and positive alcohol expectancies (b (SE)=-0.347 (0.138), $p=0.013$) than those who received placebo. Genotype did not moderate the effects of topiramate on any outcomes examined ($p>0.05$). [150]

### HLA-A & HLA-B, Human Leukocyte Antigen, Class I, A & B

The HLA-1 class of genes includes HLA-A, HLA-B, and HLA-C and encodes the heavy chains of class I antigen presenting molecules that are expressed on most nucleated cells. These genes are highly polymorphic and code for proteins that bind and present antigens to immune cells. The variants HLA-A*31:01 and HLA-B*15:02 are associated with risk of developing Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), predominately in patients of East Asian descent when taking carbamazepine. HLA-A*31:01 has been strongly associated with only carbamazepine-induced SJS and TEN [151,152], while HLA-B*15:02 increases risk for these disorders with carbamazepine, oxcarbazepine, phenytoin, fosphenytoin, lamotrigine, and possibly eslicarbazepine and phenobarbital. [53,152,153] SJS and TEN are life-threatening conditions characterized by widespread lesions on the epidermis. Due to the severity of carbamazepine-induced SJS/TEN, the FDA label includes a boxed warning indicating that genetically at-risk populations should be screened for the presence of HLA-B*15:02 before initiation of carbamazepine therapy. [154] The Clinical Pharmacogenetics Implementation Consortium (CPIC) has prescribing guidelines for both HLA-B*15:02 and HLA-A*31:01, which include recommendations regarding carbamazepine, oxcarbazepine, phenytoin, and fosphenytoin. [53,152]

### Literature Summary: HLA-A; *31:01 allele

**HLA genotype and carbamazepine-induced cutaneous adverse drug reactions: a systematic review**
https://pubmed.ncbi.nlm.nih.gov/23132554/
HLA-A*3101 is significantly associated with all phenotypes of CBZ hypersensitivity in multiple ethnicities with a pooled OR of 9.5 (95% CI = 6.4-13.9, P < 1 × 10(-5)). Between 47 and 67 patients would need to be tested for HLA-A*3101 to prevent one episode of hypersensitivity. Our findings suggest that HLA testing before carbamazepine therapy would be effective at identifying individuals at risk of hypersensitivity and applicable to multiple populations providing hope for prevention in the future.[151]

**Clinical Pharmacogenetics Implementation Consortium guideline for HLA genotype and use of carbamazepine and oxcarbazepine: 2017 update**
https://pubmed.ncbi.nlm.nih.gov/29392710/
The variant allele HLA-A*31:01 is associated with greater risk of maculopapular exanthema, drug reaction with eosinophilia and systemic symptoms, and SJS/TEN in patients treated with carbamazepine. We summarize evidence from the published literature supporting these associations and provide recommendations for carbamazepine and oxcarbazepine use based on HLA genotypes. [152]

### Literature Summary: HLA-B; *15:02 allele

**HLA genotype and carbamazepine-induced cutaneous adverse drug reactions: a systematic review**
https://pubmed.ncbi.nlm.nih.gov/23132554/
We determined that carriage of HLA-B*1502 in Asian patients was associated with a pooled odds ratio (OR) of 113.4 (95% confidence interval (CI) = 51.2-251.0, P < 1 × 10(-5)) for CBZ-induced Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). A total of 461 patients would need to be screened for HLA-B*1502 to prevent one episode of SJS/TEN. [151]

**Association between HLA-B*15:02 and oxcarbazepine-induced cutaneous adverse reaction: a meta-analysis**
https://pubmed.ncbi.nlm.nih.gov/29629814/
Eight studies were finally included for meta-analysis, including 32 severe cutaneous adverse reaction (sCAR) cases, 112 mild cutaneous adverse reaction (mcADR) cases, 281 OXC tolerant control and 946 population control cases. In the tolerant control group, an association was found between HLA-B*15:02 genotype and OXC-induced sCAR (odds ratio [OR]: 18.13; 95% CI: 6.77-48.56), but not in mcADR (OR: 1.43; 95% CI: 0.56-3.64). In population control group, an association was found between HLA-B*15:02 genotype and OXC-induced sCAR, (OR: 8.22; 95% CI: 3.03-22.34), but not in mcADR (OR: 2.06; 95% CI: 0.91-4.67). [155]

