Cigna Medical Coverage Policy

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Subject **Pharmacogenetic Testing**

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Coverage Policy

Please refer to the applicable benefit plan document to determine benefit availability and the terms, conditions and limitations of coverage. Under some benefit plans, coverage for genetic screening and/or testing may be excluded or restricted.

Gene biomarkers or gene mutation-specific coverage criteria for pharmacogenetic testing may be described in one of the Related Coverage Policies listed. If a separate Coverage Policy does not otherwise outline coverage criteria for the specific pharmacogenetic testing, the following coverage criteria apply.

Covered

Cigna covers pharmacogenetic testing (e. g., genotyping, mutation analysis) as medically necessary when EITHER of the following criteria is met (this list may not be all inclusive):

- All of the following:

    ➢ The individual is a candidate for a targeted drug therapy associated with a specific gene
      biomarker or gene mutation.

- The results of the pharmacogenetic test will directly impact clinical decision-making AND clinical outcome for the individual.
- The testing method is considered to be scientifically valid to identify the specific gene biomarker or gene mutation.
- The testing method has been scientifically proven to show a relationship between a specific gene biomarker or gene mutation and a specific therapeutic drug target.

- Identification of the gene biomarker is noted to be clinically necessary prior to initiating therapy with the drug target as noted in the section heading "Indications and Usage" of the U.S. Food and Drug Administration (FDA)-approved prescribing label.

Cigna covers pharmacogenetic testing (e.g., genotyping, mutation analysis) for the BCR-ABL T315-I mutation in an individual with chronic myelogenous leukemia (CML) or Philadelphia chromosome positive (Ph$^+$) acute lymphoblastic leukemia (ALL) as medically necessary for the detection of resistance to imatinib mesylate (Gleevec®), dasatinib (Sprycel®) or nilotinib (Tasigna®) for ANY of the following indications:

- inadequate initial response to tyrosine kinase inhibitor therapy (i.e., failure to achieve complete hematological response at 3 months, minimal cytogenetic response at 6 months or major cytogenetic response at 12 months)
- loss of response to tyrosine kinase inhibitor therapy (i.e., hematologic relapse, cytogenetic relapse, loss of major molecular response [MMR])
- progression to accelerated or blast phase CML while on tyrosine kinase inhibitor therapy

Not Covered

Cigna does not cover pharmacogenetic testing (e.g., genotyping, mutation analysis) to detect response to targeted drug therapy for EITHER of the following because it is experimental, investigational or unproven (this list may not be all inclusive):

- ANY of the following genes or gene mutations for the specific indications as listed:

  - BCR-ABL mutation other than T315-I for imatinib [Gleevec®], dasatinib [Sprycel®], or nilotinib [Tasigna®] resistance or inhibition in an individual with chronic myelogenous leukemia (CML) or acute lymphocytic or lymphoblastic leukemia (ALL)
  - DPYD gene, for treatment with 5-fluorouracil/5-FU or capecitabine
  - CYP2D6 gene mutations for ALL of the following:
    - tamoxifen [Nolvadex®] resistance or inhibition in an individual with breast cancer
    - antidepressants, including selective serotonin reuptake inhibitors (SSRI) for the treatment of depression
    - anti-psychotics for the treatment of schizophrenia
    - opioid analgesics (e.g., codeine, morphine sulfate, oxycodone hydrochloride)

- ANY of the following genes or gene mutations, for ANY indication, including but not limited to the following:

  - CYP2C19 gene for ANY of the following drug targets:
    - clopidogrel (Plavix®) resistance or inhibition
    - proton pump inhibitors
    - antidepressants
    - barbiturates
    - mephenytoin
  - UGT1A1 or UGT1A1 gene for treatment with irinotecan (Camptosar®)
  - CYP2C9 and VKORC1 genes for warfarin metabolism
  - CYP3A4 and CYP3A5 genes, including common variants *2, *3, *4, *5, *6

Cigna does not cover genotyping for thiopurine methyltransferase (TPMT) deficiency for the management of inflammatory bowel disease (IBD) because it is considered experimental, investigational or unproven.

Cigna does not cover drug metabolizing enzyme genotyping systems (e.g., AmpliChip™ Cytochrome P450 (CYP450) Genotyping Test; Invader® UGT1A1 Molecular Assay) because such systems are considered experimental, investigational or unproven.

Cigna does not cover ANY of the following pharmacogenetic testing panels for any indication because they are experimental, investigational or unproven:

- SureGene Test for Antipsychotic and Antidepressant Response (STA^{2}R)
- Genecept™ Assay
- GeneSight® Analgesic
- GeneSight® Psychotropic
- GeneSight® ADHD

Cigna does not cover pharmacogenetic screening in the general population because such testing is considered not medically necessary.

General Background

Pharmacogenetics encompasses variation in genes encoding drug transporters, drug-metabolizing enzymes and drug targets, as well as specific genes related to the action of drugs. A slight variation in deoxyribonucleic acid (DNA), called a single nucleotide polymorphism (SNP), can result in a subtle change in a protein which translates into major differences in how the protein functions.

The study of variations in DNA sequence as related to drug response is referred to as pharmacogenetic testing (Federal Drug Administration [FDA], 2008). A pharmacogenetic test is a type of genetic test meant to guide treatment strategies, patient evaluations and decisions based on their ability to predict response to treatment in particular clinical contexts (Agency for Healthcare Research and Quality [AHRQ], 2010). When applied in a clinical setting, the information from these tests could potentially identify individual variability in drug response, including both effectiveness and toxicity.

Although genetics has an impact on drug-metabolizing genes related to inter-individual differences in drug response, it is only one of the many variables affecting these genes. Other factors include the characteristics of the condition for which the drug is prescribed, co-administration of other drugs, and non-genetic factors, including the individual's diet, weight, and smoking habits. Identification of gene variations may be clinically useful in a small number of drugs; however, it may be insufficient in others to explain complex differences in metabolism, efficacy, and toxicity. The presence of polymorphisms alone may be a poor predictor of genotype because of variability (Canadian Agency for Drugs and Technology in Health [CADTH], 2006).

Criteria for Developing Pharmacogenetic Tests: To definitively show that pharmacogenetic testing has value in clinical practice, it is not enough to demonstrate that drug response varies by genotype. There must be an alternative treatment strategy, and proof that testing for the genotype and subsequently tailoring the treatment strategy based on genetic information are more clinically effective or cost effective (or both) than merely treating everyone in the usual manner (Arnett, 2007). Use of the test to identify gene variants and affected populations must be more efficient than current practice in preventing serious adverse effects. After taking into account known non-genetic factors that cause variation in response, the remaining variability in patient response can often be managed by changing drugs or dosage. Adverse effects of available drugs are generally preventable with appropriate monitoring, or can be reversed by withdrawal of the drug (BlueCross BlueShield Association [BCBSA] Technology Evaluation Center [TEC], 2007).

A particular variant is not always phenotype specific in that it may have a different impact depending on the drug in question (National Academy of Clinical Biochemistry [NACB], 2010). Racial and ethnic differences in the frequency and nature of genetic variants also must be recognized in attempting to translate outcomes from one population to another. Pharmacogenomic relations must be validated for each therapeutic indication in different

racial and ethnic groups, as well as in different treatment and disease contexts (Kager, 2008). Pharmacogenetic testing is not currently recommended for general population screening (National Academy for Clinical Biochemistry [NACB], 2010).

According to the Secretary's Advisory Committee on Genetic Testing ([SACGT], 1999-2000), the clinical use of a genetic test should be based on analytical (i.e., analytical sensitivity and specificity), and clinical validity (i.e., clinical sensitivity and specificity), and both positive and negative predictive value. Before a genetic test can be generally accepted in clinical practice, data must be collected to demonstrate the benefits and risks from both positive and negative results (i.e., the test must have clinical utility). Clinical utility refers to the usefulness of the test and the value of the information to the person being tested (SACGT, 1999-2000). Clinical utility determines whether the use of genetic testing to change management decisions improves patient outcomes. Best evidence is prospective from randomized clinical trials of standard management procedures versus genetic test-directed management. Evidence may also be derived using banked samples from already-completed clinical trials; or by constructing an indirect chain of evidence linking test results to clinical outcome (Blue Cross and Blue Shield Association [BCBSA] Technology Evaluation Center [TEC], 2007).

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratories offering such tests as a clinical service must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA) and must be licensed by CLIA for high-complexity testing. Additionally, laboratories in the U.S. should follow the College of American Pathology Guidelines (BCBS TEC, 2010; NACB, 2010). Techniques include immunohistochemistry (IHC), fluorescent in situ hybridization (FISH), polymerase chain reaction (PCR) and microarray assays. According to the FDA, diagnostic tests that assay the presence of a particular pattern (e.g., single nucleotide polymorphism [SNP] set, haplotype pattern) should ideally be validated in a prospective clinical trial (2007).

The U.S. Food and Drug Administration (FDA) considers the use of genomic information in drug labels either to require a genetic test for prescribing a drug, to recommend the use of a genetic test prior to drug therapy, or simply to provide information about the current knowledge of genomics that is relevant to drug therapy without the requirement or recommendation of a specific action (NACB, 2010). Much of the existing research in the area of pharmacogenetic testing has been limited by study design, including uncontrolled and poorly defined case and control groups, presence of confounding variables, and the use of retrospective and non-blinded study protocols.

Gene Biomarkers: For some therapeutic target drugs, identification of the associated gene biomarker is clinically necessary prior to initiation of therapy, as noted in the Indications and Usage section of the FDA-approved prescribing label. These include, but are not limited to the following (FDA, 2012):

Gene Biomarker	Drug Target
ALK[+]	Crizotimib (Xalkori®)
BRAF[V600E]	Vemurafenib (Zelboraf®)
CD20	Tositumomab and Iodine I 131 (Bexxar®)
CTFR (G551D)	Ivacaftor (Kalydeco™)
UCD (NAGS, CPS, ASS, OTC, ASL, ARG)	Sodium phenylbutyrate (Buphenyl®)
ER	Fulvestrant (Faslodex®)
EGFR (i.e., K-RAS mutation-negative [wild-type], EGFR-expressing, metastatic colorectal cancer)	Cetuximab (Erbitux®)
EGFR	Afatinib Dimaleate (Gilotrif)
Genotype I chronic hepatitis C	Teleprevir (Incivek®)
HER2/neu	Lapatinib (Tykerb®), Trastuzumab (Herceptin®),
K-RAS	Cetuximab (Erbitux®), Panitumumab (Vectibix®)
T(15;17) translocation, PML/RAR-alpha gene expression	Arsenic trioxide (Trisenox®)

UCD (NAGS, CPS, ASS, OTC, ASL, ARG)	Sodium phenylbutyrate (Buphenyl®)

In addition, a number of specific gene biomarkers and associated drug targets have been identified and are addressed in related Coverage Policies (please see related Coverage Policy section). These include, but are not limited to the following:

Gene Biomarker	Drug Target
CCR5	Miraviroc (Selzentry®)
HLA-B*5701	Abacavir (Ziagen®, Epzicom®, Trizivir®)

Other gene biomarkers and associated drug targets that have been identified but are not otherwise described in a separate Coverage Policy include the following:

Gene Biomarker	Drug Target
BCR-ABL	Imatinib (Gleevec®), Nilotinib (Tasigna®), Dasatinib (Sprycel®)
CYP2C19	Clopidogrel bisulfate (Plavix®), proton pump inhibitors, antidepressants, barbiturates, mephenytoin
CYP2D6	Tamoxifen (Nolvadex®), antipsychotics, antidepressants, including serotonin reuptake inhibitors [SSRI]), opiod analgesics (e.g., codeine, morphine)
CYP2C9	Warfarin
CYP3A4	Codeine, cyclosporin A, diazepam, erythromycin, irinotecan (Camptosar®), statins
CYP3A5	Cyclosporine, nifedipine, statins, steroid hormones (e.g., testosterone, progesterone, androstenedione), tacrolimus
DPYD	Flourouracil (5FU), capecitabine (Xeloda®)
VKORC1	Warfarin
UGT1A1	Irinotecan (Camptosar®)

Cytochrome P450: Pharmacogenetic testing has been proposed to detect individual response to targeted drug therapy for a number of isoenzymes in the cytochrome P450 superfamily. CYP450 enzyme genes are involved in the metabolism of about 75% of commonly prescribed drugs. Polymorphisms in some of these enzymes, which can vary by ethnicity, can lead to inter-individual differences in drug exposure from standard doses, resulting in potential changes to drug metabolism.

Pharmacogenetic Testing for CYP2C19
CYP2C19 is a clinically important enzyme that metabolizes about 15% of drugs in clinical use, including clopidogrel, mephenytoin, and a number of drug classes such as proton pump inhibitors and antidepressants. The variability in CYP2C19 alleles varies significantly between ethnicities and populations (National Academy of Clinical Biochemistry [NACB], 2010). Four phenotypes have been identified: poor metabolizers, intermediate metabolizers, ultra-rapid metabolizers, and extensive metabolizers. Poor metabolizers have a deficiency in drug metabolism due to a lack of the functional enzyme. They are at increased risk of drug-induced side effects due to diminished drug elimination or lack of therapeutic effect resulting from failure to generate the active form of the drug. Intermediate metabolizers are heterozygous for one deficient allele or carry two alleles that cause reduced enzyme activity. These individuals may require lower than average drug dosages for optimal therapeutic response. Ultra-rapid metabolizers have multiple gene copies, a trait that is dominantly inherited. They have increased metabolic capacity and may require an increased dosage due to higher than normal rates

of drug metabolism. Extensive metabolizers have two normal alleles and normal drug metabolism (Ingelman-Sundberg, 2004).

Several gene variants associated with reduced or absent CYP2C19 activity exist, although the CYP2C19*2 allele accounts for more than 90% of cases of poor metabolism. Together the CYP2C19*2 and *3 alleles are responsible for the majority of reduced function alleles in Caucasian (85%) and Asian (99%) poor metabolizers, while the CYP2C19*1 allele corresponds to fully functional metabolism. Other alleles associated with absent or reduced metabolism are less frequent, and include, but are not limited to CYP2C19*4-*8 (Bristol Myers Squibb/Sanofi-Aventis, 2010). CYP2C19*17 has been associated with ultra-rapid enzyme activity.

Clopidogrel: Clopidogrel bisulfate (Plavix®, Bristol Meyers Squibb/Sanofi Pharmaceuticals, Bridgewater, NJ) is an anti-platelet drug used to prevent blood clots in individuals with existing cardiovascular disease. Clopidogrel is a prodrug that requires conversion to its active form, and is catalyzed predominantly by cytochrome P450 (CYP) 3A4 and 3A5 with contributions from 2C19, 2C9, and 1A2 enzymes.

The mechanisms leading to a poor response to clopidogrel bisulfate have not yet been fully identified. Poor response is most likely caused by many factors, including genetic variations, clinical variables such as obesity, insulin resistance, smoking, the nature of the coronary event, and noncompliance (Simon, 2009; Shuldiner, 2009). Likewise the concomitant use of other drugs such as lipophilic statins, calcium channel blockers, proton pump inhibitors and St John's Wort may also contribute to the variability in response. These factors account for only a small fraction of the variation in response.

By genome-wide association studies a number of variant CYP2C19 alleles have been implicated for anti-platelet activity in individuals receiving clopidogrel. Carriers of the loss-of-function allele display a reduced pharmacodynamic response to clopidogrel and a higher rate of recurrent cardiovascular events compared with non-carriers (Hulot, 2009).

U.S. Food and Drug Administration (FDA)
In March 2010 (updated in August 2010) the FDA approved a 'Black Box' warning label for clopidogrel noting diminished effectiveness in poor metabolizers. The Indications and Usage section of the FDA-prescribing label does not require testing for the gene variant nor does it give recommendations regarding alternative treatment or dosing.

The label states "Poor metabolizers treated with Plavix® at recommended doses exhibit higher cardiovascular event rates following acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) than patients with normal CYP2C19 function. Tests are available to identify a patient's CYP2C19 genotype and can be used as an aid in determining therapeutic strategy. Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers." In August 2010, warnings were added to the prescribing information which note, "Reduced effectiveness in impaired CYPC19 function. Avoid concomitant use with drugs that are strong or moderate CYP2C19 inhibitors (e.g., omeprazole)."

Literature Review
A number of genome-wide association studies have reported inter-individual variability in platelet response to clopidogrel (Collet, 2009; Frere, 2009; Mega, 2009; Shuldiner, 2009; Simon, 2009; Gladding, 2008). Other studies have not shown this association. Pare et al. (2010) reported results of a study analyzing the genotype/clopidogrel response of 5059 patients. These patients were participants in two randomized controlled clinical trials (i.e., CURE, Active A) which reported that clopidogrel, as compared to placebo reduced the rate of cardiovascular events among patients with acute coronary syndromes and atrial fibrillation. Patients were genotyped for three single-nucleotide polymorphisms (*2, *3, *17). Clopidogrel as compared with placebo significantly reduced the rate of the primary efficacy outcome irrespective of the genetically determined metabolizer phenotype (p = 0.12 for heterogeneity). The effect of clopidogrel was similar in patients who were heterozygous or homozygous for loss-of function alleles and in those who were noncarriers of the alleles. Gain-of-function carriers derived more benefit from clopidogrel treatment as compared with placebo than did noncarriers (p = 0.02 for interaction). The effect of clopidogrel on bleeding did not vary according to genotypic subgroups. Among 1156 genotyped patients with atrial fibrillation, there was no evidence of an interaction with respect to either efficacy or bleeding between the study treatment and the metabolizer phenotype, loss-of-function carrier status, or gain-of-function carrier status. The authors noted that for patients with acute coronary syndromes, loss-of-function allele carrier status should not preclude the use of clopidogrel at currently

recommended doses. Although similar results were noted in patients with atrial fibrillation, larger studies are needed to rule out a genetic effect of the loss-of-function alleles in this patient population. Study results suggest that the effect of clopidogrel as compared with placebo is consistent, regardless of CYP2C19 loss-of-function carrier status.

Several meta-analyses have reported an increased risk of cardiovascular-related events with the presence of CYP2C19 variants while others have not reported this association. Holmes et al. (2011) reported results of a meta-analysis and systematic review of 32 studies of 42016 patients reporting 3545 cardiovascular disease events, 579 stent thromboses, and 1413 bleeding events. Six studies were randomized trials (effect-modification) and 26 reported individuals exposed to clopidogrel using a treatment-only design. In treatment-only analysis, individuals with one or more CYP2C19 alleles associated with lower enzyme activity had lower levels of active clopidogrel metabolites, less platelet inhibition, lower risk of bleeding and higher risk of CVD events (absolute risk increase of 8-12 events per 1000 individuals). However, there was evidence of small-study bias (p=.001). In effect modification studies the CYP2C19 genotype was not associated with modification of the effect of clopidogrel on cardiovascular disease events or bleeding (p>.05 for interaction for both). Although an association between CYP2C19 genotype and clopidogrel responsiveness was noted study results suggest that there was no significant association of genotype with cardiovascular events.

