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Mercaptopurine Therapy and *TPMT* and *NUDT15* Genotype

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Introduction

Mercaptopurine (brand names Purinethol, Purixan) is an immunosuppressant and anti-neoplastic agent that belongs to the drug class of thiopurines. It is used with other drugs to treat acute lymphoblastic leukemia, which is the most common form of cancer in children (1). Common off-label uses include the treatment of inflammatory bowel disease (IBD).

Mercaptopurine is a prodrug that must first be activated to form thioguanine nucleotides (TGNs), of which 6-thioguanine triphosphate (6-TGTP) is the major active metabolite. Two of the enzymes involved in the complex pathway of these metabolites are thiopurine S-methyltransferase (TPMT) and nudix hydrolase 15 (NUDT15). Individuals with reduced activity of either enzyme will be exposed to higher levels of active metabolites, like 6-TGTP, and will be at a higher risk of side effects, such as severe bone marrow suppression (myelosuppression).

The FDA-approved drug label states that the initial dose of mercaptopurine should be reduced in individuals who are known to lack TPMT or NUDT15 activity ("homozygous deficiency") and that these individuals typically require 10% or less of the standard dose. In individuals who have reduced enzyme activity ("heterozygous deficiency"), the label states that the dose of mercaptopurine should be reduced based on tolerability. A more substantial dose reduction may be required in individuals who have reduced activity of both enzymes (Table 1) (1).

Dosing recommendations for mercaptopurine based on *TPMT* and *NUDT15* genotype have also been published by the Clinical Pharmacogenetics Implementation Consortium (CPIC, Table 2, Table 3) and the Dutch Pharmacogenetics Working Group (DPWG). These recommendations include specific dose reductions for individuals who have low or deficient enzyme activity, including starting dose and more information on how and when to adjust the dose for example, the time allowed to reach steady-state after each dose adjustment (2, 3).

Table 1. FDA Drug Label Dosage and Administration of Mercaptopurine (2020)

Deficiency	Dosage and administration
Homozygous deficiency in either TPMT or NUDT15	Individuals with homozygous deficiency of either enzyme typically require 10% or less of the standard mercaptopurine oral suspension dosage. Reduce initial dosage in individuals who are known to have homozygous TPMT or NUDT15 deficiency.

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Table 1. continued from previous page.

Deficiency	Dosage and administration
Heterozygous deficiency in TPMT and/or NUDT15	Reduce the mercaptopurine oral suspension dosage based on tolerability. Most individuals with heterozygous TPMT or NUDT15 deficiency tolerate recommended mercaptopurine doses, but some require dose reduction based on toxicities. Individuals who are heterozygous for both TPMT and NUDT15 may require more substantial dosage reductions.

This FDA table is adapted from (1). TPMT, thiopurine S-methyltransferase; NUDT15, nudix hydrolase 15

Table 2. CPIC Recommended Dosing of Mercaptopurine by *TPMT* Phenotype (2018 Update)

Phenotype	Implications for mercaptopurine phenotypic measures	Dosing recommendations for mercaptopurine	Classification of recommendations[b]
TPMT normal metabolizer	Lower concentrations of TGN metabolites, higher MeTIMP, this is the "normal" pattern. Normal risk of thiopurine-related leukopenia, neutropenia, myelosuppression.	Start with normal starting dose[a] (for example, 75 mg/m^2/day or 1.5 mg/kg/day) and adjust doses of mercaptopurine (and of any other myelosuppressive therapy) without any special emphasis on mercaptopurine compared with other agents. Allow at least 2 weeks to reach steady-state after each dose adjustment.	Strong
TPMT intermediate metabolizer Or TPMT possible intermediate metabolizer	Moderate to high concentrations of TGN metabolites; low concentrations of MeTIMP. Increased risk of thiopurine-related leukopenia, neutropenia, myelosuppression.	Start with reduced starting doses (30–80% of normal dose) if normal starting dose[a] is ≥75 mg/m^2/day or ≥1.5 mg/kg/day (for example, start at 22.5–60 mg/m^2/day or 0.45–1.2 mg/kg/day) and adjust doses of mercaptopurine based on degree of myelosuppression and disease-specific guidelines. Allow 2–4 weeks to reach steady-state after each dose adjustment. If myelosuppression occurs, and depending on other therapy, emphasis should be on reducing mercaptopurine over other agents. If normal starting dose is already <75 mg/m^2/day or <1.5 mg/kg/day, dose reduction may not be recommended.	Strong
TPMT poor metabolizer	Extremely high concentrations of TGN metabolites; fatal toxicity possible without dose decrease; no MeTIMP metabolites. Greatly increased risk of thiopurine- related leukopenia, neutropenia, myelosuppression.	For malignancy, start with drastically reduced doses (reduce daily dose[a] by 10-fold and reduce frequency to thrice weekly instead of daily (for example, 10 mg/m^2/day given just 3 days/week) and adjust doses of mercaptopurine based on degree of myelosuppression and disease-specific guidelines. Allow 4–6 weeks to reach steady-state after each dose adjustment. If myelosuppression occurs, emphasis should be on reducing mercaptopurine over other agents. For nonmalignant conditions, consider alternative nonthiopurine immunosuppressant therapy.	Strong