**Clinical Pharmacogenetics Implementation Consortium guideline for HLA genotype and use of carbamazepine and oxcarbazepine: 2017 update**
https://pubmed.ncbi.nlm.nih.gov/29392710/
The variant allele HLA-B*15:02 is strongly associated with greater risk of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) in patients treated with carbamazepine or oxcarbazepine... We summarize evidence from the published literature supporting these associations and provide recommendations for carbamazepine and oxcarbazepine use based on HLA genotypes. [152]

**The association between *HLA-B*15:02* and phenytoin-induced severe cutaneous adverse reactions: a meta-analysis**
https://pubmed.ncbi.nlm.nih.gov/34816768/
A total of 11 studies on 1389 patients, were included for the analyses. There was a significant association between *HLA-B*15:02* and PHT-induced severe cutaneous adverse reactions (pooled OR = 2.29, 95% CI: 1.25-4.19, p = 0.008). Furthermore, there was a significant association regarding Stevens-Johnson syndrome/toxic epidermal necrolysis (OR = 3.63, 95% CI: 2.15-6.13, p < 0.001) but no association regarding drug reaction with eosinophilia and systemic symptom. [156]

**Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2C9 and HLA-B genotypes and phenytoin dosing: 2020 update**
https://pubmed.ncbi.nlm.nih.gov/32779747/
The variant allele HLA-B*15:02 is associated with an increased risk of Stevens-Johnson syndrome and toxic epidermal necrolysis in response to phenytoin treatment. We summarize evidence from the published literature supporting these associations and provide therapeutic recommendations for the use of phenytoin based on CYP2C9 and/or HLA-B genotypes. [53]

**Dutch Pharmacogenetic Working Group (DPWG) risk analysis document for lamotrigine and HLA**
https://www.g-standaard.nl/risicoanalyse/B0006932.PDF
Four meta-analyses of which two identical (with a total of 12, 17, 17 and 54 Asian SJS/TEN cases per meta-analysis), one case-control study with 28 Iranian SJS/TEN cases, and two pooled case-control studies with a total of 7 Han Chinese SJS/TEN cases showed that HLA-B*15:02 increased the risk of lamotrigine-induced SJS/TEN (OR = 2.4-7.9, with the OR in the meta-analyses decreasing with increasing number of total SJS/TEN cases) (Deng 2018, Zeng 2015, Bloch 2014, Cheung 2013, Sabourirad 2021, and Hung 2010). [157]

### HTR2A, Serotonin Receptor 2A

The single nucleotide polymorphism rs7997012 was originally identified as a marker of citalopram response in the seminal Sequenced Treatment Alternatives for Depression (STAR*D) study. Two studies using STAR*D data found an association between the A/A genotype and citalopram response in individuals of European descent, [158,159]. Studies completed in individuals of European descent with depression also found a poorer odds of remission to non-SSRI antidepressants in those with the A/A genotype. [97] More recently, updated meta-analyses showed a poorer odds of response and remission to numerous antidepressants, including SSRIs. [160,161]

### Literature Summary: Serotonin Receptor 2A (HTR2A)

**Variation in the gene encoding the serotonin 2A receptor is associated with outcome of antidepressant treatment**
https://pubmed.ncbi.nlm.nih.gov/16642436/
We searched for genetic predictors of treatment outcome in 1,953 patients with major depressive disorder who were treated with the antidepressant citalopram in the Sequenced Treatment Alternatives for Depression (STAR*D) study and were prospectively assessed. We detected significant and reproducible association between treatment outcome and a marker in HTR2A (P range 1 x 10(-6) to 3.7 x 10(-5) in the total sample). Participants who were homozygous for the A allele had an 18% reduction in absolute risk of having no response to treatment, compared with those homozygous for the other allele. [158]

