MAYO CLINIC
Mayo Medical Laboratories

TEST ID: TPNUV

THIOPURINE METHYLTRANSFERASE (*TPMT*) AND NUDIX HYDROLASE (*NUDT15*) GENOTYPING

USEFUL FOR

Predicting potential for toxicity to thiopurine drugs (6-mercaptopurine, 6-thioguanine, and azathioprine)

CLINICAL INFORMATION

The thiopurine drugs are purine antimetabolites that are useful in the treatment of acute lymphoblastic leukemia, autoimmune disorders (eg, Crohn disease, rheumatoid arthritis), and organ transplant recipients. The thiopurine drugs, 6-mercaptopurine (6-MP), 6-thioguanine (6-TG), and azathioprine (AZA) are prodrugs that require intracellular activation to 6-thioguanine nucleotides (6-TGN). This activation is catalyzed by multiple enzymes. The cytotoxic effects of thiopurine drugs are achieved mainly through incorporation of 6-TGNs into DNA and RNA. The pathway that leads to synthesis of active cytotoxic 6-TGNs is in competition with inactivation pathways catalyzed by thiopurine methyltransferase (TPMT). Evaluation of this pathway is important because the levels of 6-TGNs measured in red blood cells have been correlated with both thiopurine therapeutic efficacy and toxicity such as myelosuppression.

TPMT activity is inherited as a monogenic codominant trait and variable TPMT activity is associated with *TPMT* genetic variants. The distribution of TPMT activity in red blood cells is trimodal in Caucasian population, with approximately 0.3% of people having deficient (undetectable) TPMT activity, 11% low (intermediate) activity, and 89% normal TPMT activity. The allele for normal TPMT activity (wild-type) has been designated *TPMT*1*. Four *TPMT* alleles, comprised of a combination of 3 different single-nucleotide substitutions (SNPs), account for the majority of inactivating alleles in some ethnicities, including Caucasians: *TPMT*2*, *TPMT*3A*, *TPMT*3B*, and *TPMT*3C*. Additional less frequent TPMT alleles *TPMT*4*, *TPMT*5*, *TPMT*8*, and *TPMT*12* also have been implicated as deficiency alleles. If no *TPMT* variant alleles are detected by this assay the most likely genotype is that of *TPMT*1/*1* although the presence of other rarer alleles cannot be excluded.

NUDT15 is thought to dephosphorylate the active metabolites of thiopurines, TGTP and TdGTP, which prevents their incorporation into DNA and decreases their cytotoxic effects. Genetic variants in *NUDT15* that decrease this activity are strongly associated with thiopurine-related myelosuppression. NUDT deficiency is most common among East Asians (22.6%), followed by South Asians (13.6%), and Native American populations (12.5–21.2%). Studies in other populations are ongoing. This test evaluates variants associated with *NUDT15*2*, *NUDT15*3*, *NUDT15*4* and *NUDT15 *5*. If no NUDT15 variant alleles are detected by this assay the most likely genotype is that of *NUDT15*1/*1* although the presence of other rarer alleles cannot be excluded. Individuals with variants in both *TPMT* and *NUDT15* have been identified and were significantly more sensitive to mercaptopurine than those with variants in either gene alone. Integration of both *TPMT* and *NUDT15* testing may allow for more accurate prediction of thiopurine-related toxicity risk to guide dosing, particularly among patients from diverse populations.

REFERENCE VALUES

An interpretative report will be provided.

ANALYTIC TIME

1 day (not reported on Saturday or Sunday)

10/2017

THIOPURINE METHYLTRANSFERASE (*TPMT*) AND NUDIX HYDROLASE (*NUDT15*) GENOTYPING

TPMT ALLELE	cDNA NUCLEOTIDE CHANGE	EFFECT ON ENZYME METABOLISM
**1*	None (wild type)	Normal function
**2*	c.238G->C	No activity
**3A*	c.460G->A and c.719A->G	No activity
**3B*	c.460G->A	No activity
**3C*	c.719A->G	No activity
**4*	c.626-1G->A	No activity
**5*	c.146T->C	No activity
**8*	c.644G->A	Reduced activity
**12*	c.374C->T	Reduced activity

The US Food and Drug Administration, the Clinical Pharmacogenetics Implementation Consortium, and some professional societies recommend consideration of *TPMT* genotype or TPMT erythrocyte testing prior to the initiation of therapy with thiopurine drugs. There is substantial evidence linking *TPMT* genotype to phenotypic variability. Dose adjustments based upon *TPMT* genotype have reduced thiopurine-induced adverse effects without compromising desired antitumor and immunosuppressive therapeutic effects in several clinical settings. Complementary clinical tests are available to measure TPMT enzymatic activity in erythrocytes. Genotyping is not impacted by other medications known to inhibit TPMT activity. This testing can be complemented by the TPMT erythrocyte phenotype testing if the clinician wants to check for lower TPMT enzyme activity, regardless of cause. Although there currently aren't guidelines or professional society recommendations related to *NUDT15* genotyping to guide thiopurine use, this practice is substantially supported by the literature. TPMT enzyme activity testing is not impacted by variants in *NUDT15*.

NUDT15 ALLELE	cDNA NUCLEOTIDE CHANGE	EFFECT ON ENZYME METABOLISM
**1*	None (wild type)	Normal activity
**2 or *3*	c.415C>T	No activity
**4*	c.416G>A	No activity
**5*	c.52G>A	No activity

INTERPRETATION

An interpretive report will be provided.

The *TPMT* genotype, with associated star alleles, is assigned using standard allelic nomenclature as published by the TPMT Nomenclature Committe. *NUDT15* genotype and associated star alleles are as described by Moriyama et al.

For additional information regarding pharmacogenomic genes and their associated drugs, see the **Pharmacogenomics Associations Tables** in Special Instructions. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.