Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for thiopurine dosing based on *TPMT* and *NUDT15* genotypes: 2025 Update

CPIC members call

August 7th, 2025

Kelly Caudle, Jun J Yang, Maud Maillard & Bailey Tibben

On behalf of the CPIC TPMT/NUDT15 guideline and PCEP committees

Outline of the presentation

Why is it the right time to update the guideline?

Who participated in this update?

What are the major changes made to the previous guideline?

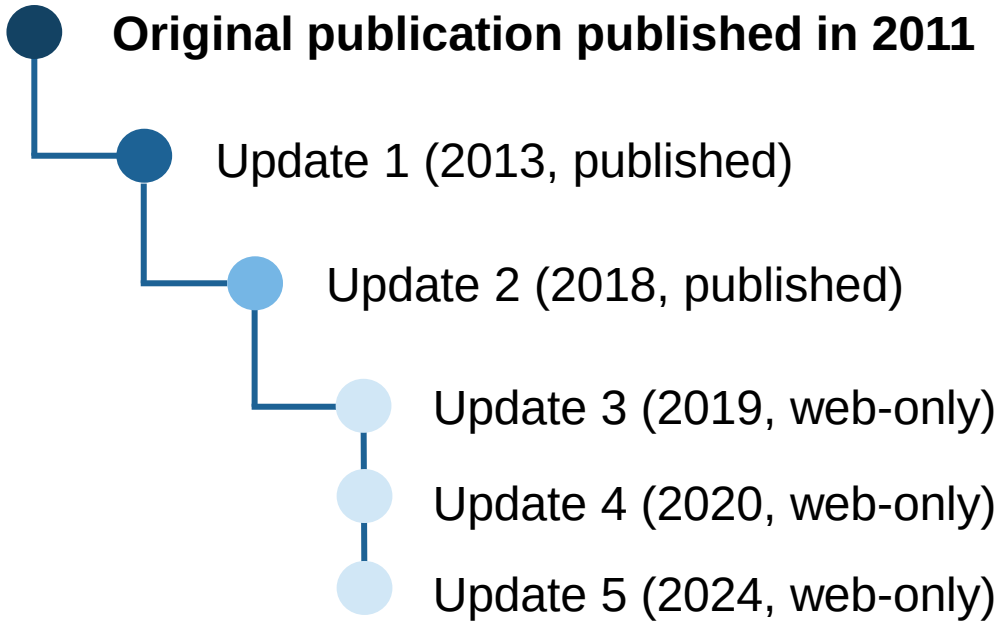
What is the role of the new PCEP committee?

Which new alleles have been incorporated?

It is time to update the TPMT/NUDT15 guideline

- A brief history of the guideline

Clinical Pharmacology & Therapeutics



TPMT-genotype guided dosing recommendations

It is time to update the TPMT/NUDT15 guideline

- A brief history of the guideline

Clinical Pharmacology & Therapeutics

CPIC UPDATE

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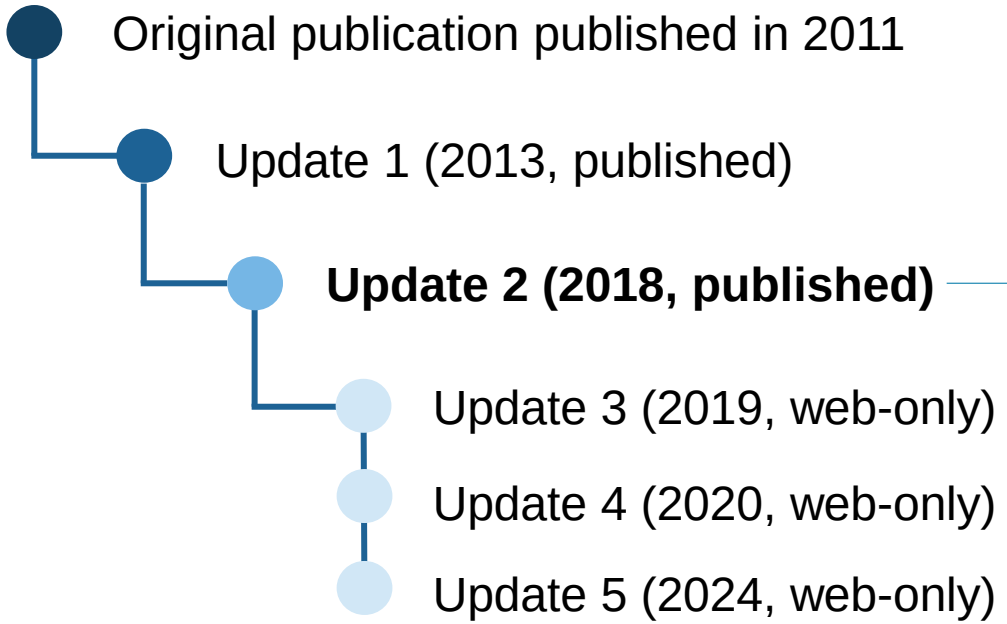
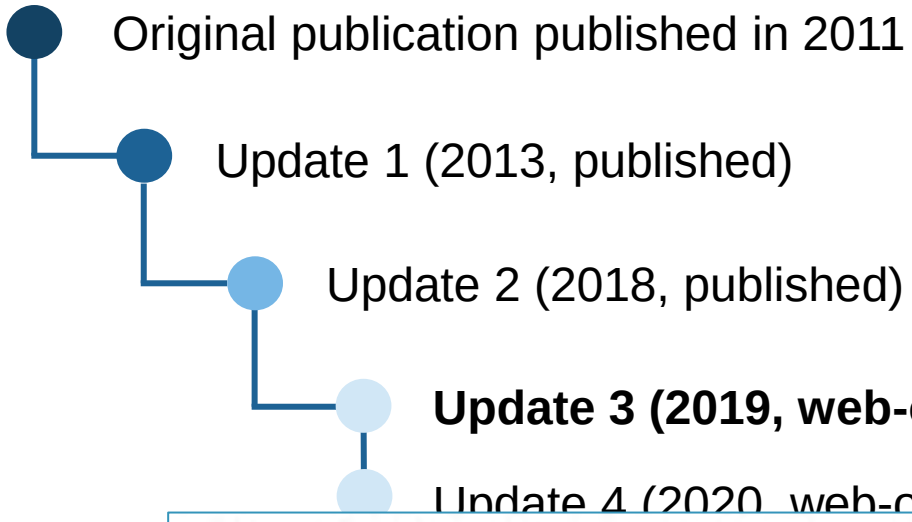
CPIC UPDATE



Introduction of *NUDT15* into the guideline (~3 years after the first genome wide association studies)

It is time to update the TPMT/NUDT15 guideline

- A brief history of the guideline

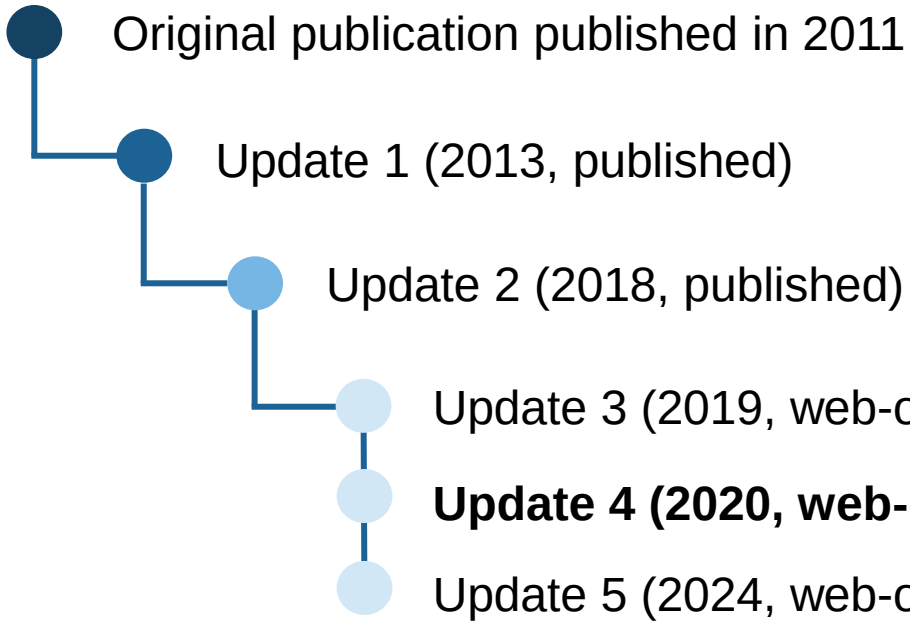


Allele function assignment for *NUDT15 *9*

February 2019: Based on a recent publication confirming *NUDT15*9* function and association with toxicity to thiopurines, *NUDT15*9* function has been changed from "uncertain function" to "no function" (PMID: 30728528). The *NUDT15* allele definition table, *NUDT15* allele functionality table, *NUDT15* diplotype-phenotype table and *NUDT15* frequency table have been updated accordingly.

It is time to update the TPMT/NUDT15 guideline

- A brief history of the guideline

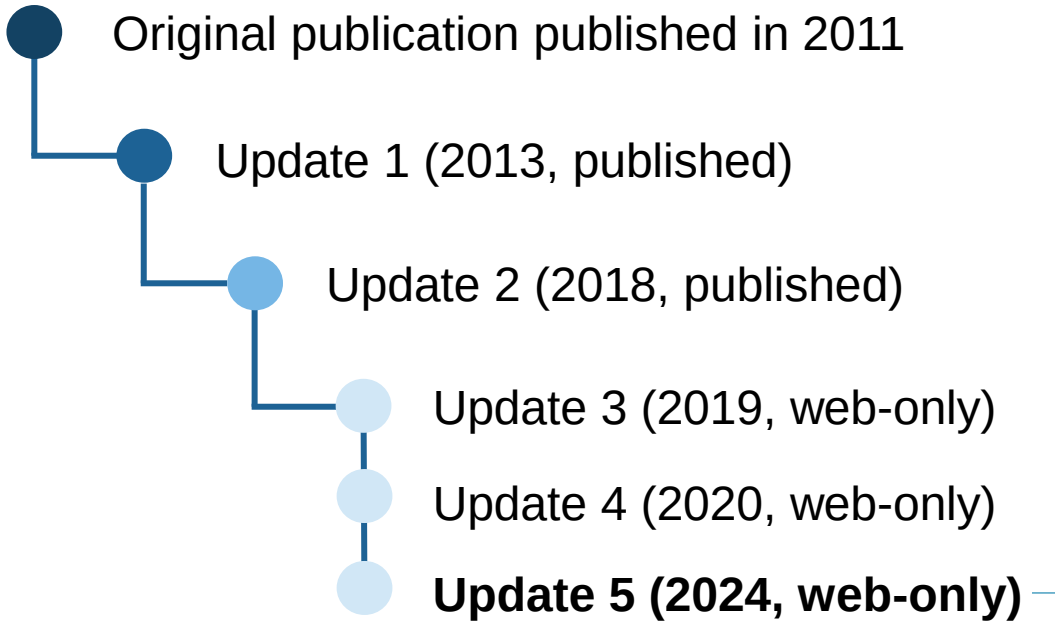


→ Recommendation for TPMT and NUDT15 indeterminate phenotype

April 2020: The authors of this guideline have added recommendations for TPMT and NUDT15 indeterminate phenotypes (i.e. combination of uncertain and/or unknown function alleles). TPMT indeterminate: Consider evaluating TPMT erythrocyte activity to assess TPMT phenotype. NUDT15 indeterminate: If thiopurines are required and NUDT15 status is unknown, monitor closely for toxicity. See here for updated recommendation tables (azathioprine, mercaptopurine, thioguanine). The diplotype-phenotype tables and pre- and post-tests alert tables have been updated accordingly below.