**Resequencing of serotonin-related genes and association of tagging SNPs to citalopram response**

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2896826/
An additional SNP in *HTR2A* (rs7997012), previously reported to be associated with outcome of citalopram treatment in this sample, but not well tagged by any of the other SNPs we studied, was also genotyped, and was associated with citalopram response (*P*=0.0002), strongly supporting the previous observation in the same STAR*D sample. [159]

**Pharmacogenetics in major depression: a comprehensive meta-analysis**
https://pubmed.ncbi.nlm.nih.gov/23733030/
We performed a comprehensive meta-analysis of published candidate gene studies focused on AD efficacy in MD to evaluate the cumulative evidence. A random-effect model was applied to study the polymorphisms with genotypic counts available from at least three independent studies…. Regarding rs7997012, 3 studies and the STAR*D data including a total of 2195 subjects, and 5 studies and the 25 STAR*D data including a total of 2704 subjects were analyzed for response and remission phenotypes, respectively… In non-SSRIs/mixed ADs subgroup… associations with remission were found in the pooling G/G and G/A versus A/A (OR = 3.19, 95%CI: 1.57–6.46, p = 0.001; Supplementary Fig. 5.1), and in the pooling G/G versus A/A (OR = 3.40, 95%CI: 1.69–6.85, p=0.0006; Supplementary Fig. 5.2), with null-to-low heterogeneity across studies (I2 within 0 and 9%). [97]

**Influence of 5-HTR2A genetic polymorphisms on the efficacy of antidepressants in the treatment of major depressive disorder: a meta-analysis**
https://pubmed.ncbi.nlm.nih.gov/25108775/
Eleven studies with a total of 1775 MDD patients met the inclusion criteria of this meta-analysis. Three common polymorphisms in the 5-HTR2A gene were assessed, including rs6311 C>T, rs7997012 G>A, and rs6313 T>C… The rs7997012 G>A polymorphism was also associated with a higher response rate to antidepressants in MDD patients under the dominant model (OR=1.92, 95% CI=1.02-3.61, P=0.044). [160]

**Associations between the 1438A/G, 102T/C, and rs7997012G/A polymorphisms of HTR2A and the safety and efficacy of antidepressants in depression: a meta-analysis**
https://pubmed.ncbi.nlm.nih.gov/33097827/
This meta-analysis ascertained forty-two studies on the efficacy (including response and remission) and side-effect issued before February 2020. Pooled analyses indicated significant associations of rs7997012G/A polymorphism (nine studies, 1434 subjects) and higher remission in overall models (dominant model: OR: 1.30, 95% CI: 1.01-1.66; recessive model: OR: 2.20, 95% CI: 1.53-3.16; homozygote model: OR: 2.73, 95% CI: 1.78-4.17). [161]

### HTR2C, Serotonin Receptor 2C

The serotonin receptor 2C (HTR2C) is a site of action of various antipsychotic medications. Serotonin activity at this receptor is involved in the regulation of appetite and is one mechanism utilized to signal satiety. [162] Inhibition of this signaling pathway via 5HT2C antagonism has been shown in clinical studies to lead to increased food intake [163]. Several meta-analyses have found an association with the HTR2C-759C/T polymorphism and antipsychotic-induced weight gain. Individuals with the T allele have a decreased risk of weight gain compared to individuals with the C/C genotype. [163,164]

### Literature Summary: Serotonin Receptor 2C (HTR2C)

**Polymorphisms of the HTR2C gene and antipsychotic-induced weight gain: an update and meta-analysis**
https://pubmed.ncbi.nlm.nih.gov/21121776/
An updated meta-analysis of nine previous studies plus our current sample suggest that the -759C allele is associated with antipsychotic-induced weight gain. In particular, individuals with the T allele had a decreased risk of weight gain to second generation antipsychotics compared to those with the C/C genotype. (OR 3.20 (1.15-5.09). [163]