Sofi et al. (2010) performed a meta-analysis of seven prospective cohort studies involving a total of 8043 patients followed for a period ranging from one month to 8.3 years. Enrolled individuals had diagnoses including acute coronary syndromes or stable coronary atherosclerotic disease. Loading dose of clopidogrel varied among studies. All of the studies reported a maintenance dose of 75mg/day. There was significant statistical heterogeneity across the studies (p<0.0001). Statistical analysis in only four of seven studies was adjusted for confounding variables. In studies with stent thrombosis as the primary outcome (n=4975), the presence of the CYP2C19*2 variant allele was associated with an increased risk of stent thrombosis (p<0.00001). Patients carrying the CYP2C19*2 allele had an increased risk of a subsequent cardiovascular event in spite of clopidogrel treatment (p=0.004). No standard dose regimen or alternative therapy was recommended as a result of the findings. Limitations include the uncontrolled design of included studies.

Mega et al. (2010) reported the results of a meta-analysis attempting to define the risk of major adverse cardiovascular outcomes among carriers of one or two reduced-function CYP2C19 genetic variants in patients treated with clopidogrel. Investigators from nine participating studies evaluating CYP2C19 genotype and clinical outcomes in patients treated with clopidogrel contributed the relevant hazard ratios (HRs) and 95% confidence intervals for specific cardiovascular outcomes by genotype. Overall, 71.5% of study participants were CYP2C19 noncarriers (n=6923), 26.3% had one reduced-function allele (n=2544), and 2.2% had two reduced-function alleles (n=218). A significantly increased risk of the composite end point (i.e., cardiovascular death, myocardial infarction, or stroke) was found evident in both carriers of one reduced-function allele (p=.01) and two reduced-function alleles (p=.002) compared with noncarriers. There was a significantly increased risk of stent thrombosis in both carriers of one (p<.0001) and two (p=.001) CYP2C19 reduced-function alleles, compared with noncarriers.

Hulot et al. (2009) performed a meta-analysis of 23 studies involving 48674 patients treated with clopidogrel. Ten studies (n=11959) assessed the impact of CYP2C19 and 13 studies assessed the impact of co-administration of proton pump inhibitors (PPI) and ischemic outcomes (i.e., major adverse cardiovascular events [MACE]). Eighteen studies were of observational design from prospective or retrospective registries, and five provided re-analyzed data from randomized clinical trials. Carriers of the CYP2C19*2 allele displayed a 30% increase in the risk for MACE compared with non-carriers (p<0.001) and this variant was also associated with an increase in mortality (n=6225, p=0.019) and stent thrombosis (n=4905, p<0.001). The increased risk was apparent in both heterozygote and homozygotes and was independent of the baseline cardiovascular risk. The impact of PPI use was significantly influenced by baseline cardiovascular risk but only in high-risk patients. When combining all data, clopidogrel-treated patients who presented with CYP2C19 deficits or drug-drug interaction with proton pump inhibitors (PPIs) had a 42% increase in the risk for occurrence for major adverse cardiovascular events (MACE). Limitations include the use of observational data for analysis.

A number of studies have attempted to determine the most effective dosing for clopidogrel in individuals with reduced-function alleles; however, at this time a standard dosing schedule has not been established. Prospective randomized clinical trials are also needed to confirm the merits of a genotype-focused dosing approach over individualized treatment based on either laboratory or point-of-care platelet function analysis.

Bhatt et al. (2012) reported on a cohort (n=4819) of the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) study who consented to genotyping. The rates of ischemic and bleeding events were compared between carriers and non-carriers of loss-of-function and gain-of-function alleles in patients randomized to clopidogrel vs. placebo. Carriers of CYP2C19 loss-of-function alleles did not have an increased rate of ischemic events. Clopidogrel-treated patients who were carriers had a significantly lower rate of bleeding compared with noncarriers (p=0.003). The CYP2C19 gain-of-function alleles did not affect ischemic or bleeding endpoints.

Mega et al. (2011) published results of a multi-center randomized double-blind trial (ELEVATE-TIMI 56) involving 335 patients with known cardiovascular disease who were on a 75mg/day dose of clopidogrel prior to study initiation. At baseline each patient underwent blinded genotyping and platelet function testing. A total of 333 were successfully genotyped and were confirmed for CYP2C19*2 carrier (n=86) or non-carrier (n=274) status. Patients were allocated to a blinded sequence of maintenance doses of clopidogrel for four treatment periods, each of approximately 14 days duration. Drug doses varied depending on whether the patient was a carrier or non-carrier of CYP2C19*2. Clinical outcomes for death, cardiac ischemic events, cerebrovascular events, and bleeding scales were assessed by dose for CYP2C19*2 carriers and non-carriers using an intention-to-treat approach. The authors reported that among patients with stable cardiovascular disease, tripling the maintenance dose of clopidogrel to 225 mg daily in CYP2C19*2 heterozygotes achieved levels of platelet reactivity similar to that seen with the standard 75-mg dose in noncarriers; in contrast, for CYP2C19 homozygotes, doses as high as 300 mg daily did not result in comparable degrees of platelet inhibition. Study limitations include the lack of information regarding long-term tolerability of higher doses as treatment periods were limited to 14 days, and the interaction of proton pump inhibitors (PPI) as individuals using PPI were excluded from this study.

Professional Societies/Organizations
American College of Cardiology Foundation/American Heart Association: The ACCF/AHA published a focused update regarding the management of patients with unstable angina/non-ST elevation myocardial infarction (2012). The Guideline notes that genotyping for a CYP2C19 loss of function variant in patients with unstable angina/non-ST-elevation myocardial infarction, (or after acute coronary syndrome and with percutaneous coronary intervention) on $P2Y_{12}$ receptor inhibitor therapy might be considered if results of testing may alter management. The Guideline is a Level of Evidence: C, class IIB recommendation. Level of evidence: C is defined by the Guideline as: very limited populations evaluated, only consensus opinion of experts, case studies, or standard of care. Class IIB is defined as: recommendations usefulness/efficacy less well-established, only diverging expert opinion, case studies, or standard of care.

Canadian Agency for Drugs and Technologies in Health (CADTH): CADTH (2007) notes "Prospective studies are needed to determine whether pharmacogenomic testing improves patient outcomes, identify which subgroups of patients may benefit, and clarify the risks and costs associated with the use of these tests."

Summary for Clopidogrel: Several prospective and retrospective studies have evaluated the association between the presence of CYP2C19 variants and response to clopidogrel; however, there is not yet consensus regarding the "gold standard" test, or the definition of non-response (Cuissett, 2009). Data are also limited regarding alternative treatment options if variants are identified; clinical trials with alternative therapies are ongoing. Data are limited regarding standard dosing recommendations, and an appropriate dose regimen for this patient population has not been established in clinical outcome trials. Although an association between CYP2C19 and response to various drugs, including clopidogrel is suggested, at this time the clinical utility of pharmacogenetic testing for CYP2C19 gene variants has not been established.

Proton Pump Inhibitors: Proton pump inhibitors are indicated for the treatment of a number of gastric acid-related disorders (e.g., duodenal ulcer, gastric ulcer, gastroesophageal reflux disease). They are also used in combination with one or two antibiotics (e.g., triple therapy) for the eradication of helicobactor pylori (Ma, 2012). Several PPIs are metabolized by CYP2C19; however the extent of metabolism by CYP2C19 is variable between individual PPIs. There are scarce data in the published peer-reviewed scientific literature regarding PPI dosing strategies in clinical practice based on CYP2C19 genotype. The majority of clinically relevant data have focused on the effect of CYP2C19 genotypes on H pylori eradication, with little attention to adverse effect risk (Ma, 2012).

U.S. Food and Drug Administration (FDA)
PPIs approved by the FDA include dexlansoprazole (Dexilant, Takeda Pharmaceuticals North America, Inc., Deerfield, IL), lansoprazole (Prevacid®, Takeda Pharmaceuticals North America, Inc., Deerfield, IL), esomeprazole magnesium (Nexium®), AstraZeneca Pharmaceuticals LP, Wilmington, DE), and omeprazole (Prilosec®), AstraZeneca Pharmaceuticals, LP, Wilmington, DE). These drugs are listed in the FDA Table of Pharmacogenomic Biomarkers in Drug Labels with CYP2C19 noted to be the biomarker for each drug target. The Indications and Usage section of the FDA-approved prescribing label for each drug does not require CYPC19 genotyping prior to initiation of therapy.

Literature Review
Zhao et al. (2008) conducted a systematic review and meta-analysis of 20 randomized controlled trials (n=44–459) to determine if CYP2C19 polymorphism affected helicobacter pylori (H. pylori) eradication rates obtained with first-line proton pump inhibitor (PPI)-based triple therapies (i.e., PPI and amoxicillin and clarithromycin or PPI and amoxicillin and metronidazole). Patients had tested positive for H. pylori, had not previously been treated and had an established CYP2C19 genotype. Eradication rates were significantly different between poor metabolizers (PM) (i.e., *2/*2, *1/*2 and *1/*3, or *3/*3) and heterozygous extensive metabolizers (HetEM) (i.e., *1/*2 or *1/*3) (p=0.002), between PM and homozygous extensive metabolizers (HomEM) (i.e., *1/*1) (p<0.0001) and between HetEM and HomEM (p<0.0001). Significantly higher H. pylori eradication rates were achieved in PM compared to HomEM metabolizers with triple omeprazole (p=0.0005) and lansoprazole (p=0.001) therapies and with HetEM compared to HomEM (p<0.0001 for omeprazole and p=0.040 for lansoprazole). Rabeprazole therapies had no significant effect on H. pylori eradication rates between PM and HomEM (p=0.610) and between HetEM and HomEM (p=0.190). No significant differences in H. pylori eradication rates between PM and HetEM were observed in the three individual PPI therapies. A limitation of the study is the small patient population that did not allow subanalyses to reach statistical significance.

In a technology assessment (2008) the Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) stated that there was insufficient evidence to permit conclusions on the effect of pharmacogenomics-based treatment of H. pylori on health outcomes. Only one randomized controlled trial using CP2C19 testing met inclusion criteria.

Professional Societies/Organizations
The American Gastroenterological Association does not have published guidance regarding proton pump inhibitors and CYP2C19 genotyping.

Summary for Proton Pump Inhibitors: Although published literature suggests that a number of proton pump inhibitors (PPI) are metabolized by CYP2C19, data are limited regarding the effect of CYP2C19 genotyping on health outcomes, including reduction in adverse drug reactions. Furthermore, genotyping is not required by the U.S. Food and Drug Administration (FDA) prior to initiating therapy. At this time the clinical utility of pharmacogenetic testing for CYP2C19 has not been established for this indication.

Metabolism of Other Drug Targets
Mutations in the CYP2C19 gene have been associated with variability in the metabolism of a number of other drugs, including certain antidepressants, barbiturates, and mephenytoin, resulting in poor metabolizer and extensive metabolizer phenotypes (Genetics Home Reference, 2013).

Food and Drug Administration (FDA)
At present, genotyping is not required prior to the initiation of therapy for these drugs.

Literature Review
Randomized controlled trial data are lacking to demonstrate the clinical utility of genotyping to determine CYP2C19 polymorphisms for these drug targets. At this time the role of CYP2C19 genotyping has not been established.

Summary for Pharmacogenetic Testing for CYP2C19
Peer-reviewed published literature suggests that CYP2C19 is implicated in the variability of metabolism of a number of drug targets including clopidogrel, proton pump inhibitors, mephenytoin, and certain antidepressants and barbiturates. However, at this time there is insufficient evidence to determine that pharmacogenetic testing improves health outcomes. The role of pharmacogenetic testing has not yet been established.

Pharmacogenetic Testing for CYP2D6
Cytochrome P450 2D6 (CYP2D6) is also a part of the P450 gene superfamily and exhibits a high degree of polymorphism. More than 90 allelic variants have been identified. Twenty to 25% of available drugs are subject to metabolism by the CYP2D6 gene. Drugs metabolized by CYP2D6 include anti-cancer agents, such as tamoxifen, antidepressants, antipsychotics, certain narcotics, and beta-blockers. The impact on therapy is related to the resulting metabolizer status that the polymorphism(s) cause in the individual receiving therapy, and whether the parent drug is active, or requires CYP2D6 to metabolize it into an active metabolite (Pharmacogenomics Knowledge Base [PharmGKB], 2001-2010).

Alleles vary by ethnicity. The most prevalent alleles are CYP2D6 *1 and *2, which produce an enzyme with normal activity. Among reduced function variants, *17, *10, and *8 are the most important in African-Americans, Asians, and Caucasians, respectively (Blue Cross and Blue Shield Association [BCBSA] Technology Evaluation Center [TEC], 2008). Phenotypes that have been identified and associated with CYP2D6 include poor, intermediate, extensive, and ultra-rapid metabolizers. Frequency of the poor metabolizer phenotype is 7%–10% in Caucasians, 1.9%–7.3% in African Americans, and ≤ 1% in most Asian populations studied (National Academy of Clinical Biochemistry [NACB], 2010; Blue Cross and Blue Shield Association [BCBSA] Technology Evaluation Center [TEC], 2008). The extensive metabolizer phenotype is the most common in Caucasian populations, and accounts for 50% of the population (NACB, 2010).

Therapy with CYP2D6 substrates can be complex, not only due to genetic variation, but also due to drug-drug interactions. For example, an extensive metabolizer can appear to be an intermediate or poor metabolizer because most of the available enzyme is being inhibited by a confounding drug. Additionally, a related phenotype can occur with chronic dosing of a CYP2D6 drug (i.e., autophenocopying), in which a CYP2D6 substrate can inhibit its own metabolism over time as the concentration of the drug approaches steady state (PharmGKB, 2001-2010). Pharmacogenetic testing has been proposed to predict inter-individual response to a variety of CYP2D6-metabolized drugs including tamoxifen, antidepressants, including selective serotonin reuptake inhibitors (SSRI), antipsychotics for the treatment of schizophrenia, and opioid analgesics, such as codeine, and morphine.

Tamoxifen: CYP2D6 is a key enzyme in the metabolism of tamoxifen, a selective estrogen receptor modulator which is important for the treatment and prevention of breast cancer. Tamoxifen is a pro-drug and is extensively metabolized by the cytochrome P450 system to several primary and secondary metabolites, including tamoxifen 4-hydroxylation and endoxifen. Because the CYP2D6 enzyme has known inter-individual variability, it has been hypothesized that breast cancer patients with poor and intermediate metabolizer genotypes who are treated with tamoxifen may have worse clinical outcomes compared to patients with extensive metabolizer genotypes (Agency for Healthcare Research and Quality [AHRQ], 2010; Dezentje, 2009; Blue Cross and Blue Shield Association [BCBSA] Technology Evaluation Center [TEC], 2008). A substantial portion of the variability in metabolite concentrations is not explained by the CYP2D6 genotype, however. Additional polymorphic enzymes play a role in the metabolism of tamoxifen including CYP2C9, CYP2C19, CYP3A, SULT1A1 and UGT2B15. Polymorphisms in the genes for these enzymes may also have an effect on overall tamoxifen efficacy. Additionally, a number of drugs known to inhibit CYP2D6 and reduce tamoxifen metabolite concentrations are often prescribed with this population. These include selective-serotonin reuptake inhibitors and statins.

U.S. Food and Drug Administration (FDA)
The Indications and Usage section of the FDA-approved prescribing label does not require CYP2D6 genotyping prior to initiation of therapy with tamoxifen citrate (Nolvadex[®], AstraZeneca, Wilmington, DE) or its generic versions.

Literature Review
Several studies focus on the association of CYP2D6 genetic variants and tamoxifen. The Agency for Healthcare Research and Quality (AHRQ, 2010) performed a systematic review of the published literature and reported the results of 16 studies. No consistent associations were found between CYP2D6 polymorphisms and tamoxifen treated women with breast cancer across these studies. The AHRQ noted limitations in the study designs; ten studies were retrospective, and the studies included in the review were generally small in size, followed poor analytic practices, and differed both in the direction and in the formal statistical significance of their results. There was complete or extensive overlap in patient populations of six studies. AHRQ documented extensive heterogeneity in the definitions of CYP2D6-derived metabolizer categories across eligible studies; different

studies classified the same genotypes into different categories of predicted enzymatic activity. Seven studies reported analyses on overall survival outcomes. The majority of studies (n=9) assessed the ability of CYP2D6 testing to predict outcomes only in women who received tamoxifen. None of the included studies performed analyses for interaction to predict response to therapy. No study demonstrated a statistically significant relationship between CYP2D6-defined metabolizer status and overall survival or mortality in either adjusted or unadjusted analyses. No study explicitly reported details on changes in treatment plans before and after testing as a result of genotyping.

AHRQ (2010) noted "It is unclear whether pharmacogenetic testing of germline (heritable) mutations in CYP2D6 can predict differential response to adjuvant tamoxifen in women with non-metastatic breast cancer. Further, evidence is severely limited for tamoxifen-treated women with metastatic disease." They further noted "We found no evidence on whether patient or disease relevant factors affect the association between CYP2D6-derived metabolizer status and outcomes in tamoxifen treated women. Several studies performed simple adjustments for patient level factors. This is not only noninformative, but also questionable from an analytic standpoint." "Most studies were relatively small and thus underpowered to detect what would be a plausible effect size for the modification of response to tamoxifen by a single polymorphism."

An update of the technology assessment by the Blue Cross and Blue Shield Association [BCBSA] Technology Evaluation Center [TEC], 2014) evaluated the evidence for CYP2D6 genotyping, compared to no testing, to direct treatment regimen choices and improve survival outcomes for patients at high risk for primary breast cancer or breast cancer recurrence. The study reviewed full-length, peer-reviewed papers reporting studies of postmenopausal women undergoing endocrine therapy whose treatment regimen selection was based on CYP2D6 genotyping versus usual selection methods and studies of the association of CYP2D6 genotype with intermediate (e.g., tamoxifen active metabolite levels) or final outcomes (e.g., time to recurrence, survival).

The assessment noted "There is no direct evidence of clinical utility. Two indirect evidence chains can be constructed. One depends on demonstrating a significant association between endoxifen and clinical outcomes; this evidence does not exist. The other depends on the association of genotype with clinical outcomes; there are several limitations to this evidence, and, as a result, it is judged insufficient to support clinical utility. There was no direct evidence of clinical utility." The assessment further noted "There is insufficient evidence to permit conclusions regarding the use of CYP2D6 genotyping for directing endocrine therapy regimen selection for women at high risk for or with breast cancer." "Whether or not the use of CYP2D6 genotyping for directing endocrine therapy regimen selection for women at high risk for or with breast cancer improves health outcomes has not been demonstrated in the investigational setting."