MeTIMP, metabolites of thiopurine methyltransferase; TGN, thioguanine nucleotides; TPMT, thiopurine methyltransferase.
[a]Normal starting doses vary by race/ethnicity and treatment regimens. If the standard dose is below the normal recommended dose, dose reduction might not be recommended for intermediate metabolizers.
[b] Rating scheme described in Supplemental Material (2).
This CPIC table is adapted from (2).
Note, CPIC have also published recommendations for thiopurine dosing when the status of both *TPMT* and *NUDT15* is known. Please see (2).

Table 3. CPIC Recommended Dosing of Mercaptopurine by *NUDT15* Phenotype (2018 Upate)

Phenotype	Implications for mercaptopurine phenotypic measures	Dosing recommendations for mercaptopurine	Classification of recommendations[b]
NUDT15 normal metabolizer	Normal risk of thiopurine-related leukopenia, neutropenia, myelosuppression	Start with normal starting dose[a] (for example, 75 mg/m^2/day or 1.5 mg/kg/day) and adjust doses of mercaptopurine (and of any other myelosuppressive therapy) without any special emphasis on mercaptopurine compared with other agents. Allow at least 2 weeks to reach steady-state after each dose adjustment.	Strong
NUDT15 intermediate metabolizer OR NUDT15 possible intermediate metabolizer	Increased risk of thiopurine-related leukopenia, neutropenia, myelosuppression	Start with reduced starting doses (30–80% of normal dose) if normal starting dose[a] is ≥75 mg/m^2/day or ≥1.5 mg/kg/day (for example, start at 22.5–60 mg/m^2/day or 0.45–1.2 mg/kg/day) and adjust doses of mercaptopurine based on degree of myelosuppression and disease-specific guidelines. Allow 2–4 weeks to reach steady-state after each dose adjustment. If myelosuppression occurs, and depending on other therapy, emphasis should be on reducing mercaptopurine over other agents. If the normal starting dose is already <75 mg/m^2/day or <1.5 mg/kg/day, dose reduction may not be recommended.	Strong
NUDT15 poor metabolizer	Greatly increased risk of thiopurine-related leukopenia, neutropenia, myelosuppression	For malignancy, initiate dose at 10 mg/m^2/day and adjust dose based on myelosuppression and disease-specific guidelines. Allow 4–6 weeks to reach steady-state after each dose adjustment. If myelosuppression occurs, emphasis should be on reducing mercaptopurine over other agents. For nonmalignant conditions, consider alternative nonthiopurine immunosuppressant therapy.	Strong

[a] Normal starting doses vary by race/ethnicity and treatment regimens. If the standard dose is below the normal recommended dose, dose reduction might not be recommended for intermediate metabolizers.
[b] Rating scheme described in Supplemental Material.
This CPIC table is adapted from (3).
Note, CPIC have also published recommendations for thiopurine dosing when the status of both *TPMT* and *NUDT15* is known. Please see (3). TPMT, thiopurine S-methyltransferase; NUDT15, nudix hydrolase 15

Drug Class: Thiopurines

Thiopurines are used as anticancer agents and as immunosuppressants in transplantation, inflammatory bowel disease, rheumatoid arthritis, and other autoimmune conditions. Three thiopurine derivatives are used in clinical practice: thioguanine, mercaptopurine, and azathioprine (a prodrug for mercaptopurine).

All 3 agents have similar effects but are typically used for different indications. Thioguanine is most commonly used in the treatment of myeloid leukemias, mercaptopurine is used for lymphoid malignancies, whereas all 3 drugs are used for a variety of autoimmune conditions.

There is increasing evidence that DNA testing for *NUDT15* and *TPMT* before initiating thiopurine therapy is clinically useful. In Europeans and Africans, inherited TPMT deficiency is the primary genetic cause of

thiopurine intolerance, whereas for Asians, risk alleles in *NUDT15* explains most thiopurine-related myelosuppression (4, 5). Current clinical practice in some countries (in the absence of enzymatic testing) is to initiate therapy and monitor for changes in liver function and complete blood count parameters, which some studies suggest may be similarly beneficial to preemptive testing (6).