**Association of the HTR2C-759C/T polymorphism and antipsychotic-induced weight gain: a meta-analysis**
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7232784/
A meta-analysis of 17 studies with 3170 patients with schizophrenia has shown that the association between the -759 C/T polymorphism and antipsychotic-induced weight gain (AIWG) is statistically significant (OR 0.34, 95% CI: 0.20

to 0.57, z=4.11, p<0.001), with T allele carriers being less likely to have AIWG. The subgroup analyses revealed significant correlations between the -759 C/T polymorphism and AIWG in the Caucasian population (OR 0.33, 95% CI: 0.14 to 0.77, z=2.55, p=0.011), the Asian population (OR 0.31, 95% CI: 0.18 to 0.52, z=4.46, p<0.001), the patients with antipsychotic drug administration (CT/TT/T vs CC/C: OR 0.63, 95% CI: 0.40 to 1.00, z=1.97, p=0.049) and the patients with atypical antipsychotic drug administration (CT/TT/T vs CC/C: OR 0.21, 95% CI: 0.09 to 0.47, z=3.83, p<0.001). [164]

### MC4R, Melanocortin 4 Receptor

MC4R is expressed in various sites of the brain, including the hypothalamus, and has a central role in the regulation of satiety, body weight and energy balance. Over 70 variations in MC4R have been identified, and about half of these variants result in partial or total loss of function, which may lead to hyperphagia, hyperinsulinemia, and increased fat mass. [165,166] Moreover, studies have shown that a particular variation in this gene, the A/A genotype, is associated with increased risk of weight gain and adverse changes in metabolic indices among individuals receiving second generation antipsychotics. [167–170]. Clinicians should use caution when prescribing second generation antipsychotics to individuals with the homozygous risk genotype. In general, those drugs that pose the highest risk for weight gain are clozapine and olanzapine, while aripiprazole, iloperidone, olanzapine/samidorphan, paliperidone, quetiapine and risperidone are medium-risk medications, and asenapine, brexpiprazole, cariprazine, lumateperone, lurasidone and ziprasidone tend to be lower-risk medications. [171–174]

### Literature Summary: Melanocortin R Receptor (MC4R)

**MC4R rs489693: a clinical risk factor for second generation antipsychotic-related weight gain?**
**https://pubmed.ncbi.nlm.nih.gov/23920449/**

The rs489693 polymorphism near the MC4R gene was associated with SGA-related weight gain in a genome-wide association study. We tried to replicate these results in our independent naturalistic study population. From 341 Caucasian inpatients receiving at least one SGA drug (olanzapine, clozapine, risperidone, paliperidone, quetiapine or amisulpride), carriers homozygous for the rs489693 A-allele (n = 35) showed a 2.2 times higher weight increase (+2.2 kg) than carriers of the CC-genotype (+1 kg) after 4 wk. of treatment (analysis of covariance, p = 0.039). We revealed an even stronger effect in a subpopulation without weight gain inducing co-medication (factor 3.1, +2.8 kg, p = 0.044, (n = 16 of 169)) and in first episode patients (factor 2.7, +2.7 kg, p = 0.017, (n = 13 of 86)). Our results confirm the rs489693 A-allele as a possible risk factor for SGA-related weight gain. [167]

**Association between common variants near the melanocortin 4 receptor gene and severe antipsychotic drug-induced weight gain**
**https://pubmed.ncbi.nlm.nih.gov/22566560/**

Our genome-wide association study yielded 20 single-nucleotide polymorphisms at a single locus exceeding a statistical threshold of P<10(-5). This locus, near the melanocortin 4 receptor (MC4R) gene, overlaps a region previously identified by large-scale genome-wide association studies of obesity in the general population. Effects were recessive, with minor allele homozygotes gaining extreme amounts of weight during the 12-week trial. These results were replicated in 3 additional cohorts, with rs489693 demonstrating consistent recessive effects; meta-analysis revealed a genome-wide significant effect (P=5.59 X 10 (-12). Moreover, we observed consistent effects on related metabolic indices, including triglyceride, leptin, and insulin levels. These data implicate MC4R in extreme SGA-induced weight gain and related metabolic disturbances. A priori identification of high-risk subjects could lead to alternative treatment strategies in this population. [168]