It is time to update the TPMT/NUDT15 guideline

- A brief history of the guideline



→ Recommendation for TPMT/NUDT15 compound intermediate metabolizers

March 2024: At the time of guideline publication, the extent of dosage reduction for thiopurines recommended for patients with intermediate metabolism for both TPMT and NUDT15 was unclear. A recent publication (PMID: 38230823) found that these individuals need a substantial dose reduction to mitigate toxicity in TPMT/NUDT15 IM/IM patients. The recommendation for a TPMT intermediate metabolizer/NUDT15 intermediate metabolizer has been updated for all thiopurines to recommend a starting dose at 20%-50% of normal dosages, depending on the starting dose. See here for updated recommendation tables (azathioprine, mercaptopurine, thioguanine). The pre- and post-tests alert tables have been updated accordingly.

It is time to update the TPMT/NUDT15 guideline

- Rationale of the update : an opportunity to align evidence-based PG recommendations with real-world clinical practice.

Clinical Integration of *TPMT* and *NUDT15* Genotyping

–

Most of clinical practices now **routinely incorporate *TPMT* and/or *NUDT15*** genotyping to guide thiopurine therapy.

Accumulation of Clinical Evidence in the Literature

–

The systematic testing of *TPMT* (and, in some cases, *NUDT15*) before or after initiating thiopurine treatment has led to the accumulation of **significant clinical data** supporting pharmacogenetic associations.

The Use of Sequencing Technologies

–

The adoption of sequencing methods enables a **more comprehensive assessment of genetic associations**, including the identification of rare variants.

Variants characterization and function assignment

–

The development of ***in silico* prediction and scalable experimental functional assays** provided additional evidence to determine the allele impact on the protein.

Discovery of New Variants Across Diverse Populations

–

New clinically relevant variant associations have been identified in **diverse populations** and these specificities need to be assessed in the guideline.

Contributors to the 2025 guideline

- Collaborative work between:
  - Physicians
  - Clinical pharmacists
  - Researchers
- Different medical areas:
  - Pediatric oncology
  - Gastroenterology
  - Neurology
- From all around the world

Contributors to the 2025 guideline

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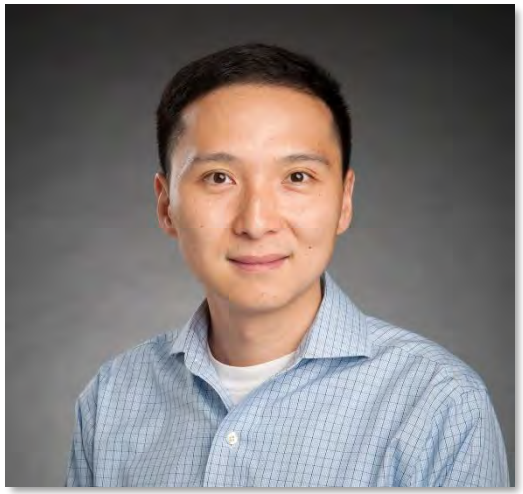
Full Member
St. Jude Children's Research Hospital
CPIC guideline update corresponding author



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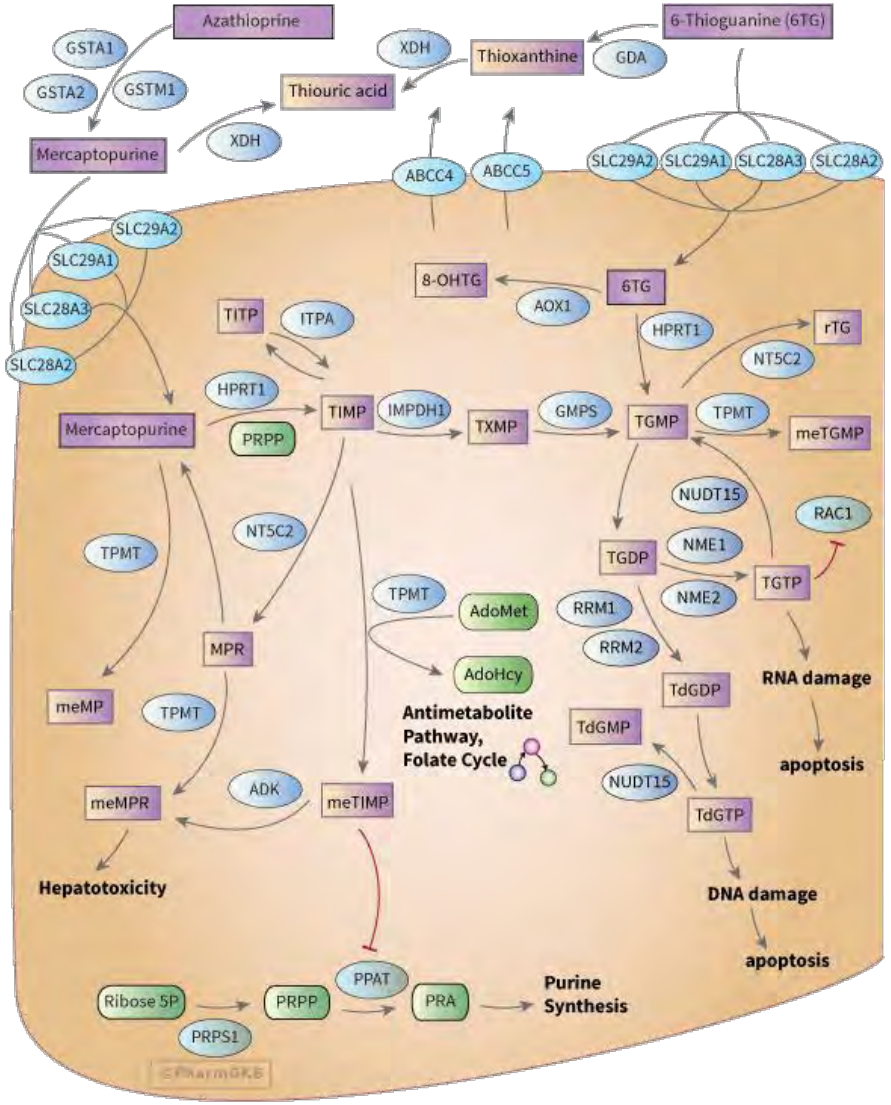
TPMT and NUDT15, it takes two to tango

- Pharmacology
  - Thiopurines: azathioprine, mercaptopurine and thioguanine
  - TPMT and NUDT15 are involved in the inactivation of thiopurines:
    - Methylation of MP and metabolites (MMPNs)
    - De-phosphorylation of thioguanine nucleotides (TGNs)

- Pharmacogenetic associations (toxicity and efficacy)
  - TPMT deficiency: ↑6-TGN & ↓ MMPNs.
  - NUDT15 deficiency: ↑ TGTP incorporation into DNA (DNA-TG).
  - Preemptive testing ↓ risk of thiopurine induced myelosuppression, without impairing their efficacy.

- Key aspects related to ethnicity
  - TPMT deficiency is more frequent in individuals of African or European descent.
  - NUDT15 deficiency mostly found in individuals of Asian and Hispanic descent.



Major changes to the previous guideline

Recommendation tables from the 2018 guideline

One table for *TPMT*…

Table 2 Recommended dosing of thiopurines by TPMT phenotype

	Mercaptopurine			Azathioprine		Thioguanine		
Phenotype	Implications for mercaptopurine and azathioprine phenotypic measures	Dosing recommendations for mercaptopurine	Classification of recommendations	Dosing recommendations for azathioprine	Classification of recommendations	Implications for thioguanine phenotypic measures	Dosing recommendations for thioguanine	Classification of recommendations[b]

… and one for *NUDT15*.

Table 3 Recommended dosing of thiopurines by NUDT15 phenotype

	Mercaptopurine			Azathioprine		Thioguanine	
Phenotype	Implications for thiopurine phenotypic measures	Dosing recommendations for mercaptopurine	Classification of recommendations	Dosing recommendations for azathioprine	Classification of recommendations	Dosing recommendations for thioguanine	Classification of recommendations[b]

Limits:

- Does not account for combination of phenotypes between TPMT and NUDT15
- No disease-specific recommendation
- Variance in recommendation based on TPMT vs NUDT15 even though both genes have comparable effects on toxicity

Relling, CPT, 2019

Major changes to the previous guideline

Recommendation workflow from the 2018 guideline

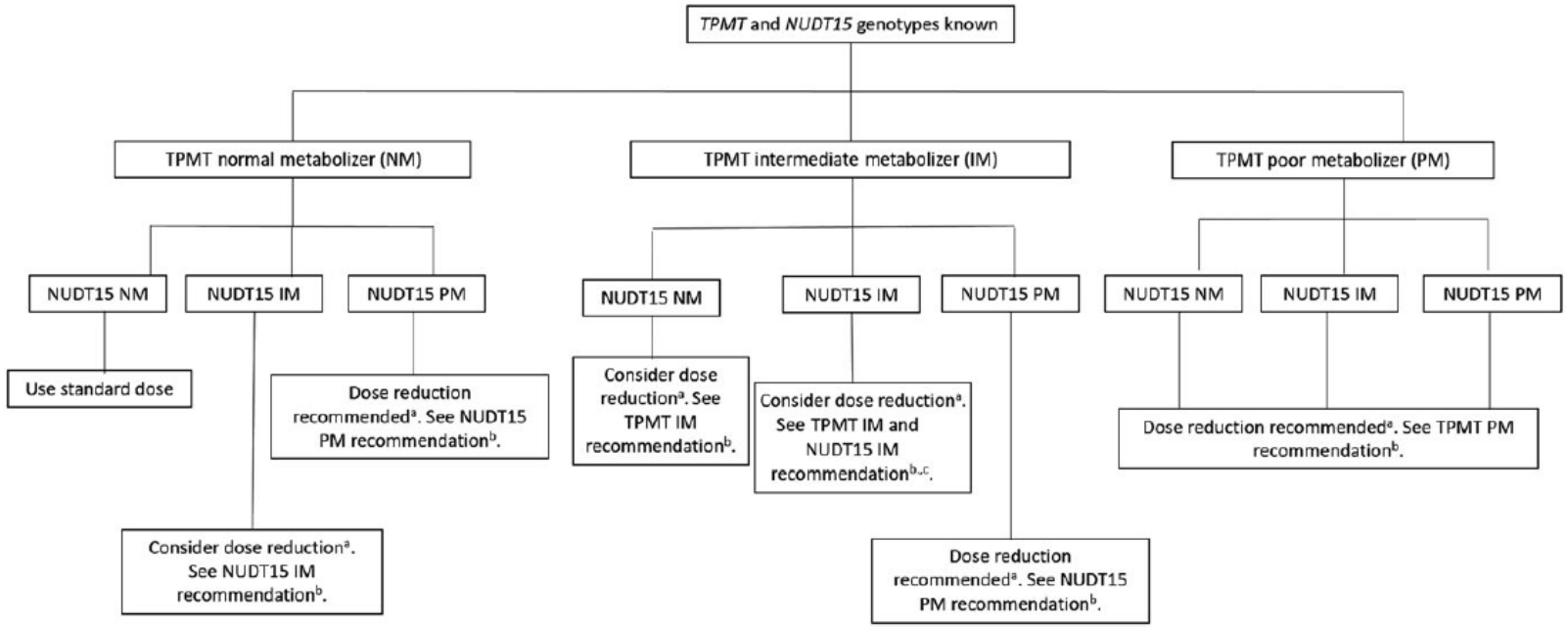


Figure 2 Recommended starting doses of thiopurines by thiopurine methyltransferase (TPMT) and NUDT15 phenotype. [a]Whether a dose reduction is recommended from the starting dose depends on the level of the standard starting dose; for example, if the standard starting dose of mercaptopurine is 75 mg/m^2/day or higher, then a lower starting dose may be considered in intermediate metabolizers and would be recommended in poor metabolizers, whereas if the starting dose is 50 mg/m^2/day or lower, a reduced starting dose may not be necessary in intermediate metabolizers. [b]See **Table 2** for recommendation. [c]For patients who are intermediate metabolizers for both TPMT and NUDT15, further dose reduction might be needed compared with those who are only intermediate metabolizers with respect to one gene (*TPMT* or *NUDT15*).