Drug: Mercaptopurine

Mercaptopurine is an anti-neoplastic agent and an immunosuppressive agent that is used in the treatment of acute lymphoblastic leukemia (ALL) as part of a combination regimen. Acute lymphoblastic leukemia is the most common form of cancer in children, accounting for approximately 30% of childhood malignancies with a peak incidence occurring at 3–5 years of age (1).

An off-label use of mercaptopurine is the treatment of IBD. Along with the closely related prodrug azathioprine (that is metabolized to mercaptopurine), mercaptopurine is used as an "immunomodulator" and as a "steroid-sparing agent" in the treatment of Crohn's disease and ulcerative colitis.

Mercaptopurine is a slow-acting drug used in IBD, which typically takes at least 3 months before a therapeutic effect is observed. Therefore, mercaptopurine is used as a maintenance therapy of IBD rather than as a monotherapy for induction of remission. Because the discontinuation of mercaptopurine is associated with a high rate of relapse of IBD, mercaptopurine is usually continued long term if there are no adverse effects (7-9).

The efficacy of mercaptopurine in individuals with IBD has been well established. However, there remain questions on the safety of long-term mercaptopurine treatment, as there have been reports of an increased risk of lymphoma in these individuals (10, 11).

Like all thiopurines, mercaptopurine is a purine analogue, and acts as an antimetabolite by interfering with nucleic acid synthesis and inhibiting purine metabolism. Activation of mercaptopurine occurs via hypoxanthine phosphoribosyltransferase (HPRT) followed by a series of reactions to form TGNs. The cytotoxicity of mercaptopurine is due, in part, to the incorporation of 6-thioguanosine triphosphate (6-TGTP) into DNA.

Inactivation of mercaptopurine occurs via 2 major pathways: via methylation, which is catalyzed by TPMT, and via oxidation, which is catalyzed by xanthine oxidase (XO). In individuals who take an XO inhibitor, such as allopurinol (used to manage gout), the dose of mercaptopurine must be reduced to one-third or one-quarter of the usual dose to avoid severe toxicity (1, 12, 13). In individuals with normal TPMT metabolization and myelo- or hepatotoxicity, allopurinol may be initiated to slow the breakdown of mercaptopurine, leading to higher concentrations of TGNs(14).

The NUDT15 enzyme has an impact on the incorporation of 6-TGTP into DNA –– this enzyme is involved in the breakdown of the deoxy-thioguanosine triphosphate metabolite 6-TGTP to the inactive monophosphate metabolite, 6-thioguanine monophosphate (6-TGMP) (1).

One of the most frequent adverse reactions to mercaptopurine is myelosuppression, which can occur in any individual and can usually be reversed by decreasing the dose of the drug. However, this risk is increased in individuals who have reduced or absent TPMT, NUDT15, or both, activity (1).

Determining genotype is helpful before initiating thiopurine therapy, but it does not replace the need for regular monitoring. One study reported that in individuals with IBD receiving thiopurine therapy, *TPMT* polymorphisms were associated with the overall incidence of adverse reactions and with bone marrow toxicity, but not with other adverse reactions such as liver damage and pancreatitis. Therefore, regular blood tests to monitor for side effects are still needed during therapy (15).

Gene: *TPMT*

The *TPMT* gene encodes thiopurine S-methyltransferase, which is historically classified as a phase II metabolism enzyme. Importantly, TPMT is one of the main enzymes involved in the metabolism of thiopurines, including thioguanine.

The *TPMT* gene is highly polymorphic, with over 40 reported variant star (*) alleles (16-19). The *TPMT*1* allele is associated with normal enzyme activity (wild type).

The *TPMT*1* is considered the wild type allele when no variants are detected and is associated with normal enzyme activity and the "normal metabolizer" phenotype. Individuals who are normal metabolizers are more likely to have a typical response to thioguanine and a low risk of myelosuppression; however, all individuals receiving thioguanine require close monitoring (20-23).

Most individuals are TPMT normal metabolizers (~86–97%). A handful of variant *TPMT* alleles account for over 90% of the reduced or absent enzyme activity (2, 20, 21, 24):

- *TPMT*2* (c.238G>C)
- *TPMT*3A* (*TPMT*3B* c.460G>A and *TPMT*3C* c.719A>G in *cis*)
- *TPMT*3B* c.460G>A
- *TPMT*3C* (c.719A>G)
- *TPMT*4* (c. 626-1G>A)

Individuals who are TPMT poor metabolizers (~0.3% of individuals of European ancestry) have 2 non-functional *TPMT* alleles (Table 4). When treated with standard doses of azathioprine or mercaptopurine, these individuals will probably experience life-threatening bone marrow suppression because of high levels of TGNs (1).

