Supplemental Material

Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for thiopurine dosing based on *TPMT* and *NUDT15* genotypes: 2018 update

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CPIC UPDATES

Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines are published in full on www.cpicpgx.org. Information will be reviewed and updated periodically on that website.

LITERATURE REVIEW

For TPMT, we searched the PubMed database from 1966 to October 2012 for the original guideline and then Oct 1, 2012 to June 6, 2017 for this guideline update for keywords ((TPMT) AND ((TPMT) AND thiopurine) AND ((TPMT) AND azathioprine) AND ((TPMT) AND mercaptopurine) AND ((TPMT) AND thioguanine) for the contribution TPMT genotype and phenotype had on predicting a thiopurine-related adverse drug event (ADE) or outcome. Using these search terms, 139 publications were identified and following application of the inclusion criteria 133 were reviewed and included in the evidence table (**Table S1**).

For NUDT15, we searched the PubMed database (no start date to May 25, 2017) for keywords (NUDT15) for the contribution NUDT15 genotype had on predicting a thiopurine-related adverse drug event (ADE) or outcome. Using these search terms, 41 publications were identified and following application of the inclusion criteria, 21 were reviewed and included in the evidence table (**Tables S2**).

To construct a *TPMT* minor allele frequency table based on ethnicity, PubMed was searched up to 1/31/2018. Studies were considered for inclusion if: (1) the ethnicity of the population was clearly indicated and (2) allele frequencies for *TPMT* genotypes were reported. Additionally, allele frequencies reported in the gnomAD browser (http://gnomad.broadinstitute.org/ - exomes and genomes) and ensembl (grch37.ensembl.org - exomes or genomes) were also included. Many *TPMT* allele frequencies could not be found through a PubMed search, so the gnomAD frequencies were the only frequencies available for many alleles. The same approach was used for *NUDT15* allele frequencies. Very little allele frequency information could be found

through a PubMed search, so gnomAD and ensembl allele frequencies were used for several population groups.

GENETIC TEST INTERPRETATION

The haplotype, or star (*) allele name, is determined by a specific SNP or a combination of SNPs that are interrogated in the genotyping analysis. The genotypes that constitute the haplotype, or star (*) alleles for *TPMT* and *NUDT15*, and the rs# for each of the specific genomic nucleotide alterations that define the alleles (if available), are described in the **TPMT Allele Definition Table** and **NUDT15 Allele Definition Table** found at https://cpicpgx.org/guidelines/guideline-for-thiopurines-and-tpmt/.

For *TPMT*, the genotype results are generally reported as a diplotype, which includes one maternal and one paternal star allele (e.g., **1/*3A*). The TPMT activity associated with each of the common * alleles is summarized in ***TPMT* Allele Functionality Table** ((1, 2); https://cpicpgx.org/guidelines/guideline-for-thiopurines-and-tpmt/). The most common no function allele among Caucasians for TPMT is designated as **3A*; other alleles predominate in other ethnic/ancestral groups (see **TPMT Frequency Table**; https://cpicpgx.org/guidelines/guideline-for-thiopurines-and-tpmt (1, 2). The **3A* allele designation for *TPMT* is assigned based on the SNP genotypes and the very strong linkage disequilibrium that has been established between two of the most common inactivating *TPMT* SNPs: Ala154Thr (rs1800460; c.460G>A) and Tyr240Cys (rs1142345; c.719A>G); when the rare genotype is present at these two SNP positions in the heterozygous state, the assumption is that the rare genotypes are in cis (on the same allele) and the diplotype call is **1/*3A*. However, each of these SNPs have been observed to exist on their own allele (**3B* and **3C*, respectively) in some populations (**TPMT Frequency Table**; https://cpicpgx.org/guidelines/guideline-for-thiopurines-and-tpmt/))(1, 2) with the rare genotypes present on their own; if these rare genotypes are present on opposite alleles in the same individual, the diplotype call should be that of a compound heterozygote diplotype (*3B/*3C)—a call consistent with homozygous TPMT deficiency. If one assumes that the frequency of the *3B-defining variant in Caucasians is 0.0063, and of the *3C-defining variant is 0.004205, the probability of finding such a