Limits:

- No numbered dose reduction
- Refers to the table & causes a lot of back and forth
- Does not account for disease-specific recommendation.

Relling, CPT, 2019

Recommendation tables for the 2025 guideline

Drug-specific recommendations and account for their respective clinical indications:

- Mercaptopurine for malignancies (e.g., leukemia) and non malignancies (e.g., auto-immune disorders)
- Thioguanine for malignancies (e.g., leukemia)
- Azathioprine for auto-immune disorders

- **4 phenotype classes:**

I. TPMT and NUDT15 normal metabolizer (NM)

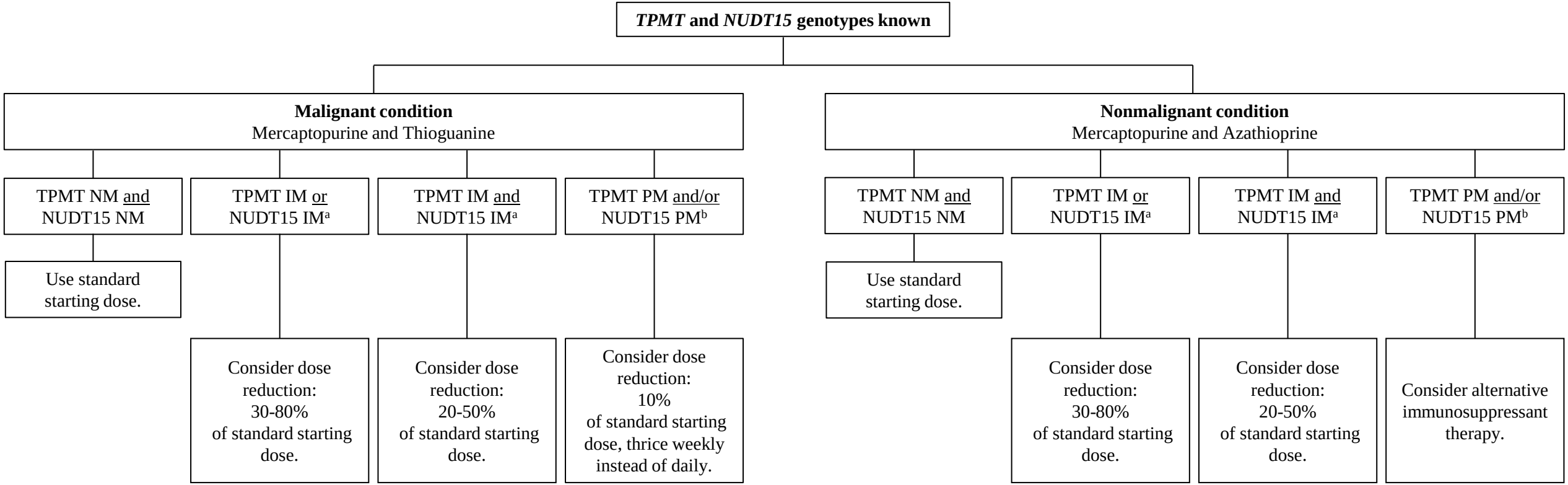
II. TPMT NM and NUDT15 (possible) intermediate metabolizer (IM)

OR TPMT (possible) IM and NUDT15 NM

III. Any combination with TPMT poor metabolizer (PM) and/or NUDT15 PM

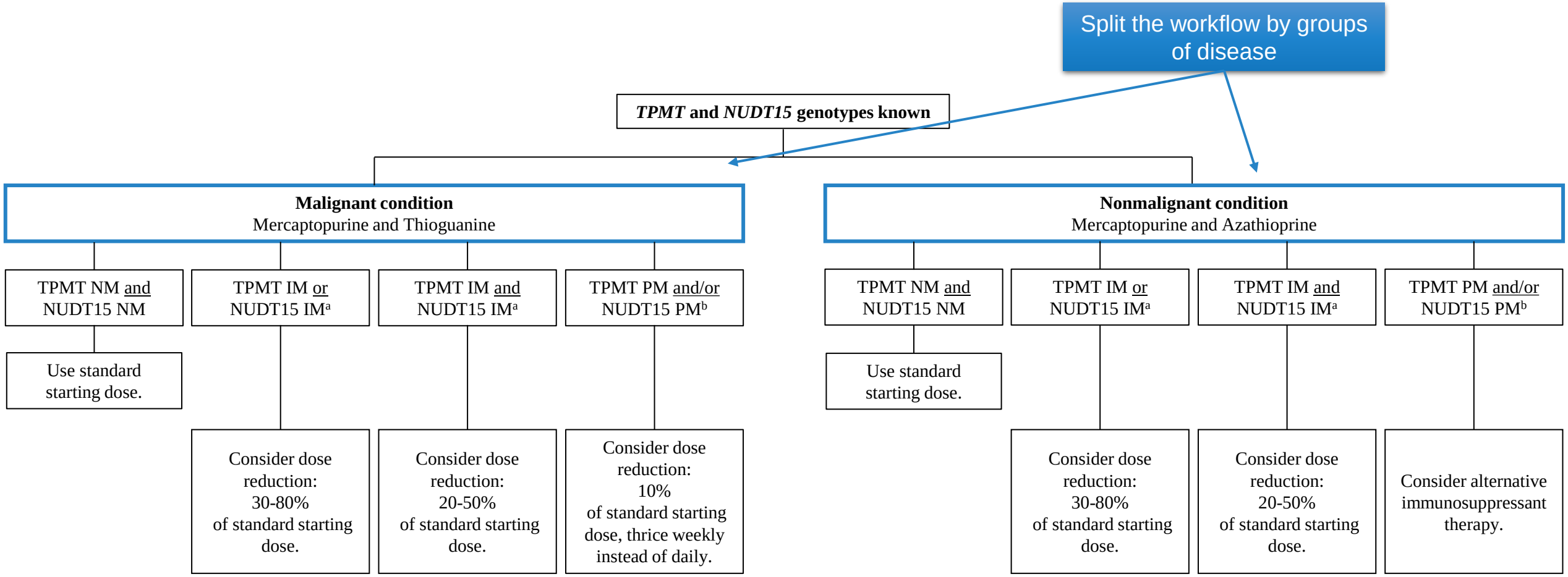
IV. TPMT IM and NUDT15 IM (i.e., TPMT/NUDT15 compound IM phenotype)

New recommendation workflow



[a] Also applies for TPMT or NUDT15 possible IM.
[b] For any combination with a TPMT or NUDT15 PM metabolizer phenotype, consider PM recommendation.

New recommendation workflow



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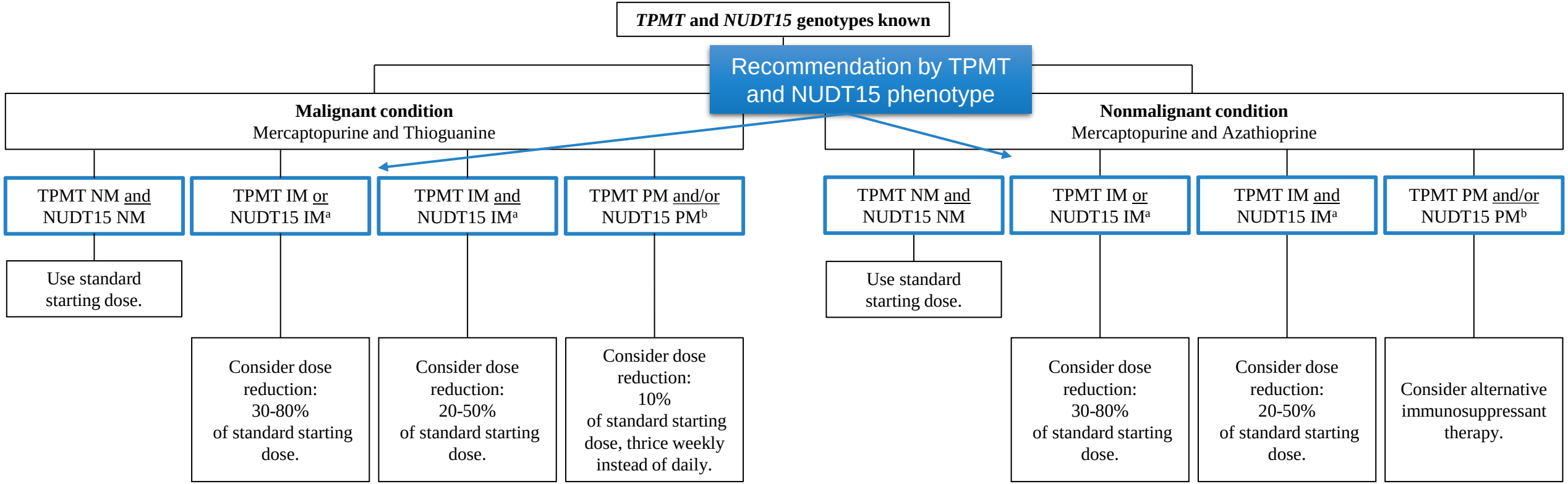
New recommendation workflow



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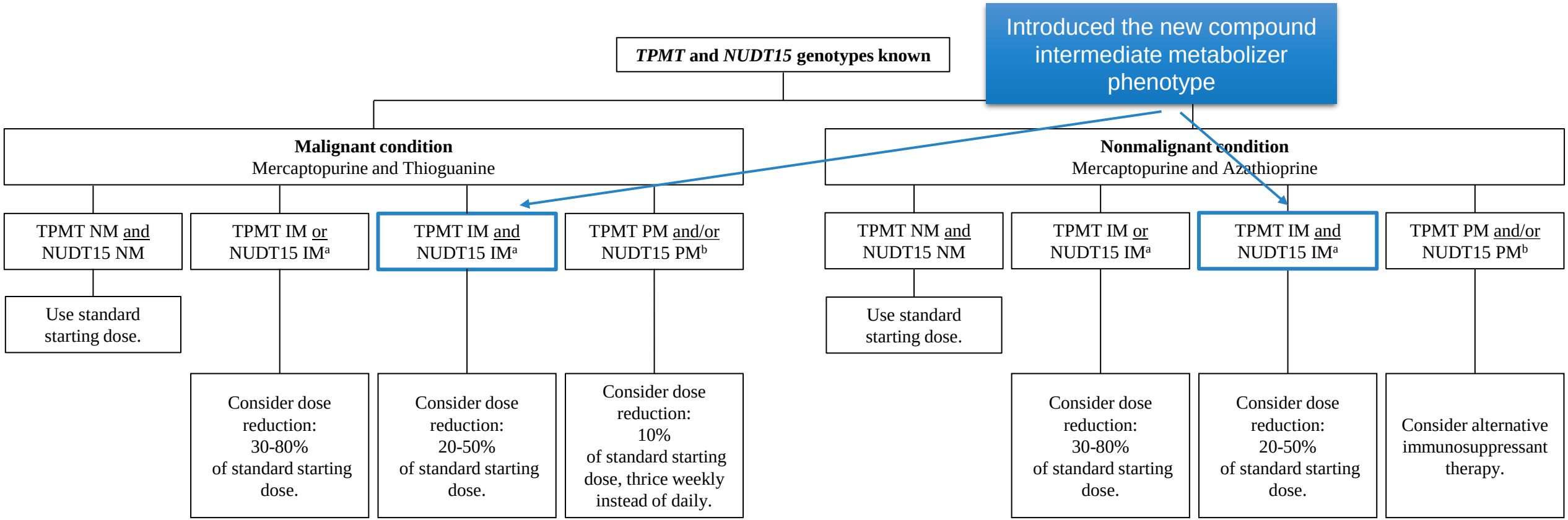

