Table of Pharmacogenetic Associations

February 20, 2020[1]

Pharmacogenetic tests, along with other information about patients and their disease or condition, can play an important role in drug therapy. When a health care provider is considering prescribing a drug, knowledge of a patient's genotype may be used to aid in determining a therapeutic strategy, determining an appropriate dosage, or assessing the likelihood of benefit or toxicity.

The table below lists pharmacogenetic associations that FDA has evaluated and believes there is sufficient scientific evidence to suggest that subgroups of patients with certain genetic variants, or genetic variant-inferred phenotypes (i.e., affected subgroup in the table below), are likely to have altered drug metabolism, and in certain cases, differential therapeutic effects, including differences in risks of adverse events. The fact that FDA has included a particular gene-drug interaction in the table does not necessarily mean FDA advocates using a pharmacogenetic test before prescribing the corresponding medication, unless the test is a companion diagnostic. Tests that are essential for the safe and effective use of a therapeutic product, including those that identify patients for which the drug is contraindicated, are companion diagnostics. This table is not intended to affect current regulatory requirements or policies, including FDA's policy regarding companion diagnostics.[2] Nor is the table intended to make an assessment on the safe and effective use of, or regulatory requirements for, tests that

detect variants in the referenced genes, or to provide comprehensive information on the described gene-drug interactions.

Specific information regarding therapeutic management is provided for some pharmacogenetic associations listed in the table, but most of the associations listed have not been evaluated in terms of the impact of genetic testing on clinical outcomes, such as improved therapeutic effectiveness or increased risk of specific adverse events. In addition, clinical studies, if available, may only have linked genetic variation to a drug's pharmacokinetics (i.e., the way in which the drug is metabolized), and differences in drug efficacy or safety across different genotype subgroups may not be known. If no statements related to efficacy or toxicity are provided, the scientific evidence FDA reviewed was considered insufficient to support such associations.

FDA recognizes that practitioners will take into account different sources and strengths of evidence and will make prescribing decisions based on their judgment about which treatments are appropriate for individual patients. In particular, each patient's genetic makeup is only one of many factors that may impact drug concentrations and response, highlighting the fact that information provided in this table is limited to certain pharmacogenetic associations only and does not provide comprehensive information needed for safe and effective use of a drug. Accordingly, health care providers should refer to FDA-approved labeling for prescribing information, including monitoring instructions and information on other factors that may affect drug concentrations, benefits, and risks. In this context, the information in this Table is intended primarily for prescribers, and patients should not adjust their medications without consulting their prescriber.

This version of the table is limited to pharmacogenetic associations that are related to drug metabolizing enzyme gene variants, drug transporter gene variants, and gene variants that have been related to a predisposition for certain adverse events. FDA recognizes that various other pharmacogenetic associations exist that are not listed here, and this table will be updated periodically with additional pharmacogenetic associations supported by sufficient scientific evidence. FDA has opened a docket (https://www.regulations.gov/docket?D=FDA-2020-N-0839) for stakeholders—including scientific and medical communities, patients, providers, and industry—to offer specific comments on pharmacogenetic associations that FDA should or should not include in this table, along with the rationale and underlying evidence that supports the pharmacogenetic association.

Please submit all comments to the open docket (https://www.regulations.gov/docket?D=FDA-2020-N-0839). Please submit any questions to PGx@fda.hhs.gov (mailto:PGx@fda.hhs.gov).

Pharmacogenetic associations for which the data support therapeutic management recommendations

Drug	Gene	Affected Subgroups+	Description of Gene-Drug Interaction
Abacavir	HLA-B	*57:01 allele positive	Results in higher adverse reaction risk (hypersensitivity reactions). Do not use abacavir in patients positive for HLA-B*57:01.
Amifampridine	NAT2	poor metabolizers	Results in higher systemic concentrations and higher adverse reaction risk. Use lowest recommended starting dosage and monitor for