### MTHFR, Methylenetetrahydrofolate Reductase

MTHFR is an enzyme responsible for catalyzing the conversion of folic acid to methylfolate. Methylfolate is the active form of folic acid, a vital cofactor for the synthesis of norepinephrine, dopamine and serotonin[175] Two variations are tested within this gene. The T allele of C677T and C allele of the A1298C lead to reduced enzymatic activity of MTHFR, resulting in inefficient folic acid metabolism and production of methylfolate. [176–180] Studies analyzing the therapeutic efficacy of l-methylfolate in depression found superior outcomes when SSRI/SNRI treatment was supplemented with l-methylfolate compared with SSRIs/SNRIs alone. [181,182] A 2016 study utilizing a methylfolate B-vitamin complex as monotherapy showed depression remission rates of 42% when MTHFR genotype was taken into consideration. [183]

Preliminary data also suggest that other biomarkers may be associated with greater response to l-methylfolate, including BMI ≥ 30 kg/m$^2$ and/or high C-reactive protein levels (≥ 2.25 mg/L). [184]

### Literature Summary: Methylenetetrahydrofolate Reductase (MTHFR)

**Correlation of clinical response with homocysteine reduction during therapy with reduced B vitamins in patients with MDD who are positive for MTHFR C677T or A1298C polymorphism: a randomized, double-blind, placebo-controlled study**

https://pubmed.ncbi.nlm.nih.gov/27035272/

330 adult patients with MDD (DSM-5) and positive for either MTHFR C677T or A1298C polymorphism were enrolled in a trial conducted between August 1, 2014, and April 3, 2015. 160 patients received placebo, while 170 received a capsule containing a combination of reduced B vitamins. Plasma homocysteine levels were measured at baseline and week 8. The Montgomery-Asberg Depression Rating Scale (MADRS) was used to evaluate efficacy for MDD.

159 of 170 vitamin-treated patients and 123 of 160 placebo-treated patients were completers. Of the active treatment group, 131 (82.4%) showed a reduction in homocysteine (for a mean in this subgroup of 25%, P < .001), while 28 (17.6%) showed no significant change. Placebo patients demonstrated a small elevation in homocysteine. Active-treatment patients demonstrated, on average, a 12-point reduction on the MADRS by week 8, and 42% achieved full remission (P < .001). No side effect was significantly different between groups. No patients experienced mania. [183]

**Effect of adjunctive L-methylfolate 15 mg among inadequate responders to SSRIs in depressed patients who were stratified by biomarker levels and genotype: results from a randomized clinical trial**

https://pubmed.ncbi.nlm.nih.gov/24813065/

The double-blind, randomized, placebo-controlled trial used the sequential parallel comparison design. Outpatients with SSRI-resistant MDD (DSM-IV criteria) received L-methylfolate 15 mg/d for 60 days, placebo for 30 days followed by L-methylfolate 15 mg/d for 30 days, or placebo for 60 days…Seventy-five patients were enrolled. Patients with specific biological (body mass index ≥ 30 kg/m², elevated plasma levels of high-sensitivity C-reactive protein or 4-hydroxy-2-nonenal, low S-adenosylmethionine/S-adenosylhomocysteine ratio) and genetic markers at baseline had significantly (P ≤ .05) greater pooled mean change from baseline on the HDRS-28 with L-methylfolate versus placebo. Pooled mean change from baseline on the Clinical Global Impressions-Severity of Illness scale was significantly (P < .05) greater with L-methylfolate versus placebo for most genetic markers. Most combinations of baseline biological and genetic markers predicted significantly (P ≤ .05) greater reductions in pooled mean change from baseline in HDRS-28 scores with L-methylfolate versus placebo. [184]