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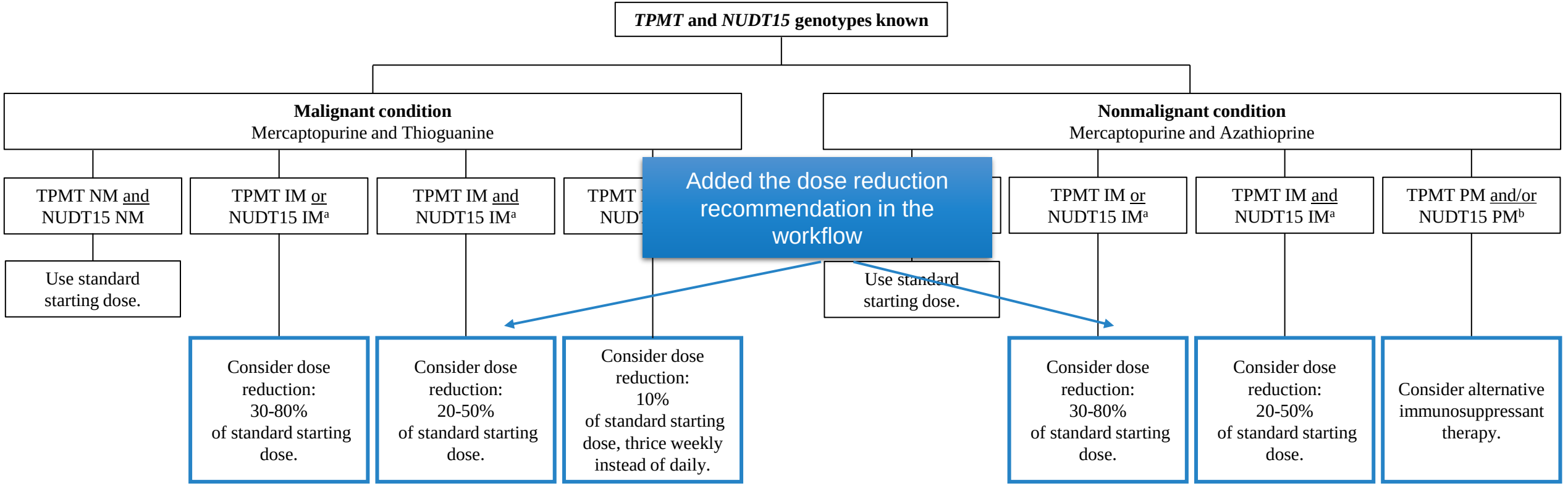


[a] Also applies for TPMT or NUDT15 possible IM.
[b] For any combination with a TPMT or NUDT15 PM metabolizer phenotype, consider PM recommendation.

TPMT/NUDT15 compound IM dosing recommendation

- A phenotype that is likely to be rare

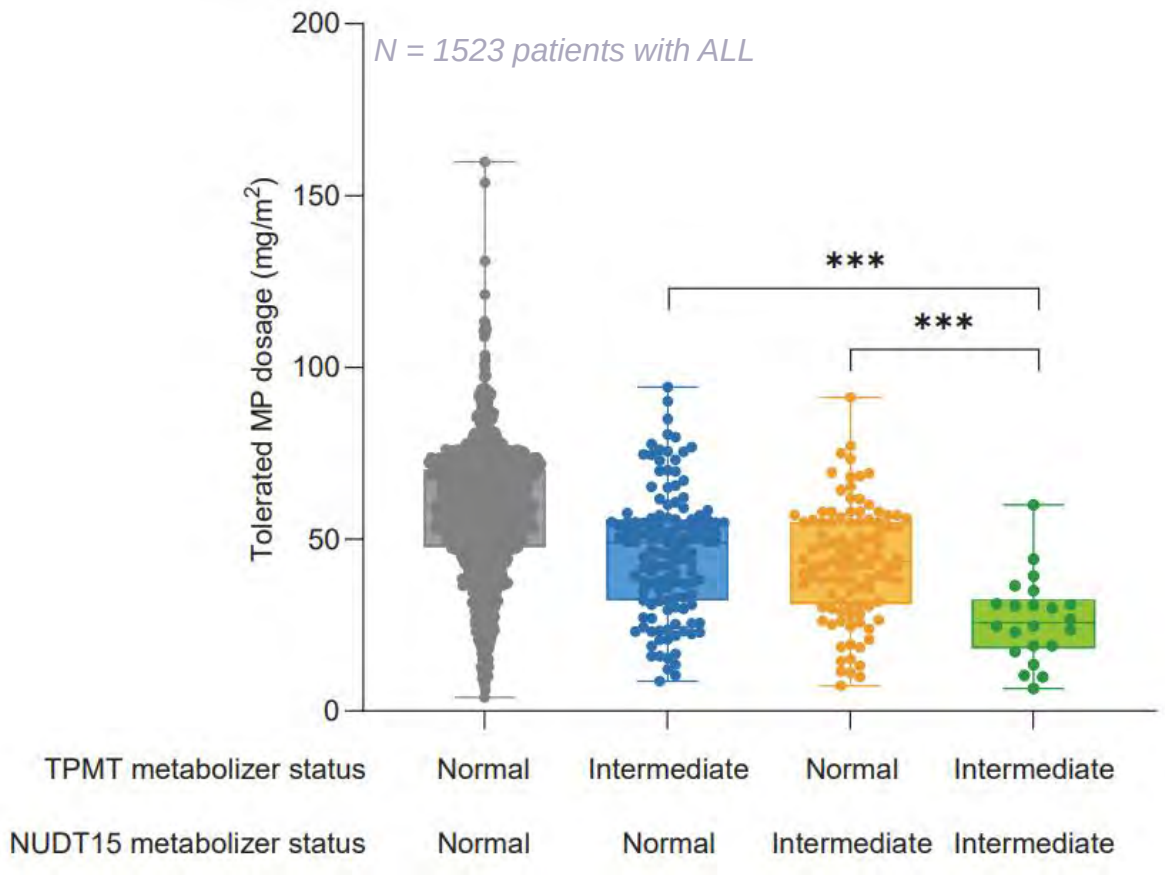
	TPMT Phenotype Frequencies				NUDT15 Phenotype Frequencies				Compound Phenotype Estimated Frequencies*			
Phenotype	**Central Asian**	**East Asian**	**European**	**Hispanic**	**Central Asian**	**East Asian**	**European**	**Hispanic**	**Central Asian**	**East Asian**	**European**	**Hispanic**
Normal metabolizer (NM)	96.3%	96.0%	90.9%	89.0%	86.5%	77.2%	98.6%	87.7%	83.3%	74.1%	89.7%	78.0%
Intermediate metabolizer (IM)	3.4%	3.3%	8.4%	10.1%	12.6%	16.8%	0.76%	8.3%	**0.43%**	**0.56%**	**0.06%**	**0.84%**
Possible IM	0.004%	0.01%	0.02%	0.03%	0.03%	0.50%	0.002%	0.17%	<0.001%	<0.001%	<0.001%	<0.001%
Poor metabolizer (PM)	0.03%	0.03%	0.19%	0.29%	0.46%	0.91%	0.001%	0.2%	<0.001%	<0.001%	<0.001%	<0.001%
Indeterminate	0.24%	0.65%	0.49%	0.59%	0.46%	4.59%	0.6%	3.7%	0.001%	0.03%	0.003%	0.02%

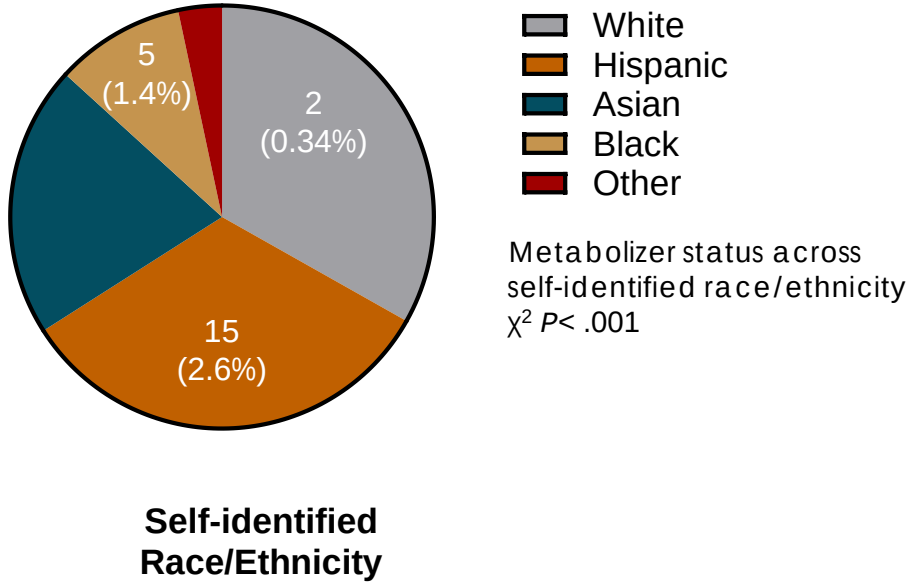
Overall estimation: <0.2%

*Compound IM freq. = TPMT IM freq. x NUDT15 IM freq.

TPMT/NUDT15 compound IM dosing recommendation

- Clinical evidence of the additive effects of the deficiencies in both TPMT and NUDT15

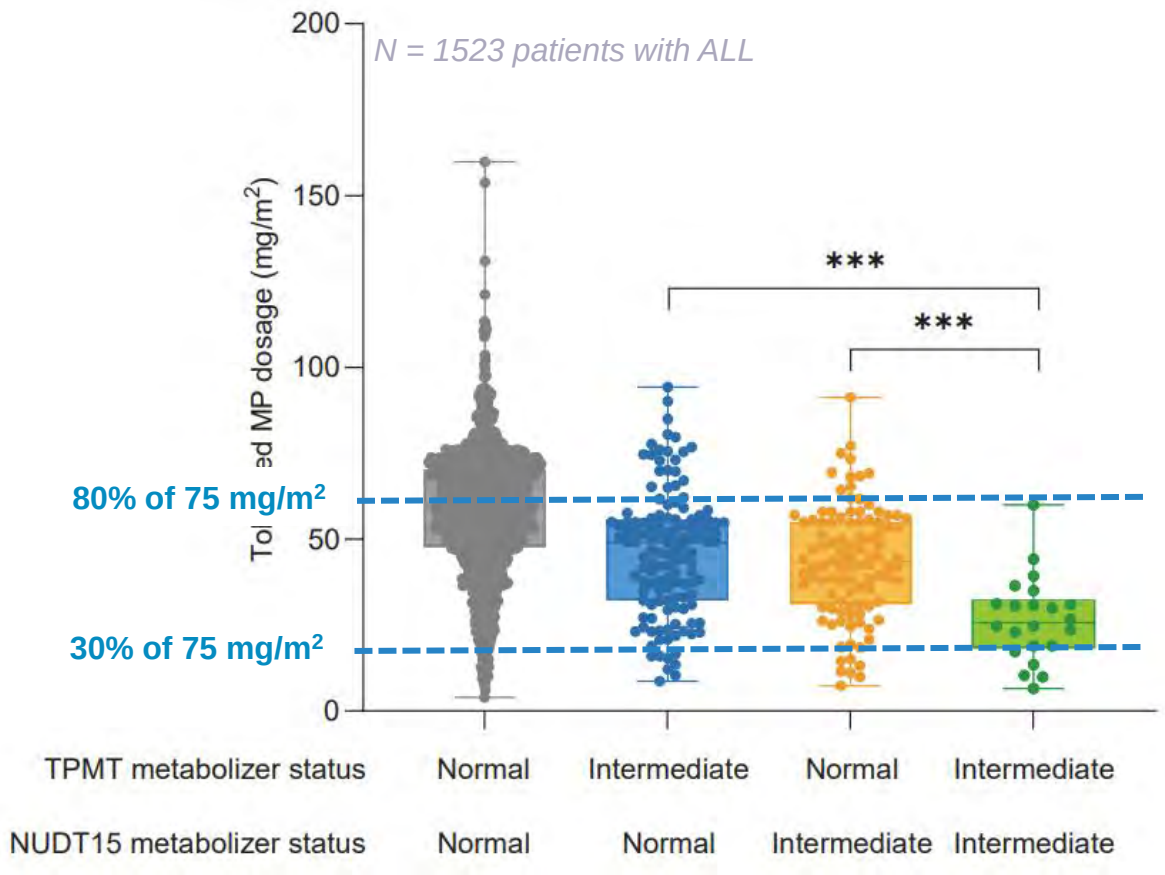




Maillard, JNCI, 2024

TPMT/NUDT15 compound IM dosing recommendation

- Clinical evidence of the additive effects of the deficiencies in both TPMT and NUDT15