			adverse reactions. Refer to FDA labeling for specific dosing recommendations.
Amifampridine Phosphate	NAT2	poor metabolizers	Results in higher systemic concentrations. Use lowest recommended starting dosage (15 mg/day) and monitor for adverse reactions.
Amphetamine	CYP2D6	poor metabolizers	May affect systemic concentrations and adverse reaction risk. Consider lower starting dosage or use alternative agent.
Aripiprazole	CYP2D6	poor metabolizers	Results in higher systemic concentrations and higher adverse reaction risk. Dosage adjustment is recommended. Refer to FDA labeling for specific dosing recommendations.
Aripiprazole Lauroxil	CYP2D6	poor metabolizers	Results in higher systemic concentrations. Dosage adjustment is recommended. Refer to FDA labeling for specific dosing recommendations.
Atomoxetine	CYP2D6	poor metabolizers	Results in higher systemic concentrations and higher adverse reaction risk. Adjust titration interval and increase dosage if tolerated. Refer to FDA labeling for specific dosing recommendations.
Azathioprine	TPMT and/or NUDT15	intermediate or poor metabolizers	Alters systemic active metabolite concentration and dosage requirements. Results in higher adverse reaction risk (myelosuppression). Consider alternative therapy in poor metabolizers. Dosage reduction is recommended in

			intermediate metabolizers for NUDT15 or TPMT. Intermediate metabolizers for both genes may require more substantial dosage reductions. Refer to FDA labeling for specific dosing recommendations.
Belinostat	UGT1A1	*28/*28 (poor metabolizers)	May result in higher systemic concentrations and higher adverse reaction risk. Reduce starting dose to 750 mg/m2 in poor metabolizers.
Brexpiprazole	CYP2D6	poor metabolizers	Results in higher systemic concentrations. Dosage adjustment is recommended. Refer to FDA labeling for specific dosing recommendations.
Brivaracetam	CYP2C19	intermediate or poor metabolizers	Results in higher systemic concentrations and higher adverse reaction risk. Consider dosage reductions in poor metabolizers.
Capecitabine	DPYD	intermediate or poor metabolizers	Results in higher adverse reaction risk (severe, life-threatening, or fatal toxicities). No dosage has proven safe in poor metabolizers, and insufficient data are available to recommend a dosage in intermediate metabolizers. Withhold or discontinue in the presence of early-onset or unusually severe toxicity.
Carbamazepine	HLA-B	*15:02 allele positive	Results in higher adverse reaction risk (severe skin reactions). Avoid use unless potential benefits outweigh risks and consider risks of alternative therapies. Patients

			positive for HLA-B*15:02 may be at increased risk of severe skin reactions with other drugs that are associated with a risk of Stevens Johnson Syndrome/Toxic Epidermal necrolysis (SJS/TEN). Genotyping is not a substitute for clinical vigilance.
Celecoxib	CYP2C9	poor metabolizers	Results in higher systemic concentrations. Reduce starting dose to half of the lowest recommended dose in poor metabolizers. Consider alternative therapy in patients with juvenile rheumatoid arthritis.
Citalopram	CYP2C19	poor metabolizers	Results in higher systemic concentrations and adverse reaction risk (QT prolongation). The maximum recommended dose is 20 mg.
Clobazam	CYP2C19	intermediate or poor metabolizers	Results in higher systemic active metabolite concentrations. Poor metabolism results in higher adverse reaction risk. Dosage adjustment is recommended. Refer to FDA labeling for specific dosing recommendations.
Clopidogrel	CYP2C19	intermediate or poor metabolizers	Results in lower systemic active metabolite concentrations, lower antiplatelet response, and may result in higher cardiovascular risk. Consider use of another platelet P2Y12 inhibitor.
Clozapine	CYP2D6	poor metabolizers	Results in higher systemic concentrations. Dosage reductions may be necessary.

