



# Nudix Hydrolase 15 (NUDT15) Genotyping

NUDT15 encodes an enzyme (nudix hydrolase) that is a negative regulator of thiopurine (e.g. 6-mercaptopurine, azathioprine, thioguanine, etc.) activation and toxicity. Genetic variants in the NUDT15 gene can lead to changes in enzymatic activity and the metabolism of thiopurines<sup>1-3</sup>. Pharmacogenetic testing for these variants can identify individuals who may have an increased risk of adverse drug reactions or failure to respond to standard dosages of drugs metabolized by NUDT15.

## Alleles Detected

Normal function allele: \*1  
 No function allele: \*2, \*3  
 Uncertain function allele: \*4, \*5, \*6, \*7, \*8, \*9

## In Vitro Function/Predicted Activity for Alleles with CPIC Function Assignment of “Uncertain”

\*4, \*5, \*7, \*8, \*9: Severely decreased activity with TGTP or TdTP as substrate  
 \*6: Significantly decreased function with TGTP; decrease more pronounced with TdTP as substrate

## Phenotype Categories

- Normal Metabolizer:** This phenotype indicates the presence of two copies of a normal function allele in the NUDT15 gene.  
*Diplotype:* \*1/\*1
- Intermediate Metabolizer:** Presence of one copy of a normal function allele and one copy of a no function allele in the NUDT15 gene. This is consistent with intermediate activity of NUDT15. Such patients are at risk for myelosuppression with normal doses of drugs in the thiopurine class.  
*Diploypes:* \*1/\*2 or \*1/\*3\*
- Poor Metabolizer:** This phenotype indicates low or absent activity of NUDT15. This phenotype includes individuals with two copies of no function alleles (i.e., \*2, \*3) in the NUDT15 gene. This is consistent with low or absent activity of NUDT15. These patients **are at high risk** for toxicity with normal doses of drugs in the thiopurine class.  
*Diploypes:* \*2/\*2, \*2/\*3, \*3/\*3
- Possible Intermediate Metabolizer:** Presence of one copy of a normal function allele and one copy of an uncertain function allele in the NUDT15 gene (alleles that have not yet been assigned a CPIC function but have predicted low or deficient activity of NUDT15 (in vitro function/predicted activity) based on the current literature<sup>4</sup>). Such patients **may be at risk** for myelosuppression with normal doses of drugs in the thiopurine class.  
*Diploypes:* \*1/\*4, \*1/\*5, \*1/\*6, \*1/\*7, \*1/\*8, \*1/\*9
- Possible Poor Metabolizer:** This phenotype indicates the presence of two copies of uncertain function alleles (alleles that have not yet been assigned a CPIC function but have predicted low or deficient activity of NUDT15 (in vitro function/predicted activity) based on the current literature<sup>4</sup>) or the presence of one copy of an uncertain function allele and one no function allele in the NUDT15 gene. These patients **may be at high risk** for toxicity with normal doses of drugs in the thiopurine class.  
*Diploypes:* \*2/\*4, \*2/\*5, \*2/\*6, \*2/\*7, \*2/\*8, \*2/\*9  
 \*3/\*3, \*3/\*4, \*3/\*5, \*3/\*6, \*3/\*7, \*3/\*8, \*3/\*9  
 \*4/\*4, \*4/\*5, \*4/\*6, \*4/\*7, \*4/\*8, \*4/\*9  
 \*5/\*5, \*5/\*6, \*5/\*7, \*5/\*8, \*5/\*9  
 \*6/\*6, \*6/\*7, \*6/\*8, \*6/\*9  
 \*7/\*7, \*7/\*8, \*7/\*9  
 \*8/\*8, \*8/\*9  
 \*9/\*9
- Indeterminate-Phasing Positive:** This phenotype represents the detection of an uncharacterized allele composition. If rs116855232 and rs147390019 variants are detected on the same allele, then this genotype has currently not been characterized, and thus the function of this allele is unknown.

## Limitations

The presence of other NUDT15 variants that are not detected in this assay may influence drug metabolism. Additional variants that are not detected but located proximally to variants interrogated may affect the assay's ability to detect the above listed alleles.

Please consider all relevant patient information (including but not limited to additional medications, gender, weight, etc.) when making any dosing decisions.

## Methodology

Real-time polymerase chain reaction with fluorescence detection.

## Informed Consent

If required by your state, please obtain informed consent for genetic testing. Please document in the appropriate location on the test request form or order if informed consent has been obtained and filed.

## Ordering

<b>Test Name</b>	CNT or NT Panel
<b>CPT Code</b>	81335
<b>Collection</b>	3-5mL peripheral whole blood in EDTA tube Saliva in Oragene Dx, Part # OGD-500
<b>Labeling</b>	Must label with the patient name plus one additional unique identifier, such as date of birth, medical record number, or date of collection
<b>Stability</b>	Samples must be received by RPRD within 7 days of collection. Ambient or refrigerated storage is acceptable
<b>Shipping</b>	Ambient temperature. Ship for RPRD receipt on Monday through Friday only
<b>Rejection</b>	Blood sample may be rejected if frozen, hemolyzed, or clotted

## About RPRD Diagnostics

RPRD Diagnostics specializes in providing innovative and end-to-end pharmacogenomics solutions, including diagnostic, analysis and consulting services to clinicians, researchers and drug developers. With decades of combined experience, RPRD's team of experts strives to improve patient lives using pharmacogenomics to enable precision medicine.

## References

1. Moriyama T, et al, *Nat Genet.* 2016; 48(4): 367-73.
2. Singh M, et al, *Leuk Res.* 2017; 62: 17-22.
3. Kakuta Y, et al, *J Gastroenterol.* 2018; 53(2):172-80.
4. Yang J, et al, *Clin Pharmacol Ther.* 2018: Manuscript accepted. Paper #2018-0518CR

## For More Information

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