Regardless of the condition and the drug

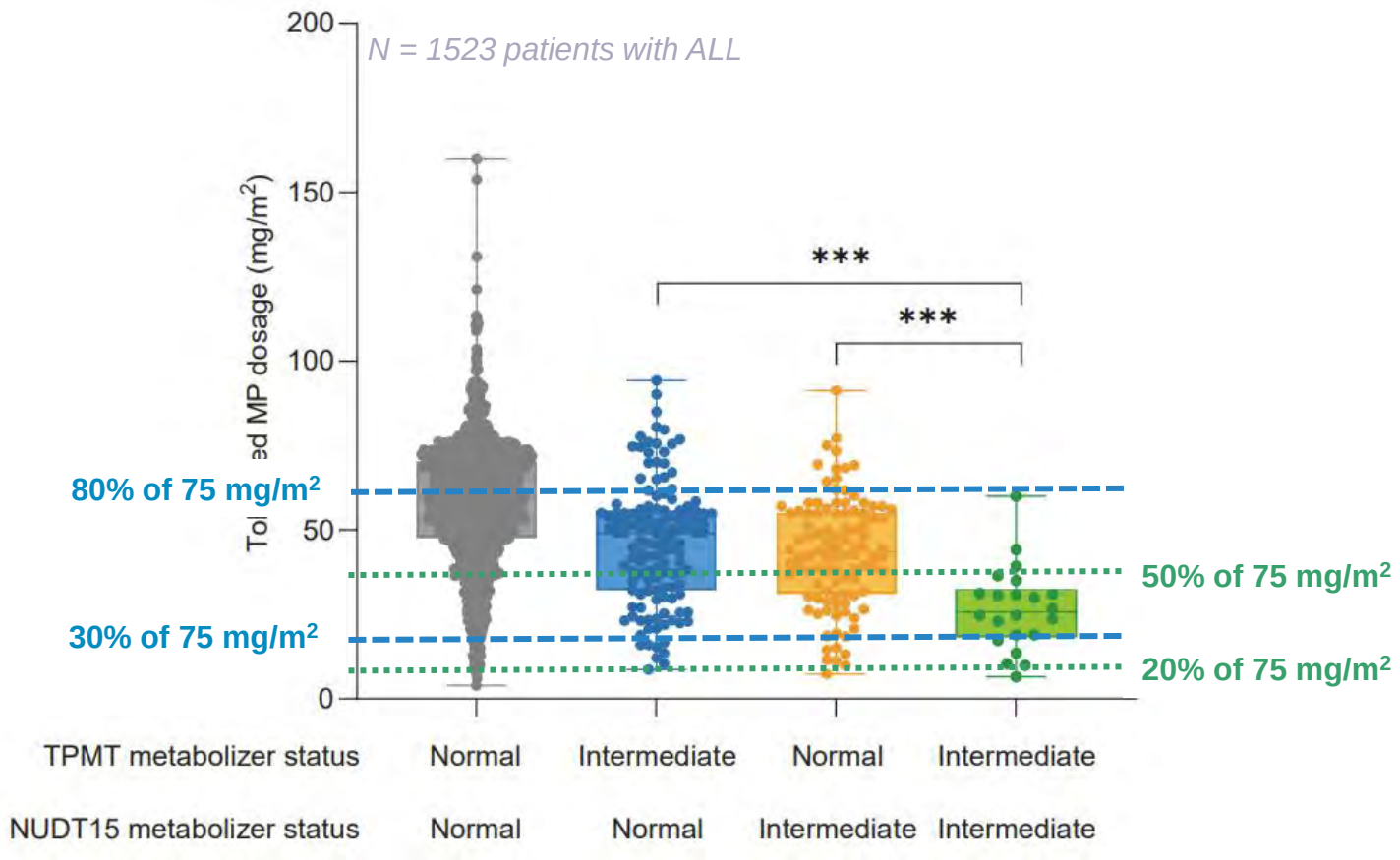
TPMT IM **or** NUDT15 IM[a]

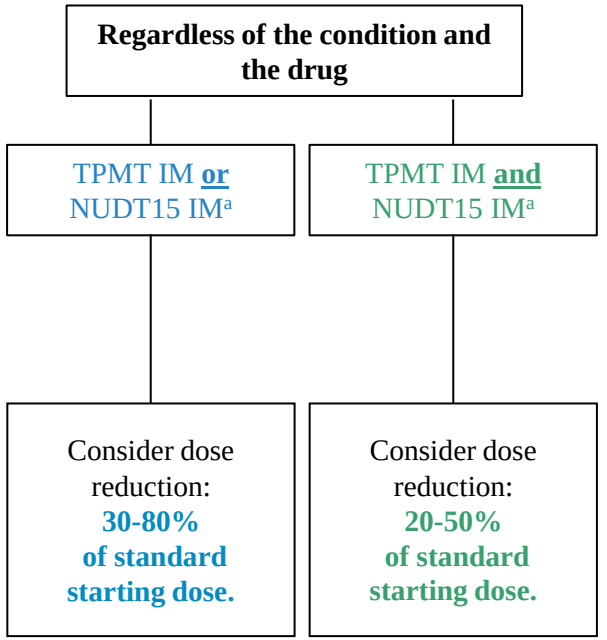
Consider dose reduction: **30-80% of standard starting dose.**

Maillard, JNCI, 2024

TPMT/NUDT15 compound IM dosing recommendation

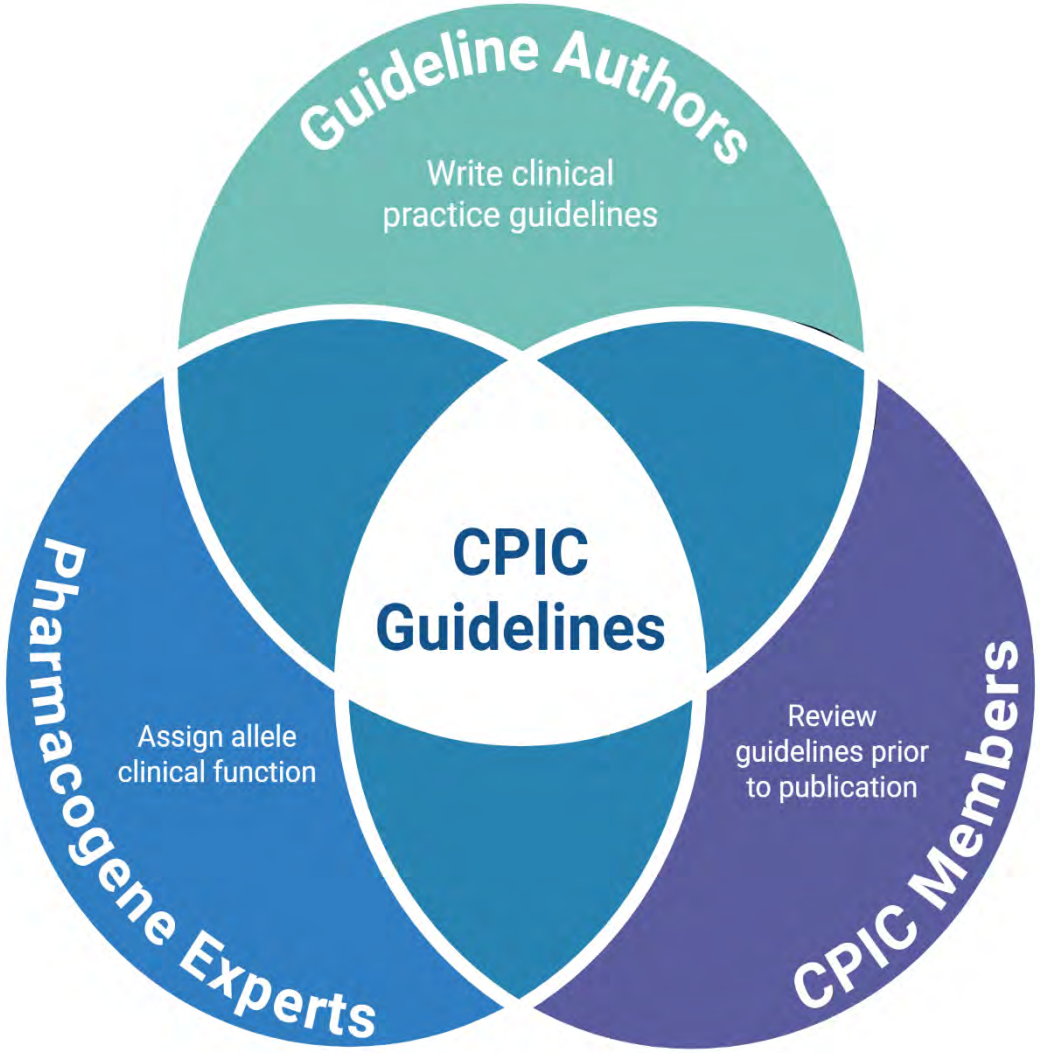
- Clinical evidence of the additive effects of the deficiencies in both TPMT and NUDT15





Maillard, JNCI, 2024

CPIC Pharmacogene Curation Expert Panels (PCEP)



Inclusion of Alleles

TPMT Allele Nomenclature Committee

- As of November 2022
- Excluded **1A*, **1S*, **3D*, and **3E*
- 5 new star alleles

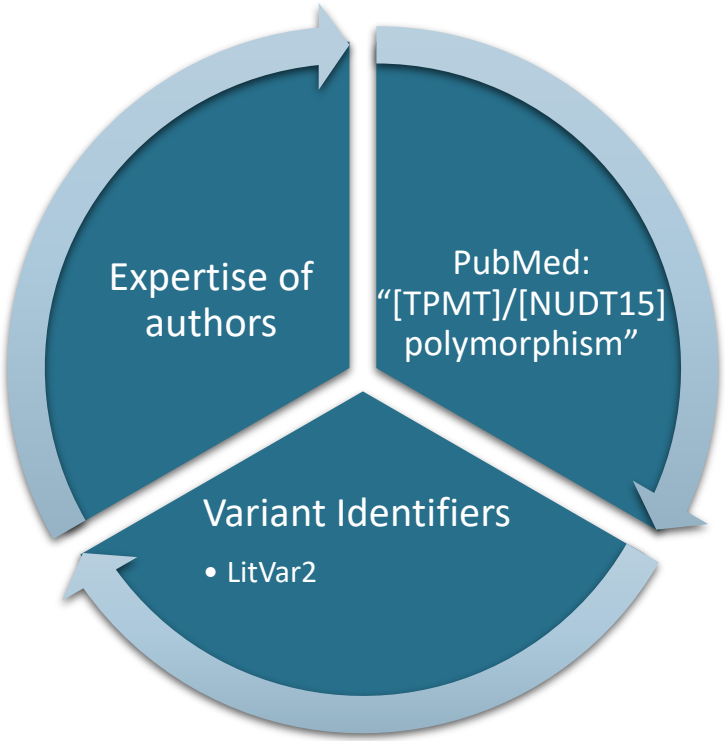
NUDT15 nomenclature validated by PharmVar

