# Selected Personalized Medicine Drugs and Relevant Genes

## Adjuvant Therapy

<table>
<thead>
<tr>
<th>Drug name (Brand name)</th>
<th>Biomarker</th>
<th>Indication</th>
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</thead>
<tbody>
<tr>
<td>Cevimeline (Evoxac®)</td>
<td>CYP2D6</td>
<td>Dry mouth: Cevimeline should be used with caution in individuals known or suspected to be deficient in CYP2D6 activity, based on previous experience, as they may be at a higher risk of adverse events.</td>
</tr>
<tr>
<td>Rasburicase (Elitek®)</td>
<td>G6PD</td>
<td>Hyperuricemia: Rasburicase administered to patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency can cause severe hemolysis. Do not administer the drug to patients with G6PD deficiency. Screen patients at higher risk for G6PD deficiency (e.g., patients of African or Mediterranean ancestry) prior to using the drug.</td>
</tr>
<tr>
<td>Sodium phenylacetate &amp; sodium benzoate (Ammonul®)</td>
<td>NAGS; CPS; ASS; OTC; ASL; ARG</td>
<td>Urea cycle disorders: Urea cycle disorders can result from decreased activity of any of the following enzymes: N-acetylglutamate synthetase (NAGS), carbamyl phosphate synthetase (CPS), argininosuccinate synthetase (ASS), ornithine transcarbamylase (OTC), argininosuccinate lyase (ASL), or arginase (ARG). Sodium phenylacetate and sodium benzoate are metabolically active compounds that can serve as alternatives to urea for the excretion of waste nitrogen.</td>
</tr>
<tr>
<td>Sodium phenylbutyrate (Buphenyl®)</td>
<td>CPS; OTC; ASS</td>
<td>Urea cycle disorders: Indicated as adjunctive therapy in the chronic management of patients with urea cycle disorders involving deficiencies of carbamylphosphate synthetase (CPS), ornithine transcarbamylase (OTC), or argininosuccinate synthetase (ASS).</td>
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## Analgesia & Anesthesiology

<table>
<thead>
<tr>
<th>Drug name (Brand name)</th>
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<tbody>
<tr>
<td>Celecoxib (Celebrex®)</td>
<td>CYP2C9</td>
<td>Pain: Patients who are known or suspected to be CYP2C9 poor metabolizers based on a previous history should be administered celecoxib with caution as they may have abnormally high plasma levels due to reduced metabolic clearance.</td>
</tr>
<tr>
<td>Codeine</td>
<td>CYP2D6</td>
<td>Pain: Some individuals may be ultra-rapid metabolizers because of a specific CYP2D6 genotype. These individuals convert codeine into its active metabolite, morphine, more rapidly and completely than other people. This rapid conversion results in higher than expected serum morphine levels. Even at labeled dosage regimens, individuals who are ultra-rapid metabolizers may have life-threatening or fatal respiratory depression or experience signs of overdose (such as extreme sleepiness, confusion, or shallow breathing). Some individuals may be poor metabolizers because of a specific genotype. These individuals do not convert codeine to morphine sufficiently and may have no pain relief.</td>
</tr>
<tr>
<td>Mivacurium (Mivacron®)</td>
<td>Cholinesterase gene</td>
<td>Anesthesia adjunct: Is metabolized by plasma cholinesterase and should be used with great caution, if at all, in patients known to be or suspected of being homozygous for the atypical plasma cholinesterase gene.</td>
</tr>
<tr>
<td>Tramadol (Ultram®)</td>
<td>CYP2D6</td>
<td>Pain: Based on a population pharmacokinetic analysis of Phase 1 studies in healthy subjects, concentrations of tramadol were approximately 20% higher in “poor metabolizers” versus “extensive metabolizers,” while M1 concentrations were 40% lower.</td>
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## Cardiovascular (CV)

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<thead>
<tr>
<th>Drug name (Brand name)</th>
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<tbody>
<tr>
<td>Carvedilol (Coreg®)</td>
<td>CYP2D6</td>
<td>Retrospective analysis of side effects in clinical trials showed that poor CYP2D6 metabolizers had a higher rate of dizziness during up-titration, presumably resulting from vasodilating effects of the higher concentrations of the D-blocking R(+)-enantiomer.</td>
</tr>
<tr>
<td>Drug name (Brand name)</td>
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<tr>
<td>Clopidogrel (Plavix®)</td>
<td>CYP2C19</td>
<td>CYP2C19 poor metabolizer status is associated with diminished antiplatelet response to clopidogrel. Although a higher dose regimen in poor metabolizers increases antiplatelet response, an appropriate dose regimen for this patient population has not been established. Poor metabolizers with acute coronary syndrome or undergoing percutaneous coronary intervention treated with the drug at recommended doses exhibit higher cardiovascular event rates than do patients with normal CYP2C19 function.</td>