Individuals who are TPMT intermediate metabolizers (approximately 3–14% of the general population) are heterozygous for one no function *TPMT* allele. These individuals may also be unable to tolerate conventional doses of thiopurines due to increased levels of TGNs and are at an increased risk of moderate to severe bone marrow suppression. However, some of these individuals, approximately 40–70%, can tolerate the full dose of mercaptopurine or other thiopurines. This may be because heterozygous-deficient individuals have lower concentrations of less active metabolites, such as methylmercaptopurine nucleotides (MeMPN), which is formed by TPMT, as compared with wild type individuals (20, 21). There are additional known *TPMT* alleles with uncertain function, including *TPMT*6, *7* and **8* (2). Individuals with these alleles in conjunction with an allele of known function are assigned to "possible intermediate metabolizer" or "indeterminate" categories as shown in Table 4. Additional details on these *TPMT* alleles is provided in the Nomenclature table below.

Table 4 Assignment of likely TPMT Phenotype based on Genotype (CPIC, 2018).

Likely phenotype[a]	Genotype	Examples of diplotype
Normal metabolizer	An individual with 2 normal function alleles	*1/*1
Intermediate metabolizer	An individual with one normal function allele PLUS one no function allele	*1/*2, *1/*3A, *1/*3B, *1/*3C, *1/*4
Possible intermediate metabolizer	An individual with one uncertain/unknown function allele PLUS one no function allele	*2/*8, *3A/*7
Poor metabolizer	An individual with 2 no function alleles	*3A/*3A, *2/*3A, *3A/*3C, *3C/*4, *2/*3C, *3A/*4

Table 4 continued from previous page.

Likely phenotype[a]	Genotype	Examples of diplotype
Indeterminate	An individual with 2 uncertain/unknown function alleles OR one normal function allele plus one uncertain allele function allele	*6/*8 *1/*8

TPMT, thiopurine methyltransferase.
[a] See TPMT and NUDT15 Frequency Table and Diplotype-Phenotype Table (3) for estimates of phenotype frequencies among different ethnic/geographic groups and for a more comprehensive list of predicted metabolizer phenotypes.
This CPIC table is adapted from (3). TPMT, thiopurine S-methyltransferase; NUDT15, nudix hydrolase 15

The frequency of *TPMT* variant alleles vary among different ethnic populations. In the United States, the most common low-activity allele in the Caucasian population is *TPMT*3A* (~5%). This allele is also found in individuals who originate from India and Pakistan, though with a lower frequency (16).

In East Asian, African-American, and some African populations, the most common variant is *TPMT*3C* (~2%), although *TPMT*8* may be more common in African populations than previously thought (~2%). In general, *TPMT*2* occurs less commonly, and *TPMT*3B* is also rare (16, 25). The *TPMT*4* allele is seen in fewer than 0.01% of Europeans and not detected in other ethnic groups, as reported by CPIC (2).

Gene: *NUDT15*

The *NUDT15* gene encodes an enzyme that belongs to the nudix hydrolase superfamily. Members of this superfamily catalyze the hydrolysis of deoxynucleoside diphosphates and triphosphates, which are created as a result of oxidative damage.

The NUDT15 enzyme is directly involved in the metabolism of thiopurines, as it catalyzes the conversion of active metabolites 6-TGTP to the less toxic metabolites 6-TGMP and 6-thioguanine diphosphate (6-TGDP) and in doing so, prevents the incorporation of the toxic metabolites into DNA and RNA (26).

In individuals with reduced or absent NUDT15 activity (intermediate or poor metabolizers, Table 5), the reduction in NUDT15-mediated degradation of 6-TGTP results in more 6-TGTP available for incorporation into DNA, leading to increased DNA damage and cell death. These individuals subsequently have increased sensitivity to thiopurines at standard doses, including an increased risk of severe myelosuppression (27).

Similar to *TPMT*, *NUDT15* is polymorphic, as the PharmVar Consortium currently has catalogued 21 variant alleles. However, most variants are rare, and the clinical significance of many *NUDT15* star (*) alleles is currently unclear.

The first *NUDT15* variant associated with thiopurine toxicity is commonly known as p.R139C (rs116855232), which is present in both the *NUDT15**2 and *NUDT15**3 haplotypes. This amino acid change results in an unstable protein with almost no enzymatic activity. The *NUDT15*2* variant haplotype also includes an insertion (see Nomenclature table and (2)).

Deficiency of NUDT15 is rare among in individuals with European or African ancestry (found in less than 1%); however, NUDT15 deficiency is more common in individuals with East Asian ancestry (for example, Korea, China, Japan, Vietnam), with a complete deficiency found in as much as 2% of these populations (2).