### OPRM1, μ Opioid Receptor

OPRM1 is a gene that encodes for the μ opioid receptor, which regulates the analgesic response to pain via endogenous and exogenous opioids which act as agonists at the μ opioid receptor. The most extensively studied genetic polymorphism *A118G* has been linked to reduced μ opioid receptor expression. Studies have demonstrated that individuals who carry at least one copy of the A118G allele exhibit higher pain scores and greater opioid consumption compared to the homozygous AA genotype [185–189]. However, those with the GG genotype have been observed to have more significant differences in the sensitivity to opioids, especially morphine, compared to those with the AA and AG genotypes. [190,191] The most recent Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for opioids states that there is insufficient evidence to provide a specific dose recommendation based on OPRM1 genotype at this time. [62]

### Literature Summary: μ opioid receptor (OPRM1)

**Pain polymorphisms and opioids: an evidence based review**

https://pubmed.ncbi.nlm.nih.gov/30592275/

Genetic variation of the μ-opioid receptor may contribute to interindividual differences in morphine consumption (with recommendation grade A for OPRM1 A118G rs1799971) but there are more than 100 polymorphisms identified in the human μ opioid peptide receptor (OPRM1) gene…Individualization of pain treatment in terms of response to

treatment and adverse events. If OPRM1 G/G genotype consider initiating morphine at a higher dose and/or more aggressive dose titration. May also influence tramadol/acetaminophen analgesic response. [190]

**Effects of the OPRM1 A118G polymorphism (rs1799971) on opioid analgesia in cancer pain**
https://pubmed.ncbi.nlm.nih.gov/30028366/
Our analysis indicates that those patients who have a homozygous (GG) polymorphism at A118G on the OPRM1 gene required higher amounts of opioids to obtain the same level of pain relief as those who had a heterozygous (AG) polymorphism (SMD = −0.51; P=0.06; I2= 44%). The patients homozygous for AA allele required less analgesic than those with homozygous AG allele, but the SMD of −0.23 was very small, denoting only a little difference between the AA and AG groups. When we compared the homozygous GG group polymorphism with homozygous AA group, we observed that the GG group had a dramatically increased opioid dose for cancer pain analgesia (SMD =−0.79; P=0.04; I2=48%)…All these results suggest that the A118G polymorphism might be associated with a decreased sensitivity to opioid analgesia in cancer pain, and these effects are more significant in GG homozygous than heterozygote carriers. [191]

### SLC6A4, Serotonin Transporter

The SLC6A4 gene, or the solute carrier family 6, member 4 gene, encodes for a protein that transports serotonin from the synapse back into the neuron to halt signaling. The antidepressant activity of selective serotonin reuptake inhibitors (SSRIs) is achieved through inhibition of this transporter, allowing serotonin to remain in the synapse longer. [192] A polymorphism within the promoter region of this gene, i.e. 5-HTTLPR, is a 44 base pair deletion that influences production of the serotonin transporter (SERT), with the long (L) allele associated with twice the basal expression as the short (S) allele. A single nucleotide polymorphism (SNP) within the L allele (rs25531A/G) causes impaired expression similar to the S variant. [193]

Several studies have shown that individuals who are homozygous for the L(A) allele demonstrate improved response to SSRIs and lower likelihood of side effects. A meta-analysis of 6 studies in patients of European descent with depressive disorders showed that individuals with the S/S genotype were significantly less likely to respond to SSRIs than those with the L/L genotype (OR=1.71, p=0.003). [194] This is consistent with results from a previous meta-analysis. [195] Individuals who carry only a single risk variant (S or L(G) alone) appear to be at increased risk of adverse effects, particularly gastrointestinal side effects, whereas those who carry two risk alleles [(S/S, S/L(G), and L(G)/L(G)] are at a greater risk of non-response and adverse effects, as compared to those who do not have these variants. [193–200] Additionally, these homozygous risk allele carriers have been shown to have an increased risk for abnormal cortisol release in response to stressors. [201]