- 12 new star alleles

New Alleles

TPMT	• **42, *43, *44, *45, *46*
NUDT15	• **10, *11, *12, *13, *14, *15, *16, *17, *18, *19, *20, *21*

Evidence Review



I HAVE A QUESTION OR COMMENT ABOUT ALLELE FUNCTION OR DIPLOTYPE-PHENOTYPE TABLES

Contact us with questions specifically about CPIC alleles

Contact about functions or diplotype-phenotypes

https://cpicpgx.org/contact/

PCEP Evidence Criteria

TPMT

- *In vivo* activity measures
- Thiopurine tolerance and toxicity
- *In vitro* functional studies
- LOF variants
  - Nonsense, frameshift, splice variants, and loss of translation initiation codon

NUDT15

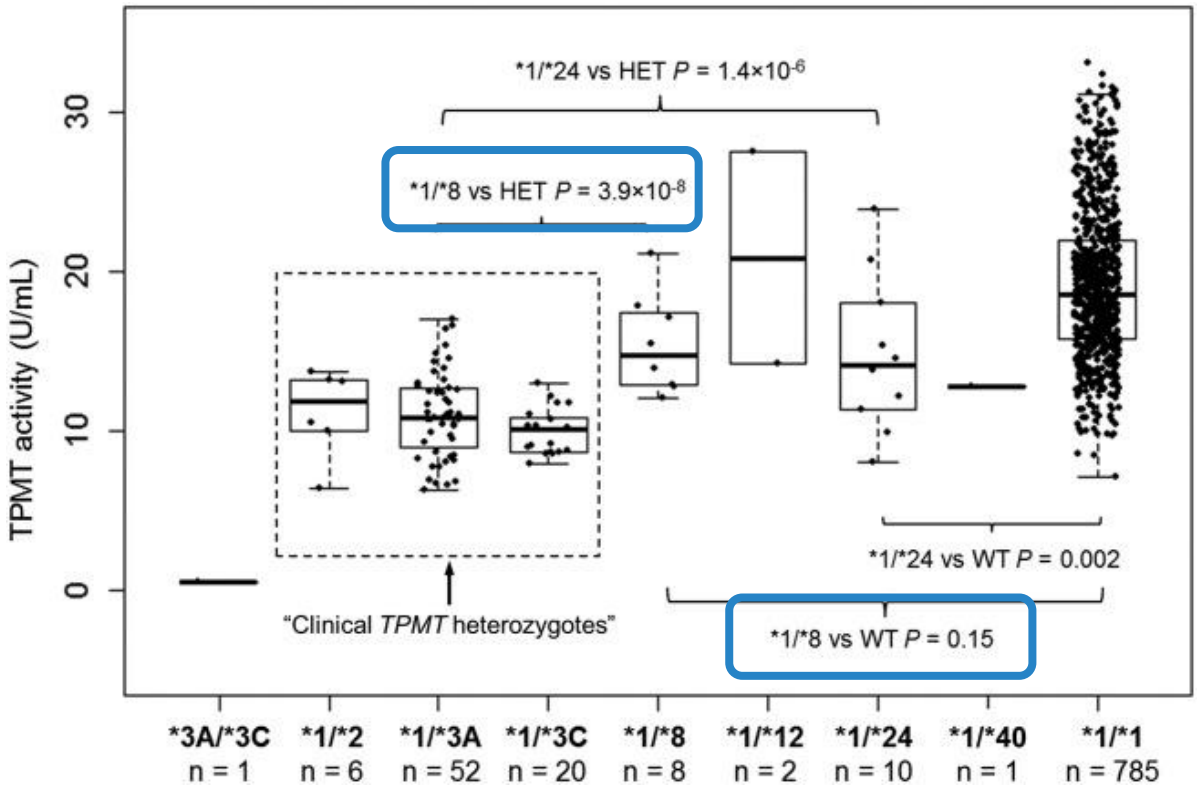
- Thiopurine tolerance and toxicity
- *In vitro* functional studies
- LOF variants
  - Nonsense, frameshift, splice variants, and loss of translation initiation codon

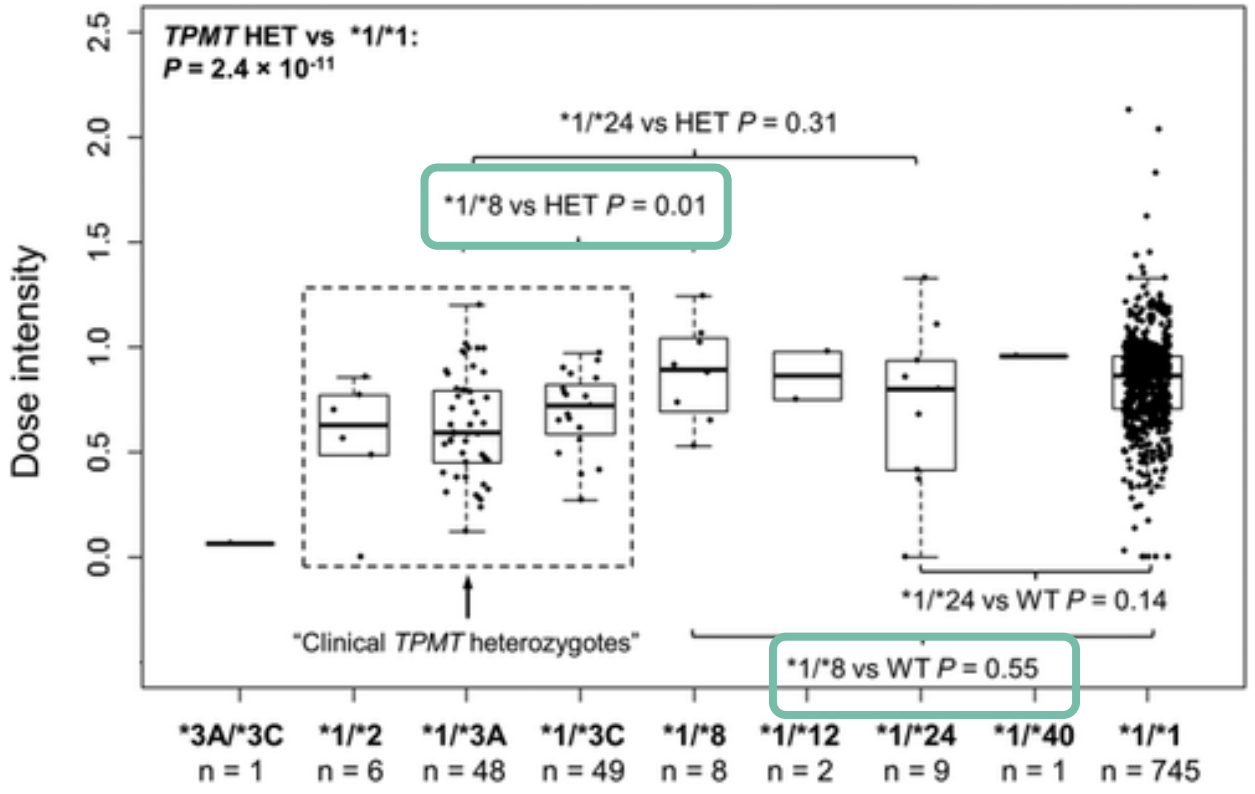
Strength of Evidence	Evidence Criteria	Examples
Definitive	For ***TPMT*** and ***NUDT15***, alleles that have consistent evidence of potential thiopurine-related toxicity, thiopurine tolerance, and enzymatic activity, as observed in patients and *in vitro* studies	*TPMT*2, TPMT*3A, NUDT15*3*
Strong	• ≥2 independent clinical studies providing evidence for the allele's role in drug phenotype • Case reports • *In vitro* data support the variant-drug phenotype association For ***TPMT***, presumed loss-of-function (LOF) alleles with additional *in vitro* or *in vivo* data to support LOF.	*NUDT15*4, NUDT15*9* *TPMT*37, TPMT*42*
Moderate	For ***TPMT***, two or more cases with clinically determined TPMT activity AND evidence of potential thiopurine-related toxicity or thiopurine tolerance. For ***NUDT15***, two or more cases observed with evidence of thiopurine-related toxicity or thiopurine tolerance and *in vitro* functional evidence.	*TPMT*16, TPMT*25,* *NUDT15*6, NUDT15*7*
Limited	For ***TPMT***, at least one case with clinically determined TPMT activity and/or evidence of potential thiopurine-related toxicity or thiopurine tolerance. For ***NUDT15***, at least one case observed with evidence of potential thiopurine-related toxicity, thiopurine tolerance or *in vitro* functional evidence. Additionally, for both ***TPMT*** and ***NUDT15***, alleles which alter function due to effects on protein translation in the absence of additional clinical or *in vitro* evidence.	*TPMT*5, TPMT*17,* *NUDT15*13, NUDT15*19*
Inadequate – Uncertain Function	For **TPMT and *NUDT15***, absence of clinical data (including TPMT activity, thiopurine tolerance, and toxicity) or conflicting *in vitro* and *in vivo* data.	*TPMT*19, TPMT*40 NUDT15*11, NUDT15*20*
No Evidence – Unknown Function	There is no literature describing function.	*TPMT*35, TPMT*36*

Updates to Allele Function Assignments for *TPMT*

TPMT Allele	Function 2018	Function 2025
**5*	Uncertain function	No function
**6*	Uncertain function	No function
**7*	Uncertain function	No function
**8*	Uncertain function	Decreased function
**10*	Uncertain function	No function
**13*	Uncertain function	No function
**16*	Uncertain function	No function
**17*	Uncertain function	No function
**18*	Uncertain function	No function
**20*	Uncertain function	No function
**21*	Uncertain function	No function
**22*	Uncertain function	No function
**25*	Uncertain function	No function
**26*	Uncertain function	No function
**27*	Uncertain function	No function
**28*	Uncertain function	No function
**31*	Uncertain function	No function
**33*	Uncertain function	No function
**34*	Uncertain function	No function
**37*	Uncertain function	No function
**38*	Unknown function	No function
**39*	Uncertain function	No function

