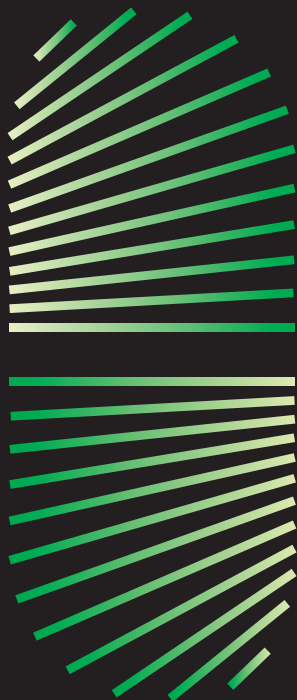
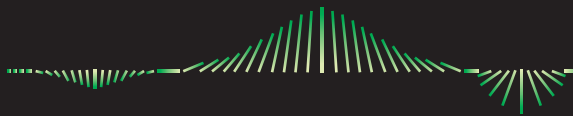


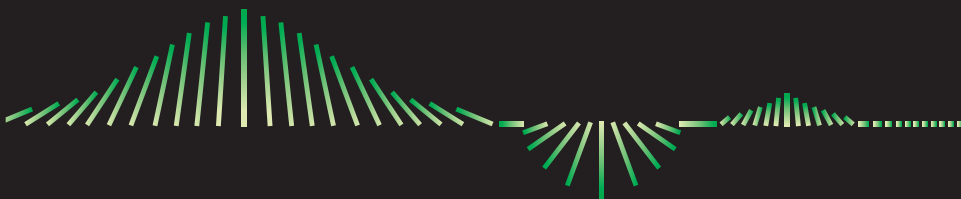
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# CUREGEN

Oncopharmacogenomics  
of Thiopurines



## What are Thiopurines?

Antimetabolites are a class of anticancer drugs that interfere with the process of cell division.<sup>1</sup>

Thiopurines are purine antimetabolites used as anti-cancer and immunosuppressive agents.

Azathioprine (AZA), 6-mercaptopurine and 6-thioguanine are thiopurines used widely in clinical practice.

## Intended therapeutic use<sup>2</sup>

Thiopurines are used in the treatment of

- Non-malignant immunological disorders, lymphoid malignancies and myeloid leukaemias
- Inflammatory bowel disease, rheumatoid arthritis and organ transplantation as immunosuppressant
- Neck cancer

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## Adverse events

**1/3<sup>rd</sup>**

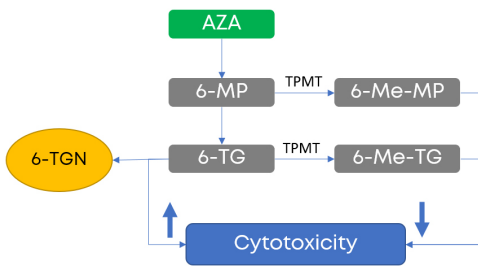
of patients administered with thiopurines experience one of more of the following side effects<sup>3</sup>

- Leucopenia
- Hair loss
- Hepatotoxicity
- Pancreatitis
- Gastric intolerance

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## Pharmacokinetics of Thiopurines

Prodrug azathioprine is converted to mercaptopurine that gets metabolized into thioguanine nucleotides (TGN). These disrupt DNA replication in rapidly dividing cells such as T cell lymphocytes thereby interfering with cell division<sup>3</sup>. However excessive formation of TGN results in cytotoxicity and thereby thiopurine related adverse events.



AZA – Azathioprine  
 MP- mercaptopurine  
 TG – thioguanine  
 TGN – Thioguanine nucleotides  
 Me-MP – methyl mercaptopurine  
 Me-TG – methyl thioguanine

## Pharmacogenetics of Thiopurine metabolism

The genes Thiopurine S-methyl transferase (*TPMT*) and nudix hydrolase 15 (*NUDT15*) code for enzymes that act on metabolites of mercaptopurine thereby leaving less parent drug for formation of TGN, resulting in less cytotoxicity.

### *TPMT*<sup>4,5</sup>:

Genetic variations in *TPMT* have been associated with varied metabolism of thiopurines and resultant side effects, mostly in Caucasian population.

Among about 20 genetic variations, 3 single nucleotide polymorphisms, namely *TPMT\*2*, *TPMT\*3B* and *TPMT\*3C* account for about 90% of low activity phenotypes.

### *NUDT15*<sup>4,6</sup>:

Variations in *NUDT15* gene is said to be more prevalent in Asian population.

Several variations associated with reduced gene function have been identified, amongst which R139C is the most common variation.

## Classification of phenotype based on genotype<sup>4</sup>

Likely phenotype	Likely phenotype
Normal metabolizer	An individual carrying two normal function alleles
Intermediate metabolizer	An individual carrying one normal function allele and one no function allele
Possible intermediate metabolizer	An individual carrying one uncertain/unknown function allele PLUS one no function allele
Poor metabolizer	An individual carrying two no function alleles

## Dosage recommendation

Dosage recommendation for thiopurine drugs is provided based on the phenotype observed in accordance with CPIC guidelines.

### CUREGEN advantage

Curegen, powered by MedGenome, is a precision pharmacogenomics test for individuals that checks for metabolism of more than 46 drugs/drug classes.

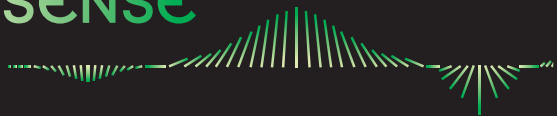
TEST CODE	SAMPLE TYPE	TURN AROUND TIME
GES002 - Curegen	Saliva/ Blood	14 working days
MGM1135 - <i>TPMT</i> and <i>NUDT15</i> gene analysis	Blood	12 working days

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