Goetz et al. (2007) performed a retrospective review of the combined effect of CYP2D6 and HOXB13/IL17BR in the outcomes of disease-free survival (DFS) and overall survival (OS) in a cohort of 160 women with lymph node–negative breast cancer treated with adjuvant tamoxifen monotherapy. In 110 of 160 women the HOXB13/IL17BR gene expression data and a comprehensive assessment of CYP2D6*4 genotype and medication history were known. The combined CYP2D6:HOXB13/IL17BR risk factor was significantly associated with DFS (p = 0.004) and OS (p = 0.009). Relative to women with extensive CYP2D6 metabolism and low HOXB13/IL17BR, those with either decreased metabolism or a high HOXB13/IL17BR ratio had significantly worse OS (p = 0.031), whereas women with both decreased metabolism and high HOXB13/IL17BR ratio had the shortest survival (p= 0.024). The authors suggest that a combined index of inherited CYP26 and tumor HOXB13/IL17BR variation may identify individuals with varying degrees of tamoxifen resistance.

In an earlier retrospective study, Goetz et al. (2005) evaluated the tumor specimens of a cohort of 223 women with resected estrogen receptor (ER)-positive breast cancer, who had participated in a tamoxifen-only arm of a randomized phase III clinical trial. The buccal swabs of 17 living women with the disease were also evaluated for CYP2D6 (*4 and *6) and CYP3A5 (*3). The concordance rate between the tumor and buccal types was 100%. Women with the CYP2D6*4/*4 genotype had a worse relapse-free time (p=0.23) and DFS (p=0.12) but not OS (p=0.169). In multivariate analysis individuals with the CYP2D6*4 genotype had worse relapse-free survival (RFS, p=0.176) and DFS (p=0.089). The CYP3A5 variant was not associated with any of these clinical outcomes.

Wegman et al. (2007) retrospectively evaluated 677 tamoxifen-treated postmenopausal patients with breast cancer who were genotyped for CYP3A5, CYP2D6, SULT1a1, or UGT2B15. Two hundred thirty-eight patients had been randomized to either three or five years of tamoxifen, Significantly better DFS was noted in individuals

homozygous for CYP2D6*4. No prognostic significance was noted for SULT1A1 or UGT2B15. No reliable differences were noted between treatment duration and the genotypes of CYP2D6. Significantly improved relapse-free survival (RFS) was noted in individuals with CYP3A5 who received prolonged tamoxifen therapy. No differences were noted for individuals with CYP2D6, SULT1A1, or UGT2b15.

Nowell et al. (2005) performed a retrospective review of 162 women with primary invasive breast cancer who received tamoxifen and 175 women who did not receive hormonal therapy. Paraffin-embedded archived tissues were used for DNA analysis. Tissue was genotyped for CYP2D6*3, CYP2D6*4, and CYP2D6*6 polymorphisms and UT2B15 and SULT1A1alleles. After adjusting for age, race, stage of disease at diagnosis, and hormone receptor status, no significant association was found between CYP2D6 genotype and overall survival in either group of breast cancer patients. Tamoxifen treated patients with UGT2B15 high activity genotypes had increased risk of recurrence and poorer survival. When UGT2B15 and SULT1A1 'at-risk' alleles were combined, women with two variant alleles had significantly greater risk of recurrence and poorer survival than those with common alleles.

Professional Societies/Organizations
American Society of Clinical Oncology (ASCO): In the Guideline titled "Update on the Use of Pharmacologic Interventions Including Tamoxifen, Raloxifene, and Aromatase Inhibition for Breast Cancer Risk Reduction" , ASCO (2009) notes "The guideline does not recommend testing for variants in the risk reduction setting at the present time."

National Comprehensive Cancer Network™ (NCCN™): In the 2013 Clinical Practice Guidelines in Oncology on Breast Cancer, the NCCN states "At this time based on current data the panel recommends against CYP2D6 testing for women being considered for tamoxifen therapy."

Summary for Tamoxifen: The metabolism of tamoxifen is complex and the mechanisms responsible for the resistance are unlikely to be explained by a single polymorphism; instead it is a combination of several mechanisms (Wegman, 2007). Data are limited regarding alternative dosing recommendations, and an appropriate dose regimen for this patient population has not been established in clinical outcome trials. Data are also limited regarding alternative treatment options if variants are identified. Randomized controlled trials are needed to determine if pharmacogenetic testing will lower the incidence of adverse drug reactions by detecting patients with CYP2D6 mutations. At this time there are insufficient data regarding the clinical utility of pharmacogenetic testing for CYP2D6 as related to the effectiveness of tamoxifen therapy in individuals with breast cancer.

Antidepressants, Including Selective Serotonin Reuptake Inhibitors: Despite the number of readily available antidepressant pharmacotherapies, a significant portion of patients do not respond adequately to treatment and/or experience tolerability or safety problems that can lead to the discontinuation of treatment. Antidepressants, in particular, are often metabolized by CYP2D6. The impact of CYP2D6 activity differs on a drug-by-drug basis, depending on whether CYP2D6 is involved in the activation or inactivation of the drug. Selective serotonin reuptake inhibitors (SSRIs) may be used as antidepressants to treat clinical depression, and anxiety and panic disorders, as well as personality, obsessive-compulsive, and eating disorders. Pharmacogenetic testing to determine metabolizer status of CYP2D6 has been proposed to inform dosage, choice of antidepressant drug therapy, and reduce adverse drug reactions.

Inter-individual variability in response to antidepressant pharmacotherapy suggests that these drugs do not have a uniform effect across patient populations. Published data indicate that there is a higher prevalence of CYP2D6 poor metabolizers in psychiatric populations than in the population at large. Consistent with this finding, it has been suggested that CYP2D6 may have an indirect effect on neurophysiologic functioning because of its involvement in the generation of serotonin (D'Empaire, 2011).

Ina review of the published literature D'Empaire et al. (2011) investigated the effect of altered CYP2D6 activity on the efficacy and tolerability of antidepressants that are CYP2D6 substrates. The authors noted the clinical effect of altered CYP2D6 metabolism on patients treated with antidepressants has not been widely studied in large scale prospective trials. The literature suggests that altered CYP2D6 metabolism, involving genetic polymorphisms or phenoconversion is associated with a less favorable treatment experience. Future clinical trials investigating the efficacy and tolerability of pharmacotherapies should be designed to allow for the assessment of pharmacogenetic factors on treatment outcomes.

U.S. Food and Drug Administration (FDA)
A number of antidepressants have received FDA approval including clomipramine (Anafranil®, Mallinckroft LLC, St Louis, MO), desipramine (Norpramin®), Sanofi Aventis US, Bridgewater, NJ), imipramine (Tofrani^l®), Novartis, Cambridge, MA), paroxetine (Paxil®), GlaxoSmithKline, Philadelphia, PA) and fluroxetine (Prozac®), Eli Lilly and company, Indianapolis, IN) . The Indications and Usage section of the FDA-approved prescribing label does not require genetic testing prior to initiating treatment with these antidepressants.

Literature Review
Serretti et al. (2009) investigated the role of CYP450, CYP1A2, CYP2C9, CYP2C19, and CYP2D6 in antidepressant treatment response and remission rates in patients diagnosed with major depression (n=278) who were recruited from four centers. Samples from a previous study were taken from patients classified as responders (n=81), nonresponders (n=197), remitters (n=31) (i.e., those in remission) and nonremitters (n=247). Nonresponders were patients with a Hamilton Rating Scale for Depression (HAM-D) score ≥ 17 after completing a minimum of four weeks of one antidepressant treatment given for the current or most recent major depressive episode and nonremitters had an HMA-D score > 8. The analyses revealed that the alleles were not associated with response or remission. When the analyses were repeated by class of antidepressant no association was found. The study was limited by the lack of information on the antiplasma levels, dosages, co-medications, and any adverse reaction to drug therapy, and the fact that the patients were not specifically recruited for pharmacogenetic analyses.

The Agency for Healthcare Research and Quality (AHRQ, 2007) published an evidence report/technology assessment regarding testing for cytochrome P450 polymorphisms in adults entering selective serotonin reuptake inhibitor treatment for non-psychotic depression. Methodological issues related to the studies included the use of single dose studies in healthy volunteers, small sample sizes, heterogeneity, not accounting for multiple CYP enzymes that may be involved in metabolism of a certain SSRI, and diet was not taken into account in any study.

After an analysis of 32 studies the AHRQ reported "There is mixed evidence regarding the association between CYP450 genotypes and SSRI metabolism, efficacy, and tolerability in the treatment of depression. There are no data regarding whether testing for CYP450 polymorphisms in adults entering SSRI treatment for non-psychotic depression leads to improvement in outcomes versus not testing, or if testing results are useful in medical, personal, or public health decision-making; if CYP450 testing influences depression management decisions by patients and providers in ways that could improve or worsen outcomes; or if there are direct or indirect harms associated with testing for CYP450 polymorphisms or with subsequent management options." AHRQ concluded "There is a paucity of good-quality data addressing the questions of whether testing for CYP450 polymorphisms in adults entering SSRI treatment for non-psychotic depression leads to improvement in outcomes." "In depressed patients treated with SSRIs, the existing data (a series of heterogeneous studies in small samples) do not support a clear correlation between CYP metabolizer status as predicted by genotyping and SSRI concentrations."

Professional Societies/Organizations
Evaluation of Genomic Applications in Practice and Prevention Project (EGAPP): In 2007, the EGAPP made the following statement regarding CYP450 genetic testing in adult patients beginning SSRI treatment: "The EGAPP Working Group found insufficient evidence to support a recommendation for or against use of CYP450 testing in adults beginning SSRI treatment for non-psychotic depression. In the absence of supporting evidence, and with consideration of other contextual issues, EGAPP discourages use of CYP450 testing for patients beginning SSRI treatment until further clinical trials are completed."

The American Psychiatric Association has not published guidance regarding CYP2D6 genotyping.

Summary for Antidepressants, Including Selective Serotonin Reuptake Inhibitors: While a number of studies have demonstrated an association with CYP2D6 and metabolism of antidepressants, there are scarce prospective randomized trial data regarding the effect of genotyping as used to establish dosing regimens. Likewise, there is insufficient evidence to inform reduced adverse events and improved health outcomes. At this time the clinical utility of CYP2D6 genotyping has not been established for this indication.

Anti-Psychotics for Schizophrenia: Antipsychotics are used to treat conditions such as schizophrenia. CYP2D6 genotyping has been proposed as a means to determine metabolizer status in individuals initiating antipsychotic drug therapy. A number of studies have demonstrated an association of CYP2D6 with this class of drugs; however, there are scarce data in the published, peer-reviewed scientific literature regarding the impact of genotyping to inform dosing or to reduce adverse drug events, and this is not yet part of clinical practice.

U.S. Food and Drug Administration (FDA)
The FDA has approved a number antipsychotics drugs including amitryptiline (Abilify®), Bristol-Myers Squibb, New York, NY/ Otsuka American Pharmaceuticals, Inc), and haloperidol (Haldol®), Ortho-McNeil, Raitan, NJ). The Indications and Usage section of the FDA-approved prescribing label does not require CYP2D6 genotyping prior to initiating therapy with these antipsychotics.

Literature Review
Jurgens et al. (2012) reported results of a retrospective cross sectional study to determine the clinical impact of the CY2D6 genotype. Antipsychotics were classified into first or second generation. Subsequently all antipsychotics were classified into CYP2D6 dependent or independent based on their metabolic profile and, secondly, according to the impact of the genotype on the pharmacokinetic differences between poor metabolizers (PM) and extensive metabolizers (EMs) where antipsychotics with less than 20% differences were classified as CYP2D6 independent. All samples were genotyped for the nonfunctional alleles CYP2D6*3, *4, *5 (gene deletion), and *6, and CYP2D6 gene duplications/multiplication. In the observation period, 968 (22.5%) of 4311 admitted patients were CYP2D6 genotyped. Five hundred seventy-six had a diagnosis within the schizophrenic spectrum. The logistic regression analysis including all 576 patients showed no significant association with the CYP2D6 genotype (P = 0.79), treatment with CYP2D6 inhibitors (P = 0.46) or the interaction of both variables (P = 0.57). The study shows a paradox result indicating that patients with deviant CYP2D6 metabolizer status are difficult to identify clinically. Furthermore, it shows that we do not know the clinical consequences of patients' CYP2D6 metabolizer status yet and emphasizes the need for prospective clinical trials.

In a health technology assessment (2010), the National Institute for Health Research (NIHR) conducted a systematic review and meta-analysis of analytical validity, clinical validity, and clinical utility of CYP testing to determine whether testing for cytochrome P450 polymorphisms in adults entering antipsychotic treatment for schizophrenia leads to improvement in outcomes, is useful in medical, personal or public health decision-making, and is a cost-effective use of health-care resources. A total of 46 studies, of a number of genotypes, most commonly CYP2D6, met inclusion criteria and reported a sensitivity and specificity of 99%–100%. One small unpublished study met the inclusion criteria for clinical utility. The authors noted that tests for determining genotypes appear to be highly accurate although not all aspects of analytical validity were reported in the tests. To date the research is limited regarding the links between genotype, metabolism and adverse drug reactions. For clinical validity (i.e., "how well do particular CYP genotypes predict metabolism of antipsychotics" and how well does CYP testing predict drug efficacy and adverse drug reactions [ADRs]") 51 studies met inclusion criteria and focused mainly on ADRs. There was some evidence that patients with wild type (wt)/mutant type (mut) and mut/mut + wt/mut genotypes had an increased risk of tardive dyskinesia and patients with mut/mut + wt/mut genotype were significantly more likely to develop Parkinsonism. One study met inclusion criteria for clinical utility. Although the CYP450 tests appeared to be accurate, there was an absence of convincing evidence from clinical validity studies, a lack of evidence of clinical utility, and unsuitability of published schizophrenia models. The current evidence base does not support the use of pharmacogenetic testing in this area.

Professional Societies/Organizations
The American Psychiatric Association has not published guidance regarding CYP2D6 genotyping.

Summary for Anti-Psychotics for Schizophrenia: There are scarce data regarding the clinical utility of CYP2D6 genotyping to improve health outcomes in individuals requiring antipsychotic drug therapy. Well-designed prospective clinical trials are necessary to demonstrate the role of genotyping for this indication.

Opioid Analgesia: Codeine analgesia is closely related to CYP2D6 pharmacogenetics; the association between CYP2D6 metabolizer phenotype and the formation of morphine from codeine is well defined. The analgesic properties of codeine stem from its conversion to morphine and morphine-6-glucuronide. Both codeine and morphine also have antitussive effects. The most common adverse reactions to codeine include

drowsiness, lightheadedness, dizziness, sedation, shortness of breath, nausea, vomiting, and sweating. Serious adverse reactions include respiratory depression and, to a lesser degree, circulatory depression, respiratory arrest, shock, and cardiac arrest (Crews, 2012). Codeine and morphine are widely used. Most patients receive codeine and morphine without prior CYP2D6 genotyping.

U.S. Food and Drug Administration (FDA)
The Indications and Usage section of the FDA-approved prescribing label does not require CYP2D6 genotyping prior to the initiation of therapy with opioid analgesics, such as codeine, morphine sulfate, and oxycodone hydrochloride.

Literature Review
Evidence regarding the effect of CYP2D6 polymorphisms on codeine toxicity is primarily derived from case reports. Andreassen et al. (2012) conducted a multicenter, prospective case series (n=450) to assess the relationship of oxycodone and CYP2D6 genotypes. A total of 27 patients were genotyped as poor metabolizers (PM), 413 as extensive metabolizers (EM) and ten as ultra-rapid metabolizers (URM). There were no significant differences in pain intensity (p=0.8), tiredness (p=0.7) and nausea (p=0.6) between the groups. CYP2D6 genotypes did not influence pain control, nausea or fatigue in this patient population.

Using AmpliChip, Candiotti et al. (2009) retrospectively analyzed data on 142 women to evaluate the potential impact of CYP2D6 on postoperative morphine consumption. The study group was divided into low morphine consumers (LMC) (≤10 milligrams [mg] per hour [hr]) (n=80) and high morphine consumers (HMC) (>10 mg/4 hrs) (n=62). The eight subjects identified as ultrarapid metabolizers (UM) were all in the LMC group. No significant differences were reported for poor, intermediate and extensive metabolizers. The patients in the LMC group had significantly lower pain scores than the overall group (p=0.0019) and received less fentanyl intraoperatively (p=0.0178). These results suggested that UM require less morphine than other metabolizers. Limitations of the study include the retrospective study design, small patient population, lack of a control group, and subjects who underwent various types of surgeries (e.g., abdominal, gynecological, ear/nose/throat).

Professional Societies/Organizations
Clinical Pharmacogenetics Implementation Consortium: On behalf of the Consortium, Crews et al. (2012 published dosing guidelines for codeine therapy in the context of cytochrome P450 2D6 (CYP2D6) based on ultrarapid, extensive, intermediate and poor metabolizer phenotypes.

Summary for Opioid Analgesia: Controlled clinical trial data are lacking regarding the clinical utility of CYP2D6 genotyping to inform improved health outcomes, including a reduction of adverse drug events, for individuals on opioid analgesic drug therapy. At this time the role of genotyping has not been established for this indication.

Summary for Pharmacogenetic Testing for CYP2D6
Peer-reviewed published literature suggests an association with CYP2D6 and the variability to metabolize a number of drug targets including tamoxifen, antidepressants, including selective serotonin reuptake inhibitors (SSRIs), anti-psychotics, and opiod analgesia. However, at this time there is insufficient evidence to determine the clinical utility of pharmacogenetic testing, including its impact on health outcomes.

Pharmacogenetic Testing for CYP3A4 and CYP3A5
CYP3A4, cytochrome P450, family 3, subfamily A, polypeptide 4, is one of the most abundant CYP enzymes expressed in the liver and small intestines (Ulvestad, 2012) and is part of a cluster of cytochrome P450 genes on chromosome 7q21. The enzyme catalyzes many reactions involved in the synthesis of cholesterol, steroids and other lipids and the metabolism of approximately 60% of the drugs in clinical use, including acetaminophen, codeine, cyclosporin A, diazepam, erythromycin, irinotecan, and statins. The enzyme also metabolizes some steroids and carcinogens (National Center for Biotechnology Information [NCBI], Online Mendelian Inheritance in Man [OMIN], 2008). Generally, variants in the coding regions of CYP3A4 occur at allele frequencies of <5% and appear as heterozygous with the wild-type allele. These coding variants may contribute to, but are not likely to be the major cause of inter-individual differences in CYP3A-dependent clearance, because of the low allele frequencies and limited alterations in enzyme expression or catalytic function (Lamba, 2002).

CYP3A5, cytochrome P450, family 3, subfamily A, polypeptide 5, is also found in the adult liver and intestine, and in the fetal liver (Lamba, 2002). CYP3A5 is also part of a cluster of genes on chromosome 7q21. Like CYP3A4, CYP3A5 catalyzes many reactions involved in synthesis of cholesterol, steroids and other lipids, the

metabolism of many drugs such as nifedipine, and statins, as well as the steroid hormones testosterone, progesterone and androstenedione. (National Center for Biotechnology Information [NCBI]). Additionally, CYP3A4 and CYP3A5 metabolize a number of immunosuppressive drugs, including cyclosporin and tacrolimus (MacPhee, 2008).

Pharmacogenetic testing of the CYP3A4 and CYP3A5 genes has been proposed as a means to improve health outcomes by allowing dose adjustment based on genotype, thereby preventing or minimizing adverse drug reactions.