compound heterozygote deficient diplotype is estimated 1 in 515,861 Caucasian individuals. It is controversial whether an individual with the **3B/*3C* genotype has ever been identified (3, 4), but the **3B* allele is very rare, and given the frequency of **3C*, a very large sample size would be needed to have a high probability of detecting the **3B/*3C* diplotype. Phenotypic tests could distinguish between the **1/*3A* and the **3B/*3C* diplotypes and should be employed if a homozygous deficient genotype is suspected. One of the two phenotyping tests (measuring erythrocyte TPMT activity or thiopurine metabolites after thiopurine dosing) can differentiate a **1/*3A* diplotype (TPMT intermediate metabolizer) from a very rare **3B/*3C* diplotype (TPMT poor metabolizer). TPMT activity would be extremely low in the latter case and intermediate in the former case; erythrocyte thiopurine metabolites would indicate a low but detectable MeTIMP/TGN ratio for a *1/*3A diplotype and the *3B/*3C diplotype would be consistent with undetectable MeTIMP (or MeMPN) levels.

For *NUDT15*, there have been nine * alleles (haplotypes) reported thus far based on seven known variants (2 indels and 5 SNPs). The p.R139C (rs116855232; c.415C>T) variant is the most common polymorphism and can be observed either alone (**3* allele) or together with the p.V18_V19dup (rs869320766; c.50_55dup) variant as a distinctive haplotype (**2* allele). No significant linkage disequilibrium is present amongst other *NUDT15* variants and all other *alleles are defined by a single variant. The p.V18_V19ins variants can be present without the p.R139C SNP (**6* allele) but is exceedingly rare based on the 1000 Genomes data. In East Asians for whom *NUDT15* variants are more common, 6.0% of individuals are heterozygous for both the p.R139C and the p. V18_V19insGV variants, of which 5.8% are **1/*2* and 0.2% are **3/*6*. Therefore, while it is advisable to resolve **1/*2* vs **3/*6* diplotypes, the probability for the former is overwhelming. The p.R139H (rs147390019; c.416G>A) variant that defines the **4* allele is only one base pair from the p.R139C variant. Thus, genotyping can be challenging in patients heterozygous for both variants because of interference between the two (e.g., during PCR amplification and/or probe hybridization). However, **3/*4* is exceedingly rare (0.01% in East Asians or Hispanics).

AVAILABLE GENETIC TEST OPTIONS

Commercially available genetic testing options change over time. Below is some information that may assist in evaluating options.

Desirable characteristics of pharmacogenetic tests, including naming of alleles and test report contents, have been extensively reviewed by an international group, including CPIC members (5). CPIC recommends that clinical laboratories adhere to these test reporting standards. CPIC gene-specific tables (see **Allele Definition Table**, **Allele Functionality Table** and **Frequency Table** (https://cpicpgx.org/guidelines/guideline-for-thiopurines-and-tpmt/)) adhere to these allele nomenclature standards (5). Moreover, the **Allele Definition**, **Functionality**, and **Frequency Tables** may be used to assemble lists of known functional and actionable pharmacogenetic variants and their population frequencies, which may inform decisions as to whether tests are adequately comprehensive in interrogations of alleles.

For *TPMT*, it has been demonstrated that the vast majority of low-activity phenotypes are accounted for by the three SNPs that constitute the **2*, **3A*, **3B*, and **3C* alleles, and that sequencing yields few new important low-function variants (6, 7). For *NUDT15*, it is not yet clear the extent to which multiple rare variants may account for low NUDT15 activity, and thus the need for sequencing-based approaches cannot be ignored.

The Genetic Testing Registry (GTR) provides a central location for voluntary submission of genetic test information by providers and is available at http://www.ncbi.nlm.nih.gov/gtr/.

Many commercially available tests for *TPMT* include only **2*, **3A*, **3B* and **3C*, although the rare **4* allele is also inactivating. Many methods are available for more comprehensive *TPMT* genotyping of additional alleles (8), and some are being adapted for clinical use.

There is an increasing demand for *NUDT15* tests which are now already available at a number of commercial laboratories. The p.R139C (rs116855232) variant is most commonly tested but some assays can determine **1-*6* alleles.

LEVELS OF EVIDENCE LINKING GENOTYPE TO PHENOTYPE

The evidence summarized in **Table S1** and **S2** is graded using a scale modified slightly from Valdes et al. (9)

High: Evidence includes consistent results from well-designed, well-conducted studies.

Moderate: Evidence is sufficient to determine effects, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of the evidence.

Weak: Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information.

