Clinical Utility
The cytochrome P450 1A2 (CYP1A2) accounts for 13% of total CYP in the human liver and is responsible for metabolizing 8-10% of commonly used drugs as well as natural compounds such as caffeine. A large inter-individual variability in the elimination of drugs that are metabolized by CYP1A2 has been observed, which has been ascribed to both genetic variations and environmental factors including smoking (tobacco), some drugs, and several dietary compounds (cruciferous vegetables).

Useful For:
- Identifying patients who are poor, intermediate, extensive, or ultrarapid metabolizers of drugs metabolized by CYP1A2
- Adjusting dosages for drugs that are metabolized by CYP1A2

Assay Interpretation
Primary metabolism of many drugs is performed by cytochrome P450 (CYP), a group of oxidative/dealkylating enzymes localized in the microsomes of many tissues including the intestines and liver. One of these CYP enzymes, CYP1A2, is wholly or partially responsible for the hydroxylation or dealkylation of many commonly prescribed drugs. The current clinical application of this test is focused on the impact of allelic variation on antidepressant and antipsychotic metabolism.

CYP1A2-mediated drug metabolism is highly variable. CYP1A2*1A is the wild type or normal allele. Some individuals have altered CYP1A2 gene sequences that result in synthesis of a defective enzyme. These individuals metabolize CYP1A2 substrates poorly. Changes in the promoter impacting gene induction of the CYP1A2 gene has been observed, which results in either an increase or decrease of overall metabolic activity. Dosing of drugs that are metabolized through CYP1A2 may require adjustment based on the individual patient’s genotype. Patients who are poor metabolizers may require lower than usual doses to achieve optimal response. Patients who are ultrarapid metabolizers may benefit from increased doses. Patients with either ultrarapid or poor metabolism may also benefit by conversion to other comparable drugs that are not primarily metabolized by CYP1A2.

More than 20 different alleles have been characterized for the CYP1A2 gene and some have been shown to affect enzyme activity and its sensitivity towards inducers (inducibility). The CYP1A2*1F is the most studied allele and results into a rapid metabolizer phenotype in presence of inducers while CYP1A2*1K and *1C alleles result in enzymes that are less active and less sensitive to induction. The CYP1A2*1F allele is found in 25-50% of Caucasians, 30% of Asians, and 50% of Ethiopians. The genotype-phenotype relationship for CYP1A2 is not well established and can be expressed in terms of metabolic capacity as well as sensitivity towards induction (inducibility). Individuals are predicted to have normal, intermediate, or poor metabolic CYP1A2 capacity with high, possible, or low inducibility depending on their genotype.

Drugs and Substances That Undergo Metabolism by CYP1A2
- Acetaminophen
- Amitriptyline
- Caffeine
- Chlorzepate
- Clozapine
- Cyclobenzaprine
- Estradiol
- Fluvoxamine
- Haloperidol
- Imipramine
- Mexiletine
- Naproxen
- Olanzapine
- Ondansetron
- Phencetin
- Propranolol
- Riluzole
- Ropivacaine
- Tacrine
- Theophylline
- Tizanidine
- Verapamil
- R-Warfarin
- Zileuton
- Zolmitriptan

Drugs and Substances Known To Increase CYP1A2 Activity
- Broccoli
- Brussels Sprouts
- Char-grilled meat
- Insulin
- Methylcholanthrene
- Modafinil
- Nafcinil
- Beta-Naphthoflavone
- Omeprazole
- Tobacco

Drugs Known To Decrease CYP1A2 Activity
- Amiodarone
- Cimetidine
- Ciprofloxacin
- Fluoroquinolones
- Fluoxymesterone
- Furafylline
- Interferon
- Methoxsalen
- Mibefradil

The reference range for CYP1A2 metabolic status is CYP1A2*1A/*1A which is consistent with a normal metabolizer that is possibly inducible.
Clinical Implications
CYP1A2 genotype can help identify patients with high or low sensitivity to inducing agents especially those released during smoking. The clinical relevance of this sensitivity becomes important in patients who are smokers or who quit smoking. Patients with the highly inducible genotype CYP1A2*1F/*1F can experience loss of response to drug substrates while they are exposed to dietary or environmental inducers and therefore may require higher doses.

References