U.S. Food and Drug Administration (FDA)
At present, the Indications and Usage section of the FDA-approved prescribing label does not require CYP3A4 genotyping prior to the initiation of any drug therapy, including codeine, cyclosporin A, diazepam, erythromycin, irinotecan, and statins. Likewise, the FDA does not require genotyping of CYP3A5 prior to the initiation of drug therapy with nifedipine, cyclosporine, statins, steroid hormones (e.g., testosterone, progesterone and androstenedione), or tacrolimus..

Literature Review
Randomized controlled trial data comparing conventional trial and error dosing with genotype-based dosing are scarce in the published, peer-reviewed literature. In one study, Van der Bol et al. (2010) reported outcomes of randomized trial designed to assess the utility of an algorithm for individualized irinotecan dose calculation based on a priori CYP3A4 activity measurements by a midazolam clearance test. Forty cancer patients were randomized to receive irinotecan at a conventional dose level (group A) or doses based on an equation consisting of midazolam clearance, γ-glutamyltransferase, and height (group B). The mean absolute dose and area under the curve of irinotecan was not significantly different in either group ($p > 0.18$). In group B, the interindividual variability in the area under the curve of irinotecan was reduced by 19% ($p > 0.22$). Compared with group A, the incidence of grades 3 to 4 neutropenia was >4-fold lower in group B (45 versus 10%; $p = 0.013$). The incidence of grades 3 to 4 diarrhea was equal in both groups (10%). Data suggests that CYP3A4 phenotyping in dose calculation resulted in a lower incidence of severe neutropenia. CYP3A4 phenotype determination should be explored further in larger randomized clinical trials as a strategy for the individualization of irinotecan treatment.

Several genome-wide association studies, as well as prospective clinical trials and literature review articles have suggested an association of CYP3A4 and CYP3A5 related to the metabolism of various drug targets (Potkin, 2013; Terrazzino, 2012; Samer, 2010; Staatz, 2010; Wang, 2010; Zhao, 2009; MacPhee, 2008, Lamba, 2002). Common variants under study include CYP3A4 *2, *3, *4, *5, and *6, and CYP3A5 *2, *3, *4, *5, and *6.

Terrazzino et al. (2012) published a systematic review and meta-analysis of the effect of CYP3A5 6986A>G (19 studies; 2028 patients) and ABCB1 3435C>T (15 studies; 1386 patients) on tacrolimus dose-adjusted trough levels and acute rejection rates in adult renal transplant patients (10 studies, 1246 patients and four studies, 524 patients for CYP3A5 6986A>G and ABCB1 3435C>T, respectively). No evidence of an effect of the ABCB1 3435C>T variant on tacrolimus dose-adjusted trough levels was found except for a modest effect limited to the first month after renal transplantation. There were significantly higher tacrolimus dose-adjusted trough levels in CYP3A5*3/*3 compared with CYP3A5*1 allele carriers in the overall analysis, and when stratifying for ethnicity and time of post-transplantation. Patients carrying the CYP3A5*3/*3 genotype required a lower dose of tacrolimus to achieve the same blood concentrations when compared with the CYP3A5*1/*1 or CYP3A5*1/*3 carriers. No differences were found in the acute rejection rate between CYP3A5*3/*3 and CYP3A5*1 allele carriers. None of the studies had an individually large effect on the impact of CYP3A5 6986A>G on the risk of acute rejection (sensitivity pooled OR: 0.695–0.829). No indication of significant publication bias was found. Sensitivity analysis showed no significant difference in the rates of acute rejection over the first month after transplantation between CYP3A5 expressers and nonexpressers.

Overall, recipient CYP3A5 6986A>G and ABCB1 3435C>T polymorphisms seem to have little or no effect on the acute rejection rates in renal transplant patients under immunosuppressive therapy with tacrolimus. The authors note given study limitations, including that few studies included were prospective in nature, prospective large studies are still required to explore the impact of ABCB1 3435C>T and CYP3A5 6986A>G, alone or in combination in both donors and recipients, on long-term outcome of immunosuppressive therapy with tacrolimus.

Wang et al. (2010) published results of a study evaluating the expression of allelic CYP3A4 heteronuclear RNA (hnRNA) and mRNA in 76 human liver samples and the association between intron 6 SNP genotype and stable statin dose in 273 patients who were taking stable doses of an HMG-CoA reductase inhibitor (statin) for lipid control. Regarding stain dosing, lipid levels were measured at the time of enrollment and after reaching stable dose of statins. However, the lipid levels at the time of enrollment did not represent the basal level in all patients because the documentation of any prior medication was incomplete. Seven SNPs in CYP3A4/3A5 were genotyped in gDNA from 273 patients. The stable titrated statin doses were significantly lower in intron 6 SNP carriers than in non-carriers (p=0.039). After controlling for different statins, carriers of the intron 6 minor T allele were less likely to take a higher statin dose (p=0.014). In contrast, in Caucasian patients, CYP3A4*1B and CYP3A5*3 did not show any significant associations. The authors note several study limitations including the need to test other genes involved in pharmacokinetics processes of statins, the small sample size with statistical analysis limited to Caucasians, and consideration of the induction and inhibition of concomitant drugs. Dosing recommendations based on genotype were not included in the study. Larger, prospective controlled clinical trials including recommendations for dosing methodology bases on genotyping are necessary to determine the clinical utility of genotyping related to statin dosing.

Zhao et al. (2009) reported outcomes of an observational study designed to determine variables for dosing of tacrolimus, including genotyping for CYP3A4 and CYP3A5, in 50 children who underwent kidney transplantation. Blood samples were obtained before the administration of tacrolimus and at one, two, three, six, nine, and 12 hours after dosing. Dosage adjustment was based on clinical and biological follow-up and tacrolimus monitoring in order to maintain the recommended therapeutic range of 5–15 ng/ml. CYP3A4, CYP3A5, ABCB1, and ABCC2 polymorphisms were determined using the TaqMan allelic discrimination technique. The plots of individual pharmacokinetic parameters versus potential covariates indicated that apparent oral clearance was related to age, sex, time elapsed since transplantation, hemoglobin and hematocrit levels, and CYP3A5 and ABCB1 3435C>T polymorphisms. Apparent oral clearance was significantly related to body weight; in addition, it was higher in patients with low hematocrit levels and lower in patients with CYP3A5*3/*3. Oral clearance was lower in patients with CYP3A5 *3/*3 compared to patients with the CYP3A5 *1 allele (p=0.013). Regarding pharmacogenetics and clinical outcomes, creatinine clearance at one month after transplantation was compared among genotype groups with respect to CYP3A4, CYP3A5, ABCB1, and ABCC2 polymorphisms. Creatinine clearance was higher in patients with the CYP3A5*1 allele than in those with CYP3A5*3/*3 but this did not reach statistical significance (p = 0.06). While data suggest inter-individual differences in apparent oral clearance, these were not limited to CYP3A5 polymorphisms. The authors noted the population pharmacokinetic–pharmacogenetic model developed in this pediatric kidney transplant population demonstrated that, in children, tacrolimus dosage should be based on weight, hematocrit levels, and CYP 3A5 polymorphism.

Summary
Although data suggests an association of CYP3A4 and CYP3A5 and the metabolism of certain drugs, there is insufficient evidence to demonstrate the clinical impact of genotyping on dosing, including the reduction of adverse drug events and improved net health outcomes. At present support by expert professional societies/organizations as evidenced by published practice guidelines is lacking. Generally accepted dosing algorithms are also lacking; genotyping as a means to determine dose and prevent adverse drug reactions is not yet considered a standard of care. The clinical utility of pharmacogenetic testing for CYP3A4 and CYP3A5 has not yet been established. Additional large scale, prospective randomized controlled clinical trials measuring impact of these genes on drug type, dose, and concomitant use of other drugs are needed to determine the clinical utility of pharmacogenetic testing.

Pharmacogenetic Testing for UGT1A1
Cancer of the colon is a highly treatable and often curable disease when localized to the bowel. Irinotecan (Captosar®), Sargent Pharmaceuticals, Schaumburg, IL) is one of several drugs indicated for treatment of colon cancer. Irinotecan is inactivated by the enzyme uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1). Deficiencies in UGT1A1 can be caused by certain polymorphisms and can result in conditions associated with hyperbilirubinemia such as types I and II Crigler-Najjar syndrome and Gilbert syndrome. At least 63 UGT-UGT1A1 variant alleles have been described, including single base pair changes, frame shift mutations, insertions, and deletions of the gene (EGAPP, 2009). As a result, irinotecan should be used with caution and at decreased dose in individuals who have Gilbert's syndrome and or elevated serum bilirubin. Additionally polymorphisms encoding the gene for UGT1A1 can result in an increased accumulation of irinotecan (National

Comprehensive Cancer Network [NCCN], 2012). Pharmacogenetic testing to determine the presence of the UGT1A1*28 allele has been proposed for individuals who are undergoing irinotecan therapy.

U.S. Food and Drug Administration (FDA)
Irinotecan (Captosar®), Sargent Pharmaceuticals, Schaumburg, IL) has been approved for the treatment of metastatic cancer of the colon or rectum. The Indications and Usage section of the FDA-approved prescribing label does not recommend genotyping for UGT1A1 polymorphisms prior to the use of irinotecan.

Literature Review
Hu et al. (Aug 2010) conducted a systematic review and meta-analysis to evaluate the relationship between UGT1A1 and neutropenia in patients treated with irinotecan. Overall analysis (n=15 trials) resulted in a statistically significant difference in an increased risk of neutropenia among UGT1A1*28/*28 genotypes compared to UGT1A1*1/*1 or UGT1A1*1/*28 (p<0.001). In 14 trials, a significantly increased risk was seen in UGT1A1*28/*28 compared to UGT1A1*1/*1 at medium and high doses of irinotecan (p<0.001, each). No significant difference was seen in the risk of neutropenia in UGT1A1*1/*28 vs. UGT1A1*1/*1 genotypes. Overall analyses of nine studies suggested a significant increased relative extent of glucuronidation (REG) of SN-38 with the UGT1A*1*1 genotype compared to UGT1A1*28/*28 (p<0.001) .The weighted mean difference of REG (UGT1A1*1/*1 or UGT1A1*1/*28 vs. UGT1A1*28/*28) increased with increasing dose of irinotecan. The analysis suggested that an increased risk of neutropenia existed for the UGT1A1*28/*28 genotype at all doses of irinotecan. Limitations of the meta-analysis included: three of the included studies were abstracts; inclusion of retrospective study designs; possibility of publication bias (p=0.43); and heterogeneity of study designs, chemotherapy regimens, irinotecan dosages (p=0.003), patient populations, types of tumors, stages of diseases, and mutation detection methods.

In a second systematic review and meta-analysis, Hu et al. (Jul 2010) evaluated the relationship between UGT1A1 and severe diarrhea in cancer patients treated with irinotecan. Twenty prospective and retrospective clinical trials met inclusion criteria. Pooled data from all studies showed a significantly increased risk of toxicity in patients with UGT1A1*1/*28 or UGT1A1*28/*28 compare to UGT1A1*1/*1 (p<0.001). When UGT1A1*1/*28 was compared to a wild-type (wt) genotype (n=15 trials) an increased risk was seen with UGT1A1*1/*28 (p=0.001). UGT1A1*28/*28 compared to wt genotype (n=11 trials) also revealed increased toxicity in UGT1A1*28/*28 genotype. At medium and high doses, analyses stratified by dose suggested an increased risk of severe diarrhea with UGT1A1*28/*28 compared to wild type. There were no significant differences at low doses. Data from 11 trials compared UGT1A1*28/*28 vs. UGT1A1*1/*1 or UGT1A1*1/*28 also showed an increased risk of severe diarrhea for UGT1A1*28/*28 genotypes at medium and high doses (p=0.001). Based on this analysis, patients with UGT1A1*28/*28 and UGT1A1*1/*28 are at a higher risk of developing severe diarrhea treated with medium and high doses of irinotecan. Limitations of the meta-analysis included the small (n=20-218), heterogeneous patient populations, inclusion of retrospective study designs, possible publication bias, significant heterogeneity of irinotecan dosages (p=0.013), and the inability to determine what dose of irinotecan increased the risk of toxicity.

Schulz et al. (2009) retrospectively evaluated (n=105) "the correlation between UGT1A1 and irinotecan-associated side effects and parameters of drug efficacy in patients with metastatic colorectal cancer." The patients were a subset of a previous phase III randomized controlled trial that evaluated the effectiveness of irinotecan plus oxaliplatin vs. irinotecan plus 5-fluorouracil (FU)/folinic acid as first-line treatment of metastatic colorectal cancer. Blood samples were obtained prior to the administration of chemotherapy. Within the study group, 49.5% of patients had a heterozygous genotype (6/7), 39.0% had a wild type genotype (6/6) and 9.5% had a homozygous genotype (7/7). There were two single cases of the rare genotype (5/7) which were excluded from further evaluation. There were no statistically significant differences between patients with genotypes 6/7, 7/6 and 6/6 in overall response rates (p=0.75); overall survival (p=0.73) or time to progression (p=0.97) in genotype 6/6 compare to 6/7 and 7/7; and in 6/6 and 6/7 compared to 7/7 in delayed diarrhea (p=0.08), treatment delays (p=0.24) and dose reductions (p=0.07). The results of this study indicated that there is a non-significant influence of UGT1A1 on efficacy and rate of irinotecan toxicities in patients treated with low-dose irinotecan.

Hoskins et al. (2007) conducted a meta-analysis of nine studies (n=821) that assessed the association of irinotecan dose with the risk of irinotecan-related hematologic toxicities (grade III-IV neutropenia) for patients with a UGT1A1*28/*28 genotype. According to the authors, those patients with the UGT1A1*28/*28 genotype had a higher risk of toxicity than those patients with the UGT1A1*1/*1 or UGT1A1*1/*28 genotypes at high

doses (200-350 mg/m² every 21 days) (p=0.005) and at medium doses (180 mg/m² every two weeks) (p=0.008). At low doses (80-125 mg/m² weekly), the risk was similar for all genotypes. The authors stated that initial studies found UGT1A1*28 genotype to be associated with the risk of toxicity, subsequent studies have been inconsistent. They also indicated that analysis of the studies was limited by the many sources of heterogeneity among the studies. This data suggested that there may be an association between the UGT1A1*28 genotype and irinotecan-induced toxicity at higher irinotecan doses. Further, well-designed studies are warranted to address many unanswered questions including those regarding dosing strategies based on the UGT1A1*28 genotype.

In an evidence report/technology assessment, the Evaluation of Genomic Applications in Practice and Prevention Project (EGAPP) (2009) conducted a systematic review of the literature and published recommendations on UGT1A1 genotyping in colorectal cancer patients treated with irinotecan. The quality of evidence for analytic validity was considered adequate and the overall sensitivity for UGT1A1 was 100% for genotypes containing the *28 and *6 alleles. Few data were available to support *36, *37, *6, and *27 variants. The overall estimated specificity was 100%. Failure rates for the Invader ranged from 5.4%–7.6%, some resolved with retesting. The EGAPP reported that there was convincing evidence for a significant association between UGT1A1*28 genotypes and the incidence of severe neutropenia at standard doses of irinotecan. The association between genotype and severe diarrhea was not as strong. In terms of tumor response, there was a significantly higher tumor response rate in *28 homozygous individuals compared to wild genotype individuals. Finally, no evidence was found to support clinical utility. The EGAPP notes "Although there appears to be a clear relationship between UGT1A1 genotype and severe neutropenia, and some evidence of a relationship with severe diarrhea, there is no evidence to support or refute the hypothesis that a modified initial and/or subsequent dose of irinotecan will change the rate of these severe adverse drug reactions." The EGAPP also noted "If the test were recommended for use in clinical practice, additional studies would be needed to understand the potential effects of alleles that are rare in Caucasians but more common in other racial/ethnic groups (e.g., *6 in Asians).

Professional Societies/Organizations
National Comprehensive Cancer Network® (NCCN®): In their discussion of the toxicities associated with irinotecan (Camptosar®), Sargent Pharmaceuticals, Schaumburg, IL), NCCN Clinical Practice Guidelines in Oncology™: Colon Cancer (2013) stated that a commercial test is available for the detection of UGT1A1*28 allele and a warning has been put in the Camptosar label that "indicates that a reduced starting dose of the drug should be used in patients known to be homozygous for UGT1A1*28", but guidelines for the use of this test in clinical practice have not been established. NCCN also noted that "UGT1A1 testing on a patient who has experienced irinotecan toxicity is not recommended since the patient will require a dose reduction regardless of the UGT1A1 test result."

Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group (EGAPP): The EGAPP published its recommendations regarding the use of UGT1A1 testing for individuals undergoing treatment with irinotecan (2009). This paper concluded, "The evidence is currently insufficient to recommend for or against the routine use of UGT1A1 genotyping in patients with metastatic colorectal cancer who are to be treated with irinotecan, with the intent of modifying the dose as a way to avoid adverse drug reactions (severe neutropenia)."

Summary for Pharmacogenetic Testing for UGT1A1
Although commercial testing is available, the clinical utility of testing has not been established for improving health outcomes for an individual with colon cancer. According to the NCCN (2012) testing on a patient who has experienced irinotecan toxicity is not recommended as the patient will require a dose reduction regardless of the outcome of testing.

Pharmacogenetic Testing for BCR-ABL Resistance or Inhibition
The breakpoint cluster region (BCR)-Abelson (ABL) fusion gene is a cancer-causing gene (i.e., oncogene) generated when a part of the ABL gene on chromosome 9 and a part of chromosome 22 break off and swap places (i.e., balanced translocation). The ABL gene relocates to the BCR gene on chromosome 22; the resulting chromosome is known as the Philadelphia chromosome (Ph, t(9;22). This chromosome is found in about 95% of individuals with chronic myelogenous leukemia (CML), and 30% of adults with acute lymphoblastic leukemia (ALL) and is important both in terms of diagnosis and for monitoring response to treatment (Agency for Healthcare Research and Quality [AHRQ], 2010; National Cancer Institute [NCI], 2013;Najfeld, 2008; National

Institute for Clinical Excellence [NICE], 2002). In CML, the standard method for monitoring response to therapy is conventional cytogenetic analysis of metaphase chromosomes obtained from marrow aspirate (Najfeld, 2008; NICE, 2002). The test can also identify additional chromosome abnormalities which may be important indicators of prognosis; however, because of the relatively small numbers of cells examined the sensitivity is approximately 5% if 20 metaphases are examined (National Institute for Clinical Excellence [NICE], 2002).