</tr>
<tr>
<td>Isosorbide and hydralazine (Bidil®)</td>
<td>NAT1, NAT2</td>
<td>In patients with heart failure, mean absolute bioavailability of a single dose of hydralazine 75mg varies from 10 to 26%, with higher percentages in slow acetylators. About 50% of patients are fast acetylators and have lower exposure.</td>
</tr>
<tr>
<td>Metoprolol (Toprol-XL®)</td>
<td>CYP2D6</td>
<td>Metoprolol is metabolized predominantly by CYP2D6, an enzyme that is absent in about 8% of Caucasians (poor metabolizers) and about 2% of most other populations. CYP2D6 can be inhibited by a number of drugs. Poor metabolizers as well as extensive metabolizers who concomitantly use CYP2D6 inhibiting drugs will have increased (several-fold) metoprolol blood levels, decreasing metoprolol's cardiovselectivity.</td>
</tr>
<tr>
<td>Mipomersen sodium (Kynamro®)</td>
<td>ApoB (Apolipoprotein B)</td>
<td>Indicated as an adjunct to lipid-lowering medications and diet to reduce low density lipoprotein-cholesterol (LDL-C), ApoB, total cholesterol (TC), and non-high density lipoprotein-cholesterol (non HDL-C) in patients with homozygous familial hypercholesterolemia (HoFH).</td>
</tr>
<tr>
<td>Propafenone (Rythmol SR®)</td>
<td>CYP2D6</td>
<td>The combination of CYP3A4 inhibition and either CYP2D6 deficiency or CYP2D6 inhibition with the simultaneous administration of propafenone may significantly increase the concentration of propafenone and thereby increase the risk of pro-arrhythmia and other adverse events.</td>
</tr>
<tr>
<td>Warfarin (Coumadin®)</td>
<td>CYP2C9</td>
<td>Patients with one or more variant CYP2C9 alleles have decreased S-warfarin clearance. The frequencies of these alleles in Caucasians are approximately 11% and 7% for CYP2C9<em>2 and CYP2C9</em>3, respectively.</td>
</tr>
<tr>
<td>Protein C or S deficiencies</td>
<td></td>
<td>Hereditary or acquired deficiencies of protein C or its cofactor, protein S, have been associated with tissue necrosis following warfarin administration.</td>
</tr>
<tr>
<td>Dermatology</td>
<td>DPD</td>
<td><strong>Contraindication:</strong> 5-FU should not be used in patients with dihydro-pyrimidine dehydrogenase (DPD) enzyme deficiency. A large percentage of the drug is catabolized by DPD. DPD enzyme deficiency can result in shunting of 5-FU to the anabolic pathway leading to cytotoxic activity and potential toxicities.</td>
</tr>
<tr>
<td>Gastroenterology</td>
<td>CYP2C19</td>
<td>GERD: Systemic exposure of deslansoprazole is generally higher in intermediate and poor metabolizers.</td>
</tr>
<tr>
<td>Esomeprazole (Nexium®)</td>
<td>CYP2C19</td>
<td>GERD: CYP2C19 isoenzyme exhibits polymorphism in the metabolism of esomeprazole, since some 3% of Caucasians and 15 to 20% of Asians lack CYP2C19 and are termed poor metabolizers. At steady state, the ratio of area under the curve (AUC) in poor metabolizers to AUC in the rest of the population (extensive metabolizers) is approximately 2.</td>
</tr>
<tr>
<td>Rabeprazole (Aciphex®)</td>
<td>CYP2C19</td>
<td>GERD: Gastric acid suppression was higher in poor metabolizers as compared to extensive metabolizers. This could be due to higher rabeprazole plasma levels in poor metabolizers.</td>
</tr>
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<td>Drug name (Brand name)</td>
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<tr>
<td><strong>Orphan disease</strong></td>
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<tr>
<td>Ivacaftor (Kalydeco®)</td>
<td>G551D mutation in the CFTR gene</td>
<td>Cystic Fibrosis: Indicated for the treatment of cystic fibrosis (CF) in patients age 6 years and older who have one of the following mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R. If the patient’s genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of a CFTR mutation followed by verification with bidirectional sequencing when recommended by the mutation test instructions for use.</td>
</tr>
<tr>
<td><strong>Hematology</strong></td>
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<tr>
<td>Eltrombopag (Promacta®)</td>
<td>Factor-V-Leiden ATIII deficiency</td>
<td>Potential for an increased risk of thromboembolism when administering eltrombopag to patients with known risk factors for thromboembolism (e.g. Factor-V-Leiden, ATIII deficiency, antiphospholipid syndrome, chronic liver disease). Follow dose adjustment guidelines to achieve and maintain target platelet counts.</td>
</tr>
<tr>
<td>Lenalidomide (Revlimid®)</td>
<td>5q deletion</td>