### Literature Summary: Serotonin Transporter (SLC6A4)

**Association between a functional serotonin transporter promoter polymorphism and citalopram treatment in adult outpatients with major depression**
https://pubmed.ncbi.nlm.nih.gov/17606812/
A clinical effectiveness trial, Sequenced Treatment Alternatives to Relieve Depression, collected DNA samples from outpatients with nonpsychotic major depressive disorder who received citalopram in the first treatment step…. Expression-based grouping produced a significant finding of association between the L(A) allele and adverse effect burden in the entire sample (P = .004 [genotype frequency]; P < .001 [allele frequency]). To control for bias from population stratification, a white American subsample was analyzed. A lesser adverse effect burden was associated with L(A)L(A) genotype frequency (P = .03) or L(A) allele frequency (P = .007). These findings in white patients did not hold when the L allele was undifferentiated. No association was observed between treatment outcome phenotypes and HTTLPR. Development of diarrhea and the presence of the low-expression S or L(G) alleles were the strongest risk factors associated with adverse effect burden. [193]

**Meta-analysis of serotonin transporter gene promoter polymorphism (5-HTTLPR) association with antidepressant efficacy**
https://pubmed.ncbi.nlm.nih.gov/22137564/

A total of 19 studies performed in Caucasians were included. A significant association was found between l allele and response rate for SSRIs (OR=1.58, C.I. 95% 1.16-2.16, p=0.004), and it survived removing single studies one at a time, the only exception being the study by Huezo-Diaz et al. (2009) (in this case p=0.05)….Considering all antidepressant classes taken together and only non-SSRI antidepressants, no association was detected. On the other hand, pooling the 1/1 genotype versus the s/s one, we found evidence of association both considering all antidepressant classes (OR= 1.62, C.I. 95% 1.22-2.16, p=0.0008) and SSRIs only (OR=1.71, C.I. 95% 1.20-2.45, P=0.003), but not for other/mixed antidepressants. These two associations were heavily influenced by one study (Huezo-Diaz et al., 2009), which exclusion made the effect size on the edge of significance (p=0.04 and p=0.02, respectively for all antidepressants and SSRIs only) [194]

**Serotonin transporter genetic variation and antidepressant response and tolerability: a systematic review and meta-analysis**
**https://pubmed.ncbi.nlm.nih.gov/34945806/**
We performed a systematic review and meta-analysis to assess 5-HTTLPR associations with antidepressants: (1) response in psychiatric disorders other than major depressive disorder (MDD) and (2) tolerability across all psychiatric disorders... Carriers of the 5-HTTLPR LL or LS genotypes were more likely to respond to antidepressant therapy, compared to the SS carriers in the total and European ancestry-only study populations. Long (L) allele carriers taking selective serotonin reuptake inhibitors (SSRIs) reported fewer ADRs relative to short/short (SS) carriers. European L carriers taking SSRIs had lower ADR rates than S carriers. [196]

**The serotonin transporter gene-linked polymorphic region (5-HTTLPR) and cortisol stress reactivity: a meta-analysis**
**https://pubmed.ncbi.nlm.nih.gov/22945032/**
We evaluated the association of 5-HTTLPR genotype and cortisol reactivity to acute psychosocial stress by applying a meta-analytical technique based on eleven relevant data sets (total N=1686), which were identified through a systematic literature search up to October 2011. This meta-analysis indicates a small (d=0.27), but significant association between 5-HTTLPR genotype and HPA-axis reactivity to acute psychosocial stress with homozygous carriers of the S allele displaying increased cortisol reactivity compared with individuals with the S/L and L/L genotype. The latter association was not further moderated by participants' age, sex or the type of stressor. Formal testing revealed no evidence for a substantial selection or publication bias. Our meta-analytical results are consistent with a wide variety of experimental studies indicating a significant association between 5-HTTLPR genotype and intermediate phenotypes related to stress sensitivity. [201]

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