U.S. Department of Veterans Affairs
Veterans Health Administration
PBM Academic Detailing Services

CLINICIAN GUIDE

Applying Pharmacogenomics (PGx) to Thiopurine Dosing

Using PGx testing to improve safety

Utilizing PGx testing reduces the risk of life-threatening myelosuppression related to thiopurine therapy.

Thiopurines are a class of medications with several indications.[1-4]

Azathioprine

- Inflammatory bowel disease (IBD)†
- Post-transplant immunosuppression
- Rheumatoid and psoriatic arthritis

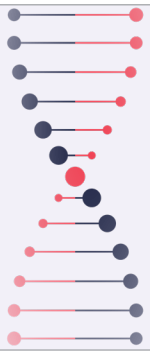
Mercaptopurine

- IBD†
- Lymphoid malignancies

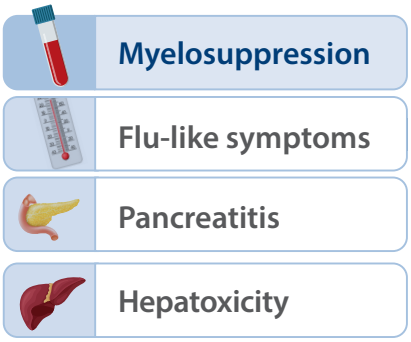
Thioguanine

- Myeloid leukemias

†Off-label indication



Thiopurine Side Effects



- **Myelosuppression** from thiopurine therapy has been linked to 6-thioguanine nucleotides, an active metabolite of thiopurine metabolism.[5]
- **Thiopurine methyltransferase (TPMT)** and the **nudix-type motif 15 (NUDT15)** enzyme metabolizes thiopurines and its metabolites into less toxic substances. Polymorphisms in either or both enzymes can result in **increased toxic metabolite concentration and increased risk of myelosuppression**.[1]

An estimated **4 to 11% of the population have intermediate TPMT function** and roughly 0.3% have very low or absent activity.[5] **NUDT15 polymorphisms are seen in up to 10%** of certain ancestral populations.[6]

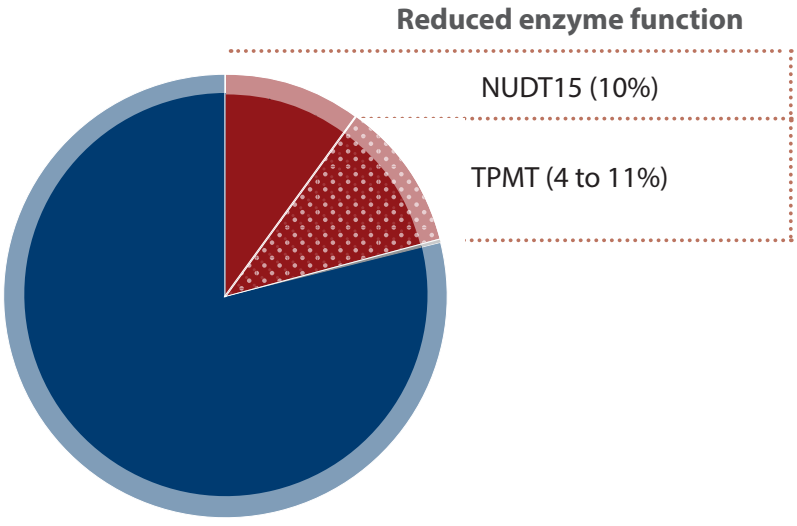
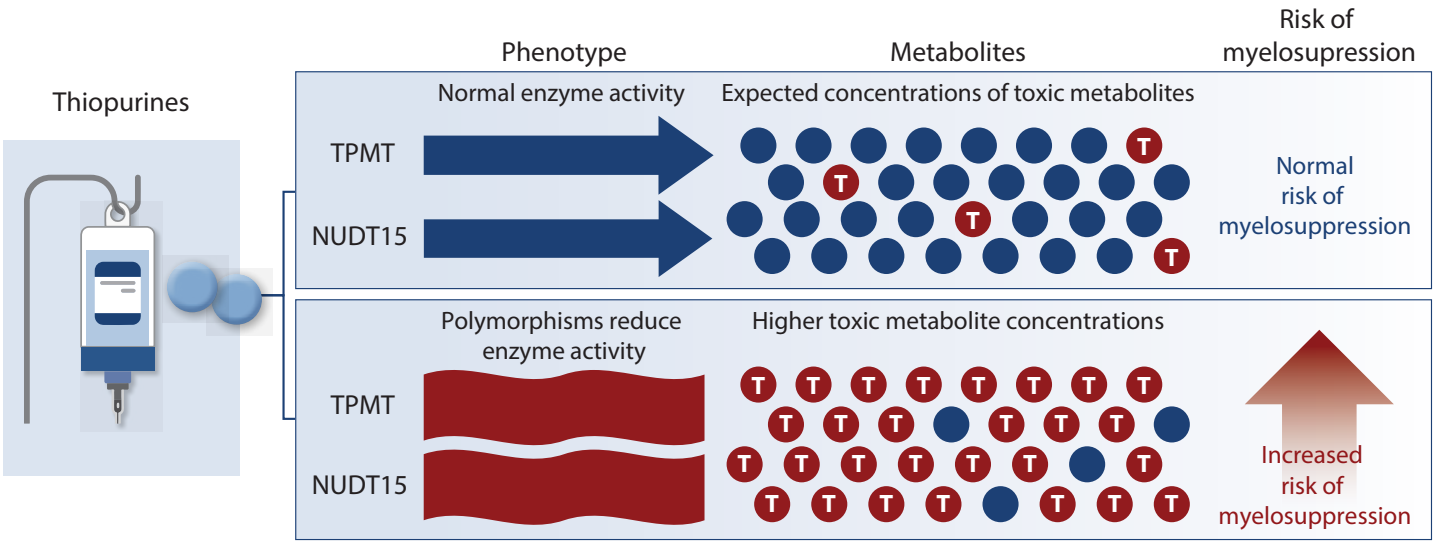