<td>Myelodysplastic syndrome: For patients with transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes (MDS) associated with a deletion 5q abnormality with or without additional cytogenetic abnormalities.</td>
</tr>
<tr>
<td><strong>Immunology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indacaterol (Arcapta®)</td>
<td>UGT1A1</td>
<td>COPD: The pharmacokinetics of indacaterol were prospectively investigated in subjects with the UGT1A1 (TA)7/(TA)7 genotype (low UGT1A1 expression; also referred to as *28) and the (TA)6, (TA)6 genotype. Steady-state AUC and Cmax of indacaterol were 1.2-fold higher in the [(TA)7, (TA)7] genotype, suggesting no relevant effect of UGT1A1 genotype on indacaterol exposure.</td>
</tr>
<tr>
<td>Mycophenolic acid (Myfortic®)</td>
<td>HGPRT</td>
<td>Transplantation: Patients with Hereditary Deficiency of Hypoxanthine-Guanine Phosphoribosyl-transferase (HGPRT): May cause exacerbation of disease symptoms; avoid use.</td>
</tr>
<tr>
<td><strong>Infectious disease</strong></td>
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<tr>
<td>Abacavir (Ziagen®)</td>
<td>HLA-B*57:01</td>
<td>HIV: Patients who carry the HLA-B<em>57:01 allele are at high risk for experiencing a hypersensitivity reaction to abacavir. Prior to initiating therapy with abacavir, screening for the HLA-B</em>57:01 allele is recommended.</td>
</tr>
<tr>
<td>Boceprevir (Victrelis®)</td>
<td>IL28B</td>
<td>Hepatitis C: A genetic variant near the gene encoding interferon-lambda-3 (IL28B rs12979860, a C to T change) is a strong predictor of response to PegInterferon alfa-2b/Ribavirin. Among subjects that received at least one dose of placebo or boceprevir, sustained virological response rates tended to be lower in subjects with the C/T and T/T genotypes compared to those with the C/C genotype, particularly among previously untreated subjects receiving 48 weeks of PegInterferon alfa-2b and Ribavirin.</td>
</tr>
<tr>
<td>Chloroquine (Aralen®)</td>
<td>G6PD</td>
<td>Malaria: The drug should be administered with caution to patients having G-6-PD deficiency.</td>
</tr>
<tr>
<td>Isoniazid (Nydrazid®)</td>
<td>NAT</td>
<td>Tuberculosis: Slow acetylation may lead to higher blood levels of the drug, and thus, an increase in toxic reactions.</td>
</tr>
<tr>
<td>Maraviroc (Selzentry®)</td>
<td>CCR5 receptor</td>
<td>HIV: In combination with other antiretroviral agents, it is indicated for treatment experienced adult patients infected with only CCR5-tropic HIV.</td>
</tr>
<tr>
<td>Peginterferon alfa-2b (Pegasys®)</td>
<td>IL28B</td>
<td>Hepatitis C: A single nucleotide polymorphism near the gene encoding interferon-lambda-3 (IL28B) was associated with variable sustained virological response rates.</td>
</tr>
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<tr>
<td>Pyrazinamide (Rifater®)</td>
<td>NAT</td>
<td><strong>Tuberculosis:</strong> Slow acetylation may lead to higher blood levels of the drug, and thus, an increase in toxic reactions.</td>
</tr>
<tr>
<td>Rifampin (Rifadin®)</td>
<td>NAT</td>
<td><strong>Tuberculosis:</strong> Slow acetylation may lead to higher blood levels of the drug, and thus, an increase in toxic reactions.</td>
</tr>
<tr>
<td>Telaprevir (Incivek®)</td>
<td>IL28B</td>
<td><strong>Hepatitis C:</strong> A genetic variant near the gene encoding interferon-lambda-3 (IL28B rs12979860, a C to T change) is a strong predictor of response to peginterferon alfa and ribavirin (PR). SVR rates tended to be lower in subjects with the CT and TT genotypes compared to those with the CC genotype, particularly among treatment-naïve subjects receiving PR48. Among both treatment-naïve and previous treatment failures, subjects of all IL28B genotypes appeared to have higher SVR rates with regimens containing telaprevir.</td>
</tr>
<tr>
<td>Voriconazole (Vfend®)</td>
<td>CYP2C19</td>
<td><strong>Antifungal:</strong> Studies conducted in Caucasian and Japanese healthy subjects have shown that poor metabolizers have, on average, 4-fold higher voriconazole exposure (AUCt) than their homozygous extensive metabolizer counterparts. Subjects who are heterozygous extensive metabolizers have, on average, 2-fold higher voriconazole exposure than their homozygous extensive metabolizer counterparts.</td>
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### Neurology

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<tr>
<th>Drug name (Brand name)</th>
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<tbody>
<tr>
<td>Carbamazepine (Tegretol®)</td>
<td>HLA-B*15:02</td>
