Thiopurine S-Methyltransferase (TPMT): Pharmacogenetic Competency

Updated on 6/2015

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Pre-test Question # 1

Approximately 10% of patients have a (an) _____ TPMT phenotype.

a) Normal/high function
b) Intermediate function
c) Low/absent function
d) Ultra-rapid function

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Pre-test Question # 2

Which one of the following is NOT currently a recognized TPMT phenotype?

a) Normal/high function
b) Intermediate function
c) Low/absent function
d) Ultra-rapid function

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Pre-test Question # 3

In patients with high or normal TPMT function, how much time is needed to reach steady state after each dose adjustment?

a) 5 days
b) 1 week
c) 2 weeks
d) 4-6 weeks

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Pre-test Question # 4

Which of the following mercaptopurine dosing adjustments is correct for a leukemia patient with low or absent TPMT function?

a) Reduce the dose by 90% and give daily
b) Reduce the dose by 50% and give daily
c) Reduce the dose by 50% and give three times a week
d) Reduce the dose by 90% and give three times a week

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Pre-test Question # 5

What is the predicted TPMT phenotype for a patient with a *TPMT* genotype of **1/*2*?

a) Normal/high function
b) Intermediate function
c) Low/absent function
d) Ultra-rapid function

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Objectives

- **Upon completion of this competency, participants will be able to:**
  - **Recognize the different *TPMT* allele variants**
  - **Recognize the different TPMT phenotypes**
  - **Assign the correct phenotype based upon the allele variants**
  - **Make therapeutic recommendations for thiopurines based on a patient's predicted TPMT phenotype**

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Patient Case

- A 12-year-old patient was receiving azathioprine for auto-immune liver disease.
- He presented to the hospital for a workup of pediatric leukemia because of a CBC that revealed severe myelosuppression.
- Upon further work up, it was revealed that the patient had a TPMT genotype of *2/*2.
- Given that genotyping revealed that the patient had deficient TPMT function, azathioprine was discontinued. He was switched to another myelosuppressive agent.
- Blood counts slowly returned to normal after discontinuation of the azathioprine.

TPMT Pharmacogenetics

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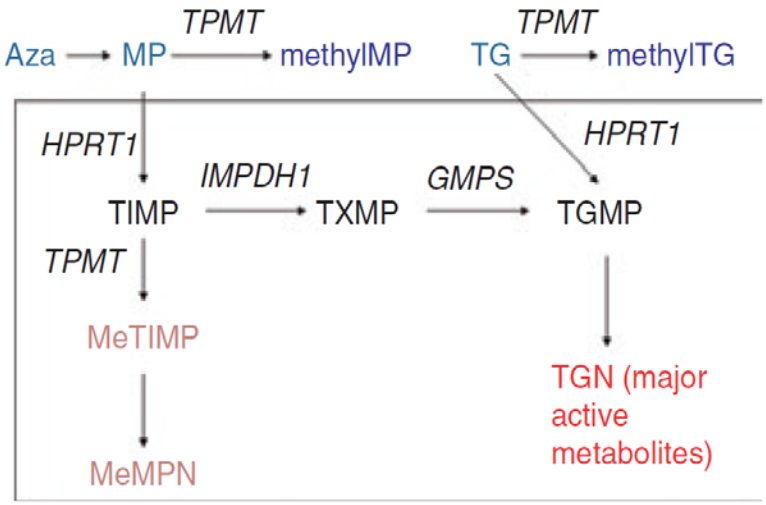
TPMT

- **Azathioprine (Aza), mercaptopurine (MP), and thioguanine (TG) are all prodrugs inactivated by *TPMT***
- ***TPMT* catabolizes MP and TG to inactive methyl-metabolites**
- **This leaves less parent drug available for metabolism to active thioguanine nucleotide (TGN) metabolites**
- **There is an inverse relationship between TPMT function and TGN metabolites**



Relling MV, et al. *Clin Pharmacol Ther* 2011;89(3):387-91.

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TPMT Function

- There are three ways to assess TPMT status
  - *TPMT* genotype (from DNA)
  - TPMT function or phenotype (using RBCs)
  - Thiopurine metabolites (TGN and MMPNs in RBCs)
- This competency will focus on *TPMT* genotype

RBC: Red Blood Cell
MMPN: 6-methylmercaptopurine ribonucleotide

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TPMT Allele Variants

- **Genetic variations in the *TPMT* gene may lead to changes in metabolic activity of the TPMT enzyme**
- **The following table summarizes the most common TPMT allele variants and likely TPMT enzyme activity**

Functional status	Alleles
Functional/ normal activity/ wild-type	*1, *24
Non-functional/ variant /no activity	*2, *3A, *3B, *3C, *4
Probable reduced function/ decreased activity (these are very rare)	*6, *8, *9, *10, *11, *12, *13, *16, *17, *18

Adapted from Relling MV, et al. *Clin Pharmacol Ther.* 2011;89(3):387-91.