Codeine	CYP2D6	ultrarapid metabolizers	Results in higher systemic active metabolite concentrations and higher adverse reaction risk (life-threatening respiratory depression and death). Codeine is contraindicated in children under 12 years of age.
Deutetrabenazine	CYP2D6	poor metabolizers	Results in higher systemic concentrations and adverse reaction risk (QT prolongation). The maximum recommended dosage should not exceed 36 mg (maximum single dose of 18 mg).
Dronabinol	CYP2C9	intermediate or poor metabolizers	May result in higher systemic concentrations and higher adverse reaction risk. Monitor for adverse reactions.
Eliglustat	CYP2D6	ultrarapid, normal, intermediate, or poor metabolizers	Alters systemic concentrations, effectiveness, and adverse reaction risk (QT prolongation). Indicated for normal, intermediate, and poor metabolizer patients. Ultrarapid metabolizers may not achieve adequate concentrations to achieve a therapeutic effect. The recommended dosages are based on CYP2D6 metabolizer status. Coadministration with strong CYP3A inhibitors is contraindicated in intermediate and poor CYP2D6 metabolizers. Refer to FDA labeling for specific dosing recommendations.
Erdafitinib	CYP2C9	*3/*3 (poor metabolizers)	May result in higher systemic concentrations and higher adverse reaction risk. Monitor

			for adverse reactions.
Flibanserin	CYP2C19	poor metabolizers	May result in higher systemic concentrations and higher adverse reaction risk. Monitor patients for adverse reactions.
Flurbiprofen	CYP2C9	poor metabolizers	Results in higher systemic concentrations. Use a reduced dosage.
Fluorouracil	DPYD	intermediate or poor metabolizer	Results in higher adverse reaction risk (severe, life-threatening, or fatal toxicities). No dosage has proven safe in poor metabolizers and insufficient data are available to recommend a dosage in intermediate metabolizers. Withhold or discontinue in the presence of early-onset or unusually severe toxicity.
Gefitinib	CYP2D6	poor metabolizers	Results in higher systemic concentrations and higher adverse reaction risk. Monitor for adverse reactions.
Iloperidone	CYP2D6	poor metabolizers	Results in higher systemic concentrations and higher adverse reaction risk (QT prolongation). Reduce dosage by 50%.
Irinotecan	UGT1A1	*28/*28 (poor metabolizers)	Results in higher systemic active metabolite concentrations and higher adverse reaction risk (severe neutropenia). Consider reducing the starting dosage by one level and modify the dosage based on individual patient tolerance.
Lofexidine	CYP2D6	poor metabolizers	Results in higher systemic concentrations and higher

			adverse reaction risk. Monitor for orthostatic hypotension and bradycardia.
Meclizine	CYP2D6	ultrarapid, intermediate, or poor metabolizers	May affect systemic concentrations. Monitor for adverse reactions and clinical effect.
Metoclopramide	CYP2D6	poor metabolizers	Results in higher systemic concentrations and higher adverse reaction risk. The recommended dosage is lower. Refer to FDA labeling for specific dosing recommendations.
Mercaptopurine	TPMT and/or NUDT15	intermediate or poor metabolizers	Alters systemic active metabolite concentration and dosage requirements. Results in higher adverse reaction risk (myelosuppression). Initial dosages should be reduced in poor metabolizers; poor metabolizers generally tolerate 10% or less of the recommended dosage. Intermediate metabolizers may require dosage reductions based on tolerability. Intermediate metabolizers for both genes may require more substantial dosage reductions. Refer to FDA labeling for specific dosing recommendations.
Mivacurium	BCHE	intermediate or poor metabolizers	Results in higher systemic concentrations and higher adverse reaction risk (prolonged neuromuscular blockade). Avoid use in poor metabolizers.
Pantoprazole	CYP2C19	poor metabolizers	Results in higher systemic concentrations. Consider dosage reduction in children

			who are poor metabolizers. No dosage adjustment is needed for adult patients who are poor metabolizers.
Pimozide	CYP2D6	poor metabolizers	Results in higher systemic concentrations. Dosages should not exceed 0.05 mg/kg in children or 4 mg/day in adults who are poor metabolizers and dosages should not be increased earlier than 14 days.
Piroxicam	CYP2C9	intermediate or poor metabolizers	Results in higher systemic concentrations. Consider reducing dosage in poor metabolizers.
Propafenone	CYP2D6	poor metabolizers	Results in higher systemic concentrations and higher adverse reaction risk (arrhythmia). Avoid use in poor metabolizers taking a CYP3A4 inhibitor.
Siponimod	CYP2C9	intermediate or poor metabolizers	Results in higher systemic concentrations. Adjust dosage based on genotype. Do not use in patients with CYP2C9 *3/*3 genotype. Refer to FDA labeling for specific dosing recommendations.
Succinylcholine	BCHE	intermediate or poor metabolizers	Results in higher systemic concentrations and higher adverse reaction risk (prolonged neuromuscular blockade). Avoid use in poor metabolizers. May administer test dose to assess sensitivity and administer cautiously via slow infusion.
Tacrolimus	CYP3A5	intermediate or normal	Results in lower systemic concentrations and lower