<td><strong>Epilepsy and bipolar disorder:</strong> Serious dermatologic reactions are associated with the HLA-B<em>15:02 allele in patients treated with carbamazepine. Patients with ancestry in genetically at-risk populations should be screened for the presence of HLA-B</em>15:02 prior to initiating treatment with Carbamazepine. Patients testing positive for the allele should not be treated with the drug unless the benefit clearly outweighs the risk.</td>
</tr>
<tr>
<td>Carisoprodol (Soma®)</td>
<td>CYP2C19</td>
<td><strong>Musculoskeletal pain:</strong> Patients with reduced CYP2C19 activity have higher exposure to carisoprodol. Caution should be exercised in administration of carisoprodol to these patients as it has been shown that CYP2C19 poor metabolizers have a 4-fold increase in exposure to carisoprodol compared to normal CYP2C19 metabolizers.</td>
</tr>
<tr>
<td>Clobazam (Onfi®)</td>
<td>CYP2C19</td>
<td><strong>Lennox-Gastaut syndrome:</strong> Concentrations of clobazam’s active metabolite, N-desmethylclobazam, are higher in CYP2C19 poor metabolizers than in extensive metabolizers. For this reason, dosage modification is recommended.</td>
</tr>
<tr>
<td>Dextrometorphan &amp; Quinidine (Nuedexta®)</td>
<td>CYP2D6</td>
<td><strong>Neurological disorders:</strong> Approximately 7-10% of Caucasians and 3-8% of African Americans lack the capacity to metabolize CYP2D6 substrates and are classified as poor metabolizers. The quinidine component is not expected to contribute to the effectiveness in poor metabolizers, but adverse events of the quinidine are still possible. In those patients who may be at risk of significant toxicity due to quinidine, genotyping to determine if they are poor metabolizers should be considered prior to making the decision to treat with dextromethorphan and quinidine.</td>
</tr>
<tr>
<td>Divalproex (Depakote®)</td>
<td>UCD (NAGS; CPS; ASS; OTC; ASL; ARG)</td>
<td><strong>Bipolar disorder (antiepileptic drug):</strong> Hyper-ammonemic encephalopathy, sometimes fatal, has been reported following initiation of valproate therapy in patients with urea cycle disorders, particularly ornithine transcarbamylase deficiency.</td>
</tr>
<tr>
<td>Phenytoin (Dilantin®)</td>
<td>HLA-B*15:02</td>
<td>Studies have found an association between the risk of developing Stevens Johnson Syndrome/Toxic Epidermal Necrolysis and the presence of the HLA-B<em>15:02 variant in patients using another anticonvulsive drug. Consideration should be given to avoid use of drugs associated with SJS/TEN, including phenytoin, in HLA-B</em>15:02 positive patients when alternative therapies are otherwise equally available.</td>
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<tr>
<td><strong>Tetrabenazine</strong> (Xenazine®)</td>
<td>CYP2D6</td>
<td><strong>Huntington's disease</strong>: Patients who require doses of tetrabenazine greater than 50 mg per day, should be first tested and genotyped to determine if they are poor or extensive metabolizers by their ability to express the drug metabolizing enzyme, CYP2D6. The dose of tetrabenazine should then be individualized accordingly to their status as either poor or extensive metabolizers.</td>
</tr>
<tr>
<td><strong>Valproic acid</strong> (Depakene®)</td>
<td>UCD; especially OTC</td>
<td><strong>Epilepsy</strong>: Hyper-ammonemic encephalopathy, sometimes fatal, has been reported following initiation of valproate therapy in patients with urea cycle disorders, a group of uncommon genetic abnormalities, particularly ornithine transcarbamylase deficiency.</td>
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<tr>
<td><strong>Oncology</strong></td>
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<tr>
<td>ado-trastuzumab emtansine (Kadcyla®)</td>
<td>ERBB2 (HER2)</td>
<td><strong>Breast cancer</strong>: Indicated, as a single agent, for the treatment of patients with HER2-positive metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination.</td>
</tr>
<tr>
<td>Afatinib (Gilotrif®)</td>
<td>EGFR</td>
<td><strong>NSCLC</strong>: Indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test.</td>
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<tr>
<td>cf. Table 2</td>
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<tr>
<td>Anastrozole (Arimidex®)</td>
<td>HR</td>
<td><strong>Breast cancer</strong>: Indicated for i) adjuvant treatment of postmenopausal women with Hormone receptor (HR)-positive early breast cancer; ii) first-line treatment of postmenopausal women with HR-positive or HR unknown locally advanced or metastatic breast cancer.</td>
</tr>
<tr>
<td>Arsenic trioxide (Trisenox®)</td>
<td>PML / RARα</td>
<td><strong>Leukemia</strong>: For induction of remission and consolidation in patients with acute promyelocytic leukemia (APL) whose APL is characterized by the presence of the t (15;17) translocation or PML / RAR-alpha gene expression.</td>