Figure 1. TPMT and NUDT15 polymorphisms result in life-threatening myelosuppression[1]



DID YOU KNOW

Poor and intermediate TPMT or NUDT15 metabolizers are **19 times more likely to experience myelotoxicity** and subsequently discontinue treatment compared to normal metabolizers when treated with standard dosing regimens.[5,7]

In a randomized, controlled trial of 783 patients with IBD, **genotype-guided thiopurine dosing** resulted in an **89% decreased risk** of myelotoxicity in intermediate and poor TPMT metabolizers.[8]

Reduce severe thiopurine toxicity by ordering PGx testing prior to therapy initiation.

Order PGx testing to confirm metabolizer status and inform risks.

Enzyme or activity assay provides information on TPMT function but will not provide information on NUDT15 genotype. Refer to the National Pharmacogenomics SharePoint for up-to-date PGx testing capabilities within VA. VA PGx tests currently take up to 10 to 20 days to come back.

You will be notified when PGx test results are available, and the patient will receive a copy in the mail. The results report will indicate the patient's phenotype, or metabolizer status, and provide therapeutic dosing recommendations.

For more information about interpreting PGx test results,

- Refer to An Introduction to Pharmacogenomics Clinician Guide
- Consult your PGx Clinical Pharmacist Practitioner (CPP)

See the Resources section on page 4 for more information.

Table 1. Azathioprine dosing recommendations based on TPMT and NUDT15 metabolizer status and malignant v. non-malignant indication[1]

Phenotype	NUDT15 normal or unknown	NUDT15 intermediate or possible intermediate	NUDT15 poor
TPMT normal	Use standard starting dose of 2-3 mg/kg/day	Reduce starting dose to 0.6-2.4 mg/kg/day Adjust every 2-4 weeks based on degree of myelosuppression	For **non-malignant conditions**, consider a non-thiopurine alternative agent Reduce daily dose by 10-fold Adjust every 4-6 weeks based on degree of myelosuppression
TPMT intermediate or possible intermediate	Reduce starting dose to 0.6-2.4 mg/kg/day Adjust every 2-4 weeks based on degree of myelosuppression		
TPMT poor	For **non-malignant conditions**, consider a non-thiopurine alternative agent Reduce starting dose by 10-fold and give three times/week rather than daily (e.g., 10 mg/m^2/day three days/week) Adjust every 4-6 weeks based on degree of myelosuppression		

Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines give the above therapeutic management recommendations a classification of **strong**.