*TPMT*8* activity and thiopurine dose tolerance





Liu et al 2017, *Clinical Pharmacology and Therapeutics*

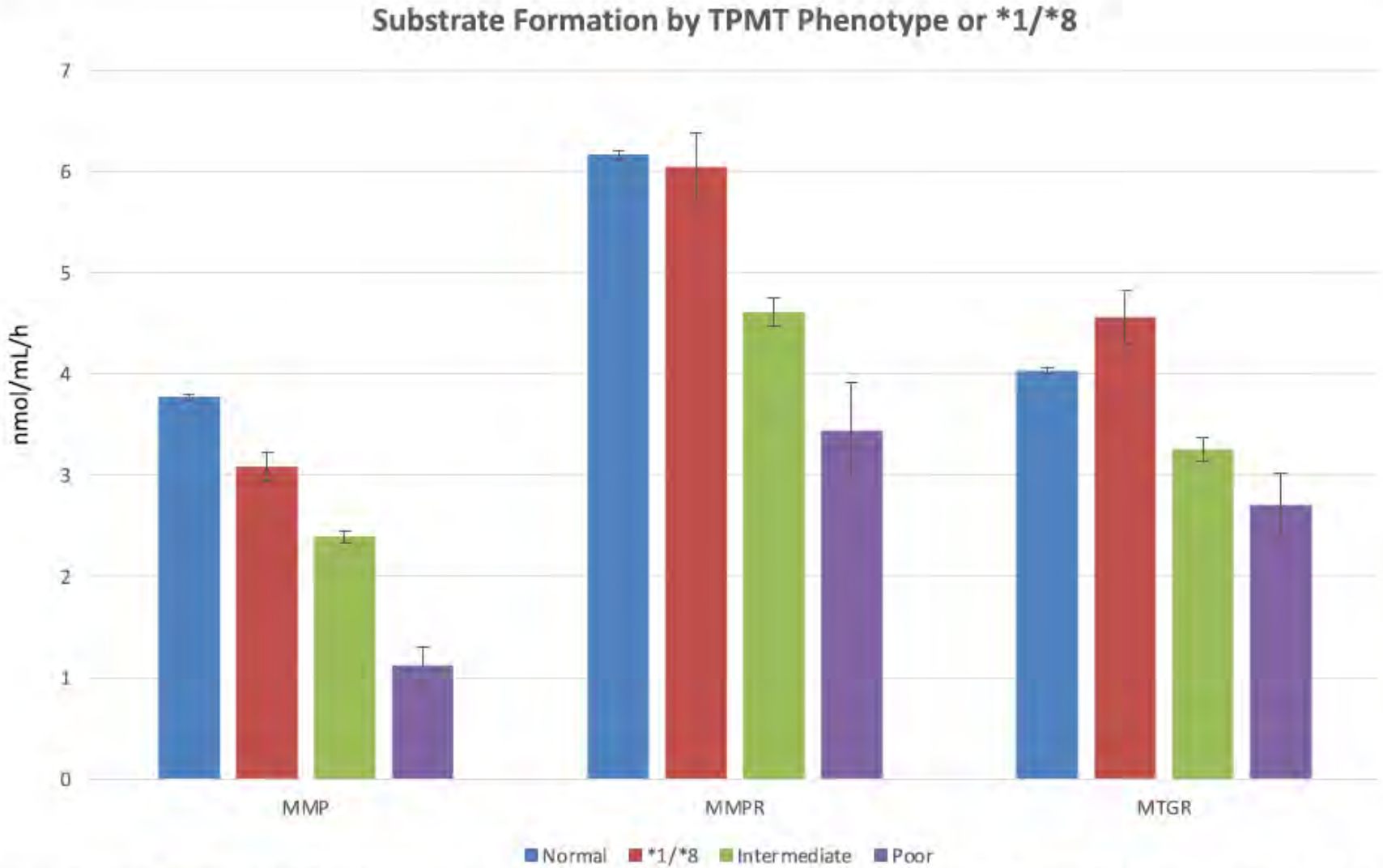


Figure 2 MMP, MMPR, and MTGR production for thiopurine methyl transferase (TPMT)*1/*8 versus phenotype. The production of MMP, MMPR, and MTGR are shown according to the TPMT phenotype, along with production for individuals with a *1/*8 genotype. TPMT activity is provided on the y-axis. The error bars represent SEM.

Sterner et al 2024, *Journal of Molecular Diagnostics*

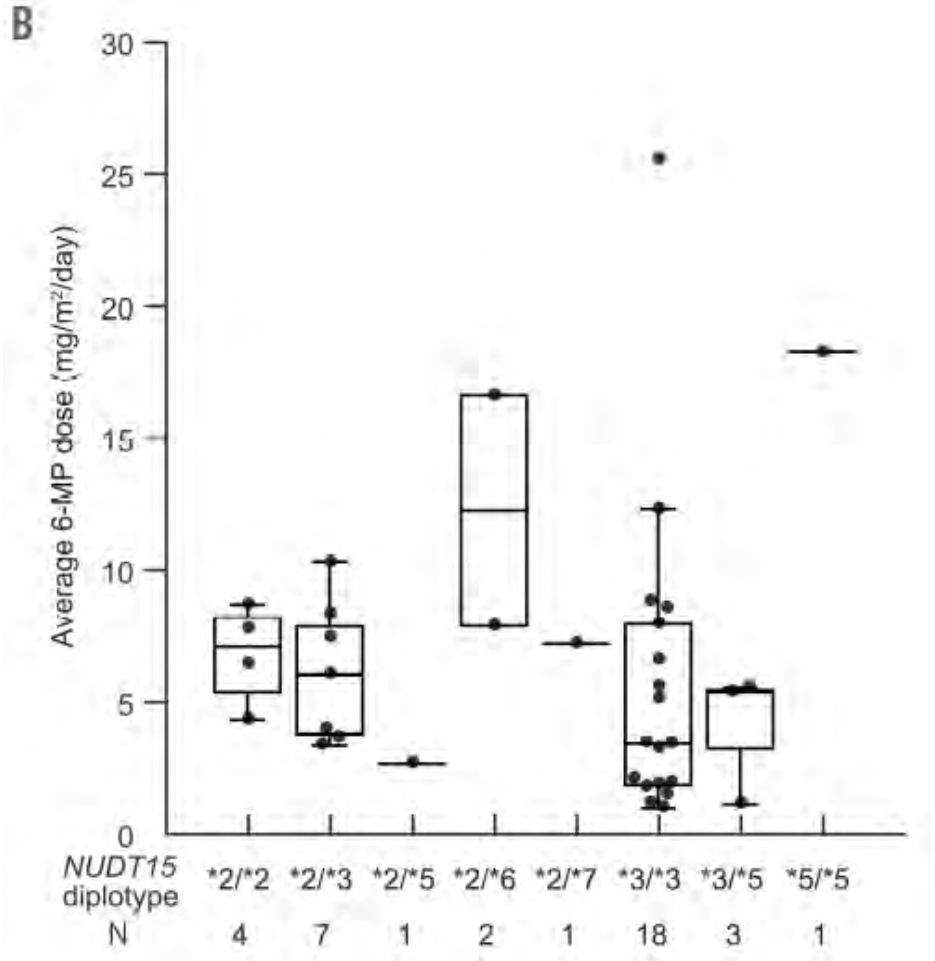
TPMT diplotype to phenotype translation

Assignment of likely TPMT phenotypes based on genotypes		
Likely Phenotype	**Genotypes**	**Example Diplotypes***
Normal Metabolizer (NM)	an individual carrying two normal function alleles OR one normal function allele PLUS one decreased function allele	**1/*1* **1/*8*
Intermediate Metabolizer (IM)	an individual carrying one normal function allele PLUS one no function allele OR two decreased function alleles	**1/*2, *1/*3A, *1/*3B, *1/*3C, *1/*4* **8/*8*
Possible Intermediate Metabolizer	an individual carrying one uncertain/unknown function allele PLUS one no function allele OR one no function allele PLUS one decreased function allele	**2/*9, *3A/*12* **3A/*8*
Poor Metabolizer (PM)	an individual carrying two no function alleles	**3A/*3A, *2/*3A, *3A/*3C, *3C/*4, *2/*3C, *3A/*4*
Indeterminate	one normal function allele PLUS one uncertain function allele OR one decreased function allele PLUS one uncertain function allele OR two uncertain/unknown function alleles	**1/*19* **8/*30* **19/*40*
*See CPIC® Guideline for Thiopurines and TPMT and NUDT15 for a full list of possible diplotypes and assigned phenotypes		

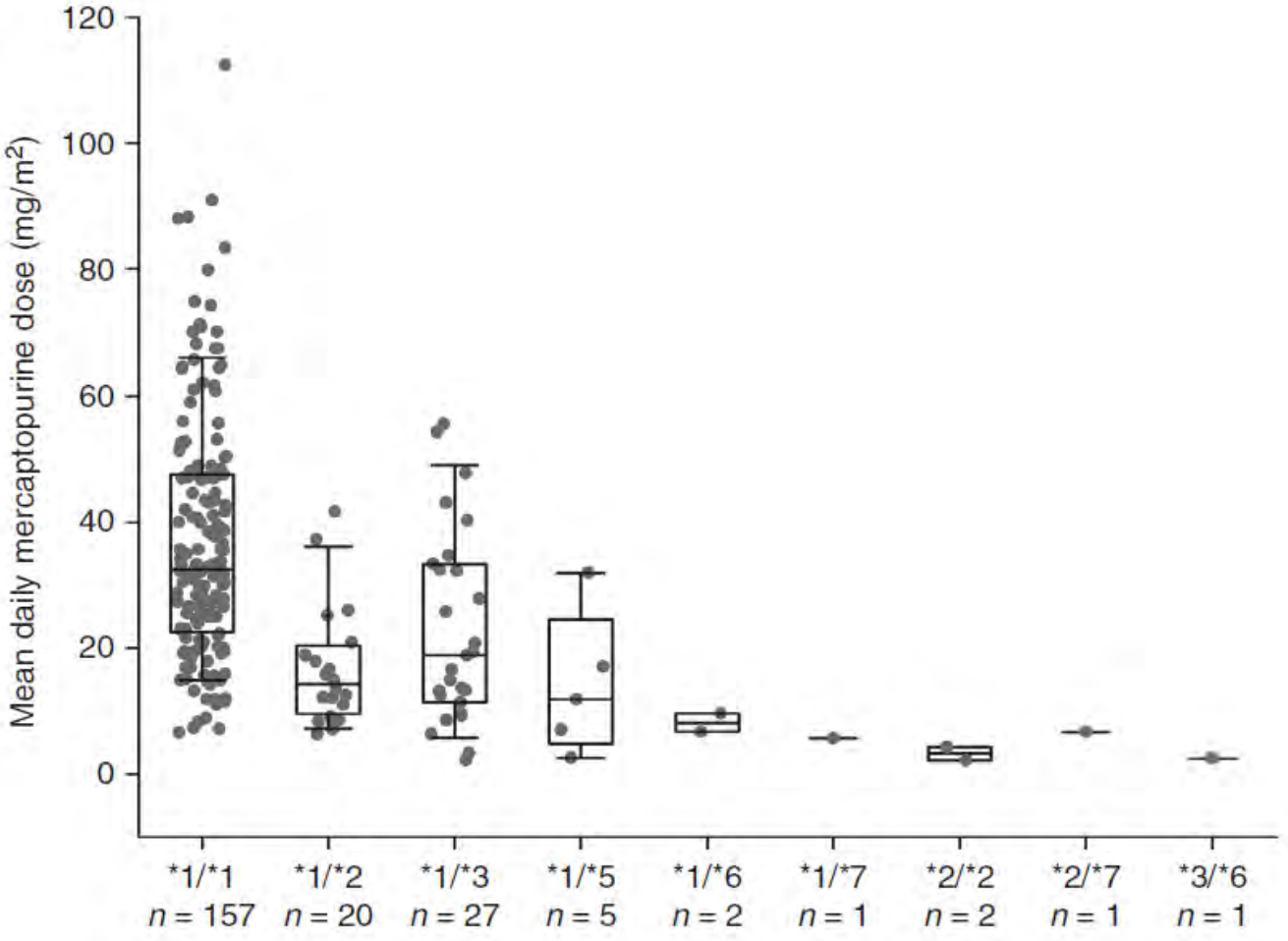
Updates to Allele Function Assignments for *NUDT15*

NUDT15 Allele	Function 2018	Function 2025
**4*	Uncertain function	No function
**5*	Uncertain function	Decreased function
**6*	Uncertain function	No function
**7*	Uncertain function	No function
**8*	Uncertain function	Decreased function