Table 5 Assignment of likely *NUDT15* Phenotype based on Genotype (CPIC, 2018)

Likely phenotype[a]	Genotype	Examples of diplotype
Normal metabolizer	An individual with 2 normal function alleles	*1/*1

Table 5 continued from previous page.

Likely phenotype[a]	Genotype	Examples of diplotype
Intermediate metabolizer	An individual with one normal function allele PLUS one no function allele	*1/*2, *1/*3
Possible intermediate metabolizer	An individual with one uncertain/unknown function allele PLUS one no function allele	*2/*5, *3/*6
Poor metabolizer	An individual with 2 no function alleles	*2/*2, *2/*3, *3/*3
Indeterminate	An individual with 2 uncertain function alleles OR one normal function allele plus one uncertain function allele	*1/*4, *1/*5 *4/*5, *5/*6

NUDT15, Nudix (Nucleoside Diphosphate Linked Moiety X)-Type Motif 15
[a] See *TPMT* and *NUDT15* Frequency Table and Diplotype-Phenotype Table (3) for estimates of phenotype frequencies among different ethnic/geographic groups and for a more comprehensive list of predicted metabolizer phenotypes.
This CPIC table is adapted from (3). TPMT, thiopurine S-methyltransferase; NUDT15, nudix hydrolase 15

Linking Gene Variation with Treatment Response

Genetic variation in the *TPMT* and *NUDT15* genes strongly influences the safety of thiopurine therapy, specifically, influencing the risk of treatment-related bone marrow suppression (28).

Thiopurine S-methyltransferase deficiency is the primary genetic cause of thiopurine intolerance in Europeans and Africans, and NUDT15 deficiency is a more common cause in Asians and Hispanics.

The clinical impact of variant *NUDT15* alleles was discovered more recently than for *TPMT*, and there is less evidence available to guide dose adjustments, but studies support genotyping *NUDT15* to improve the safety of thiopurine therapy. However, there is one clinical trial in progress that addresses azathioprine dosing guided by the status of both *TPMT* and *NUDT15* genotyping for the treatment of IBD (4, 5, 29-31).

Currently, *TPMT* and *NUDT15* testing is not required by the FDA before starting treatment with any thiopurine (azathioprine, mercaptopurine, or thioguanine); however, both genes were listed in the recently published FDA Association tables as pharmacogenetic associations with data supporting therapeutic management recommendations (32). Consequently, routine genotyping for *TPMT* and *NUDT15* variants has not been universally adopted (33). For homozygous or compound heterozygous deficiency of either *TPMT* or *NUDT15*, reconsider the use of thiopurines in non-neoplastic conditions, such as IBD, as potentially less toxic alternatives are available.(14)

Genetic Testing

The NIH Genetic Testing Registry, GTR, displays genetic tests that are available for the azathioprine drug response, and the genes *TPMT* and *NUDT15*. The genes may be tested separately, or together, as part of test panel that evaluates the drug response to thiopurines.

As with many tests, only the most common variants are usually tested (for example, for *TPMT*, the *2, *3A*, *3B* and *3C* alleles, which account for more than 90% of known inactivating alleles). This means that rare or previously undiscovered variants will not be detected by variant-specific genotyping methods (20, 21, 34-37).

It is important to note that for *TPMT*3A*, 2 variants, c.460G>A and c.719A>G, are in *cis*. The variant, c.460G>A by itself is *TPMT*3B* and c.719A>G by itself is *TPMT*3C*. Most clinical laboratories are unable to phase the 2 variants. In most cases, especially if the individual is of European ancestry, the laboratory will assume the 2 variants are in *cis*, though the possibility of the variants being in *trans* cannot be ruled out.

For TPMT, phenotype testing is also available. Phenotype tests directly measure TPMT enzyme activity in red blood cells but accurate phenotyping is not possible in individuals who have recently received blood transfusions (22). However, one study reported that *TPMT* genotyping was more reliable than phenotyping in identifying individuals at risk of adverse reactions from thiopurine treatment, and several studies reported that the *TPMT* genotype is a better indicator than TPMT activity for predicting TGN accumulation or treatment outcome (23, 38-40).

Therapeutic Recommendations based on Genotype

This section contains excerpted[1] information on gene-based dosing recommendations. Neither this section nor other parts of this review contain the complete recommendations from the sources.

2020 Statement from the US Food and Drug Administration (FDA):

Dosage Modifications in Patients with TPMT and NUDT15 Deficiency

Consider testing for TPMT and NUDT15 deficiency in patients who experience severe myelosuppression or repeated episodes of myelosuppression.