</tr>
<tr>
<td>Azathioprine (Imuran®)</td>
<td>TPMT</td>
<td><strong>Leukemia</strong>: Guides adjustment of dose in treatment of acute lymphoblastic leukemia: Patients with inherited little or no thiopurine S-methyl-transferase (TPMT) activity are at increased risk for severe drug toxicity from conventional doses. It is recommended that consideration be given to either genotype or phenotype patients for TPMT.</td>
</tr>
<tr>
<td>Busulfan (Busulfex® &amp; Myleran®)</td>
<td>Philadelphia Chromosome/ BCR-ABL</td>
<td><strong>Leukemia</strong>: Busulfan is clearly less effective in patients with chronic myelogenous leukemia who lack the Philadelphia (Phi) chromosome.</td>
</tr>
<tr>
<td><strong>Bosutinib</strong> (Bosulif®)</td>
<td>BCR-ABL1</td>
<td><strong>Leukemia</strong>: The molecular response measured by BCR-ABL1 RT-qPCR assists in identifying suboptimal responses and can help inform the decision to switch to alternative therapies that may be more efficacious (or to pursue more stringent monitoring). Furthermore, the tyrosine kinase inhibitor-mediated molecular response provides valuable risk stratification and prognostic information on long-term outcomes.</td>
</tr>
<tr>
<td>Brentuximab Vedotin (AdcetrisTM)</td>
<td>CD30</td>
<td><strong>Lymphoma</strong>: Targets CD30 protein present on the surface of certain cells for the treatment of Hodgkins lymphoma and systemic anaplastic large cell lymphoma.</td>
</tr>
<tr>
<td>Capecitabine (Xeloda®)</td>
<td>DPD</td>
<td><strong>Multiple cancers</strong>: Contraindicated in patients with known DPD deficiency.</td>
</tr>
<tr>
<td>Carboplatin (Daraplatin®)</td>
<td>RRMI</td>
<td><strong>Lung cancer</strong>: Low levels of RRMI gene expression are associated with improved response to platin therapy.</td>
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</tr>
<tr>
<td>Cetuximab (Erbitux®)</td>
<td>EGFR, KRAS</td>
<td>Colon cancer: treatment of K-Ras mutation-negative (wild-type), EGFR-expressing, metastatic colorectal cancer as determined by FDA-approved tests.</td>
</tr>
<tr>
<td>Crizotinib (Xalkori®)</td>
<td>ALK</td>
<td>Lung cancer: Indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test. The ALK abnormality occurs in 1-7% of NSCLC patients.</td>
</tr>
<tr>
<td>Dabrafenib (Tafinlar®)</td>
<td>BRAF</td>
<td>Melanoma: Indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test.</td>
</tr>
<tr>
<td>Dasatinib (Sprycel®)</td>
<td>Philadelphia Chromosome/ BCR-ABL</td>
<td>Leukemia: Indicated for the treatment of adults with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) with resistance or intolerance to prior therapy.</td>
</tr>
<tr>
<td>Denileukin diftitox (Ontak®)</td>
<td>CD25</td>
<td>Lymphoma: Indicated for the treatment of patients with persistent or recurrent cutaneous T-cell lymphoma whose malignant cells express the CD25 component of the IL-2 receptor.</td>
</tr>
<tr>
<td>Erlotinib (Tarceva®)</td>
<td>KRAS</td>
<td>Lung cancer: EGFR activating mutations occur in approximately 10% of Caucasian patients with NSCLC and up to 50% of Asian patients. Data from multiple studies indicate a predictive role for EGFR activating mutations with respect to response rate and progression-free survival with tyrosin kinase inhibitor therapy, particularly in the first-line setting.</td>
</tr>
<tr>
<td>Everolimus (Afinitor®)</td>
<td>HR</td>
<td>Breast cancer: Indicated for the treatment of postmenopausal women with advanced HR positive, HER2-negative breast cancer (advanced HR+ breast cancer) in combination with exemestane after failure of treatment with letrozole or anastrozole.</td>
</tr>
<tr>
<td>Exemestane (Aromasin®)</td>
<td>ER</td>
<td>Breast cancer: Indicated for adjuvant treatment of postmenopausal women with Estrogen Receptor (ER)-positive early breast cancer who have received two to three years of tamoxifen and are switched to the drug for completion of a total of five consecutive years of adjuvant hormonal therapy.</td>
</tr>
<tr>
<td>5-Fluorouracil (5-FU) (Efudex®)</td>
<td>DPD</td>
<td>Warnings: Rarely, unexpected, severe toxicity (e.g. stomatitis, diarrhea, neutropenia and neurotoxicity) associated with 5-FU has been attributed to deficiency of DPD activity.</td>
</tr>
</tbody>
</table>
|                       | TS        | Multiple cancers:  
Gastrointestinal cancers: High levels thymidylate synthetase (TS) gene expression correlate with tumor resistance (low response) to 5-FU in gastric and colon cancers.  
Lung cancer: Patients with high levels of TS in their tumors tend to respond less favorably to TS inhibitors such as 5-FU and pemetrexed.  