STRENGTH OF DOSING RECOMMENDATIONS

CPIC's dosing recommendations are based on weighting the evidence from a combination of preclinical functional and clinical data (**Tables S1 and S2**), as well as on some existing disease-specific consensus guidelines **(10, 11)**. Some of the factors that are taken into account in evaluating the evidence supporting dosage recommendations include: *in vivo* clinical outcome data for thiopurines, *in vivo* pharmacokinetic and pharmacodynamic data for thiopurines, *in vitro* enzyme activity of expressed wild-type or variant-containing TPMT or NUDT15 (with thiopurines or TGTP as substrate, respectively), *in vitro* TPMT enzyme activity from tissues isolated from individuals of known *TPMT* genotypes, *in vivo* pre-clinical pharmacokinetic and pharmacodynamic studies, and *in vitro* studies of TPMT or NUDT15 protein stability.

Overall, the therapeutic recommendations are simplified to allow rapid interpretation by clinicians. CPIC uses a slight modification of a transparent and simple system for just three categories for recommendations adopted from the rating scale for evidence-based recommendations on the use of antiretroviral agents (12):

Strong recommendation for the statement: "The evidence is high quality and the desirable effects clearly outweigh the undesirable effects."
Moderate recommendation for the statement: "There is a close or uncertain balance" as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects.
Optional recommendation for the statement: The desirable effects are closely balanced with undesirable effects, or the evidence is weak or based on extrapolations. There is room for differences in opinion as to the need for the recommended course of action.
No recommendation: There is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time.

OTHER CONSIDERATIONS

Complementary clinical laboratory tests are available to measure thiopurine metabolites in erythrocytes: TGNs (for mercaptopurine, azathioprine, and thioguanine) and MeMPNs (or MeTIMP) for those on mercaptopurine or azathioprine. These tests can be useful to confirm TPMT phenotype and to test for patient adherence with oral medication regimens, but the values are dependent upon the prior thiopurine dosing. TPMT phenotype can also be assessed by measuring erythrocyte TPMT activity; however, activity measures must be interpreted with caution because TPMT activity increases after exposure to thiopurines. Thus, TPMT measured at diagnosis may not reflect TPMT activity later in therapy. This is one reason the TPMT genotype is a useful measure, as genotype does not change during therapy. Although there may be some settings in which aminosalicylates affect TPMT activity, other studies clearly show no in vivo drug interactions. (13-17) TPMT may be spuriously altered from baseline if the patient has recently received allogeneic erythrocyte transfusions or if the patient has previously received an allogeneic hematopoietic stem cell transplant (10, 18-22). Furthermore, because TPMT activity is similar to other erythrocyte enzymes that decrease during the red cells' life-span, the erythrocyte TPMT activity in a wild-type patient with bone-marrow insufficiency (e.g., as is true at diagnosis of ALL) may be within the expected range of a healthy TPMT heterozygote patient, and a TPMT heterozygous patient with a

rapid red cell turn-over (e.g. as seen during hemolysis) may have erythrocyte TPMT activity within the TPMT wild-type range.(23)

Conflicts between phenotype and genotype results (e.g. a low TPMT activity in an individual with a wild-type genotype) may be resolved with additional testing. Because most commercial genotyping assays test only the three most common inactivating SNPs, if a rare inactivating (and untested-for) SNP is present, a spurious wild-type genotype assignment could be made although phenotype tests indicate low TPMT activity or low MeTIMP/TGN ratio. Another rare possibility would be that two inactivating SNP variants are mistakenly assumed to reside on the same allele, when they in fact reside on opposite alleles; phenotypic tests can distinguish these two possibilities.

As indicated in the main manuscript, there is a wide variety of starting, target, and usual doses of thiopurines for different diseases (24, 25) or for the same disease by different groups (25, 26). Patients with an intermediate metabolizer TPMT phenotype will be more likely to require a thiopurine dosage decrease if the starting, target, or usual dosage is on the higher end of the usual range. Also, as indicated below, heterozygotes are more likely to need a decrease of their thiopurines if other concurrent therapy (such as methotrexate) has overlapping adverse effects (such as myelosuppression). Some have suggested that combining thiopurines with allopurinol minimizes methylated active metabolites (27-30), an interaction that will depend upon TPMT phenotype/genotype.

Because clinical assays for TGNs do not distinguish tri- from di- from mono-phosphates, TGN levels cannot be used to identify low NUDT15 activity. There is a growing body of research data indicating that thioguanine incorporated into blood cell DNA may be an indicator of NUDT15 status in patients receiving thiopurines (31), but there are not enough data at present to know if this assay will be a useful adjunct it were available in the clinic.