Homozygous Deficiency in either TPMT or NUDT15

Patients with homozygous deficiency of either enzyme typically require 10% or less of the recommended dosage. Reduce the recommended starting dosage of mercaptopurine tablets in patients who are known to have homozygous TPMT or NUDT15 deficiency.

Heterozygous Deficiency in TPMT and/or NUDT15

Reduce the mercaptopurine tablets dose based on tolerability. Most patients with heterozygous TPMT or NUDT15 deficiency tolerate the recommended dosage, but some require a dose reduction based on adverse reactions. Patients who are heterozygous for both TPMT and NUDT15 may require more substantial dose reductions.

[…]

Several published studies indicate that patients with reduced TPMT or NUDT15 activity receiving usual doses of mercaptopurine, accumulate excessive cellular concentrations of active 6-TGNs, and are at higher risk for severe myelosuppression. In a study of 1028 children with ALL, the approximate tolerated mercaptopurine dosage range for patients with TPMT and/or NUDT15 deficiency on mercaptopurine maintenance therapy (as a percentage of the planned dosage) was as follows: heterozygous for either TPMT or NUDT15, 50-90%; heterozygous for both TPMT and NUDT15, 30- 50%; homozygous for either TPMT or NUDT15, 5-10%.

Approximately 0.3% (1:300) of patients of European or African ancestry have two loss-of-function alleles of the *TPMT* gene and have little or no TPMT activity (homozygous deficient or poor metabolizers), and approximately 10% of patients have one loss-of-function TPMT allele leading to intermediate TPMT activity (heterozygous deficient or intermediate metabolizers). The *TPMT*2*, *TPMT*3A*, and *TPMT*3C* alleles account for about 95% of individuals with reduced levels of TPMT activity. NUDT15 deficiency is detected in < 1% of patients of European or African ancestry. Among patients of East Asian ancestry (i.e., Chinese, Japanese, Vietnamese), 2% have two loss-of-function alleles of the *NUDT15* gene, and approximately 21% have one loss-

[1] The FDA labels specific drug formulations. We have substituted the generic names for any drug labels in this excerpt. The FDA may not have labeled all formulations containing the generic drug. Certain terms, genes and genetic variants may be corrected in accordance to nomenclature standards, where necessary. We have given the full name of abbreviations, shown in square brackets, where necessary.

of-function allele. The p.R139C variant of *NUDT15* (present on the *2 and *3 alleles) is the most commonly observed, but other less common loss-of-function *NUDT15* alleles have been observed.

Consider all clinical information when interpreting results from phenotypic testing used to determine the level of thiopurine nucleotides or TPMT activity in erythrocytes, since some coadministered drugs can influence measurement of TPMT activity in blood, and blood from recent transfusions will misrepresent a patient's actual TPMT activity.

[…]

Consider testing for TPMT or NUDT15 deficiency in patients with severe myelosuppression or repeated episodes of myelosuppression. *TPMT* genotyping or phenotyping (red blood cell TPMT activity) and *NUDT15* genotyping can identify patients who have reduced activity of these enzymes. Patients with heterozygous or homozygous TPMT or NUDT15 deficiency may require a dose reduction.

Please review the complete therapeutic recommendations that are located here: (1).

2018 Statement from the Clinical Pharmacogenetics Implementation Consortium (CPIC)

***TPMT* recommendation**

If starting doses are already high (e.g., 75 mg/m^2 of mercaptopurine), as is true in some ALL treatment regimens, lower than normal starting doses should be considered in TPMT intermediate metabolizers and markedly reduced doses (10-fold reduction) should be used in TPMT poor metabolizers. This approach has decreased the risk of acute toxicity without compromising relapse rate in ALL. Even at these markedly reduced dosages, erythrocyte TGN concentrations in TPMT poor metabolizers remain well above those tolerated and achieved by the majority of patients (who are TPMT normal metabolizers).

In some nonmalignant conditions, alternative agents may be chosen for TPMT intermediate or poor metabolizers rather than reduced doses of thiopurines; if thiopurines are used, full starting doses are recommended for TPMT normal metabolizers, reduced doses (30–80% of target dose) in TPMT intermediate metabolizers, and substantially reduced doses (or use of an alternative agent) in TPMT poor metabolizers.

Some of the clinical data upon which dosing recommendations are based rely on measures of TPMT phenotype rather than genotype; however, because TPMT genotype is strongly linked to TPMT phenotype, these recommendations apply regardless of the method used to assess TPMT status.