Table 2. Mercaptopurine dosing recommendations based on TPMT and NUDT15 metabolizer status and malignant v. non-malignant indication[1]

Phenotype	NUDT15 normal or unknown	NUDT15 intermediate or possible intermediate	NUDT15 poor
TPMT normal	Use standard starting dose of 75 mg/m^2/day **or** 1.5 mg/kg/day	Reduce starting dose to 22.5-60 mg/m^2/day[†] **or** 0.45-1.2 mg/kg/day Adjust every 2-4 weeks based on degree of myelosuppression	For **non-malignant conditions**, consider a non-thiopurine alternative agent Reduce starting dose to 10 mg/m^2/day Adjust every 4-6 weeks based on degree of myelosuppression
TPMT intermediate or possible intermediate	Reduce starting dose[†] to 22.5-60 mg/m^2/day **or** 0.45-1.2 mg/kg/day Adjust every 2-4 weeks based on degree of myelosuppression		
TPMT poor	For **non-malignant conditions**, consider a non-thiopurine alternative agent Reduce starting dose by 10-fold and give three times/week rather than daily (e.g., 10 mg/m^2/day three days/week) Adjust every 4-6 weeks based on degree of myelosuppression		

CPIC guidelines give the above therapeutic management recommendations a classification of **strong**.

[†]If normal starting dose is already <75 mg/m^2/day or <1.5 mg/kg/day, dose reduction may not be recommended.

Table 3. Thioguanine dosing recommendations based on TPMT and NUDT15 metabolizer status and malignant v. non-malignant indication[1]

Phenotype	NUDT15 normal or unknown	NUDT15 intermediate or possible intermediate	NUDT15 poor
TPMT normal	Use standard starting dose of 40-60 mg/m^2/day	Reduce starting dose to 20-48 mg/m^2/day Adjust every 2-4 weeks based on degree of myelosuppression	For **non-malignant conditions**, consider a non-thiopurine alternative agent Reduce to 25% of normal dose Adjust every 4-6 weeks based on degree of myelosuppression
TPMT intermediate or possible intermediate	Reduce starting dose to 20-48 mg/m^2/day Adjust every 2-4 weeks based on degree of myelosuppression		
TPMT poor	For **non-malignant conditions**, consider a non-thiopurine alternative agent Reduce starting dose by 10-fold and give three times/week rather than daily Adjust every 4-6 weeks based on degree of myelosuppression		

CPIC guidelines give the above therapeutic management recommendations a classification of **strong** for normal and poor metabolizers. For intermediate and possible intermediate metabolizers, the strength of recommendation is classified as **moderate**.

For more information

RESOURCES:

- Up-to-date PGx testing capabilities within VA:
  - National Pharmacogenomics SharePoint (http://tinyurl.com/bdft5zd8)
- Information about interpreting PGx test results:
  - An Introduction to Pharmacogenomics Clinician Guide (http://tinyurl.com/2juazb6v)
  - Consult your PGx Clinical Pharmacist Practitioner (CPP) (http://tinyurl.com/47zzsb8p)

REFERENCES:‡ **1.** Relling MV, Schwab M, Whirl-Carrillo M, et al. Clinical Pharmacogenetics Implementation Consortium Guideline for Thiopurine Dosing Based on TPMT and NUDT15 Genotypes: 2018 Update. Clin Pharmacol Ther. May 2019;105(5):1095-1105. doi:10.1002/cpt.1304. **2.** Product Information: IMURAN (azathioprine) (2011). **3.** Highlights of Prescribing Information: PURINETHOL® (mercaptopurine) (2020). **4.** Prescribing Information: TABLOID® (thioguanine) (2018). **5.** Booth RA, Ansari MT, Loit E, et al. Assessment of thiopurine S-methyltransferase activity in patients prescribed thiopurines: a systematic review. *Annals of internal medicine*. Jun 21 2011;154(12):814-23, w-295-8. doi:10.7326/0003-4819-154-12-201106210-00009. **6.** Franca R, Zudeh G, Pagarin S, et al. Pharmacogenetics of thiopurines. *Cancer Drug Resist*. 2019;2(2):256-270. doi:10.20517/cdr.2019.004. **7.** Dickson AL, Daniel LL, Zanussi J, et al. TPMT and NUDT15 Variants Predict Discontinuation of Azathioprine for Myelotoxicity in Patients with Inflammatory Disease: Real-World Clinical Results. *Clin Pharmacol Ther*. Jan 2022;111(1):263-271. doi:10.1002/cpt.2428. **8.** Coenen MJ, de Jong DJ, van Marrewijk CJ, et al. Identification of Patients With Variants in TPMT and Dose Reduction Reduces Hematologic Events During Thiopurine Treatment of Inflammatory Bowel Disease. *Gastroenterology*. Oct 2015;149(4):907-17.e7. doi:10.1053/j.gastro.2015.06.002.

‡All "**doi**'s" use NIH's NLM Pub Med to search for the article.