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TPMT Phenotypes

- There are three TPMT phenotypes
  - Normal or high function
  - Intermediate function
  - Low or absent function
- The assignment of likely TPMT phenotype is based on genotype
- Phenotype (activity and metabolites) may be combined with genotype for patients receiving thiopurines

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TPMT Phenotypes

- **Normal (or high) function**
  - **Approximately 90% of patients**
  - **An individual carrying two or more functional (*1) alleles**
  - **Example diplotype: **1/*1***

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TPMT Phenotypes

- **Intermediate function**
  - **Approximately 10% of patients**
  - **An individual carrying one functional (*1) allele and one non-functional allele (*2, *3A, *3B, *3C, *4)**
  - **Example diplotypes: **1/*2, *1/*3A, *1/*3B, *1/*3C, *1/*4***
  - **Note: **1/*8* is classified as having possible intermediate TPMT function**

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TPMT Phenotypes

- **Low or absent function**
  - **Approximately 1 in 400 patients**
  - **An individual carrying two or more non-functional alleles (*2, *3A, *3B, *3C, *4)**
  - **Example diplotypes: **2/*3A,*2/*3C, *3A/*3A, *3A/*4, *3A/*3C, *3C/*4***

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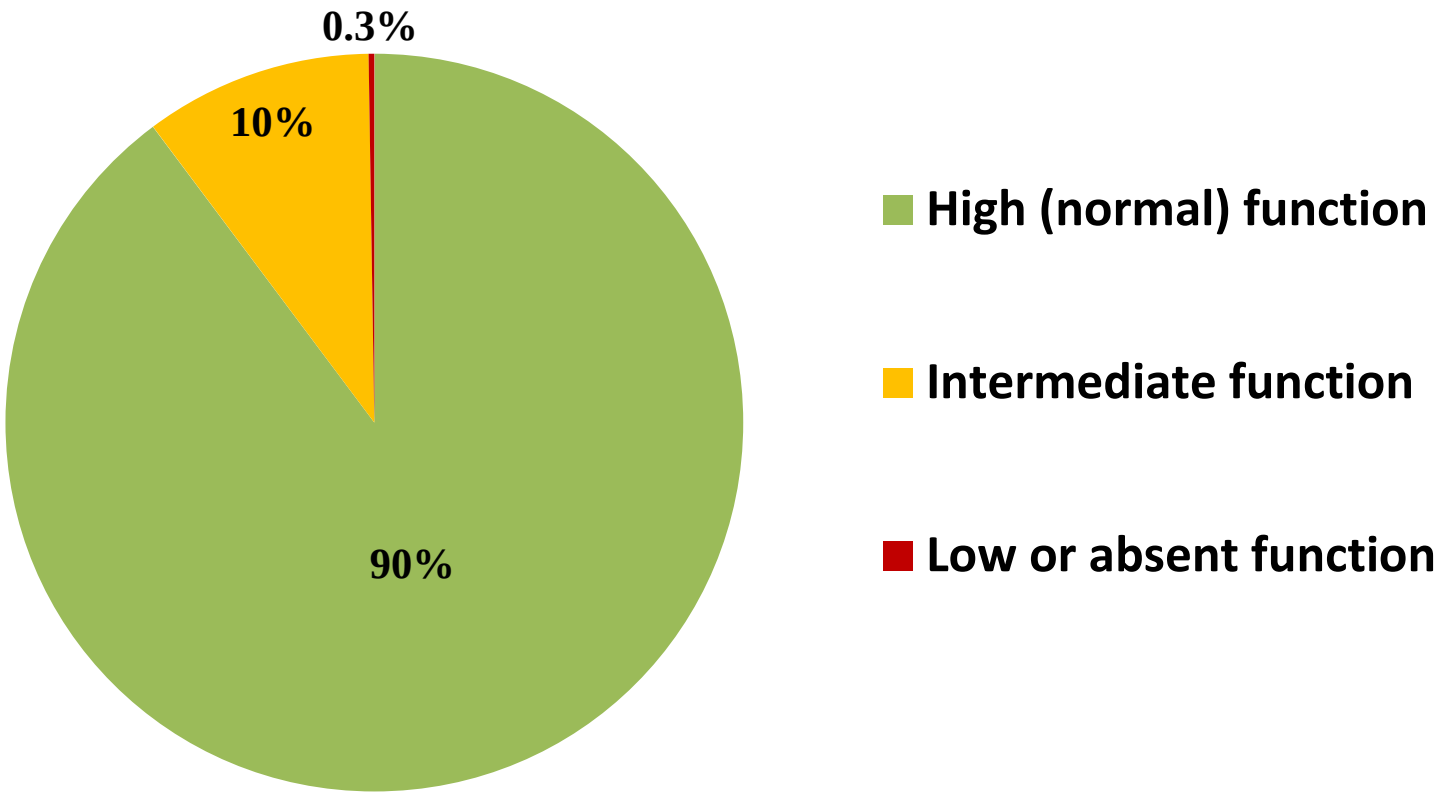
TPMT Phenotypes