One caveat to thiopurine use is that some serious long-term adverse effects (secondary tumors) have been associated with defective TPMT activity (19, 32-34) without

necessarily causing serious acute myelosuppression; whether capping doses of thiopurines in those with a TPMT defect will decrease the risk of the late effect of secondary cancer is not known. It should be noted that at least one study did not confirm a relationship between TPMT and a higher risk of second tumors (35). Veno-occlusive disease and persistent splenomegaly have been associated with low TPMT activity in a UKALL trial, although not with TPMT genotype (36, 37), but VOD was not associated with TPMT genotype in a CCG trial (38).. Thiopurine-associated pancreatitis has not been related to low TPMT activity, and hepatotoxicity (hypertransaminasemia) is more common in those with high TPMT activity (39-45).

Hepatic nodular regenerative hyperplasia (NRH) has been reported in patients treated with thiopurines for inflammatory bowel disease (IBD) (46, 47); however, only two studies reported *TPMT* genotype (48, 49). In both studies NRH was observed in patients who were heterozygous for the *TPMT*3A* allele. Further studies are needed to confirm the association between NRH and *TPMT* genotype.

The effects of NUDT15 variants on these long-term side effects of thiopurines are currently unknown.

High dose methotrexate is commonly given in combination with 6-mercaptopurine during consolidation therapy and re-inductions during maintenance therapy in patients with acute lymphoblastic leukemia. Through inhibition of purine de novo synthesis and enhancement of 6-mercaptopurine bioavailability, high dose methotrexate increases the incorporation of the cytotoxic metabolite of 6-mercaptopurine (6-thioguanine nucleotide) into DNA (50, 51).This interaction is enhanced with increasing levels of the methylated 6-mercaptopurine metabolite, MeTIMP (51). Additionally, the risk of significant bone-marrow suppression is increased if oral 6-mercaptopurine is co-administered with high dose methotrexate (52). Patients who are TPMT or NUDT15 deficient may experience life-threatening myelosuppression during combination therapy (53). Thus, reductions in the dose of concurrently given 6-mercaptopurine during high dose methotrexate therapy can significantly reduce the risk of severe myelotoxicity (50, 54).

RESOURCES TO INCORPORATE PHARMACOGENETICS INTO AN EHR WITH CDS

Clinical decision support (CDS) tools integrated within electronic health records (EHRs) can help guide clinical pharmacogenetics at the point of care (55-59). See https://cpicpgx.org/guidelines/guideline-for-thiopurines-and-tpmt/ for resources to support the adoption of CPIC guidelines within an EHR. Based on the capabilities of various EHRs and local preferences, we recognize that approaches may vary across organizations. Our intent is to synthesize foundational knowledge that provides a common starting point for incorporating the use of *TPMT* and/or NUDT15 genotype results to guide thiopurine dosing and use in an EHR.

Effectively incorporating pharmacogenetic information into an EHR to optimize drug therapy should have some key attributes. Pharmacogenetic results, an interpreted phenotype, and a concise interpretation or summary of the result must be documented in the EHR (60, 61). To incorporate a phenotype in the EHR in a standardized manner, genotype test results provided by the laboratory must be consistently translated into an interpreted phenotype (**Table 1, main manuscript**). Because clinicians must be able to easily find the information, the interpreted phenotype may be documented as a problem list entry or in a patient summary section; these phenotypes are best stored in the EHR at the "person level" rather than at the date-centric "encounter level". Additionally, results should be entered as standardized and discrete terms to facilitate using them to provide point-of-care CDS (55, 62).

Because pharmacogenetic results have lifetime implications and clinical significance, results should be placed into a section of the EHR that is accessible independent of the test result date to allow clinicians to quickly find the result at any time after it is initially placed in the EHR. To facilitate this process, CPIC is providing gene-specific information figures and tables that include full diplotype to phenotype tables, diagram(s) that illustrate how *TPMT* and/or *NUDT15* pharmacogenetic test results could be entered into an EHR, example EHR consultation/genetic test interpretation language and widely

used nomenclature systems for genes relevant to the CPIC guideline (see https://www.pharmgkb.org/page/tpmtRefMaterials and https://www.pharmgkb.org/page/nudt15RefMaterials**)** (63, 64).

Point-of-care CDS should be designed to effectively notify clinicians of prescribing implications at any time after the test result is entered into the EHR. CPIC is also providing gene-drug specific tables that provide guidance to achieve these objectives with diagrams that illustrate how point-of-care CDS should be entered into the EHR, example pre- and post-test alert language, and widely used nomenclature systems for drugs relevant to the CPIC guideline (see https://cpicpgx.org/guidelines/guideline-for-thiopurines-and-tpmt/).