		metabolizers	probability of achieving target concentrations. Measure drug concentrations and adjust dosage based on trough whole blood tacrolimus concentrations.
Tetrabenazine	CYP2D6	poor metabolizers	Results in higher systemic concentrations. The maximum recommended single dose is 25 mg and should not exceed 50 mg/day.
Thioguanine	TPMT and/or NUDT15	intermediate or poor metabolizers	Alters systemic active metabolite concentration and dosage requirements. Results in higher adverse reaction risk (myelosuppression). Initial dosages should be reduced in poor metabolizers; poor metabolizers generally tolerate 10% or less of the recommended dosage. Intermediate metabolizers may require dosage reductions based on tolerability. Intermediate metabolizers for both genes may require more substantial dosage reductions. Refer to FDA labeling for specific dosing recommendations.
Thioridazine	CYP2D6	poor metabolizers	Results in higher systemic concentrations and higher adverse reaction risk (QT prolongation). Predicted effect based on experience with CYP2D6 inhibitors. Contraindicated in poor metabolizers.
Tramadol	CYP2D6	poor metabolizers	Results in higher systemic and breast milk active metabolite concentrations, which may result in

			respiratory depression and death. Contraindicated in children under 12 and in adolescents following tonsillectomy/adenoidectomy. Breastfeeding is not recommended during treatment.
Valbenazine	CYP2D6	poor metabolizers	Results in higher systemic active metabolite concentrations and higher adverse reaction risk (QT prolongation). Dosage reductions may be necessary.
Venlafaxine	CYP2D6	poor metabolizers	Alters systemic parent drug and metabolite concentrations. Consider dosage reductions.
Vortioxetine	CYP2D6	poor metabolizers	Results in higher systemic concentrations. The maximum recommended dose is 10 mg.
Warfarin	CYP2C9	intermediate or poor metabolizers	Alters systemic concentrations and dosage requirements. Select initial dosage, taking into account clinical and genetic factors. Monitor and adjust dosages based on INR.
Warfarin	CYP4F2	V433M variant carriers	May affect dosage requirements. Monitor and adjust doses based on INR.
Warfarin	VKORC1	-1639G>A variant carriers	Alters dosage requirements. Select initial dosage, taking into account clinical and genetic factors. Monitor and adjust dosages based on INR.

Pharmacogenetic associations for which the data indicate a potential impact on safety or response

Drug	Gene	Affected Subgroups+	Description of Gene-Drug Interaction
Allopurinol	HLA-B	*58:01 allele positive	Results in higher adverse reaction risk (severe skin reactions).
Carbamazepine	HLA-A	*31:01 allele positive	Results in higher adverse reaction risk (severe skin reactions). Consider risk and benefit of carbamazepine use in patients positive for HLA-A*31:01. Genotyping is not a substitute for clinical vigilance.
Carvedilol	CYP2D6	poor metabolizers	Results in higher systemic concentrations and higher adverse reaction risk (dizziness).
Cevimeline	CYP2D6	poor metabolizers	May result in higher adverse reaction risk. Use with caution.
Codeine	CYP2D6	poor metabolizers	Results in lower systemic active metabolite concentrations and may result in reduced efficacy.
Efavirenz	CYP2B6	poor metabolizers	Results in higher systemic concentrations and higher adverse reaction risk (QT prolongation).
Isoniazid	Nonspecific (NAT)	poor metabolizers	May result in higher systemic concentrations and adverse reaction risk.
Lapatinib	HLA-DRB1	*07:01 allele positive	Results in higher adverse reaction risk (hepatotoxicity). Monitor liver function tests regardless of genotype.
Lapatinib	HLA-DQA1	*02:01 allele	Results in higher adverse