Other laboratory techniques may include hyperphase and interphase fluorescence in situ hybrization (FISH), and real-time quantitative polymerase chain reaction (RQ-PCR). These molecular assays improve the ability to measure residual disease and to estimate risk of relapse (Nashed, 2003). Real-time quantitative PCR (RQ-PCR) is by far the most sensitive method. It provides an accurate measure of the total leukemia cell mass and the degree to which breakpoint cluster region-Abelson (BCR-ABL) transcripts are reduced by therapy, and correlates with progression-free survival. Current international recommendations for optimal molecular monitoring of patients receiving imatinib treatment include an RQ-PCR assay expressing the BCR-ABL transcript levels, which is predictive of prognosis (Bhatia, 2012; Najfeld, 2008). Molecular responses at 12 and 18 months are also predictive of long-term outcome (Bhatia, 2012). In acute lymphocytic leukemia (ALL), because many patients have a different fusion protein from the one found in chronic myelogenous leukemia (CML), the BCR-ABL gene may be detectable only by pulsed-field gel electrophoresis or reverse-transcriptase polymerase chain reaction (RT-PCR). These tests should be performed whenever possible in patients with ALL, especially those with B-cell lineage disease (NCI, 2013a).

The BCR-ABL gene encodes an enzyme called tyrosine kinase. BCR-ABL tyrosine kinase is not controlled by normal cellular mechanisms and its presence leads to enhanced cell proliferation, resistance to apoptosis (i.e., programmed cell death) and altered adhesion (NICE, 2002). Unregulated tyrosine kinase activity is important to the development of several disorders including CML, and some types of ALL. Other disorders in which unregulated tyrosine activity is implicated include gastrointestinal stromal tumors (GIST), dermatofibrosarcoma protuberans, myelodysplastic syndromes, and mast cell disease. With these disorders other gene biomarkers and variants have been identified. For the purpose of this Coverage Policy, discussion is limited to the BCR-ABL fusion gene in individuals with CML and ALL.

The two major obstacles to successful TKI-based therapies are the persistence of BCR-ABL fusion-positive cells and relapse of the disease due to emergence of resistance (Najfeld, 2008; AHRQ, 2010). Acquired resistance to imatinib treatment is manifested in two ways: amplification of BCR-ABL fusion product and mutations in the ABL kinase domain. Specific mutations in BCR-ABL have been shown to confer resistance to imatinib both in vitro and in vivo, by affecting the binding of the drug to the tyrosine kinase enzyme (AHRQ, 2010). Currently 40 different ABL kinase domain mutations have been described. Of interest is the T315-I mutation which is thought to be resistant to all current TKI therapy. The mutation frequency in imatinib resistant patients with CML ranges between 2% and 20%, with variability related to detection methods as well as patient cohort characteristics and treatment. T315I mutation frequency appears to be greater in patients with Philadelphia chromosome-positive (Ph[+)] ALL and likely increases with the continuation of TKI treatment (Nicolini, 2009). The detection of mutations of the BCR-ABL gene has been proposed as a pharmacogenetic test with potential impact on management decisions (AHRQ, 2010).

U.S. Food and Drug Administration (FDA)
Several drugs have been approved by the FDA for use in selected individuals with CML and ALL, including Imatinib mesylate (Gleevec®, Novartis, East Hanover, NJ), dasatinib (Sprycel®, Bristol Myers Squibb Company, Princeton, NJ), and nilotinib hydrochloride monohydrate (Tasigna® , Novartis, East Hanover, NJ). These drugs are tyrosine kinase inhibitors (TKI), that is, drugs that bind to the tyrosine kinase enzyme and inhibit its activity (AHRQ, 2010). The goal of therapy is to achieve a molecular response as measured by the reduction or elimination of BCR-ABL transcripts. Increasing the dose schedule of TKIs can often overcome the resistance due to gene amplification. Those individuals who cannot tolerate or are resistant to imatinib may benefit from the second generation of TKIs, such dasatinib and nilotinib. Because their mechanism of action is different from imatinib they retain activity against nearly all imatinib resistant mutations (Najfeld, 2008). There are no labeling recommendations from the FDA regarding BCR-ABL genotyping for use with these drugs.

Literature Review
Several studies have reported associations between variations of BCR-ABL and response to drug therapy. AHRQ (2010) performed a systematic review of the published literature regarding variations of the BCR-ABL1 fusion gene and response to imatinib, dasatinib, and nilotinib in CML. Thirty-one studies were analyzed for

outcomes of interest including overall survival and cancer specific survival; progression-free or event-free survival (as defined by each study); and treatment failure. Typically, treatment failure is defined as absence of hematologic, cytogenetic, or molecular response to treatment, according to various criteria. Data was analyzed for first-, second-, and third- line TKI therapy. Second-line TKI therapy studies (four publications) demonstrated sensitivity and specificity ranges of 0.35 to 0.83 and from 0.58 to 1.00, respectively, for high-dose imatinib and imatinib-based combination. These studies were small, the calculated sensitivity and specificity values have wide confidence intervals, and a range of different mutations was identified in each of them. No robust conclusions could be made. Eight studies (9 publications) pertained to dasatinib; some had overlapping populations. Sensitivities and specificities ranged from 0.27 to 0.90 and from 0.14 to 0.87, respectively. A lack of predictive ability is suggested. For nilotinib, three studies had relevant data. Sensitivity ranged from 0.56 to 0.71 and specificity ranged from 0.42 to 0.56 for all identified mutations. Only one included study reviewed overall survival (OS). No statistically significant differences in the time-to-death among patients with, versus without mutations were found. When any breakpoint cluster region- Abelson (BCR-ABL1) mutation was considered, almost all studies reported sensitivity and specificity values that are not suggestive of strong predictive ability. The Agency for Healthcare Research and Quality (AHRQ) notes that no study explicitly reported details on changes in treatment plans before or after testing.

AHRQ determined "The presence of any BCR-ABL mutation does not appear to differentiate response to tyrosine kinase inhibitor (TKI) treatment (i.e., imatinib, dasatinib, nilotinib)." AHRQ also notes "the majority of evidence pertains to the short term surrogate outcomes of hematologic, cytogenetic or molecular response. Data on overall or progression-free survival are sparse. "There is consistent evidence that presence of the relatively rare T315-I mutation can predict TKI treatment failure, mainly in terms of hematologic and cytogenetic response."

Jabbour et al. (2009) studied 169 patients with chronic myelogenous leukemia (CML) after imatinib failure. The goals of the study were to investigate whether in vitro sensitivity of kinase domain mutations could be used to predict the response to therapy as well as the long-term outcome of patients receiving second-generation TKIs after imatinib failure. Treatment failure was defined as loss of a cytogenetic, or complete hematologic response (CHP), or failure to achieve a CHR or any hematologic response (for patients in accelerated phase or blast phase after 3 months of therapy, or persistence of 100% Philadelphia chromosome (Ph)–positive metaphases after 6 months of therapy, or more than or equal to 35% after 12 months). Fifty-seven patients (66%) had received prior therapy with interferon-alpha before the start of imatinib; 29 (34%) had received imatinib as their first-line therapy for CML. Mutations were detected by cDNA sequencing for mutations in the kinase domain of BCR-ABL before a change to dasatinib or nilotinib in 86 patients. Ninety-four mutations were identified in 86 patients with imatinib failure. Seven patients harbored more than 1 mutation. There was no difference in patient characteristics between those with mutations at the time of imatinib failure versus those with no mutations. Forty-one patients received dasatinib and 45 received nilotinib after developing failure to imatinib therapy. Hematologic and cytogenetic response rates were similar for patients without or with KD mutations. After a median follow-up of 23 months, 48 (58%) of patients without baseline mutations were alive compared with 52 (60%) with any mutation.

Nicolini et al. (2009) reported the results of a retrospective observational study of 222 patients with CML in chronic-phase, accelerated-phase, or blastic-phase and Philadelphia chromosome-positive (Ph$^+$) ALL patients with the BCR-ABL T315I mutation. After T315I mutation detection, second-generation TKIs were used in 56% of cases, hydroxyurea in 39%, imatinib in 35%, cytarabine in 26%, MK-0457 in 11%, stem cell transplantation in 17%, and interferon-alpha in 6% of cases. Median overall survival from T315I mutation detection was 22.4, 28.4, 4.0, and 4.9 months, and median progression-free survival was 11.5, 22.2, 1.8, and 2.5 months, respectively, for chronic phase, accelerated phase, blastic phase, and Ph(+) ALL patients. These results suggest that survival of patients harboring a T315I mutation is dependent on disease phase at the time of mutation detection.

In an earlier study by Jabbour et al. (2006) 171 patients were screened for mutations after failing TKI therapy with a median follow-up of 38 months from start of therapy. Sixty-six mutations impacting 23 amino acids in the BCR-ABL oncogene were identified in 62 (36%) patients. Factors associated with the development of mutations were older age, previous interferon therapy and accelerated or blast phase at the start of TKI therapy. By multivariate analysis, factors associated with a worse survival were development of clonal evolution and a higher percentage of peripheral blood basophils. The presence of a BCR-ABL kinase domain mutation had no impact on survival. When survival was measured from the time therapy started, non-P-loop mutations were associated with a shorter survival than P-loop mutations. The authors concluded that BCR-ABL P-loop

mutations were not associated with a worse outcome. This study suggests that outcomes of individuals who fail TKI therapy may be influenced by multiple factors.

Nicolini and colleagues (2006) retrospectively analyzed the predictive impact of 94 breakpoint cluster region (BCR) - Abelson (ABL) kinase domain mutations found in 89 protein tyrosine kinase inhibitor (TKI) resistant chronic myelogenous leukemia (CML) individuals. With a median follow-up of 39 months, overall survival was worse for P-loop and another point mutation (T315-I), but not for other BCR-ABL mutations. For individuals in chronic phase only, analysis demonstrated a worse overall survival for P-loop and worse progression free survival for T315-I mutations.

Professional Societies/Organizations
National Cancer Institute (NCI): Regarding BCR-ABL mutation analysis in individuals with chronic myelogenous leukemia (CML), the NCI notes "In case of treatment failure or suboptimal response, patients should undergo BCR/ABL kinase domain mutation analysis to help guide therapy with the newer tyrosine kinase inhibitors or with allogeneic transplantation (2013b)."

National Comprehensive Cancer Network™ (NCCN™): Regarding kinase domain mutation testing, the NCCN notes "Kinase domain mutation analysis is recommended in chronic phase CML if there is inadequate initial response (failure to achieve complete hematological response at 3 months, minimal cytogenetic response at 6 months or major cytogenetic response at 12 months or any sign of loss of response (defined as hematologic relapse, cytogenetic relapse or 1 log increase in BCR-ABL transcript ratio and loss of MMR)." The NCCN also recommends that "KD mutation testing be performed for progression to accelerated or blast phase CML (2011)." The NCCN panel does not endorse routine CYP2D6 testing for women being considered for tamoxifen therapy (2011).

Summary for Pharmacogenetic Testing for BCR-ABL Resistance or Inhibition
Although certain BCR-ABL mutations may be associated with TKI therapy resistance, sensitivity and specificity values in outcome studies are not suggestive of strong predictive ability, with the exception of the T315-I mutation. Early identification of this mutation may allow for alternative treatment regimens including increased dose scheduling and drug selection. Data in the published peer-reviewed scientific literature supports the clinical utility of testing for the presence of the T315-I mutation as evidence of TKI resistance. At this time the clinical utility of testing for other mutations to determine TKI resistance has not been established.

Pharmacogenetic Testing for the Dihydropyrimidine Dehydrogenase (DPYD) Gene
DPD deficiency is a disorder characterized by a wide variation of neurological symptoms and is inherited in an autosomal recessive fashion. It is caused by mutations in the DPYD gene. Individuals may have a severe form of the disorder which becomes apparent in infancy, others may be asymptomatic. Individuals with DPD are vulnerable to severe, potentially life-threatening toxic reactions to certain drugs called fluoropyrimidines that are used to treat cancer. Because fluoropyrimidine drugs are also broken down by the dihydropyrimidine dehydrogenase enzyme, deficiency of this enzyme leads to the drug buildup that causes fluoropyrimidine toxicity. Common examples of these drugs are fluorouracil (Fluorouracil (Adrucil®) Pharmacia & Upjohn, Bridgewater, NJ) and capacitating (Xeloda®), Genetech, South San Francisco, CA. Fluoropyrimidine toxicity may lead to neutropenia, and thrombocytopenia (Genetics Home Reference [GHR], 2012). The gene test identifies the IVS14+1G>A mutation, which accounts for approximately 50% of DPD deficiency alleles.

U.S. Food and Drug Administration (FDA)
Capecitabine (Xeloda®) Genetech, South San Francisco, CA) has been approved for the treatment of Duke's C colon cancer, metastatic colorectal cancer, and metastatic breast cancer. It is contraindicated for use in individuals with DPD deficiency. Flourouracil (5FU) (Teva Parenteral Medicines, Inc, Irvine, CA) is indicated for the palliative management of carcinoma of the colon, rectum, breast, stomach and pancreas. DPD genotyping is not required in the Indication and Usage section of the FDA-approved prescribing labels prior to the use of either of these drugs.

Literature Review
Prospective controlled data are limited in the published peer-reviewed literature regarding the improvements in health outcomes for an individual with DPD deficiency that undergoes genotyping. Deenen and others conducted a retrospective nested case-control study of 45 subjects with colorectal cancer (CRC) who had capecitabine-related toxicity and 100 randomly selected controls (2011). All subjects were selected from a

sample of 568 individuals with previously untreated colorectal cancer enrolled in the CAIRO2 trial and were tested for DPYD genetic variants. From this data genotype frequencies of polymorphisms were calculated. The authors reported that 4 variant alleles (IVS14+1G>A, 1236G>A, 2846G>A, and 2194G>A) were significantly associated with severe diarrhea when carriers were treated with capecitabine-based chemotherapy. Furthermore, heterozygous carriers of IVS14+1G>A were significantly at risk for developing grade III to IV toxicity. No association with overall survival was noted for any specific allele. While this study did identify a role of several alleles in capecitabine-related toxicity, no data regarding outcomes benefit of screening for DYPD genotypes was provided. Further investigation is warranted.

Professional Societies/Organizations
Neither the NCCN nor the National Cancer Institute has published guidance regarding DPYD genotyping.

Summary for Pharmacogenetic Testing of the DPYD Gene: There is insufficient evidence regarding the published peer-reviewed scientific literature to inform improved health outcomes as a result of DPYD genotyping in an individual receiving . There is a lack of prospective randomized trials; data are limited to case studies with small study populations. At this time the role of genotyping has not been established for this indication.

Pharmacogenetic Testing of CYP2C9 and VKORC1 for Warfarin Metabolism
CYP2C9 metabolizes approximately 10% of clinically prescribed drugs. Several variant alleles or single nucleotide polymorphisms (SNPs) of the CYP2C9 gene have been identified as affecting the metabolism of warfarin in the liver. Individuals with CYP2C9*2 and CYP2C9*3 metabolize coumarins slowly and may require a lower initial dose of the drug. Other CYP2C9 alleles also associated with reduced enzymatic activity but occurring at lower frequencies include the *5,*6, *9 and *11 alleles.

Mutations in the VKORC1 (vitamin K epoxide reductase complex 1) gene has been associated with deficiencies in vitamin-K-dependent clotting factors, and with warfarin resistance. Variation in the VKORC1 gene is believed to be the most important individual predictor of warfarin dose, accounting for about 30% of the variance observed in dosing (Online Mendelian Inheritance in Man [OMIN], 2012). The VKORC1 genotype has also been shown to be the strongest predictor of warfarin dosage in those of Japanese heritage.

There are population and racial differences in minor allele frequencies of important variants as well as sensitivity to warfarin dosage requirements. The CYP2C9*2 and *3 alleles and VKORC1-1639G>A genotype explain approximately 50–60% of the variability in dosage in Caucasians but only 20–25% of variability in African Americans.

Clinical Utility: Although pharmacogenetic-based testing has the potential to identify sources of interindividual variability in drug response, at this time the standard of care mechanism by which warfarin dosage is determined remains close monitoring of the INR.

The objective of using pharmacogenetics-based warfarin therapy is to improve the safety and effectiveness of anticoagulant therapy by decreasing number of adverse events caused by bleeding and reducing the time to stable INR. It is theorized that the use of pharmacogenetic testing in warfarin therapy will affect the initial warfarin dose but will have less effect once the therapeutic dose is known (Gage, 2006). A number of dosing algorithms which incorporate age, body mass index, and genetic variation as well as other factors have been developed. However, at present no single algorithm has been accepted as the standard of care to predict the best dose for stable anticoagulation. Additionally, there is a lack of data regarding the ability to use genotype to further refine warfarin dose after INRs become available.

Several large randomized controlled clinical trials comparing the safety and effectiveness of genotype-based- and standard of care dosing are ongoing. Although results of published trials are promising, at this time the clinical utility of pharmacogenetic testing to inform warfarin metabolism to predict accurate dosing is unknown.

U.S. Food and Drug Administration (FDA)
On August 16, 2007 (updated January 22, 2010), the FDA revised the drug labeling for Coumadin® (Bristol-Meyers Squibb Company, Princeton, NJ), a brand of warfarin, to include genomic information. A specific recommendation to perform testing before prescribing warfarin is not included in the labeling. In the Dosage and Administration section, it states that lower initial doses should be considered for patients with genetic variations in CYP2C9 and VKORC1; however, the dosage recommendations have not changed. In the Clinical

Pharmacology section of the labeling, evidence of reduced warfarin clearance in patients carrying mutations in the genes CYP2C9 and VKORC1 is discussed. In the Precautions section, it is stated that genetic variation in the CYP2C9 and VKORC1 enzymes may influence the response of the patient to warfarin. It is expected that generic forms of the drug will also feature revised labeling.

In addition to a number of warfarin genetic assay kits and independent laboratory-developed tests for warfarin response, there are several devices that have received pre-market clearance by the FDA. They include but are not limited to:

- Verigene Warfarin Metabolism Nucleic Acid Test[®] and the Verigene system[®] (Nanosphere Inc., Northbrook IL): this test received clearance from the FDA as a class II device in September, 2007.
- eSensor[®] Warfarin Sensitivity Test, eSensor[®] XT-8 System (GenMark DX™, Carlsbad, CA; previously marketed by Osmetech Molecular Diagnostics, Pasedena, CA): this test received clearance from the FDA in July, 2008.
- INFINITI 2C9 & VKORC1 Multiplex Assay for Warfarin (AutoGenomics, Inc., Carlsbad, CA): this test received clearance from the FDA in January, 2008.
- Rapid Genotyping Assay-CYP2C9 & VKORC1 (Paragon DX™, Morrisville, NC): this test received clearance from the FDA in April, 2008.
- eQ-PCR™ LC Warfarin Genotyping Kit (TrimGen Corporation, Sparks, MD): this test received clearance from the FDA in January, 2009.

Literature Review
In regards to warfarin dosing, a number of comparative analyses based on retrospective data have been carried out, but no single pharmacogenetic-based algorithm has emerged as the consensus choice at this time. Several small RCTs have yielded promising results; however, no adequately powered, randomized, controlled trials (RCTs) has been completed that inform whether the improvement in dosing accuracy potentially achieved with a genotype-based approach yields a reduction in serious adverse events.

Several case-controlled and retrospective studies have been published that demonstrate a correlation between CYP2C9 and VKORC1 variants and warfarin dose requirements (Freder, 2010; Zhu, 2007; Aquilante, 2006; Lindh, 2005; Reider, 2005; Veenstra, 2005; Wadelius, 2005; Joffe, 2004; Peyvandi, 2004; Higashi, 2002).

