RPRD DIAGNOSTICS
— Right Patient | Right Drug —

NT Panel

Genes (clinically relevant variants):
TPMT (10 alleles)
NUDT15 (9 alleles)

Drug dosing:
Azathioprine
Mercaptopurine
Thioguanine

Indications:
Acute lymphoblastic leukemia (ALL)
Inflammatory bowel disease (IBD)
Autoimmune disorders
Rejection after organ transplant

NT Panel

Using NUDT15 and TPMT Pharmacogenetics to Reduce Thiopurines-related Adverse Reactions

RPRD™ Diagnostics (RPRD) introduces the NT (NUDT15 and TPMT) Panel, investigating all clinically relevant variants of both NUDT15 and TPMT genes in a single test. The NT panel provides clinically actionable genetic information to help clinicians determine effective therapies and appropriate dosing of thiopurines. Thiopurines are commonly used to treat acute lymphoblastic leukemia (ALL), inflammatory bowel disease (IBD), and other autoimmune diseases, or to prevent rejection after organ transplant.

The NT Panel investigates all clinically relevant genetic variants of TPMT and NUDT15. Compared to testing only a limited number of genetic variants, RPRD's comprehensive NT Panel yields thorough dosing guidelines for thiopurines with high accuracy. Such pharmacogenomics testing has been shown to reduce adverse drug reaction, eliminate trial and error to determine the right medication and dose, and improve therapeutic outcomes for patients.

Right Patient Right Drug

UNIQUE ADVANTAGES

+ **Covers CPIC guideline-recommended genes in one test**. The NT Panel covers the complete set of Clinical Pharmacogenomics Implementation Consortium (CPIC) guideline-recommended genes (NUDT15 and TPMT) for thiopurines in a single test.

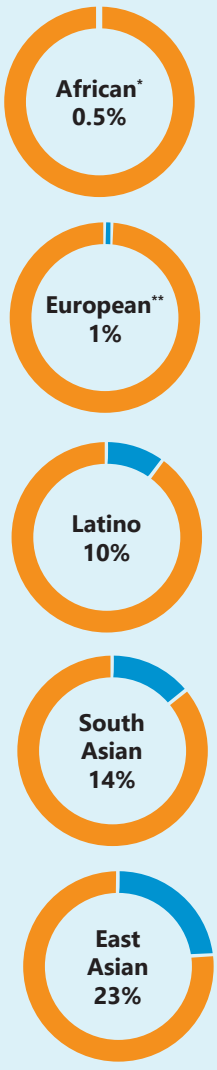
+ **Tests all clinically relevant variants**. The panel tests all clinically relevant variants of NUDT15 and TPMT genes to enhance accuracy and eliminate guesswork.

+ **Rapid turnaround time.** Highly accurate clinical results are delivered within 3-5 days to support potentially life-saving clinical decision making.

BACKGROUND

Thiopurines are a class of immunosuppression drugs that include azathioprine, mercaptopurine and thioguanine. They are frequently prescribed to treat a variety of conditions, such as ALL, myeloid leukemia, IBD, and other autoimmune diseases, or to prevent rejection after organ transplant. Thiopurines can cause severe and life-threatening toxicity in some patients. TPMT genetic variation is an important explanation for this frequently observed toxicity, and the pharmacogenomic relationship between the two is well described in the FDA thiopurines drug label. NUDT15 genetic variation is yet another critical determinant of thiopurine metabolism, and the CPIC guideline provides thiopurine dosage recommendations for individuals with TPMT and NUDT15 variants[1]. Several NUDT15 variants are highly penetrant and confer sensitivity to thiopurines, with effect sizes comparable to variants found in TPMT[2]. In addition, whereas TPMT variants are primarily found in those of European descent, genetic variants in NUDT15 are found in many populations[3] (see Fig. 1). Individuals with variants in both TPMT and NUDT15 are significantly more sensitive to thiopurines than individuals with variants in only one gene[2]. Therefore, genotyping both TPMT and NUDT15 allows for a more accurate prediction of each patient's thiopurine-related toxicity risk to guide dosing, particularly among patients from diverse populations.

FIGURE 1. NUDT15 DIPLOTYPE VARIANTS' FREQUENCY IN MULTIPLE ETHNICITIES[3]



Wildtype

Variants

** African includes American of African ancestry.*

*** European includes American of European ancestry.*

WHY TEST ALL CLINICALLY RELEVANT GENETIC VARIANTS & COMBINATIONS?

The combination of each patient's TPMT and NUDT15 variants identifies whether the individual is a normal, intermediate, or poor metabolizer of thiopurines. To ensure therapeutic efficacy and patient safety, a provider must personalize the dosage of thiopurines according to the patient's genetic variants of both genes.

The NT Panel investigates all clinically relevant TPMT (10 alleles) and NUDT15 (9 alleles) genetic variants recommended by CPIC dosing guidelines for thiopurines[1]. Compared to testing only a limited number of genetic variants, as most commercially available pharmacogenomics testing does, RPRD's comprehensive NT Panel reduces the likelihood of false prediction of toxicity risks and thus yields a thorough dosing guideline with the highest accuracy.

1. Relling MV, et al., CPIC Guideline for thiopurines dosing based on TPMT and NUDT15 genotypes: 2018 update. *Clin Pharmacol Ther.* 2019 May; 105(5):1095-1105.
2. Yang JJ, et al., *J Clin Oncol.* 2015; 33:1235-42.
3. Moriyama T, et al., *Nat Genet.* 2016; 48(4):367-73.

ORDERING PANELS

Complete the Test Requisition Form located on RPRD's website and ship the sample to our CLIA-certified laboratory. The typical turnaround time to receive patient results for NT testing is three to five days from receipt of samples that meet specified requirements. Test results are reported Monday through Friday.

TEST	GENES	CPT CODE
NT Panel	TPMT, NUDT15	81335, 81306
CNT Panel	TPMT, NUDT15, CEP72	81335, 81306
WPS™ (Whole Pharmacogenomics Scan)	4,627 markers in 1,191 genes of known PGx value	81479
Custom	Custom-designed panel of genes and variants	

Specimen Requirements

COLLECTION	3-5mL peripheral whole blood in EDTA tube
	Saliva in Oragene Dx, part# OGD-500
LABELING	Must label with the patient name plus one additional unique identifier, such as date of birth, medical record number, or date of collection
SHIPPING	Ambient temperature. Ship for RPRD receipt on Monday through Friday only
STABILITY	Samples must be received by RPRD within 7 days from time of collection
REJECTION	Blood sample may be rejected if frozen, hemolyzed, or clotted

ABOUT RPRD DIAGNOSTICS

RPRD Diagnostics specializes in providing innovative and complete precision medicine solutions including diagnostics, analytical, and supporting services to clinicians, researchers, and drug developers. RPRD's team of experts strive to unlock the power of science enabling personalized care for today and accelerating personalized therapies for tomorrow.

1225 Discovery Parkway, Ste 260
Milwaukee, WI 53226 USA

RPRDx.com
info@rprdx.com
Tel: +1 (414) 316-3097
Fax: +1 (414) 777-0058