		positive	reaction risk (hepatotoxicity). Monitor liver function tests regardless of genotype.
Nilotinib	UGT1A1	*28/*28 (poor metabolizers)	Results in higher adverse reaction risk (hyperbilirubinemia).
Oxcarbazepine	HLA-B	*15:02 allele positive	Results in higher adverse reaction risk (severe skin reactions). Patients positive for HLA-B*15:02 may be at increased risk of severe skin reactions with other drugs that are associated with a risk of Stevens Johnson Syndrome/Toxic Epidermal necrolysis (SJS/TEN). Genotyping is not a substitute for clinical vigilance.
Pazopanib	HLA-B	*57:01 allele positive	May result in higher adverse reaction risk (liver enzyme elevations). Monitor liver function tests regardless of genotype.
Pazopanib	UGT1A1	*28/*28 (poor metabolizers)	Results in higher adverse reaction risk (hyperbilirubinemia).
Perphenazine	CYP2D6	poor metabolizers	Results in higher systemic concentrations and higher adverse reaction risk.
Procainamide	Nonspecific (NAT)	poor metabolizers	Alters systemic parent drug and metabolite concentrations. May result in higher adverse reaction risk.
Simvastatin	SLCO1B1	521 TC or 521 CC	Results in higher systemic concentrations

		(intermediate or poor function transporters)	and higher adverse reaction risk (myopathy). The risk of adverse reaction (myopathy) is higher for patients on 80 mg than for those on lower doses.
Sulfamethoxazole and Trimethoprim	Nonspecific (NAT)	poor metabolizers	May result in higher adverse reaction risk.
Sulfasalazine	Nonspecific (NAT)	poor metabolizers	Results in higher systemic metabolite concentrations and higher adverse reaction risk.
Tolterodine	CYP2D6	poor metabolizers	Results in higher systemic concentrations and higher adverse reaction risk (QT prolongation).

Pharmacogenetic associations for which the data demonstrate a potential impact on pharmacokinetic properties only.

The impact of these genetic variants or genetic variant inferred phenotypes on the safety or response of the corresponding drug has not been established.

Drug	Gene	Affected Subgroups+	Description of Gene-Drug Interaction
Amitriptyline	CYP2D6	ultrarapid, intermediate, or poor metabolizers	May alter systemic concentrations.
Amoxapine	CYP2D6	ultrarapid, intermediate, or poor metabolizers	May alter systemic concentrations.
Avatrombopag	CYP2C9	intermediate	Results in higher systemic

		or poor metabolizers	concentrations.
Carisoprodol	CYP2C19	poor metabolizers	Results in higher systemic concentrations. Use with caution.
Clomipramine	CYP2D6	ultrarapid, intermediate, or poor metabolizers	May alter systemic concentrations.
Darifenacin	CYP2D6	poor metabolizers	Results in higher systemic concentrations.
Desipramine	CYP2D6	ultrarapid, intermediate, or poor metabolizers	May alter systemic concentrations.
Dexlansoprazole	CYP2C19	intermediate or poor metabolizers	Results in higher systemic concentrations.
Diazepam	CYP2C19	poor metabolizers	May affect systemic concentrations.
Dolutegravir	UGT1A1	poor metabolizers	Results in higher systemic concentrations.
Donepezil	CYP2D6	ultrarapid or poor metabolizers	Alters systemic concentrations.
Doxepin	CYP2C19	intermediate or poor metabolizers	Results in higher systemic concentrations.
Doxepin	CYP2D6	ultrarapid, intermediate, or poor metabolizers	May alter systemic concentrations.
Elagolix	SLCO1B1	521 CC (poor function transporters)	Results in higher systemic concentrations.
Escitalopram	CYP2C19	poor metabolizers	May result in higher systemic concentrations.