Additionally, a number of studies have reported results regarding the development and validation of various pharmocogenetic-based dosing algorithms for warfarin. At this time there is no consensus regarding a single algorithm for warfarin dosing based on genotype.

In a large cohort study conducted by the International Warfarin Pharmacogenetics Consortium, clinical and genetic data were collected from 4043 patients to create a pharmacogenetic dose algorithm. In a validation cohort of 1009 patients the potential clinical value of each algorithm was retrospectively evaluated by calculating the percentage of patients whose predicted dose of warfarin was within 20% of the actual stable therapeutic dose. In the validation cohort, it was found that the pharmacogenetic algorithm accurately identified larger proportions of patients who required 21 mg of warfarin or less per week and of those who required 49 mg or more per week to achieve the target International Normalized Ratio (INR) than did the clinical algorithm (49.4% versus 33.3%, respectively, p<0.001, among patients requiring 21 mg or less per week; and 24.8% versus 7.2%, respectively, p<0.001, among those requiring greater than 49 mg per week). The analysis did not address the issue of whether a precise initial dose of warfarin will lead to improved clinical outcomes, such as a reduction in the time needed to achieve a stable therapeutic INR, fewer INRs that are out of range, and a reduction in bleeding or thromboembolic events (2009).

Millican et al. (2007) reported results of a retrospective analysis of two cohorts of orthopedic surgery patients (n=92) conducted with the goal of developing an algorithm for initial warfarin dose. Genotype for polymorphism in CYP2C9 and VKORC1 genes was performed. Utilizing a stepwise regression, a model was developed that refined the warfarin dose. The algorithm explained four-fifths of the variability in therapeutic dose. It was noted that significant predictors were INR value after three doses (47% reduction per 0.25 unit rise), first warfarin dose (+7% per 1 mg), CYP2C9*2 and CYP2C9*3 genotype (-38% and -17%, respectively, per allele), estimated blood loss, smoking status (+20% in current smokers), and VKORC1 (-11% per copy of haplotype A).

Tham et al. (2006) conducted a study with the aim of deriving a pharmacogenetic-based dosing algorithm by use of retrospective information and to validate it through a data-splitting method in a separate cohort of equal size. The study included 215 records of patients who had been recruited in a previous genotyping study for CYP2C9/VKORC1.The authors hypothesized that single-nucleotide polymorphisms in CYP2C9 and VKORC1, used to infer VKORC1 haplotype in combination with demographic factors, can accurately predict warfarin doses. Within the final model, only predictors reaching a statistical significance of $p < .05$ were retained. Data from 107 subjects undergoing maintenance warfarin therapy with an International Normalized Ratio (INR) between two and three were used to derive the final model, as an exponential function of age, weight, CYP2C9*3 allele, and VKORC1 381 CC and TC genotypes. This model accounted for 60.2% of the variability in daily warfarin dose requirement. A separate cohort of 108 subjects validated the model and demonstrated a mean underestimation of 0.23 ± 1.21 mg/d. The authors concluded that "Warfarin dose requirements in Asians can be accurately predicted by use of a combination of patient demographics and a simplified genotyping approach for single variants in CYP2C9 and VKORC1." A large randomized controlled clinical trial comparing the clinical benefits of such pharmacogenetics-guided dosing approaches for warfarin is required to determine the reproducibility and clinical benefits of this approach.

Several randomized controlled clinical trials, prospective cohort studies and retrospective analyses have examined genotype-based warfarin dosing compared with standard dosing methods. Although some studies suggest the ability to predict dosing requirements using genotype-based dosing, the standard of care for warfarin dosing remains measurement of INR.

Anderson et al. (2011) reported results of a randomized blinded clinical trial comparing a one-step pharmacogenetic-based (PG-1) dosing algorithm with a three-step pharmacogenetic-based algorithm (PG-2). The study also comprised a clinical effectiveness comparison of PG guidance using either algorithm (n=504) with standard dosing in a parallel control group (n=1866). Primary outcomes were percentage of out-of-range INR at one and three months, and percentage of time in therapeutic range. In the randomized comparison, PG-2 was non-inferior but not superior to PG-1 for percentage of out-of-range INR at one and three months and for percentage of time in therapeutic range at three months. However, the combined PG cohort was superior to the parallel controls in the percentage of out-of-range INR at one and three months, and percentage of time in therapeutic range (all $p < 0.001$). There were fewer percentage serious adverse events at three months ($p < 0.001$) with PG guidance. While results of this study suggest an improvement in out-of-range INR at one and three months with the use of a PG algorithm compared with standard dosing, at present there is no consensus regarding the superiority of a single PG algorithm. The standard of care for warfarin dosing remains close monitoring of the INR. The authors note that several RCTs are ongoing which seek to determine the role of genotype dosing in clinical practice.

McMillin et al. (2010) reported on a prospective, parallel cohort study comparing gene-based warfarin dosing with standard of care dosing in 229 patients receiving warfarin to prevent venous thromboembolism after joint replacement surgery. Primary endpoint in the study was reduction in the incidence of adverse events; additional endpoints included time to first therapeutic INR (1.8–2.9), time to first supratherapeutic INR, and percent of INR determinations that fell below, within, and above the therapeutic range. Initial dose for patients was determined by validated algorithms. Warfarin management was based on INR, but the dose was adjusted less aggressively for patients with CYP2C9 variants. Genetic variants were detected in 13% (n = 29) of participants for only CYP2C9, and 44% (n = 101) for only VKORC1; variants in both genes were detected in 19% (n = 44) of participants. The endpoints did not reach statistical significance. The study found that there were no statistically significant differences observed between the genotype-based and standard dosing groups in the average time required to achieve a therapeutic INR (approximately 4 days), or the time to first supratherapeutic INR (approximately 5 days). The incidence of adverse events between the standard of care and genotype-based dosing arms was found to not be statistically different ($p=0.683$).

Caraco et al. (2008) conducted a study to prospectively examine whether a priori knowledge of CYP2C9 genotype may improve warfarin therapy. Patients were randomly assigned to either the control group where they received warfarin by a validated algorithm (n=96) or to the study group where a CYP2C9 genotype-adjusted algorithms (n=95) was used. The first therapeutic INR and stable anticoagulation were reached 2.73 and 18.1 days earlier in the study group, respectively ($p<0.001$). The faster rate of initial anticoagulation was driven by a 28% higher daily dose in the study group ($p<0.001$). The study group patients spent more time within the therapeutic range (80.4 versus 63.4%, respectively; $p<0.001$) and experienced less minor bleeding (3.2% versus 12.5%, respectively; $p<0.02$).

Anderson et al. (2007) conducted a randomized trial that examined genotype-guided warfarin dosing compared to standard warfarin dosing in patients initiating oral anticoagulation. The study involved 206 patients that were randomized to either pharmacogenetic-guided or standard dosing. A buccal swab deoxyribonucleic acid (DNA) was genotyped for CYP2C9*2 and CYP2C9 *3 and VKORC1 with a rapid assay. The standard dosing followed an empirical protocol. The pharmacogenetic-guided dosing followed a regression equation including the three genetic variants and age, sex and weight. INR was measured on days 0, 3, 5, 8, 21, 60, and 90. The pharmacogenetic-guided predicted doses were noted to more accurately approximate stable doses (p<0.001), resulting in smaller (p=0.002) and fewer (p=0.03) dosing changes and International Normalized Ratios (INRs) (p=0.06). The primary end point, the percent out-of-range INRs, (pharmacogenetic=30.7%, standard=33.1%), did not differ significantly between the two arms. When restricted to wild-type patients who required larger doses (p=0.001) and multiple variant carriers (who required smaller doses (p<0.001) in exploratory analyses, the results (pharmacogenetic=29%, standard=39%) achieved nominal significance (p=0.03).

Hillman et al. (2005) reported on a prospective, randomized, single-blinded clinical pilot trial to evaluate the feasibility of applying a CYP2C9 gene-based warfarin dosing model in clinical practice. The trial included 117 patients who were recruited from a list of clinic patients with varied diagnoses who were eligible for warfarin initiation. The patients were randomized to receive either a standard initiation dose of 5 mg warfarin/day or rapid CYP2C9 genotyping and an initiation dose determined using parameters estimated from a previously published multivariate model. The parameters in this model included: age, body size, comorbidity (e.g., diabetes), clinical indication (e.g., valvuloplasty) and CYP2C9 genotype. The primary outcome measurements included patient willingness to participate, physician willingness to refer, sample processing time, ability to administer calculated dosage and adequacy of follow-up. The limitations of the trial were noted: the trial was designed to assess the feasibility of model-based warfarin dosing, and the power was insufficient for statistical comparison of adverse event rates. Six warfarin-related adverse events (in five patients) were noted in the standard dosing group with two events (in two patients) occurring in the model-based dosing group. The authors concluded that based on the results of this trial, prospective application of CYP2C9 gene-based multivariate warfarin dosing calculators are both technically feasible and acceptable to patients and providers. While feasible, additional outcome-based pilot trials are needed prior to implementing a larger study.

Epstein et al. (2010) reported on a prospective, observational study (Medco-Mayo Warfarin Effectiveness Study [MM-WES]) that compared the incidence of hospitalization in patients receiving warfarin genotyping (n=896) to a matched historical control group (n=2,688). The primary endpoint was the incident hospitalization rate (measured as event-free time) during the six months following the start of warfarin treatment. On an unadjusted basis, the patients in the intervention group showed a 28% lower rate of hospitalization for any cause, compared with patients in the historical control group (18.5% vs. 25%, p<0.001). The intervention group demonstrated a 27% reduction in hospitalization risk for bleeding or thromboembolism, compared with the controls (6.0% vs 8.1%, p=0.039). On a per-protocol analysis, the unadjusted differences between the two groups were found to be: patients in the intervention group showed a 31% lower rate of all-cause hospitalizations (14.0% vs. 20.5%, p<0.001) and a 40% lower rate of hospitalizations for bleeding or thromboembolism (3.7% vs. 6.2%, p=0.005). The study found that for the patients who were genotyped, 29.2% had normal warfarin sensitivity, 25.4% had lower-than normal sensitivity, 12.2% had mild sensitivity, and 33.2% had moderate to very high sensitivity. The study design did not include direct monitoring of treatment changes by physicians following delivery of the genotype data. Several weeks may have elapsed between the start of therapy and delivery of the genotype results to the physician; the interval ranged from 11 to 60 days, with a median of 32 days. The authors note that since the physicians in the intervention group were aware of being enrolled in a study, it is possible that they were thus more vigilant in their care. The authors note that further research is warranted to replicate and extend the findings.

Systematic Reviews/Technology Assessments: An ECRI emerging technology evidence report evaluated the results of three randomized controlled trials and two nonrandomized trials comparing genotype-based dosing in 1273 individuals to standard-care dosing in a total of 3060 individuals. An additional cohort study used clinical and genetic data from 5052 individuals. The assessment noted there was insufficient data to determine how genotype-based dosing compared with standard-based dosing relative to the number of serious warfarin-related adverse events and/or hospitalizations due to warfarin adverse events. In addition, the impact of genotype-based dosing compared with standard-based dosing on the time to therapeutic dose and time in therapeutic range could not be determined because the studies reported inconsistent results (2011).

Kangelaris et al. (2009) conducted a systematic review of randomized trials that compared a dose-selection strategy that used pharmacogenetic information to one that did not. The review included three small, single-center randomized clinical trials ranging from 38–238 patients. Follow-up ranged from 22 days to an average of 46 days. Each of these studies used different dosing models for the pharmacogenetic and control dosing arms. One study used dosing models that accounted only for CYP2C9 variants, while the other two utilized both CYP2C9 and VKORC1 variants. The pharmacogenetic dosing groups showed improvement in time to stable warfarin dose compared to the control groups in two of the three studies and was not reported in the third. Meta-analysis was not performed due to the heterogeneity of the trials. The authors concluded that the study did not find sufficient evidence to support the use of pharmacogenetics to guide warfarin therapy outside of clinical trials.

The Agency for Healthcare Research and Quality (AHRQ) published a technology assessment conducted by Tufts Evidenced-based Practice Center (Tufts-NEMC) that reviewed pharmacogenetic tests for selected conditions (Raman, et al., 2008). The report was commissioned by the Center for Medicare and Medicaid Services (CMS). For CYP2C9 genetic variants *2 and *3, 29 studies, including two recent randomized controlled trials, were included in the systematic review. Studies chosen for this systematic review focused on the induction or maintenance phases of warfarin therapy. For VKORC1 variants twenty-eight articles were retrieved and reviewed in full text, and 19 studies reported data on the correlation of common VKORC1 with outcomes of interest. Findings of the systematic review included:

- Carriers of the variant CYP2C9 alleles *2 or *3 receiving warfarin therapy were associated with lower mean maintenance warfarin dose requirements compared with the non-carriers. There was a lack of studies investigating the role of pharmacogenetic testing (CYP2C9 or VKORC1) and warfarin dose requirements in the induction phase. Carriers of the three relatively common VKORC1 variants were more likely to need lower maintenance warfarin dose requirements, on average, compared with the non-carriers.
- Carriers of CYP2C9 variants *2 and *3 were associated with an increased rate of bleeding complications during warfarin induction phase, but the studies did not report if those patients had normal or supratherapeutic range of PT/INR.
- Risk of over-anticoagulation (INR results exceeded desired upper limits) was also noted among carriers of CYP2C9 variants *2 and *3 compared with non-carriers. Significant risk increases were noted in 5 of these 6 studies reviewed.

The review noted the following regarding the published literature:

- The majority of studies evaluated the associations of pharmacogenetic test results with intermediate, not clinical, outcomes, such as the effectiveness of drug dose, and adverse clinical outcomes, such as bleeding events.
- Only a few studies evaluated the effects of patient- and disease-related characteristics on the association between test results and intermediate or clinical outcomes.
- No studies investigated the influence of gene testing on the impact of therapeutic choices and on the benefits and harms or adverse effects for patients from their subsequent therapeutic management after pharmacogenetic testing.
- No studies evaluated whether pharmacogenetic testing among patients who are on warfarin and who have supratherapeutic INRs will result in better maintenance of therapeutic INR, fewer episodes of serious bleeding, or fewer serious thrombotic events
- It is unclear whether dose-prediction algorithms using genetic information improve clinical outcomes (fewer bleeding complications and fewer thromboembolic events) over those of standard practice. Only a few clinical trials have addressed this question, essentially three randomized clinical trials, each of which has their flaws in the design, inclusion criteria and power to reach statistical conclusions.

The California Technology Assessment Forum (CTAF) published a technology assessment regarding the use of genetic testing to guide the initiation of warfarin therapy (2008). The findings noted that due to absent or insufficient evidence for improvement of outcomes, for benefit compared to established alternatives and for improvement attainable outside the investigational setting, the use of CYP2CP and VKORC1 did not meet its criteria for recommendation.

Sanderson et al. (2005) conducted a systematic review and meta-analysis to examine the strength and quality of existing evidence about CYP2C9 gene variants and clinical outcomes in warfarin-treated patients. Eleven studies were included in the review (n=3029), with nine studies included in the meta-analyses (n=2775). In order to be included, a study needed to report at least one of the following outcome measures: drug dose, indicators of anticoagulation control, and bleeding events. Results indicated that 20% of patients studied carry a variant allele: CYP2C9*2, 12.2% (9.7%–15.0%) and CYPC9*3, 7.9% (6.5%–9.7%). The mean difference in daily warfarin dose was noted to be: CYP2C9*2—reduction of 1.92 mg (1.37–2.47 mg), a 37% reduction; CYP2C9*3—reduction of 1.47 mg (1.24–1.71 mg), a 27% reduction. The study found the relative bleeding risk for CYP2C9*2 to be 1.91 (1.16–3.17) and for CYP2C9*3 to be 1.77 (1.07–2.91). The authors note that among the implications for these findings, there are two possible roles for genotyping CYP2C9:

- Testing could identify high-risk patients who may benefit from conservative induction regimens, lower maintenance doses and more frequent clinical and laboratory monitoring.
- Testing may assist in determining the choice of drug for patients considering elective anticoagulation (e.g., nonrheumatic atrial fibrillation).

The evidence presented in this review is insufficient to make a case for genotyping in routine clinical practice yet and that evidence of clinical utility is required. The authors concluded that "Patients with CYP2C9*2 and CYP2C9*3 alleles have lower mean daily warfarin doses and a greater risk of bleeding. Testing for gene variants could potentially alter clinical management in patients commencing warfarin. Evidence for the clinical utility and cost-effectiveness of genotyping is needed before routine testing can be recommended."

Professional Societies/Organizations
American College of Chest Physicians (ACCP): On behalf of the ACCP Ansell et al. (2008) published evidenced based clinical practice guidelines regarding the pharmacology and management of the vitamin K antagonists (VKA). The guidelines include the following recommendations: "At the present time, for patients beginning VKA therapy without evidence from randomized trials, we suggest against the use of pharmacogenetic-based initial dosing to individualize warfarin dosing. Grade (2C)."

The ACCP notes the following regarding the grading system used in the guidelines: the strength of any recommendation depends on two factors: the trade-off between benefits, risks, burden, and cost, and the level of confidence in estimates of those benefits and risks. If benefits do or do not outweigh risks, burden, and costs, a strong recommendation is designated as Grade 1. If there is less certainty about the magnitude of the benefits and risks, burden, and costs, a weaker Grade 2 recommendation is made. Support for these recommendations may come from high-quality, moderate-quality, or low-quality evidence, labeled, respectively, A, B, and C. The phrase "we recommend" is used for strong recommendations (Grade 1A, 1B, 1C) and "we suggest" for weaker recommendations (2A, 2B, 2C).

American College of Medical Genetics (ACMG): On behalf of the ACMG, Flockhart et al. (2008) published a policy guideline regarding pharmacogenetic testing of CYP2C9 and VKORC1 (Flockhart, et al., 2008). The policy statement is based on an evidenced-based report: Rapid-ACCE (Analytic, Clinical Validity, Clinical Utility and Ethical, Legal and Social implications) Review of CYP2C9 and VKORC1 Allele Testing to Inform Warfarin Dosing in Adults at Elevated Risk for Thrombotic Events to Avoid Serious Bleeding (McClain, et al., 2008).The ACCE review makes the following notations regarding genetic testing for warfarin dosing (McClain, et al., 2007):

- Regarding analytic validity of the testing:
  - Based on seven studies reporting performance in the analytic phase of testing, assays for the common CYP2C9 genotypes (*1/*2 and *1/*3) have an analytic sensitivity of 100% (95% confidence interval [CI] 96.7% to 100%). The analytic specificity is also 100% (95% CI 98.2% to 100%).
  - Based on sparse data for the less common CYP2C9 genotypes (*2/*2, *2/*3, and *3/*3), the analytic sensitivity of selected assay systems is still 100%, but the CI interval is wider (95%, CI 75% to 100%).
  - Too few data exist to estimate these rates for VKORC1 genotyping.
- At least 12 laboratories in the U.S. now offer CYP2C9 and/or VKORC1 genotyping for clinical use. Several manufacturers offer reagents to test for variants in both genes.