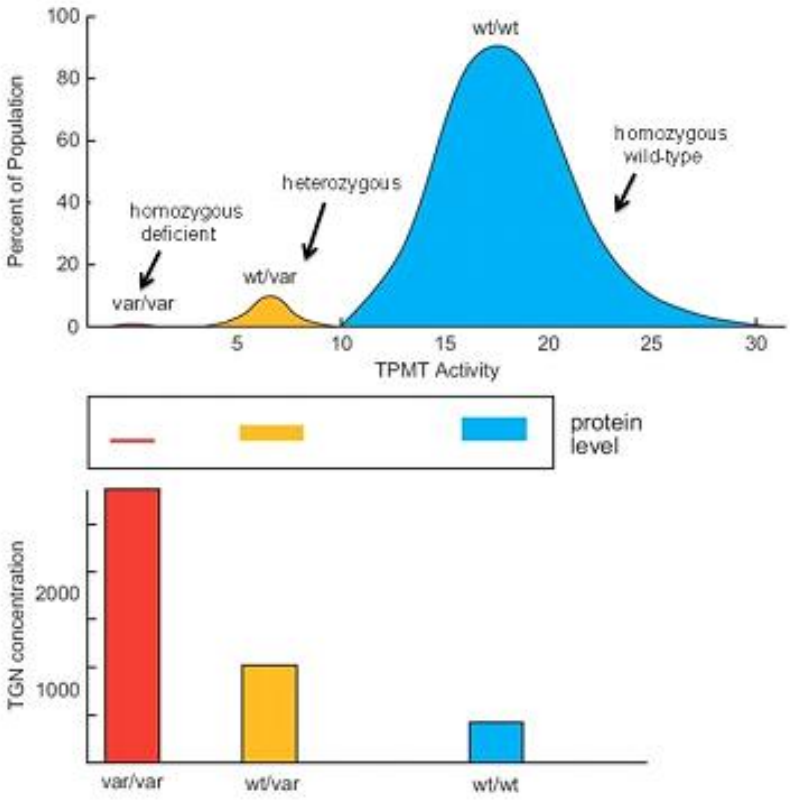

FIGURE S1. IDEALIZED DEPICTIONS OF TPMT ACTIVITY IN ERYTHROCYTES FROM A NORMAL, HEALTHY, NON-TRANSFUSED POPULATION. TPMT activity displays a trimodal frequency distribution (top) that corresponds to monogenic inheritance. Activity is generally directly related to TPMT protein levels, and inversely related to concentrations of active TGN (thioguanine nucleotide) metabolites.

TABLE S1. EVIDENCE LINKING *TPMT* GENOTYPE WITH THIOPURINE PHENOTYPE

Type of experimental model (in vitro, in vivo, preclinical or clinical)	Major findings	References	Level of evidence[a]
In vitro	MP's catabolism to methylmercaptopurine absent in human erythrocytes, lymphocytes, liver, and kidneys from TPMT homozygous deficient individuals	Weinshillboum, et al. (1980) (65) Van Loon, et al. (1982) (66) Van Loon, et al. (1990) (67) Szumlanski, et al. (1992) (68)	High
In vitro	TG's catabolism to methylthioguanine	Moore, et al. (1958) (69)	High
In vitro	Mechanisms of functional inactivation for TPMT *2, *3A, *3B, *3C, *4 demonstrated by expression of specific variant alleles	Tai, et al. (1997) (70) Tai, et al. (1999) (71) Wang, et al. (2003) (72)	High
In vitro	Heterologous expression of TPMT catabolizes mercaptopurine to methylmercaptopurine, thioguanine to methylthioguanine, and TIMP to methylTIMP	Hill, et al. (1971) (73) Krynestki, et al. (2003) (74)	High

In vitro	TPMT deficiency could lead to chronic exposure to thiopurine and could be linked to development of brain cancer (astrocytomas).	Hosni-Ahmed, et al. (2011) (75)	Low
In vitro	TPMT knock-down cells are more sensitive to 6-TG, and in some cases 6-MP, than wild type	Karim, et al. (2013) (76)	High
Preclinical	TPMT+/+ mice have higher survival with high doses of mercaptopurine but TPMT-/- mice have improved survival with lower doses.	Ramsey, et al. (2014) (77)	High
Preclinical	TPMT knock-out mice have more morbidity and mortality but better ALL efficacy from thioguanine and mercaptopurine than wild type mice; heterozygotes were at intermediate risk.	Hartford, et al. (2007) (78) Ramsey, et al. (2014) (77)	High
Clinical	Increased risk of myelosuppression in TPMT heterozygotes receiving normal doses of MP or azathioprine	Lennard, et al. (1987) (79) Lennard, et al. (1993) (80) Black, et al. (1998) (81) McLeod, et al. (1999) (82) Relling, et al. (1999) (83) Sebbag, et al. (2000) (84) Colombel, et al. (2000) (85) McBride, et al. (2000) (86) Evans, et al. (2001) (87) Schwab, et al. (2002) (88) Formea, et al. (2004) (89) Gearry, et al. (2005) (90) Zelinkova, et al. (2006) (91)	High