Esomeprazole	CYP2C19	poor metabolizers	Results in higher systemic concentrations.
Fesoterodine	CYP2D6	poor metabolizers	Results in higher systemic active metabolite concentrations.
Fluvoxamine	CYP2D6	poor metabolizers	Results in higher systemic concentrations. Use with caution.
Galantamine	CYP2D6	poor metabolizers	Results in higher systemic concentrations. Titrate dosage based on tolerability.
Hydralazine	Nonspecific (NAT)	poor metabolizers	Results in higher systemic concentrations.
Imipramine	CYP2D6	ultrarapid, intermediate, or poor metabolizers	May alter systemic concentrations.
Metoprolol	CYP2D6	poor metabolizers	Results in higher systemic concentrations.
Mirabegron	CYP2D6	poor metabolizers	Results in higher systemic concentrations.
Nebivolol	CYP2D6	poor metabolizers	May result in higher systemic concentrations.
Nortriptyline	CYP2D6	ultrarapid, intermediate, or poor metabolizers	May alter systemic concentrations.
Omeprazole	CYP2C19	intermediate or poor metabolizers	Results in higher systemic concentrations.
Paroxetine	CYP2D6	ultrarapid, intermediate, or poor metabolizers	May alter systemic concentrations.
Propranolol	CYP2D6	poor metabolizers	May affect systemic concentrations.

Protriptyline	CYP2D6	poor metabolizers	Results in higher systemic concentrations.
Rabeprazole	CYP2C19	poor metabolizers	Results in higher systemic concentrations.
Raltegravir	UGT1A1	*28/*28 (poor metabolizers)	Results in higher systemic concentrations.
Risperidone	CYP2D6	poor metabolizers	Alters systemic parent drug and metabolite concentrations.
Rosuvastatin	SLCO1B1	521 CC (poor function transporters)	Results in higher systemic concentrations.
Tamoxifen	CYP2D6	intermediate or poor metabolizers	Results in lower systemic active metabolite concentrations. The impact of CYP2D6 intermediate or poor metabolism on efficacy is not well established.
Tamsulosin	CYP2D6	poor metabolizers	Results in higher systemic concentrations. Predicted effect based on experience with CYP2D6 inhibitors. Use with caution.
Trimipramine	CYP2D6	ultrarapid, intermediate, or poor metabolizers	May alter systemic concentrations.
Voriconazole	CYP2C19	intermediate or poor metabolizers	Results in higher systemic concentrations.

+ The table describes gene-drug interactions and indicates specific affected subgroup(s) to which the interaction applies. The affected subgroup(s) may be carriers of a specific genetic variant (e.g., HLA-B*15:02), or a genotype-inferred phenotype, ultrarapid, normal, intermediate, or

poor metabolizers/function transporters of a drug metabolizing enzyme/drug transporter. Normal metabolizers or normal transporters do not have genetic variants that are expected to impact metabolism or transport function. In general, ultrarapid metabolizers have two or more copies of a genetic variant that increases metabolic function; intermediate metabolizers or reduced function transporters are individuals who have one or two copies of a genetic variant that reduces the ability to metabolize or transport a drug; and poor metabolizers or poor function transporters are individuals who generally have two copies of a genetic variant that results in little to no ability to metabolize or transport a drug.

When evaluating if a gene-drug association is supported, FDA believes it is important to ensure that there is sufficient scientific evidence to support:

- the relationship between the detected genetic variant and as appropriate, diplotypes, and the affected subgroup, and
- the association between the affected subgroup and the claimed gene-drug interaction.

In some cases, a specific genetic variant may affect the metabolism of different drugs in different ways. In cases where the association is limited to specific genetic variants and does not apply to all individuals with the genotype-inferred phenotype, the specific variants are provided in the table. In cases where individual genetic variants are not listed in the table, FDA believes there is sufficient scientific evidence to generally support the described association for the genotype-inferred phenotype subgroup, provided specific genetic variants are determined to confer the genotype-inferred phenotype based on sufficient scientific evidence.

For example, when considering, as described in the table, that poor and intermediate metabolizers of CYP2C19 have higher systemic active metabolite concentrations, higher adverse reaction risk, and dosage adjustments are recommended when taking clobazam, sufficient scientific evidence supports the following, with respect to the *2 allele:

- The functionality of the *2 variant is known, i.e., the *2 variant results in a loss of CYP2C19 enzyme function, and
- *1/*2 confers an intermediate metabolizer phenotype and *2/*2 confers a poor metabolizer phenotype.

---

[1] This version is an initial table on the corresponding state of the science; FDA will continue to review data and update this resource.

[2]Guidance for Industry and FDA Staff: In Vitro Companion Diagnostic Devices (/regulatory-information/search-fda-guidance-documents/vitro-companion-diagnostic-devices).