- Most available data are based on deoxyribonucleic acid (DNA) extracted from whole blood samples. Other sample types (e.g., mouthwash) have been mentioned, but the data are sparse for these types. .
- Regarding clinical validity of the testing:

  - International Normalized Ratio (INR) values above 3 are more likely among CYP2C9 heterozygotes (risk ratio of 2.0 or higher), and are more likely in the first and second week (induction phase) after initiation than the third week or later.
  - With all variant CYP2C9 genotypes grouped together, the clinical sensitivity of CYP2C9 to identify serious bleeding events is 46% (95% CI 32% to 60%), indicating that half of the serious bleeding occurs among wild-type individuals.
  - Clinical specificity of CYP2C9 is 69% (95% CI 62% to 75%), indicating that non-wild CYP2C9 genotypes are relatively common.
  - Relative risk for serious bleeding is 1.7 (95% CI 0.8 to 3.6).
  - The prevalence of serious bleeding among populations varies widely (<1% to 17%) depending on many factors (e.g., indication for warfarin, age, comorbidities, definition of serious bleeding and other drug use).

- Models that predict warfarin dose should consider the following characteristics:

  - Use the logarithm of the warfarin dose (not warfarin dose) as the dependent variable
  - Allow different dosages for CYP2C9 genotypes *1/*2 and *1/*3
  - Include other important factors (e.g., age, weight, height, body mass index [BMI])

- Regarding clinical utility of the testing:

  - The intended action is to compute an individual's initial warfarin dose by incorporating demographic, clinical, and gene variant data (both CYP2C9 and VKORC1) as a way to limit high INR values (over-anticoagulation) that are associated with serious bleeding events.
  - Many of these events will occur within the first few weeks of treatment. No study has yet shown this intervention to be effective in reducing the incidence of high INR values, the time to stable INR, or the occurrence of serious bleeding events.
  - There are several large randomized trials underway to determine the clinical effectiveness of CYP2C9 genotyping and VKORC1 haplotyping to inform warfarin dosing.

The ACMG position statement notes that "in the context of variable warfarin sensitivity, there is limited evidence at this time to support routine testing of the CYP2C9 and VKORC1 genes for functional polymorphisms that affect warfarin dosing. Although the analytic testing is currently being performed in a number of laboratories, there is less linkage of the genotype data produced with phenotypic warfarin dosing than is optimal for the development of recommendations for clinical practice." The policy statement includes the following recommendations (Flockhart, et al., 2008):

- There are no prospective data to recommend for or against routine CYP2C9 and VKORC1 testing in warfarin-naïve patients since there are no substantive prospective study that has yet shown this intervention to be effective in reducing the incidence of high INR values, the time to stable INR, or the occurrence of serious bleeding events, while maintaining the ability of the drug to prevent thromboembolic events.
- CYP2C9 and VKORC1 genotypes can reasonably used as part of diagnostic efforts to determine the cause of an unusually low maintenance dose of warfarin or an unusually high INR during standard dosing.
- CYP2C9 testing beyond *2 and *3 alleles involves rare alleles for which there is much more limited data available to support their inclusions.

Summary for Pharmacogenetic Testing for CYP2C9 and VKORC1
A number of comparative analyses based on retrospective data suggest a relationship between the CYP2C9 and VKORC1 genes and the metabolism of warfarin; however, the impact of this information on meaningful health outcomes has not yet been demonstrated. No single pharmacogenetic-based algorithm has emerged as the consensus choice at this time. There is insufficient evidence in the published, peer-reviewed, scientific

literature to support the clinical utility of this testing. At present there is a lack of evidence to demonstrate that the use of this testing is effective in reducing the incidence of high International Normalized Ratio (INR) values, the time to a stable INR, or the occurrence of serious bleeding events. Several large randomized controlled trials are ongoing.

Genotyping for Thiopurine Methyltransferase (TPMT) Deficiency in Individuals with Inflammatory Bowel Disease (IBD)
Genetically determined variations in the activity of thiopurine methyltransferase (TPMT) can lead to differences in response to and toxicity from thiopurines (i.e., 6-mercaptopurine [6-MP] and its pro-drug, azathioprine [AZA]). These medications are used in the treatment of inflammatory bowel disease (IBD) when steroid dependency, steroid resistance, or relapse occurs. Studies have shown a direct correlation between red blood cell 6-TG activity and the accumulation of 6-MP and AZA. Either measurement of 6-TG levels or TPMT genotyping may assist clinicians in optimizing the therapeutic response to AZA/6-MP and in identifying individuals at increased risk for drug-induced toxicity (Stenson and Korzenik, 2003). Myelotoxicity can occur when a patient is unable to metabolize 6-TG. Hepatotoxicity occurs when 6-MP is not metabolized uniformly.

TPMT genotyping identifies specific heterozygous or homozygous alleles or polymorphisms to which 6-MP and AZA react. These alleles can cause treatment failure or toxicity. Among patients with inflammatory bowel disease (IBD):

- Homozygous TPMT mutation is low or absent in 0.33%. These individuals are at extreme risk of very severe leukopenia with potential septic complications and may not be good candidates for thiopurine therapy.
- Heterozygous TPMT activity is at an intermediate level in 11%. These individuals respond to therapy, but are prone to myelotoxicity. Reducing dosages minimizes the development of this toxic effect.
- "Wild type" TPMT activity is at normal to high levels in 89%. Response to thiopurine therapy varies. Results may include normal to excessive levels of 6-methylmercaptopurine (6-MMP). High TPMT activity may require increased dosing to achieve a therapeutic response. Close monitoring is required, however, as these patients are susceptible to hepatotoxicity due to excessive 6-MMP (Regueiro and Mardini, 2002; Sandborn, 2001; Dubinsky, et al., 2000).

TPMT genotyping is reliable (90% sensitivity, 99% specificity) in identifying these polymorphisms and can therefore be used to individualize thiopurine therapy and prevent serious toxicities (Kager and Evans, 2008).

Prometheus Laboratories (San Diego, CA) provides metabolite and pharmacogenomic testing for use in the treatment of patients receiving AZA therapy. The company's PRO-Predict Rx[®] TPMT performs genotypic analysis of the TPMT enzyme, while PRO-Predict Rx[®] Metabolites measures levels of 6-TG and 6-MMP, and PRO-Predict Rx[®] EnzAct provides a quantitative analysis of TPMT enzyme activity levels.

The U.S. Food and Drug Administration (FDA) considers the use of genomic information in drug labels either to require a genetic test for prescribing a drug, to recommend the use of a genetic test prior to drug therapy, or simply to provide information about the current knowledge of genomics that is relevant to drug therapy without the requirement or recommendation of a specific action National Academy of Clinical Biochemistry [NACB], 2010). The FDA prescribing information states that patients with intermediate TPMT activity may be at an increased risk of myelotoxicity and those with low or absent TPMT activity are at an increased risk of developing severe, life-threatening myelotoxicity, if receiving conventional doses of azathioprine. TPMT testing prior to the initiation of azathioprine is recommended, not required by the FDA.

Literature Review
The available evidence examining the effectiveness and clinical utility of TPMT genotyping is primarily in the form of retrospective case series. Some studies have found minimal evidence of the effectiveness of TPMT pretesting (Fangbin, et al., 2012; Booth, et al., 2011) or no association between TPMT polymorphisms and intolerance of and toxicity from the use of AZA for IBD (De Ridder, et al., 2006 [n=72]; Sayani, et al., 2005 [n=29]; Reuther, et al., 2003 [n=71]). The results of other studies (n=71-394) suggest that TPMT genotyping predicts adverse effects and reduced chance of clinical response in AZA-treated patients (Higgs, et al., 2010; Ansari, et al., 2008, Gisbert, et al., 2006), and allows for more effective AZA dosing (Banerjee and Bishop, 2006; Reuther, et al.; 2003a; Regueiro and Mardini, 2002; Dubinsky, et al.; 2000).

Newman et al. (2011) conducted a randomized controlled trial (RCT) (n=333) to assess whether TPMT genotyping prior to azathioprine reduces adverse drug reactions. Patients with inflammatory disease primarily IBD (n=284), were randomized 1:1 to undergo TPMT genotyping prior to azathioprine or to start treatment without genotyping. There were no differences in TPMT variant genotype frequencies between the two study arms. The overall TPMT variant genotype frequencies were one homozygote in 333 individuals and 34 heterozygotes. Of the 322 individuals who provided outcome data, 91(28.3%) patients had stopped azathioprine due to adverse drug reactions at four months of follow-up. With regard to the primary end point, there was a trend to stopping azathioprine with increasing age due to adverse drug reactions ($p = 0.01$). There was no difference in the frequency of stopping azathioprine due to an adverse drug reaction in the two study arms (p=0.74). There was no increase in stopping azathioprine due to adverse drug reactions in TPMT heterozygotes compared with wild-type individuals. The single individual with TPMT variant homozygosity experienced severe neutropenia. With regard prescribing practice, in the non-genotyping arm, when clinicians did not have the patients' TPMT status, the average starting dose was similar between patients wild-type or heterozygous for TPMT variants. In the genotyping arm, when the TPMT status was available, the average starting dose of azathioprine was lower in the TPMT heterozygotes than wild-type individuals ($p = 0.007$). This indicated that, overall, the clinicians were initiating treatment at a lower dose for TPMT heterozygotes as advised by the genotype result. The prescribing dose patterns of azathioprine between initiation and at four months were not different between the two arms. There was no difference in dose at four months between the two study arms ($p = 0.25$) or between individuals heterozygous or wild-type for variant TPMT alleles ($p = 0.98$). No difference was found in the rates of remission achieved between the genotyped and non-genotyped arms. It was noted that pharmacogenetic testing for TPMT status may be important to identify variant homozygote individuals who are at high risk of severe neutropenia with standard dose azathioprine treatment. However, with only one homozygote identified, this study was not adequately powered to formally establish this relationship (Newman, et al., 2011).

A technology assessment performed by the Agency for Healthcare Research and Quality (AHRQ) evaluating TPMT in patients receiving AZA therapy. The report included 114 observational studies and one RCT. The majority of studies were rated fair quality. In general, there were few patients who were homozygous (or compound heterozygous) for TPMT variant alleles in the included studies limiting applicability. The sensitivity of genotyping to identify patients with low or intermediate TPMT enzymatic activity was reported to be imprecise, ranging from 70.7%─82.1% (95 % CI, lower bound range 37.90%─54%; upper bound range 84.6%─96.9%). Sensitivity of homozygous TPMT genotype to correctly identify patients with low to absent enzymatic activity was 87.1% (95% CI 44.3%─98.3%). Genotyping specificity approached 100%. Leukopenia was found to be significantly associated with low and intermediate enzymatic activity (low activity OR 80.00, 95 %CI 11.5 to 559; and intermediate activity OR 2.96, 95%CI 1.18 to 7.42), and homozygous and heterozygous TPMT variant allele genotype (OR 18.60, 95 percent CI 4.12 to 83.60; and 4.62, 95 percent CI 2.34 to 9.16, respectively). Indirect evidence confirmed strong association of leukopenia with lower levels of TPMT activity and carrier genotype already established in the literature. There was insufficient direct evidence found regarding the effectiveness of pretesting of TPMT status in patients with chronic autoimmune diseases (AHRQ, 2010).

Although it is recognized that patients with low TPMT activity are more susceptible to the development of bone marrow suppression side effects, the available evidence has not shown that using this information to guide treatment leads to better clinical outcomes. Studies have been of variable quality with relatively small patient populations and mixed results. TPMT testing strategy has not been adequately compared to standard CBC monitoring. There is insufficient evidence in the published peer-reviewed medical literature to support TPMT testing in patients with IBD.

Professional Societies/Organizations
The American Gastroenterological Association (AGA) issued a position statement on the use of corticosteroids, immunomodulators, and infliximab for the treatment of IBD. The document notes that the current FDA recommendations suggest that TPMT genotype or phenotype should be assessed before initiation of thiopurine therapy to detect individuals who have low enzyme activity. This would be done in an effort to avert AZA or 6-MP therapy in those patients and thereby avoid potential adverse events. Those who are found to have intermediate or normal TPMT activity (i.e., wild type or heterozygotes) need measurement of frequent CBCs in addition to TPMT assessment because the risk of myelosuppression subsequent to use of AZA or 6-MP still exists (Lichtenstein, et al., 2006).

According to the American College of Gastroenterology (ACG) clinical practice guidelines for the management of ulcerative colitis (UC) in adults, "prospective studies of dose-optimization based on measurements of TPMT, 6-TG, or 6-MP levels to monitor clinical response are still needed before the routine use of these assays can be recommended as providing much incremental benefit to the traditional routine of monitoring the complete blood count (CBC), liver associated laboratory chemistry abnormalities, and clinical response" (Kornbluth and Sachar, 2004).

Use Outside of the US
According to guidelines on the management of IBD commissioned by the British society of Gastroenterology, the precise role of measuring TPMT levels in starting AZA/MP therapy is still controversial. At the start of AZA/MP therapy, measuring TPMT has a role in identifying the one in 300 patients at risk of severe immunosuppression when treated with standard doses. Most patients who develop leukopenia will have a normal TPMT. During the initial months of AZA therapy a knowledge of low TPMT activity warns of possible early bone marrow toxicity (probability of myelotoxicity in high TPMT group is 3.5% compared 14.3% in the TPMT intermediate group. The guideline recommendation is that all patients should have measurement of TPMT levels before starting thiopurines, mainly to avoid administration to a patient with no functional TPMT in whom thiopurine administration may be fatal (Mowat, et al., 2011).

Summary for TPMT
The clinical utility of genotyping for thiopurine methyltransferase (TPMT) deficiency in patients with inflammatory bowel disease (IBD) remains controversial. The evidence in the published peer-reviewed literature evaluating the clinical utility of TPMT measurement is limited and mostly in the form of retrospective case series and cross-sectional studies. Although it has been established that determining the presence of TPMT genetic mutations identifies those who are at increased risk for drug-induced toxicity, the available evidence has failed to demonstrate that this testing results in improved patient outcomes compared to the standard practice of complete blood count (CBC). Large-scale prospective, randomized controlled trials (RCTs) are needed to further define the role of pharmacogenomics in the management of patients with IBD receiving thiopurines.

Drug Metabolizing Enzyme Genotyping Systems
Drug metabolizing enzyme genotyping systems test deoxyribonucleic acid (DNA) for the presence or absence of human genotypic markers that encode a drug metabolizing enzyme. The aim of these systems is to identify genetic mutations that affect the way the body metabolizes (i.e., too fast, too slow, or not at all) certain medications. Test results are intended to allow the clinician to predict the patient's response to pharmacotherapy, assist in making treatment choices, individualize drug dosages in order to maintain a consistent drug level in the body, and avoid adverse reactions from overdose or suboptimal effects from under medication (Al-Goul, et al., 2008).

Some systems analyze the CYP450 gene products which are a class of enzymes, found primarily in the liver where they break down toxins, drugs and compounds. CYP450 includes the CYP2D6 and CYP2C19 genotypes. CYP2D6 metabolizes antidepressants, antipsychotics, beta-blockers, opiates, antiemetics, and some chemotherapy drugs (e.g., Tamoxifen). CYP2D6 alleles determine two phenotypic types, poor metabolizers and extensive metabolizers. The enzyme encoded by CYP2C19 metabolizes anticonvulsants, proton pump inhibitors, anticoagulants, benzodiazepines and antimalarials. The allelic variants in CYP2C19 result in four phenotypes: ultrarapid (UM), extensive (EM), intermediate (IM), poor (PM) and unknown metabolizers. The phenotypes are proposed to predict how an individual will metabolize and respond to drug therapy.
Other drug metabolizing enzyme genotyping systems are used for the detection and genotyping of the *1 telomere-associated (TA) *6 and *28 (TA7) alleles of the uridine diphosphate (UDP) glucuronosyltransferase 1A1 (UGT1A1). UGT1A1 is a hepatic enzyme involved in the conjugation of bilirubin and also catalyzes the glucuronidation of SN-38. Analyzing this enzyme is proposed to aid in identifying patients at a greater risk for decreased UDP-UGT1A1 activity. UGT1A1 is responsible for producing the enzyme which influences an individual's ability to metabolize certain drugs, including irinotecan, a drug used in colorectal cancer treatment.

Although some drug metabolizing enzyme systems have been approved by the U.S. Food and Drug Administration (FDA), the clinical utility and benefit to net health outcomes have not been established.

AmpliChip™ CYP450 Test
AmpliChip™ Cytochrome P450 (CYP450) Genotyping Test (Roche Molecular Systems, Inc. Pleasanton, CA) is a microarray drug-metabolizing enzyme genotyping device that uses polymerase chain reaction (PCR)

amplification technology to prepare DNA obtained from a blood sample. The test detects genetic variations in CYP450 genotypes CYP2D6 and CYP2D19. The blood samples are analyzed on the Affymetrix GeneChip® Microarray Instrumentation System. By using tiny chips housed in a cartridge, Affymetrix microarrays allow analysis of multiple DNA fragments (i.e., olignucleotides) at one time. Amplichip predicts enzymatic activity for 27 CYP2D6 alleles and three CYP2C19 alleles. Compared to DNA sequencing, an established technology, the specificity of the AmpliChip for detection of wild-type samples (n=100; 3 different wild-type alleles) was reported at 100% and sensitivity for 22 different variant alleles in 492 alleles tested was 99.2% with no miss-calls and four no-calls. Reproducibility was reported at 99.9% (Blue Cross and Blue Shield Association (BCBSA) Technology Evaluation Center (TEC), 2008; U.S. Food and Drug Administration [FDA] 2009; FDA, 2005). The most comprehensive data were found in studies utilizing AmpliChip. Compared to polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) for CYP2D6 testing, a sensitivity of 95% and specificity of 100% were reported for AmpliChip.

U.S. Food and Drug Administration (FDA): The AmpliChip™ CYP450 Test is 510(k) approved "to identify a patient's CYP2D6 genotype from genomic DNA extracted from a whole blood sample" which may aid clinicians in determining therapeutic strategy and treatment doses for drugs that are metabolized by the CYP2D6 gene product. The FDA also approved the use of Amplichip "as an aid to clinicians in determining therapeutic strategy and treatment dose for therapeutics that are metabolized by the CYP2C19 gene product" (FDA, 2009; FDA, 2005).

The Canadian Agency for Drugs and Technologies in Health (CADTH) (2006) reported that studies have shown that AmpliChip does accurately identify CYP2D6 and CYP2C19, but have not linked its use to an improvement in patient outcomes or shown that outcomes can be predicted or altered by knowledge of drug metabolizing enzyme status.