Pancreatic cancer: High TS expression also correlates with gemcitabine and 5-FU resistance in pancreatic cancers. |
<p>| Fulvestrant (Faslodex®)| ER        | Breast cancer: Indicated for the treatment of HR-positive metastatic breast cancer in postmenopausal women with disease progression following anti-estrogen therapy. |</p>
<table>
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<tr>
<th>Drug name (Brand name)</th>
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<tbody>
<tr>
<td>Gefitinib (Iressa®)</td>
<td>KRAS</td>
<td>Colon cancer: Retrospective analyses of metastatic colorectal cancer trials have not shown a treatment benefit for the EGFR inhibitors in patients whose tumors had KRAS mutations in codon 12 or 13.</td>
</tr>
<tr>
<td>Gemcitabine (Gemzar®)</td>
<td>TS</td>
<td>Pancreatic cancer: High TS expression correlates with gemcitabine and 5-FU resistance in pancreatic cancers.</td>
</tr>
<tr>
<td></td>
<td>RRMI</td>
<td>Lung cancer: Gemcitabine interferes with the DNA synthesis function of ribonucleotide reductase through its active subunit (RRMI). Low levels of RRMI gene expression are associated with improved response to gemcitabine therapy.</td>
</tr>
<tr>
<td></td>
<td>PDGFR (platelet-derived growth factor receptor)</td>
<td>Myelodysplastic syndrome: Indicated for adult patients with myelodysplastic / myeloproliferative diseases (MDS/MPD) associated with platelet-derived growth factor receptor (PDGFR) gene re-arrangements.</td>
</tr>
<tr>
<td></td>
<td>c-KIT</td>
<td>Stomach cancer: Indicated for the treatment of patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST).</td>
</tr>
<tr>
<td>Irinotecan (Camptosar®)</td>
<td>UGT1A1</td>
<td>Colon cancer: Individuals who are homozygous for the UGT1A1<em>28 allele are at increased risk for neutropenia following initiation of irinotecan treatment. A reduction in the starting dose by at least one level of the drug should be considered for patients known to be homozygous for the UGT1A1</em>28 allele.</td>
</tr>
<tr>
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<td>ERCC1</td>
<td>Colon cancer: High expression of ERCC1 is associated with response to irinotecan therapy.</td>
</tr>
<tr>
<td>Lapatinib (Tykerb®)</td>
<td>HER2/neu receptor</td>
<td>Breast cancer: For the treatment of patients with metastatic breast cancer whose tumors overexpress the Human Epidermal growth factor Receptor 2 (HER2) protein and who have received one or more chemotherapy regimens for their metastatic disease.</td>
</tr>
<tr>
<td>Letrozole (Femara®)</td>
<td>HR</td>
<td>Breast cancer: Indicated for i) adjuvant treatment of postmenopausal women with HR-positive early breast cancer; ii) first and second-line treatment of postmenopausal women with HR-positive or unknown advanced breast cancer.</td>
</tr>
<tr>
<td>Mercaptopurine (Purinethol®)</td>
<td>TPMT</td>
<td>Leukemia: Guidance for dose adjustment during treatment of acute lymphoblastic leukemia: Patients with inherited little or no TPMT activity are at increased risk for severe drug toxicity from conventional doses. It is recommended that consideration be given to either genotype or phenotype patients for TPMT.</td>
</tr>
<tr>
<td>Nilotinib (Tasigna®)</td>
<td>UGT1A1, Ph+</td>
<td>Leukemia: Indicated for the treatment of chronic phase and accelerated phase Philadelphia chromosome positive chronic myelogenous leukemia (CML) in adults resistant to imitinab. UGT1A1*28 patients have a high risk of hyperbilirubinemia.</td>
</tr>
<tr>
<td>Omacetaxine meper-succinate (Synribo®)</td>
<td>BCR-ABL &amp; B-ALL</td>
<td>Leukemia: Treatment with omacetaxine decreased the number of leukemia stem cells and prolonged the survival of mice with BCR-ABL-induced CML or B-ALL.</td>
</tr>
<tr>
<td>Drug name (Brand name)</td>
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<tr>
<td>Panitumumab (Vectibix®)</td>
<td>EGFR</td>
<td>Colon cancer: Indicated as a single agent for the treatment of metastatic colorectal carcinoma (mCRC) with disease progression on or following fluoropyrimidine, oxaliplatin, and irinotecan chemotherapy regimens.</td>
</tr>
<tr>
<td></td>
<td>KRAS</td>
<td>Colon cancer: Is NOT indicated for the treatment of patients with KRAS mutation-positive mCRC or for whom KRAS mCRC status is unknown. Retrospective subset analyses of metastatic colorectal cancer trials have not shown a treatment benefit for the drug in patients whose tumors had KRAS mutations in codon 12 or 13.</td>
</tr>
<tr>
<td></td>
<td>BRAF</td>
<td>Colon cancer: A mutation in BRAF identifies 12-15% of metastatic colorectal cancer patients who fail to respond to TKI's. Non-mutated forms of BRAF and KRAS genes are required for response.</td>
</tr>
<tr>
<td>Pemetrexed (Alimta®)</td>
<td>TS</td>
<td>Lung cancer: Patients with high levels of TS in their tumors tend to respond less favorably to TS inhibitors such as 5-FU and pemetrexed.</td>
</tr>
<tr>
<td>Pertuzumab (Perjeta®)</td>
<td>HER2/neu receptor</td>
<td>Breast cancer: Indicated in combination with trastuzumab and docetaxel for the treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.</td>
</tr>
<tr>
<td>Platinum therapies</td>
<td>ERCC1</td>