*** The exact percent of each phenotype group varies by ethnicity**

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TPMT Phenotypes

- **In rare cases, patients may be wild-type by genotype and show intermediate function by TPMT phenotype testing requiring an additional phenotype terminology**
- **These patients are assigned a "possible intermediate function" phenotype**

Gene-Based Dosing Recommendations

Mercaptopurine

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Mercaptopurine

- **High or normal TPMT function**
  - **Initiate normal starting doses**
  - **Allow 2 weeks to reach steady state after each dose adjustment**
- **Intermediate TPMT function**
  - **Start at 30-70% of the normal starting dose**
  - **Adjust dose based on myelosuppression and disease-specific guidelines**
  - **Allow 2-4 weeks to reach steady state after each dose adjustment**
  - **Eventually, up to 65% of patients with intermediate TPMT function may tolerate full doses of mercaptopurine**

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Mercaptopurine

- **Low or absent TPMT function**
  - **For non-malignant conditions, consider alternative non-thiopurine immunosuppressants**
  - **For malignant conditions, reduce the daily dose by 90% and reduce the frequency to 3 times per week instead of daily**
  - **Allow 4-6 weeks to reach steady state after each dose adjustment**

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Azathioprine

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Azathioprine

- **High or normal TPMT function**
  - **Initiate normal starting doses and adjust based on disease-specific guidelines**
  - **Allow 2 weeks to reach steady state after each dose adjustment**
- **Intermediate TPMT function**
  - **Consider starting at 30-70% of target dose if "full doses" are to be used**
  - **Titrate doses based on tolerance**
  - **Allow 2-4 weeks to reach steady state after each dose adjustment**

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Azathioprine

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Thioguanine

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Thioguanine

- **High or normal TPMT function**
  - **Initiate normal starting doses**
  - **Allow 2 weeks to reach steady state after each dose adjustment**
- **Intermediate TPMT function**
  - **Start at 30-50% of the normal starting dose**
  - **Adjust dose based on myelosuppression and disease-specific guidelines**
  - **Allow 2-4 weeks to reach steady state after each dose adjustment**
  - **Eventually, up to 65% of patients with intermediate TPMT function may tolerate full doses of thioguanine**

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Thioguanine

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For More Information…

- **For more information about TPMT and thiopurine dosing click here.**
- **For more information about pharmacogenetics visit the following website: www.pharmgkb.org**
- **For more pharmacogenetic service implementation resources visit the following website: www.stjude.org/pg4kds/implement**

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Question # 1

Approximately 10% of patients have a (an) _____ TPMT phenotype.

a) Normal/high function
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c) Low/absent function
d) Ultra-rapid function

Correct answer: b

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Question # 2

Which one of the following is NOT currently a recognized TPMT phenotype?

a) Normal/high function
b) Intermediate function
c) Low/absent function
d) Ultra-rapid function

Correct answer: d

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Question # 3

In patients with high or normal TPMT function, how much time is needed to reach steady state after each dose adjustment?

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b) 1 week
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d) 4-6 weeks

Correct answer: c

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Question # 4

Which of the following mercaptopurine dosing adjustments is correct for a leukemia patient with low or absent TPMT function?

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b) Reduce the dose by 50% and give daily
c) Reduce the dose by 50% and give three times a week
d) Reduce the dose by 90% and give three times a week

Correct answer: d

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Question # 5

What is the predicted TPMT phenotype for a patient with a *TPMT* genotype of **1/*2*?

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d) Ultra-rapid function

Correct answer: b

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