***NUDT15* recommendation**

Similar to *TPMT*, tolerated mercaptopurine dosage is also correlated with the number of nonfunctional alleles of the *NUDT15* gene. In fact, the degree of thiopurine intolerance (e.g., for mercaptopurine) is largely comparable between carriers of TPMT vs. NUDT15 decreased function alleles, there remains a paucity of multi-ethnic studies examining both TPMT and NUDT15 variants.

Therefore, our *NUDT15* recommendations parallel those for *TPMT*. For NUDT15 normal metabolizers (NUDT15*1/*1), starting doses do not need to be altered. For NUDT15 intermediate metabolizers (e.g., NUDT15*1/*3), reduced starting doses should be considered to minimize toxicity, particularly if the starting doses are high (e.g., 75 mg/m^2/ day for mercaptopurine). For NUDT15 poor metabolizers (e.g., NUDT15*3/*3), substantially reduced doses (e.g., 10 mg/m^2/ day of mercaptopurine) or the use of an alternative agent should be considered.

As for TPMT, there is substantial variability in the tolerated thiopurine dosages within NUDT15 intermediate metabolizers, with a minority of individuals who do not seem to require significant dose reduction. Therefore,

genotype-guided prescribing recommendations apply primarily to starting doses; subsequent dosing adjustments should be made based on close monitoring of clinical myelosuppression (or disease-specific guidelines). In contrast, a full dose of mercaptopurine poses a severe risk of prolonged hematopoietic toxicity in NUDT15 poor metabolizers and pre-emptive dose reductions are strongly recommended.

The NUDT15 poor metabolizer phenotype is observed at a frequency of about 1 in every 50 patients of East Asian descent, which is more common than the TPMT poor metabolizer phenotype in Europeans, and, thus, genotyping NUDT15 in the Asian populations may be of particular clinical importance. NUDT15 deficiency is also more prevalent in individuals of Hispanic ethnicity, particularly those with high levels of Native American genetic ancestry.

Please review the complete therapeutic recommendations, which include CPIC's recommended course of action if both TPMT and NUDT15 genotypes are known, located here: (2).

2019 Summary of recommendations from the Dutch Pharmacogenetics Working Group (DPWG) of the Royal Dutch Association for the Advancement of Pharmacy (KNMP)

The Dutch Pharmacogenetics Working Group considers genotyping before starting azathioprine or 6-mercaptopurine to be essential for drug safety. Genotyping must be performed before drug therapy has been initiated to guide drug and dose selection.

TPMT Intermediate Metabolizer

Grade 2 leukopenia occurs in 23% of these patients with normal therapy for immunosuppression. The genetic variation increases the quantity of the active metabolites of azathioprine and mercaptopurine.

Recommendation:

IMMUNOSUPPRESSION

- Start with 50% of the standard dose

Adjustment of the initial dose should be guided by toxicity (monitoring of blood counts) and effectiveness.

Dose adjustment is not required for doses lower than 1.5 mg/kg per day for azathioprine or 0.75 mg/kg per day for mercaptopurine.

LEUKEMIA

- Start with 50% of the standard mercaptopurine dose, or start with the standard dose and reduce to 50% if side effects necessitate a dose reduction

It is not known whether dose reduction in advance results in the same efficacy as dose reduction based on toxicity.

The initial dose should be adjusted based on toxicity (monitoring of the blood counts) and efficacy.

Note: more stringent dose reductions are necessary if the patient is also NUDT15 IM or NUDT15 PM.

TPMT Poor Metabolizer

Grade 2 leukopenia and intolerance occurred in 98% of these patients with standard therapy. The gene variation increases the quantities of the active metabolites of azathioprine and mercaptopurine.

Recommendation:

- Choose an alternative or use 10% of the standard dose.

Any adjustment of the initial dose should be guided by toxicity (monitoring of blood counts) and effectiveness.

If the dose is decreased: advise patients to seek medical attention when symptoms of myelosuppression (such as severe sore throat in combination with fever, regular nosebleeds and tendency to bruising) occur

Background information:

Azathioprine is converted in the body to mercaptopurine. Mercaptopurine is an inactive pro-drug, which is converted to the active metabolites - thioguanine nucleotides - in the body.

Two catabolic routes reduce mercaptopurine bio-availability for thioguanine nucleotide formation. Thiopurine methyltransferase (TPMT) catalyses S-methylation of both mercaptopurine and the 6- mercaptopurine ribonucleotides formed in the metabolic pathway. In addition to this, mercaptopurine is oxidised to the inactive 6-thiouric acid by the enzyme xanthine oxidase (XO), which occurs primarily in the liver and intestines.

For more information about the TPMT phenotypes: see the general background information about TPMT on the KNMP Knowledge Bank or on www.knmp.nl (search for TPMT).