		Hindorf, et al. (2006) (92) Karas-Kuzelicki, et al. (2009) (93) Booth, et al. (2011) (94) Budhiraja, et al. (2011) (95) Fangbin, et al. (2012) (96) Colleoni, et al. (2013) (97) Hlavaty, et al. (2013) (98) Zabala, et al. (2013) (99) Lee, et al. (2013) (100) Ben Salah, et al. (2013) (101) Davavala, et al. (2014) (102) Carvalho, et al. (2014) (45) Boso, et al. (2014) (103) Chen, et al. (2014) (104) Uchiyama, et al. (2014) (105) Kim, et al. (2014) (106) Yang, et al. (2014) (107) Belen, et al. (2014) (108) Liu, et al. (2015) (44) El-Rashedy, et al. (2015) (42) Liu, et al. (2015) (43) Steponaitiene, et al. (2016) (109) Lee, et al. (2016) (110) Fangbin, et al. (2016) (111) Liu, et al. (2016) (112) Zhu, et al. (2016) (113) Jimenez-Morales, et al. (2016) (114) Di Salvo, et al. (2016) (115) Soler, et al. (2017) (116) Kim, et al. (2017) (117)	

Clinical	TPMT genotype correlates with TPMT activity measured by biochemical assay (variant genotypes have lower activity in general than *1/*1), but activity cannot be explained by genotype alone because the *1/*1 and variant (het) activities overlap	Relling, et al. (1999) (83) Ansari, et al. (2002) (118) Gearry, et al. (2005) (90) Schmiegelow, et al. (2009) (119) Booth, et al. (2011) (94) Fangbin, et al. (2012) (96) Wennerstrand, et al. (2013) (120) Ben-Salah, et al. (2013) (101) Liang, et al. (2013) (121) Demlova, et al. (2014) (122) Chen, et al. (2014) (104) Farfan, et al. (2014) (123) Chouchana, et al. (2014) (124) Karas-Kuzelicki, et al. (2014) (125) Coelho, et al. (2016) (126) Liu, et al. (2017) (6) Tamm, et al. (2017) (7)	High
Clinical	TPMT variant genotype is associated with increased TGN levels and/or lower MMPN levels	Lennard, et al. (2013) (127) Stocco, et al. (2014) (128) Uchiyama, et al. (2014) (105) Chouchana, et al. (2014) (124) Kim, et al. (2014) (106) Lee, et al. (2015) (129) Lee, et al. (2015) (130) Fangbin, et al. (2016) (111)	High
Clinical	TPMT variant genotype associated with incidence of gastrointestinal ADRs	Hlavaty, et al. (2013) (98) Ben Salah, et al. (2013) (101) Liu, et al. (2015) (44) Liu, et al. (2015) (43)	Weak

Clinical	*3C variant is associated with alopecia in patients with autoimmune disease (i.e. inflammatory bowel disease and lupus)	Chen, et al. (2014) (104) Kim, et al. (2014) (106)	Moderate
Clinical	TPMT status associated with dose reduction or cessation of therapy of AZA or 6MP	Evans, et al. (1991) (131) McLeod, et al. (1993) (132) Evans, et al. (2001) (87) Kaskas, et al. (2003) (133) Dhaliwal, et al. (2012) (134) Chisick, et al. (2013) (135) Lee, et al. (2013) (100) Ben Salah, et al. (2013) (101) Farfan, et al. (2014) (123) Kim, et al. (2014) (106) Yang, et al. (2015) (136) Lennard, et al. (2015) (137) Tanaka, et al. (2015) (138) Kim, et al. (2016) (139) Ma, et al. (2016) (140) Zgheib, et al. (2017) (141) Liu, et al. (2017) (6)	High
Clinical	TPMT activity is not associated with sinusoidal obstruction syndrome	Stoneham, et al. (2003) (37) Lennard, et al. (2006) (142) Dong, et al. (2010) (39) Wray, et al. (2014) (38)	Weak
Clinical	TPMT variant genotype is NOT associated with greater likelihood of event free survival, but studies that adjust dose based on TPMT status or tolerance may be unlikely to find such associations	Yang, et al. (2012) (143) Levinsen, et al. (2014) (144) Lennard, et al. (2015) (137) Lennard, et al. (2015) (145) Liang, et al. (2016) (146) Karol, et al. (2017) (147)	Moderate