INFINITI® CYP2C19 Assay
The INFINITI® CYP2C19 Assay (Autogenomics, Inc., Vista, CA) is a microarray qualitative assay for the identification of CYP450 2C19 genotype obtained from a whole blood sample. The Assay is comprised of the R-Chip BioFilmChip Microarray, the Intellipac Reagent Module, a polymerase chain reaction (PCR) Amplification Mix and the GAP/Header CD and is run on the AutoGenomics INFINITI Analyzer. The process involves PCR amplification of purified DNA, labeling of the amplified product, hybridization of the labeled amplified product to a microarray, scanning of the microarray and signal detection. In a study conducted by Autogenomics, the analytical sensitivity (n=1560 tests) of INFINITI was ≥ 90% with no incorrect calls. The accuracy (n=317 samples) was reported at 98.1% and inter-laboratory reproducibility was 97.6% (n=255 tests) with no incorrect calls (Autogenomics, 2011; FDA, Oct 2010).

U.S. Food and Drug Administration (FDA): The INFINITI® CYP2C19 Assay is 510(k) FDA approved and indicated "for use as an aid to clinicians in determining therapeutic strategy for therapeutics that are metabolized by the CYP450 2C19 gene product, specifically *2, *3, *17." The Assay is not indicated to be used to predict drug response or non-response (FDA, Oct 2010).

Invader® UGT1A1 Molecular Assay
The Invader® UGT1A1 Molecular Assay (Third Wave Technologies, Madison, WI) is a diagnostic pharmacogenetic test used for the detection and genotyping of UGT1A1 using a blood sample. The Invader utilizes Tecan GENios, Tecan GENios FL, or Bio-Tek FLX800 fluorometers and the Call Reporting Software (CRS). Individuals with the UGT1A1*28 allele may require dose modification for specific drugs such as the chemotherapeutic agent irinotecan. Based on the studies submitted to the FDA, inter-laboratory reproducibility was 98.1% (n=900 genotypes). The lower and upper limits of detection (analytical sensitivity) compared to bi-directional DNA sequencing was in 100% agreement and lot-to-lot reproducibility was 100% (Hologic, 2010; FDA, 2007).

Baudhuin et al. (2007) analyzed 119 DNA samples to evaluate and compare the Invader with an automated fluorescent sequencing assay and a capillary electrophoresis allelic size-based method (fragment analysis) for genotyping the UGT1A1 TATA box. The majority of the $(TA)_n$ were *6/*6 and *6/*7. There was 100% concordance in the sequencing and size-based analysis. The Invader was also concordant if genotypes *6/*6, *6/*7, or *7/*7 were present. Compared to the other two methods, the 88 samples of *6/*6, *6/*7, or *7/*7 genotypes analyzed by Invader were in 100% concordance. As it relates to failures, six samples failed using the sequencing assay, two failed using the size-base analysis, and nine failed using the Invader. Turn-around time

was five hours for the Invader, seven hours for sequencing assays, and three hours for size-based assays. The Invader method required more concentrated DNA for analysis and had a limited genotyping spectrum (i.e., *6/*6, *6/*7, or *7/*7). The authors concluded that all three methods were valuable, but the Invader had the most drawbacks.

U.S. Food and Drug Administration (FDA): The Invader® UGT1A1 Molecular Assay is 510(k) FDA approved as "an in vitro diagnostic test for the detection and genotyping of the *1 (TA6) and *28 (TA7) alleles of the UDP glucuronosyltransferase 1A1 (UGT1A1) gene in genomic DNA from whole peripheral blood as an aid in the identification of patients with greater risk for decreased UDP-glucuronosyltransferase activity" (FDA, 2007).

xTAG® CYP2D6 Kit v3
The xTAG® CYP2D6 Kit v3 (Luminex Molecular Diagnostics, Inc., Toronto, Canada) is an assay used to detect and identify a panel of nucleotide variants in the CYP2D6. The test is proposed to assist clinicians in determining therapeutic strategy for therapeutics metabolized by the CYP2D6 gene. xTAG analyzes CYP2D6 genotypes from whole blood and involves PCR reactions, multiplex allele specific primer extension, hybridization and fluorescing to determine allele status. xTAG predicts CYP2D6 enzyme activities for alleles *1–*11, *15, *17, *29, *35, *41. In studies submitted to the FDA, the overall, multi-center reproducibility (n=36 replicates for 13 genotypes) of xTAG was 94.4% with a 95% lower bound confidence interval of 91.97% and analytical specificity reported 100% agreement in six genotypes from six patient samples. In comparison to bidirectional dideoxy sequencing (n=918 alleles sequenced), xTAG had an overall 98.4% agreement in genotypes (FDA, Aug 2010; Luminex, 2011).

U.S. Food and Drug Administration (FDA): The xTAG® CYP2D6 Kit v3 is FDA 510(k) approved to "simultaneously detect and identify a panel of nucleotide variants found within the highly polymorphic CYP2D6 gene located on chromosome 22 from genomic DNA extracted from EDTA and citrate anticoagulated whole blood samples. This kit can also identify gene rearrangements associated with the deletion (*5) and duplication of genotypes." The test is not intended to be used to predict drug response or non-response (FDA, Aug 2010).

Literature Review: There is insufficient evidence in the published peer reviewed scientific literature to support the clinical utility of xTAG and its impact on net health outcomes. There is a paucity of studies comparing xTAG to conventional testing methods.

Sunmmary of Drug Metabolizing Enzyme Genotyping Systems: High-quality randomized controlled trial data are lacking to demonstrate the clinical utility of these tests in informing improving health outcomes or avoiding adverse events.

Pharmacogenetic Testing Panel Tests
Genecept™ Assay: The Genecept™ assay (Genomind LLC, Chalfont, PA) is a saliva-based test which analyzes a panel of a minimum of 10 biomarker genes associated with metabolism and response to medications for treatment of neuropsychiatric conditions, such as depression, bipolar disorder, schizophrenia, anxiety disorders, OCD or ADHD. Genes analyzed by this panel include CYP2D6, CYP2C19, CYP3A4, SLC6A4, 5HT2C, DRD2, CACNA1C, ANK3, COMT, and MTHFR. The Genecept ™ assay can only be ordered as a panel including all genes. The primary targets of the Genecept™ assay are genetic polymorphisms associated with single nucleotide, polymorphisms within genes associated with neurotransmitters and drug metabolism (i.e., Cytochrome P450 family). According to the manufacturer's website, a psychopharmacologist is available to provide a consult to the ordering clinician regarding the results.

US Food and Drug Administration (FDA): This test has not received FDA approval.

Literature Review
Data are lacking in the published peer-reviewed scientific literature regarding effectiveness of this test to inform on improved health outcomes.

Summary for Genecept assay: There is insufficient evidence in the published peer-reviewed scientific literature to determine the effectiveness of this test to inform on drug metabolism, or drug dosing in the target populations. While targeted gene testing for polymorphisms in some of the genes referenced above has been proposed to determine specific drug metabolism, the clinical utility of panel testing has been unproven in large scale population studies.

GeneSight Panel: GeneSight[®] (Assurex Health, Mason, OH) analyzes genomic variants associated with the metabolism and response to behavioral health medications. This includes the GeneSight[®] Psychotropic test, GeneSight[®] MTHFR, GeneSight[®] ADHD panel, and the GeneSight[®] Analgesic panel. Genes analyzed by these panels include, but are not limited to: CYP2D6, CYP2C19, CYP2C9,CYP1A2, SLC6A4, HTR2A, OPRM1, COMT, MTHFR and ADRA2A, many of which are associated with the CYP450 superfamily. The CYP450 gene superfamily is composed of many isoenzymes that are involved in the metabolism of up to 90% of commonly prescribed drugs (Guengerich FP, 2008). The GeneSight® Psychotropic test, GeneSight® ADHD panel, and the GeneSight® Analgesic panel can only be ordered as multigene panels. Relevant regions are amplified using polymerase chain reaction (PCR). Specific mutations for SLC6A4 are detected by gel electrophoresis of PCR products.

US Food and Drug Administration (FDA): This test has not received FDA approval.

Literature Review
Winner et al. (2013) reported results of a 10 week prospective randomized control trial of 50 patients with major depression to evaluate the benefit of a five gene pharmacogenetic test and interpretive report (i.e., GeneSight[®]) for the management of psychotropic medications. This comparison of 25 patients with 'treatment as usual' and 26 patients where treatment was informed by the GeneSight[®] panel exhibited trends of increased likelihood of response and remission in the GeneSight[®] group, however difference between groups were not statistically significant (p=0.28) (Winner 2013). **Level of evidence: 1.**

HallFlavin et al. (2013) reported an open label study for utility comparing patients with depression where use of the GeneSight[®] panel was incorporated into treatment (n=114), to those where treating physicians were unaware of GeneSight results (n=113). Depression ratings were collected at baseline and at two, four, and eight weeks. Eight week response rates were higher in the guided group in three measurements of depression (p=0.0001). Success rates were highest in patients whose baseline medication was most discordant with their pharmacogenetic results, and treatment was guided by these results (p=0.01). While data suggest improved response rates in the group guided by GeneSight, the study was limited by lack of randomization, small patient numbers and short follow-up. **Level of evidence: 3.**

Summary for GeneSight: While targeted gene testing for polymorphisms in some of the genes referenced above has been proposed to determine specific drug metabolism, the clinical utility of panel testing has been unproven in large scale randomized clinical trials or population studies. There are limited published peer-reviewed scientific data to demonstrate the effectiveness of this test to improve health outcomes. Studies are limited by short-term follow-up, small patient numbers. At this time the clinical utility and effectiveness of the GeneSight test has not yet been established.

SureGene Panel: The SureGene Test for Antipsychotic and Antidepressant Response (STA[2]R) (SureGene, LLC, Louisville, KY) assesses genetic variants associated with drug metabolism and sensitivity, especially antipsychotic and antidepressant medications. According to the manufacturer's website, the purpose of the test is to predict treatment response before initiation of therapy, identify the presence of psychiatric disorders, and predict the likely future course of psychiatric disorders. This panel includes, but is not limited to the genes CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4,CYP3A5, SLC6A4, HTR2A, COMT, ADRA2A, OPRM1 and SULT4A1. The primary targets of the SureGene assays are genetic polymorphisms associated with single nucleotide polymorphisms within genes associated with neurotransmitters and drug metabolism (Cytochrome P450 family). SureGene assays are only advertised available as panels of multiple gene assays.

US Food and Drug Administration (FDA): This test has not received FDA approval.

Literature Review
Data are lacking in the published peer-reviewed scientific literature regarding the effectiveness of this panel to inform on improved health outcomes with its use.

Summary for SureGene: While targeted gene testing for polymorphisms in some of the genes referenced above has been proposed to determine specific drug metabolism, the clinical utility of panel testing has been unproven in large scale population studies. There is insufficient evidence to demonstrate the effectiveness of

this test t inform on drug metabolism or drug dosing for the target populations or to inform on improved health outcomes with its use.

Summary
Although an increasing number of pharmacogenetic tests are available, routine testing has not yet been recommended for most genes and drug targets. Large-scale, controlled clinical trials demonstrating improved patient outcomes are lacking for many indications and the clinical utility of such tests has not been established.

Pharmacogenetic testing of specific gene biomarkers or mutations may be appropriate if an individual is a candidate for a targeted drug therapy associated with a specific gene biomarker or mutation and the results will directly impact clinical decision making and/or clinical outcomes. The testing method should be proven by scientifically valid methods to identify the specific gene biomarker or gene mutation and results should be reproducible and subject to peer review. In addition, pharmacogenetic testing may be indicated when identification of the biomarker is noted to be clinically necessary prior to initiating therapy as noted in the Indications and Usage section of the therapeutic drug target's Food and Drug Administration (FDA)-approved prescribing label. Evidence in the peer-reviewed scientific literature supports the clinical utility of pharmacogenetic testing for the BCR ABL T315-I mutation in selected individuals with chronic myelogenous leukemia or Philadelphia chromosome positive acute lymphoblastic leukemia to detect resistance to imatinib (Gleevec®), nilotinib (Tasigna®) or dasatinib (Sprycel®). The clinical utility of pharmacogenetic testing for all other indications has not been established at this time.

There is insufficient evidence in the published peer-reviewed scientific literature to support the clinical utility of drug metabolizing enzyme genotyping systems such as the AmpliChip® Cytochrome P450 (CYP450) Test and the Invader® UGT1A1 Molecular Assay. Studies are primarily in the form of small case series or retrospective reviews with heterogeneous patient population, various methodologies and outcome measures, conflicting outcomes, as well as potential bias in tissue sample selection. Systematic reviews and meta-analyses have demonstrated no significant clinical benefit in net health outcomes with the use of these genotyping systems.

There is insufficient evidence to determine the effectiveness or clinical utility in improving health outcomes with the use of panel tests such as the SureGene Test for Antipsychotic and Antidepressant Response (STA²R), Genecept™ Assay, and the GeneSight® test. Data from large randomized clinical trials are lacking to demonstrate the effectiveness of these tests to improve health outcomes.

Coding/Billing Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Covered when medically necessary when the identification of the gene biomarker is noted to be clinically necessary prior to initiating therapy with the drug target as noted in the section heading "Indications and Usage" of the U.S. Food and Drug Administration (FDA)-approved prescribing label.

CPT®* Codes	Description
81210	BRAF (v-raf murine sarcoma viral oncogene homolog B1) (eg, colon cancer), gene analysis, V600E variant
81235	EGFR (epidermal growth factor receptor) (eg, non-small cell lung cancer) gene analysis, common variants (eg, exon 19 LREA deletion, L858R, T790M, G719A, G719S, L861Q)
81275	KRAS (v-Ki-ras2 Kirsten rat sarcoma viral oncogene) (eg, carcinoma) gene analysis, variants in codons 12 and 13
81315	PML/RARalpha, (t(15;17)), (promyelocytic leukemia/retinoic acid receptor alpha) (eg, promyelocytic leukemia) translocation analysis; common breakpoints (eg, intron 3 and intron 6), qualitative or quantitative
81316	PML/RARalpha, (t(15;17)), (promyelocytic leukemia/retinoic acid receptor alpha)

81403	Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of > 10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons) • KRAS (v-Ki-ras2 Kirsten rat sarcoma viral oncogene) (eg, carcinoma), gene analysis, variant(s) in exon 2 MPL (myeloproliferative leukemia virus oncogene, thrombopoietin receptor, TPOR) (eg, myeloproliferative disorder), exon 10 sequence VHL (von Hippel-Lindau tumor suppressor) (eg, von Hippel-Lindau familial cancer syndrome), deletion/duplication analysis VWF (von Willebrand factor) (eg, von Willebrand disease types 2A, 2B, 2M), targeted sequence analysis (eg, exon 28)
81405	Molecular pathology procedure, level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons) • KRAS (v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog) (eg, Noonan syndrome), full gene sequence • OTC (ornithine carbamoy/transferase) (eg, ornithine transcarbamylase deficiency), full gene sequence
81406	Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia) • BRAF(v-raf murine sarcoma viral oncogene homolog B1) (eg, Noonan syndrome, full gene sequence
81479	Unlisted molecular pathology procedure • When used to report testing for a specific gene biomarker which is not otherwise reportable by a specific code and which is noted to be clinically necessary prior to initiating therapy with the drug target as noted in the section heading "Indications and Usage" of the U.S. Food and Drug Administration (FDA)-approved prescribing label.

Covered when medically necessary when used to report pharmacogenetic testing for the BCR-ABL T315-I mutation:

CPT®* Codes	Description
81206	BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; major breakpoint, qualitative or quantitative
81207	BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; minor breakpoint, qualitative or quantitative
81208	BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; other breakpoint, qualitative or quantitative
81401	Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat) • ABL (c-abl oncogene 1, receptor tyrosine kinase) (eg, acquired imatinib resistance), T315I variant
81403	Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of > 10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons) • ABL1 (c-abl oncogene 1, receptor tyrosine kinase) (eg, acquired imatinib tyrosine kinase inhibitor resistance), variants in the kinase domain

Experimental/Investigational/Unproven/Not Covered when used to report pharmacogenetic

testing to detect response to targeted drug therapy for ANY of the indications listed as such in this policy:

CPT* Codes	Description
81225	CYP2C19 (cytochrome P450, family 2, subfamily C, polypeptide 19) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *8, *17)
81226	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *5, *6, *9, *10, *17, *19, *29, *35, *41, *1XN, *2XN, *4XN)
81350	UGT1A1 (UDP glucuronosyltransferase 1 family, polypeptide A1) (eg, irinotecan metabolism), gene analysis, common variants (eg, *28, *36, *37)
81400	Molecular pathology procedure, Level 1 (eg, identification of single germline variant [eg, SNP] by techniques such as restriction enzyme digestion or melt curve analysis) • DPYD (dihydropyrimidine dehydrogenase) (eg, 5-fluorouracil/5-FU and capecitabine drug metabolism), IVS14+1G>A variant

Experimental/Investigational/Unproven/Not Covered when used to report pharmacogenetic testing to detect response to targeted drug therapy for ANY indication:

CPT®* Codes	Description
81225	CYP2C19 (cytochrome P450, family 2, subfamily C, polypeptide 19) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *8, *17)
81227	CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *5, *6)
81350	UGT1A1 (UDP glucuronosyltransferase 1 family, polypeptide A1) (eg, irinotecan metabolism), gene analysis, common variants (eg, *28, *36, *37)
81355	VKORC1 (vitamin K epoxide reductase complex, subunit 1) (eg, warfarin metabolism), gene analysis, common variants (eg, -1639/3673)
81401	Molecular pathology procedure, level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat) • CYP3A4 (cytochrome P450, family 3, subfamily A, polypeptide 4)(eg, drug metabolism), common variants (eg, *2, *3, *4, *5, *6) • CYP3A5 (cytochrome P450, family 3, subfamily A, polypeptide 5)(eg, drug metabolism), common variants (eg, *2, *3, *4, *5, *6)

Experimental/Investigational/Unproven/Not Covered when used to report genotyping for thiopurine methyltransferse (TPMT):

CPT®* Codes	Description
81401	Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat) • TPMT (thiopurine S-methyltransferase) (eg, drug metabolism), common variants (eg, *2, *3)

Experimental/Investigational/Unproven when used to report drug metabolizing enzyme genotyping systems (e.g., AmpliChip™ Cytochrome P450 (CYP450) Genotyping Test; Invader® UGT1A1 Molecular Assay).

81225	CYP2C19 (cytochrome P450, family 2, subfamily C, polypeptide 19) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *8, *17)
81226	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism),

	gene analysis, common variants (eg, *2, *3, *4, *5, *6, *9, *10, *17, *19, *29, *35, *41, *1XN, *2XN, *4XN)
81227	CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *5, *6)
81350	UGT1A1 (UDP glucuronosyltransferase 1 family, polypeptide A1) (eg, irinotecan metabolism), gene analysis, common variants (eg, *28, *36, *37)

Experimental/Investigational/Unproven when used to report the following pharmacogenetic testing panels: SureGene Test for Antipsychotic and Antidepressant Response (STA²R); Genecept™ Assay, GeneSight® Analgesic, GeneSight® Psychotropic or GeneSight® ADHD

81479	Unlisted molecular pathology procedure

*Current Procedural Terminology (CPT®) ©2013 American Medical Association: Chicago, IL.

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