<td>Multiple cancers: Bladder cancer: Low ERCC1 expression is associated with greater survival in bladder cancer patients treated with platinum-based therapies. Colon cancer: In a study of advanced colorectal cancer treated with 5-fluorouracil/oxaliplatin, low ERCC1 expression is associated with longer survival. High expression of ERCC1 is associated with response to irinotecan therapy. Gastric cancer: Patients treated with (5-fluorouracil/leucovorin/oxaliplatin) regimen or first-line cisplatin-based regimens respond significantly better if they show lower levels of ERCC1 expression. Lung cancer: Enzyme excision repair complementing factor 1 (ERCC1) helps repair DNA damage caused by platinum-based therapy. Low ERCC1 is a favorable indicator for response to platinum therapy.</td>
</tr>
<tr>
<td>Ponatinib (Iclusig®)</td>
<td>BCR-ABL1</td>
<td>Leukemia: The molecular response measured by BCR-ABL1 RT-qPCR assists in identifying suboptimal responses and can help inform the decision to switch to alternative therapies that may be more efficacious (or to pursue more stringent monitoring). Ponatinib is a kinase inhibitor, which inhibits the in vitro tyrosine kinase activity of ABL and T315I mutant ABL.</td>
</tr>
<tr>
<td>Tamoxifen (Nolvadex®)</td>
<td>ER</td>
<td>Breast cancer: Available evidence indicates that patients whose tumors are ER positive are more likely to benefit from tamoxifen therapy.</td>
</tr>
<tr>
<td>Thioguanine (Tabloid®)</td>
<td>TPMT</td>
<td>Leukemia: Guidance for dose adjustment during treatment of acute lymphoblastic leukemia: Patients with inherited little or no TPMT activity are at increased risk for severe drug toxicity from conventional doses. It is recommended that consideration be given to either genotype or phenotype patients for TPMT.</td>
</tr>
<tr>
<td>Tositumomab (Bexxar®)</td>
<td>CD20</td>
<td>Lymphoma: Is indicated for the treatment of patients with CD20 antigen expressing non-Hodgkin’s lymphoma.</td>
</tr>
<tr>
<td>Trametinib (Mekinist®)</td>
<td>BRAF</td>
<td>Melanoma: Indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test.</td>
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<td>Drug name (Brand name)</td>
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<tr>
<td><strong>Trastuzumab (Herceptin®)</strong>&lt;br&gt;cf. Table 2</td>
<td>HER2 / neu receptor</td>
<td><strong>Breast cancer:</strong> Indicated for i) the treatment of HER2 overexpressing breast cancer; ii) the treatment of HER2 overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma.</td>
</tr>
<tr>
<td><strong>Tretinoin (Vesanoid®)</strong></td>
<td>PML / RARα</td>
<td><strong>Leukemia:</strong> For induction of remission and consolidation in patients with acute promyelocytic leukemia (APL) whose APL is characterized by the presence of the t (15;17) translocation or PML/RAR-alpha gene expression.</td>
</tr>
<tr>
<td><strong>Vemurafenib (Zelboraf®)</strong>&lt;br&gt;cf. Table 2</td>
<td>BRAF V600E</td>
<td><strong>Melanoma:</strong> Indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test. The BRAF V600E mutation is found in about half of melanoma patients.</td>
</tr>
</tbody>
</table>

**Psychiatry**

<table>
<thead>
<tr>
<th>Drug name (Brand name)</th>
<th>Biomarker</th>
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<tbody>
<tr>
<td><strong>Aripiprazole (Abilify®)</strong></td>
<td>CYP2D6</td>
<td><strong>Psychotic disorders:</strong> Poor Metabolizers have approximately 80% increase in aripiprazole exposure and approximately 30% decrease in exposure to the active metabolite compared to extensive metabolizers, resulting in approximately 60% higher exposure to the total active moieties from a given dose of aripiprazole compared to extensive metabolizers. Poor metabolizers have higher exposure to aripiprazole compared to extensive metabolizers; hence, poor metabolizers should have their initial dose reduced by one-half. Laboratory tests are available to identify CYP2D6 poor metabolizers.</td>
</tr>
<tr>
<td><strong>Amitriptyline (Elavil®)</strong></td>
<td>CYP2D6</td>
<td><strong>Depression:</strong> Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by CYP2D6, the increase in plasma concentration may be small or quite large (8-fold increase in plasma AUC of the TCA).</td>
</tr>
<tr>
<td><strong>Atomoxetine (Strattera®)</strong></td>
<td>CYP2D6</td>
<td><strong>ADHD:</strong> Atomoxetine is metabolized primarily through the CYP2D6 enzymatic pathway. People with reduced activity in this pathway (poor metabolizers) have higher plasma concentrations of atomoxetine compared to people with normal activity (extensive metabolizers). For poor metabolizers, AUC of atomoxetine is approximately 10-fold andCss max is about 5-fold greater than in extensive metabolizers. Dose adjustment may be necessary.</td>
</tr>
<tr>
<td><strong>Citalopram (Celexa®)</strong></td>
<td>CYP2C19</td>
<td><strong>Depression:</strong> In CYP2C19 poor metabolizers, citalopram steady state Cmax and AUC was increased by 68% and 107%, respectively. 20 mg/day is the maximum recommended dose in CYP2C19 poor metabolizers due to the risk of QT prolongation.</td>
</tr>
<tr>
<td><strong>Clomipramine (Anafranil®)</strong></td>
<td>CYP2D6</td>
<td><strong>Depression:</strong> Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by CYP2D6, the increase in plasma concentration may be small or quite large (8-fold increase in plasma AUC of the TCA).</td>