Clinical	TPMT status associated with development of secondary cancer	Yenson, et al. (2008) (32) Stanulla, et al. (2009) (35) Levinsen, et al. (2014) (144) Lennard, et al. (2015) (137) Stensman, et al. (2015) (148) Nielsen, et al. (2017) (149)	Weak
Clinical	TPMT status associated with development of secondary cancer	Dhaliwal, et al. (2012) (134) Linga, et al. (2014) (150) Levinsen, et al. (2015) (151) Hoang, et al. (2015) (152) Tanaka, et al. (2015) (138) Emmungil, et al. (2015) (153) Bermejo San Jose, et al. (2017) (154)	Weak
Clinical	Personalized dose for TPMT variant genotypes significantly associated with decreased hematologic ADR risk and decreased 6-TGN levels compared with standard doses.	Coenen, et al. (2015) (155)	High
Clinical	The VNTR region in TPMT promoter correlates with TPMT expression (not statistically significant).	Kotur, et al. (2015) (156)	Weak
Clinical	TPMT wild-type patients with ALL have higher risk of relapse than those with at least one variant TPMT allele, particularly in regimens that are primarily antimetabolite-based; wild-type patients with IBD have higher risk of treatment failure	Lennard, et al. (1987) (79) Lennard, et al. (1990) (157) Ansari, et al. (2002) (118) Schmiegelow, et al. (2009) (119)	High

Clinical	TPMT homozygous deficient individuals have life-threatening toxicity (myelosuppression) from normal doses of MP, TG, and azathioprine; toxicity can be minimized with substantially decreased doses	Evans, et al. (1991) (131) Schutz, et al. (1993) (158) McLeod, et al. (1993) (132) Lennard, et al. (1993) (80) Black, et al. (1998) (81) McLeod, et al. (1999) (82) Relling, et al. (1999) (83) Sebbag, et al. (2000) (84) Colombel, et al (2000) (85) McBride, et al. (2000) (86) Schwab, et al. (2002) (88) Kaskas, et al. (2003) (133) Gearry, et al. (2005) (90) Zelinkova, et al. (2006) (91) Hindorf, et al. (2006) (92)	High
Clinical	Increased risk of leukopenia in TPMT heterozygotes and homozygotes receiving thiopurines for treatment of chronic inflammatory diseases.	Booth, et al. (2011) (94)	High
Clinical	Higher level of residual leukemia in TPMT wild- type patients than in heterozygous/homozygous deficient patients with ALL after 10 days of fixed- dose TG but not in absence of thiopurines	Stanulla, et al. (2005) (26)	High
Clinical	No change in relapse risk for heterozygous patients with ALL who receive MP doses adjusted downward for TPMT defective patients	Relling, et al. (2006) (159) Schmiegelow, et al. (2010) (160)	Moderate

Clinical	No increase in acute toxicity in heterozygous compared to homozygous wild-type patients with ALL who received MP doses adjusted downward for TPMT defective patients	Lennard, et al. (1996) (161) Evans, et al. (2001) (87) Stocco, et al. (2009) (162)	High
Clinical	Increased risk of secondary leukemia in those with low TPMT activity and in those with high thiopurine active metabolites	Relling, et al. (1998) (163) Relling, et al. (1999) (164) Bo, J. et al. (1999) (165) Yenson, et al. (2008) (32) Schmiegelow, et al. (2009) (166) Levinsen, et al. (2014) (144) Nielson, et al. (2017) (149)	Moderate
Clinical	TPMT genotyping is useful in predicting myelosuppression and likelihood of clinical response to AZA/6-MP in IBD	Dubinsky, et al. (2000) (167) Schwab, et al. (2002) (88) Gearry, et al. (2005) (90) Hindorf, et al. (2006) (92) Zelinkova, et al. (2006) (91) Hindorf, et al. (2006) (168) Winter, et al. (2007) (169) Gardiner, e al. (2008) (170) Ansari, et al. (2008) (171) Takatsu, et al. (2009) (172) Kim, et al. (2010) (173)	Moderate
Clinical	TPMT genotyping is useful in predicting myelosuppression and likelihood of clinical response to AZA in CD	Lennard, et al. (1989) (174) Colombel, et al. (2000) (85) Regueiro, et al. (2002) (175) Dubinsky, et al. (2005) (176) Gardiner, et al. (2008) (170)	Moderate