6-MP tolerance by *NUDT15* diplotype - **5*

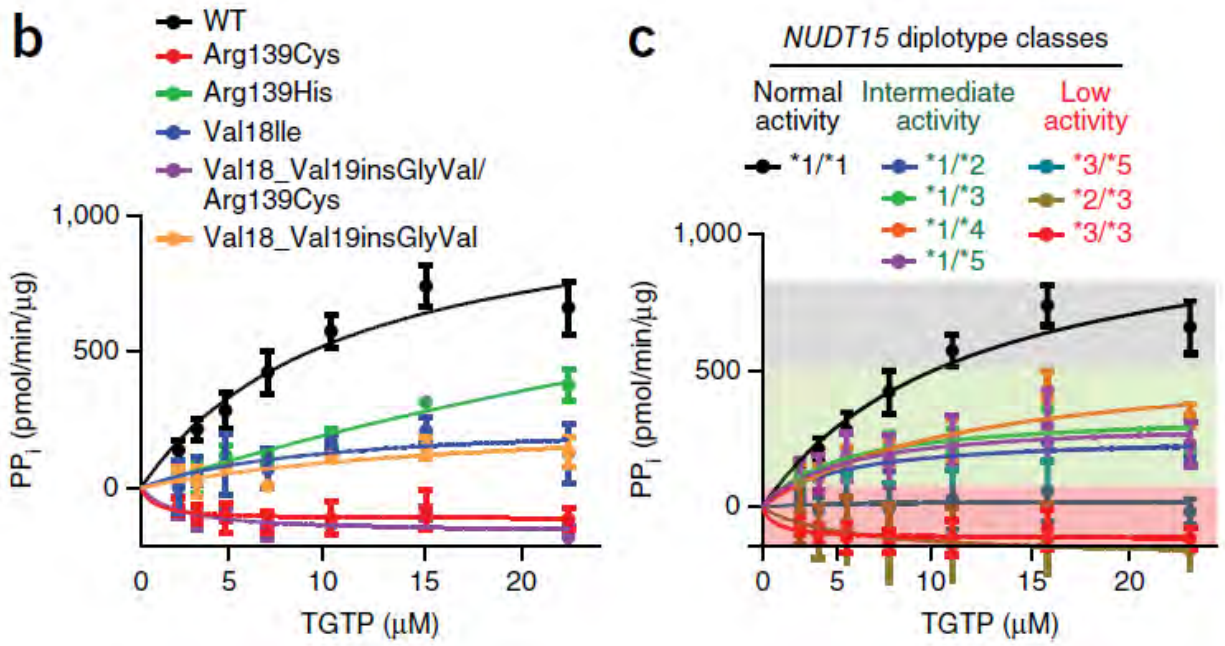


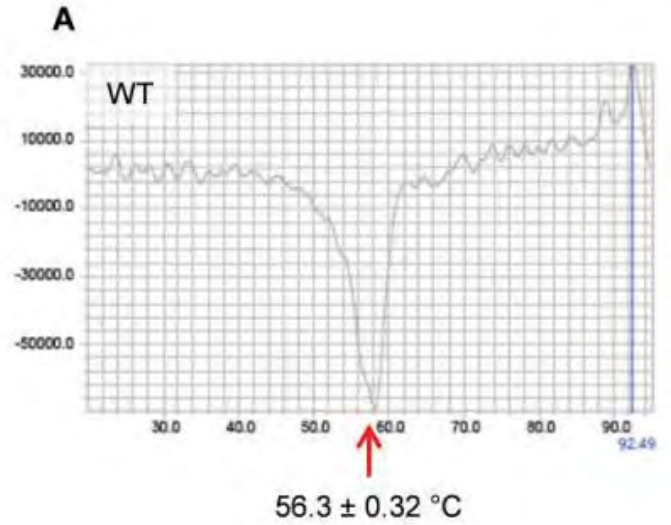
Tanaka 2021, *haematologica*

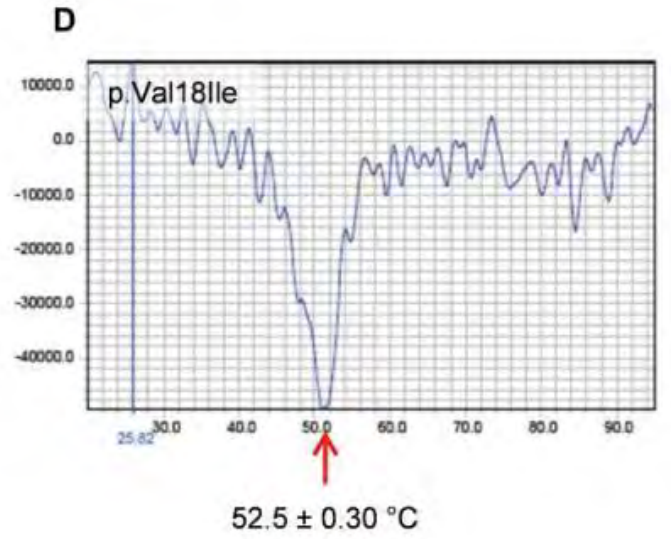


Wang 2021, *Pediatric Research*

*NUDT15*5* Biochemical Data

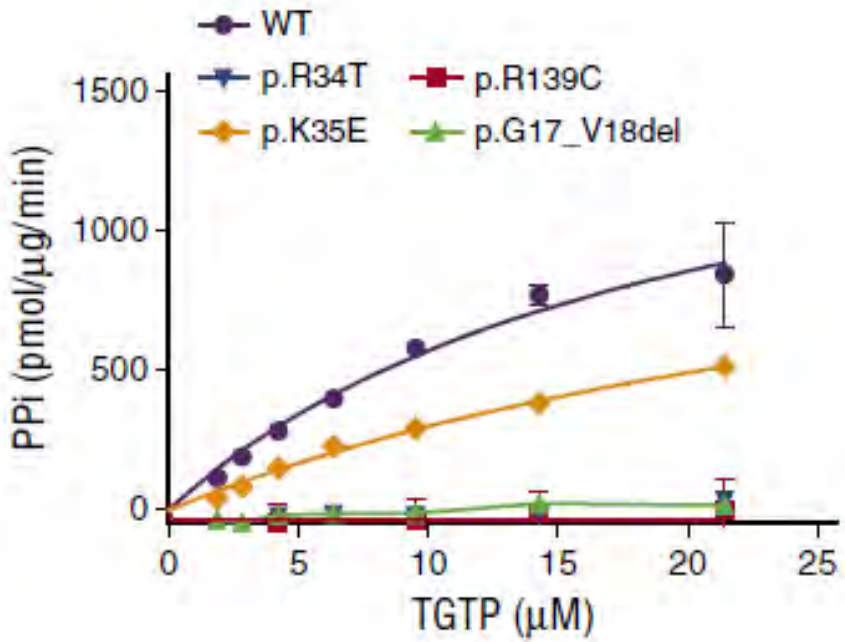


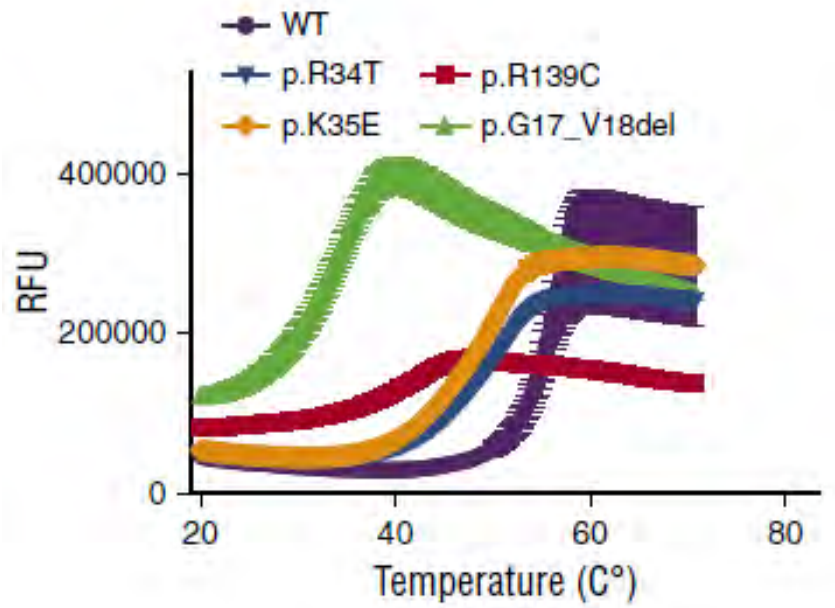




Moriyama 2016 et al, *Nature Genetics*

*NUDT15*8* Biochemical Data





Moriyama 2017 et al, *blood*

6-MP tolerance by *NUDT15* diplotype - **8*

Table 1. Patient characteristics and MP tolerance

	NUDT15 novel variant				
	c.101G>C p.R34T		c.103A>G p.K35E	c.37_42delGGAGTC p.G17_V18del	
Position at chr13	48037847		48037849	48037783-48037788	
rsID	rs766023281		NA	rs746071566	
	Subject 1	**Subject 2**	**Subject 3**	**Subject 4**	**Subject 5**
Sex	Male	Male	Male	Female	Male
Age, y	13.8	0.3	4.4	13.7	6.3
Race	East Asian	East Asian	East Asian	African	European
Diagnosis	B-ALL	B-ALL	B-ALL	T-ALL	B-ALL
Protocol	MaSpore 2003 SR	TPOG-2002-infantile ALL	MaSpore 2003 IR	TOT XIIIB HR	TOT XVI LR
NUDT15 diplotype*	*1/p.R34T	*1/p.R34T	*2/p.K35E	*1/p.G17_V18del	*1/p.G17_V18del
TPMT genotype	*1/*7 WT	*1/*7 WT	*2/*8 WT	*1/*9 WT	*1/*9 WT
4-wk tolerated MP dosage, mg/m^2 per day	17.9	16.4†	8.5	82.5 for a 1-wk period‡	43.5
Protocol MP dosage, mg/m^2 per day	50	25†	50	75 for a 1-wk period‡	75

B-ALL, B-cell acute lymphoblastic leukemia; HR, high risk; IR, intermediate risk; LR, low risk; NA, not applicable; rsID, reference SNP ID; SR, standard risk; T-ALL, T-cell acute lymphoblastic leukemia; TPOG, Taiwan Pediatric Oncology Group; WT, wild-type.

*The *1 represents the *NUDT15* wild-type haplotype, and *2 represents the haplotype with both p.V18_ V19insGV and p.R139C variants.

†Patient received MP at 17.9 and 15.2 mg/m^2 per day for 17 and 22 days, respectively, during remission, but did not complete the entire treatment regimen due to relapse.

‡Maintenance therapy (120 weeks) for TOT XIIIB HR consisted of drug pairs administered in weekly rotation. Therefore, the standard MP exposure was 75 mg/m^2 per day for only 1 week, followed by other drug pairs for the subsequent 3 weeks. With MP dosed for this short duration, the patient did not experience toxicity. It is likely her actual long-term MP tolerance would be low if MP were given in a continuous fashion similar to other ALL treatment protocols.

Moriyama 2017 et al, *blood*

NUDT15 diplotype to phenotype translation

Assignment of likely NUDT15 phenotypes based on genotypes		
Likely Phenotype	**Genotypes**	**Example Diplotypes***
Normal Metabolizer (NM)	an individual carrying two normal function alleles OR one normal function allele PLUS one decreased function allele	**1/*1* **1/*5*
Intermediate Metabolizer (IM)	an individual carrying one normal function allele PLUS one no function allele OR an individual carrying two decreased function alleles	**1/*2, *1/*3* **5/*5*
Possible Intermediate Metabolizer	an individual carrying one uncertain function allele PLUS one no function allele	**2/*15, *3/*21*
Poor Metabolizer (PM)	an individual carrying two no function alleles OR one no function allele PLUS one decreased function allele	**2/*2, *2/*3, *2/*4* **3/*5*
Indeterminate	one normal function allele PLUS one uncertain function allele OR one decreased function allele PLUS one uncertain function allele OR two uncertain function alleles	**1/*12* **5/*20* **11/*14*
*See CPIC® Guideline for Thiopurines and TPMT and NUDT15 for a full list of possible diplotypes and assigned phenotypes		

Summary and take-home messages

Why

- Widespread TPMT/NUDT15 genotyping in the context of thiopurine therapy provides an opportunity to align evidence-based PGx recommendations with real-world clinical practice.

How

- By involving experts in hematological malignancy (i.e., leukemia) and non malignancy diseases (such as IBD, myasthenia gravis, …).
- By reviewing the literature from 2018 to June 2025.

What

- TPMT/NUDT15 compound IM: we recommend to reduce the dose to 20-50% of standard dose.
- We acknowledge the <u>possible</u> IM phenotype and provide the same recommendation as for the IM patients, i.e. 30-80% of standard dose.
- Any combination with a PM allele is considered a PM.
- Novel alleles identified and characterized by the PCEP will be included in the « Assignment of likely TPMT and NUDT15 phenotypes based on genotypes » table.

When

- PCEP has finished the review and is currently drafting a functional paper (new).
- Currently drafting the guideline, goal is to submit before the end of the year.

Thank you!

We welcome questions and feedback

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