</tr>
<tr>
<td><strong>Clozapine (Clozaril®)</strong></td>
<td>CYP2D6</td>
<td><strong>Psychotic disorders:</strong> Dose reduction may be necessary in patients who are CYP2D6 poor metabolizers. Clozapine concentrations may be increased in these patients, because clozapine is almost completely metabolized and then excreted.</td>
</tr>
<tr>
<td><strong>Desipramine (Norpramin®)</strong></td>
<td>CYP2D6</td>
<td><strong>Depression:</strong> Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by CYP2D6, the increase in plasma concentration may be small or quite large (8-fold increase in plasma AUC of the TCA).</td>
</tr>
<tr>
<td><strong>Doxepin (Silenor®)</strong></td>
<td>CYP2D6</td>
<td><strong>Insomnia:</strong> Poor metabolizers of CYP2C19 and CYP2D6 may have higher doxepin plasma levels than normal subjects.</td>
</tr>
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<tr>
<td><strong>Fluvoxamine (Luvox CR®)</strong></td>
<td>CYP2D6</td>
<td><strong>Obsessive compulsive disorders</strong>: Caution is indicated in patients known to have reduced levels of cytochrome P450 2D6 activity and those receiving concomitant drugs known to inhibit this cytochrome P450 isoenzyme.</td>
</tr>
<tr>
<td><strong>Iloperidone (Fanapt®)</strong></td>
<td>CYP2D6</td>
<td><strong>Psychotic disorders</strong>: Iloperidone dose should be reduced by one-half for poor metabolizers of CYP2D6.</td>
</tr>
<tr>
<td><strong>Imipramine (Tofranil-PM®)</strong></td>
<td>CYP2D6</td>
<td>Depression: Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by CYP2D6, the increase in plasma concentration may be small or quite large (8-fold increase in plasma AUC of the TCA).</td>
</tr>
<tr>
<td><strong>Nortriptyline (Pamelor®)</strong></td>
<td>CYP2D6</td>
<td>Depression: Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by CYP2D6, the increase in plasma concentration may be small or quite large (8-fold increase in plasma AUC of the TCA).</td>
</tr>
<tr>
<td><strong>Perphenazine (Trilafon®)</strong></td>
<td>CYP2D6</td>
<td><strong>Psychotic disorders</strong>: CYP2D6 poor metabolizers will metabolize perphenazine more slowly and will experience higher concentrations compared with normal or “extensive” metabolizers.</td>
</tr>
<tr>
<td><strong>Pimozide (Orap®)</strong></td>
<td>CYP2D6</td>
<td><strong>Tourette's Syndrome</strong>: Individuals with genetic variations resulting in poor CYP2D6 metabolism (approximately 5 to 10% of the population) exhibit higher pimozide concentrations than extensive CYP2D6 metabolizers. Alternative dosing strategies are recommended in patients who are genetically poor CYP2D6 metabolizers.</td>
</tr>
<tr>
<td><strong>Protriptyline (Vivactil®)</strong></td>
<td>CYP2D6</td>
<td>Depression: Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by CYP2D6, the increase in plasma concentration may be small or quite large (8-fold increase in plasma AUC of the TCA).</td>
</tr>
<tr>
<td><strong>Thioridazine (Mellaril®)</strong></td>
<td>CYP2D6</td>
<td><strong>Psychotic disorders</strong>: Reduced CYP2D6 isozyme activity, drugs which inhibit this isozyme, and certain other drugs appear to appreciably inhibit the metabolism of thioridazine. The resulting elevated levels of thioridazine would be expected to augment the prolongation of the QTc interval associated with thioridazine and may increase the risk of serious, potentially fatal, cardiac arrhythmias, such as Torsades de pointes type arrhythmias.</td>
</tr>
<tr>
<td><strong>Trimipramine (Surmontil®)</strong></td>
<td>CYP2D6</td>
<td>Depression: Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by CYP2D6, the increase in plasma concentration may be small or quite large (8-fold increase in plasma AUC of the TCA).</td>
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<tr>
<td><strong>Rheumatology</strong></td>
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<tr>
<td><strong>Flurbiprofen (Ansaid®)</strong></td>
<td>CYP2C9</td>
<td><strong>Arthritis</strong>: Patients who are known or suspected to be CYP2C9 poor metabolizers based on previous history/experience with other CYP2C9 substrates (such as warfarin and phenytoin) should be administered flurbiprofen with caution as they may have abnormally high plasma levels due to reduced metabolic clearance.</td>
</tr>
<tr>
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<tr>
<td>Urology</td>
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<tr>
<td>Tolterodine (Detrol®)</td>
<td>CYP2D6</td>
<td><strong>Overactive bladder:</strong> A subset (about 7%) of the population is devoid of CYP2D6, the enzyme responsible for the formation of the 5-hydroxymethyl metabolite of tolterodine. The identified pathway of metabolism for these individuals (“poor metabolizers”) is dealkylation via CYP3A4 to N-dealkylated tolterodine. The remainder of the population is referred to as “extensive metabolizers.” Pharmacokinetic studies revealed that tolterodine is metabolized at a slower rate in poor metabolizers than in extensive metabolizers; this results in significantly higher serum concentrations of tolterodine and in negligible concentrations of the 5-hydroxymethyl metabolite.</td>
</tr>
</tbody>
</table>