Clinical	TPMT genotype-based dosing reduced toxicity while maintaining drug efficacy in trial of AZA for moderate-severe atopic eczema	Meggitt, et al. (2006) (177)	Moderate
Clinical	TPMT genotyping is useful in predicting myelosuppression from AZA in RA	Kerstens, et al. (1995) (178) Marra, et al. (2002) (179) Corominas, et al. (2003) (180) Clunie, et al. (2004) (181)	Moderate
Clinical	TPMT genotyping is useful in predicting myelosuppression from AZA in transplant recipients	Schutz, et al. (1993) (158) McLeod, et al. (1993) (132) Sebbag, et al. (2000) (84) Formea, et al. (2004) (89) Budhiraja, et al. (2011) (95)	High
Clinical	No change in treatment efficacy for IBD patients who receive AZA based on TPMT status or TG concentration	Gonzalez-Lama, et al. (2011) (182)	High
Clinical	Increased risk of hepatotoxicity to MP in patients with TPMT wild-type genotype and/or higher MP metabolites (6-MMPN)	Adam de Beaumais, et al. (2011) (183) Carvalho, et al. (2014) (45) Liu, et al. (2015) (44) El-Rashedy, et al. (2015) (42) Liu, et al. (2015) (43) Abdelaziz, et al. (2016) (41) Jimenez-Morales, et al. (2016) (114) Ebbesen, et al. (2017) (40)	Moderate

TABLE S2. EVIDENCE LINKING *NUDT15* GENOTYPE WITH THIOPURINE PHENOTYPE

Type of experimental model (in vitro, in vivo, preclinical or clinical)	Major findings	References	Level of evidence[a]
In Vitro	rs116855232 T allele is associated with decreased activity	Moriyama, et al. (2016) (31) Valerie, et al. (2016) (184)	High
In Vitro	rs116855232 T allele is associated with thermal instability and rapid degradation in vitro	Valerie, et al. (2016) (184)	High
Clinical	rs116855232 T allele is associated with increased risk of leukopenia, neutropenia, myelosuppression or other thiopurine toxicity	Yang, et al. (2014) (107) Tanaka, et al. (2015) (138) Cheiengthong, et al. (2016) (185) Asada, et al. (2016) (186) Lee, et al. (2016) (110) Wong, et al. (2016) (187) Kakuta, et al. (2016) (188) Ailing, et al. (2016) (189) Zhu, et al. (2016) (113) Soler, et al. (2017) (116) Yin, et al. (2017) (190) Shah, et al. (2017) (191) Tanaka, et al. (2017) (192) Zhang, et al. (2018) (193)	High
Clinical	rs116855232 T allele is associated with decreased thiopurine dose	Yang, et al. (2015) (136) Tanaka, et al. (2015) (138) Suzuki, et al. (2016) (194) Liang, et al. (2016) (146) Zgheib, et al. (2017) (141) Yin, et al. (2017) (190) Tanaka, et al. (2017) (192)	High
Clinical	rs116855232 T T genotype is associated with severe hair loss	Asada, et al. (2016) (186) Lee, et al. (2016) (110) Kakuta, et al. (2016) (188)	Moderate

		Ailing, et al. (2016) (189) Zhu, et al. (2016) (113) Shah, et al. (2017) (191)	
Clinical	rs116855232 T allele is associated with accumulation of DNA-TG in vivo	Moriyama, et al. (2017) (195)	High
Clinical	rs116855232 T allele is not associated with event free survival	Tanaka, et al. (2015) (138) Liang, et al. (2016) (146)	Weak
Clinical	rs116855232 T allele is not associated with relapse	Chiengthong, et al. (2016) (185) Suzuki, et al. (2016) (194)	Weak

*Rating Scheme for Quality of Evidence as per (196)

ALL = acute lymphoblastic leukemia; AZA = azathioprine; CD = Crohn's disease; RA = rheumatoid arthritis; IBD = inflammatory bowel disease; MP = mercaptopurine; TG = thioguanine; TPMT = thiopurine methyltransferase; 6-MMPN = 6-methylmercaptopurine nucleotides.

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