NUDT15 Intermediate Metabolizer

Grade ≥ 2 leukopenia occurs in 42% of these patients with standard immunosuppression therapy. The gene variation increases the concentration of the fully activated metabolite of azathioprine and mercaptopurine.

IMMUNOSUPPRESSION

- start with 50% of the standard dose

Adjustment of the initial dose should be performed based on toxicity (monitoring of the blood counts) and efficacy.

LEUKAEMIA

- start at 50% of the standard mercaptopurine dose, or start with the standard dose and reduce to 50% if side effects necessitate a dose reduction

It is not known whether dose reduction in advance results in the same efficacy as dose reduction based on toxicity.

Adjustment of the initial dose should be performed based on toxicity (monitoring of the blood counts) and efficacy.

Note: more stringent dose reductions are necessary if the patient is also TPMT IM or TPMT PM.

NUDT15 Poor Metabolizer

Grade ≥ 2 leukopenia occurs in 96% of these patients with standard therapy. The gene variation increases the concentration of the fully activated metabolite of azathioprine and mercaptopurine.

- avoid azathioprine and mercaptopurine
- if it is not possible to avoid azathioprine and mercaptopurine: use 10% of the standard dose and advise patients to seek medical attention when symptoms of myelosuppression (such as severe sore throat in combination with fever, regular nosebleeds and tendency to bruising) occur

Any adjustment of the initial dose should be guided by toxicity (monitoring of blood counts) and efficacy.

Background information:

NUDT15 reverses the last step in the formation of the active metabolite of mercaptopurine and its precursor azathioprine. It converts 6-thiodeoxyguanosine triphosphate (6-thio-dGTP), which is incorporated in DNA, to 6-thiodeoxyguanosine monophosphate (6-thio-dGMP). Lower metabolic activity of NUDT15 therefore leads to increased intracellular concentrations of the active metabolite 6- thio-dGTP. This increases the risk of side effects, such as myelosuppression.

For more information about TPMT and NUDT15 phenotypes: see the general background information in the KNMP Knowledge Bank or on www.knmp.nl (search for TPMT or NUDT15).

Please review the complete therapeutic recommendations that are located here: (3).

Nomenclature for Selected *TPMT* and *NUDT15* Alleles

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
*TPMT*2*	238G>C Ala80Pro	NM_000367.4:c.238G>C	NP_000358.1:p.Ala80Pro	rs1800462
*TPMT*3A*	This allele contains 2 variants in *cis*: c.460G>A and c.719A>G			
*TPMT*3B*	460G>A Ala154Thr	NM_000367.4:c.460G>A	NP_000358.1:p.Ala154Thr	rs1800460
*TPMT*3C*	719A>G Tyr240Cys	NM_000367.4:c.719A>G	NP_000358.1:p.Tyr240Cys	rs1142345
*TPMT*4*	626-1G>A	NM_000367.4:c.626-1G>A	(Splice acceptor variant)	rs1800584
*TPMT*6*	539A>T	NM_000367.4:c.539A>T	NP_000358.1:p.Tyr180Cys	rs75543815
*TPMT*7*	681T>G	NM_000367.4:c.681T>G	NP_000358.1:p.His227Gln	rs72552736
*TPMT*8*	644G>A	NM_000367.4:c.644G>A	NP_000358.1:p.Arg215His	rs56161402
*NUDT15*2*	p.R139C p.13_14GV[5]	NM_018283.4:c.415C>T NM_018283.4:c.38_43GAGTCG[4]	NP_060753.1:p.Arg139Cys NP_060753.1:p.13_14GV[5]	rs116855232 rs746071566
*NUDT15*3*	p.R139C	NM_018283.4:c.415C>T	NP_060753.1:p.Arg139Cys	rs116855232
*NUDT15*4*	p.R139H c.416G>A	NM_018283.4:c.416G>A	NP_060753.1:p.Arg139His	rs147390019
*NUDT15*5*	Val18Ile	NM_018283.4:c.52G>A	NP_060753.1:p.Val18Ile	rs186364861
*NUDT15*6*	p.13_14GV[4]	NM_018283.4:c.38_43GAGTCG[2]	NP_060753.1:p.13_14GV[4]	rs746071566

Note: the p.R139C variant of *NUDT15* is present on the *NUDT15*2* and *NUDT*3* alleles.
The TPMT Nomenclature Committee defines the nomenclature and numbering of novel TPMT variants.
Nomenclature for *NUDT15* is available from the Pharmacogene Variation (PharmVar) Consortium.
Guidelines for the description and nomenclature of gene variations are available from the Human Genome Variation Society (HGVS)

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Version History

To view the second edition of this summary (Update: May 3, 2016), please click here.
To view the first edition of this summary (Update: March 18, 2013), please click here.

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