Supplemental Table S1. Genotypes that constitute the * alleles for *TPMT*	
Allele[a]	**Constituted by genotypes at:**
*1	wild-type
*1S	G>A at rs2842934
*2	C>G at rs1800462
*3A	C>T at rs1800460 and T>C at rs1142345
*3B	C>T at rs1800460
*3C	T>C at rs1142345
*4	C >T at rs1800584
*5	A>G at rs72552740
*6	T>A at rs75543815
*7	A>C at rs72552736
*8	C>T at rs56161402
*9	T>G at rs151149760
*10	C>G at rs72552737
*11	C>T at rs72552738
*12[b]	G>A (NM_000367.2:c.374C>T)
*13	T>A at rs72552742
*14	T>C at rs9333569
*15	C>T at rs9333570
*16	C>T at rs144041067
*17[b]	G>C (NM_000367.2:c.124C>G)
*18[b]	C>T (NM_000367.2.c.211G>A)
*19[b]	T>G (NM_000367.2:c.365A>C)

*20	T>C at rs150900439
*21[b]	G>C (NM_000367.2:c.205C>G)
*22[b]	C>G (NM_000367.2:c.488G>C)
*23	G>C at rs74423290
*24	C>A at rs6921269
*25[b]	A>G (NM_000367.2:c.634T>C)
*26	A>G at rs72556347
*27[b]	A>C (NM_000367.2:c.319T>G)
*28[b]	C>G(NM_000367.2:c.349G>C)
*29	A>G at rs267607275
*30 (*24)[b]	C>T (NM_000367.2:c.106G>A)
*31 (*28)[b]	A>G (NM_000367.2:c.611T>C)

See www.pharmgkb.org for updates on *TPMT* alleles and nomenclature. Bases reported on the positive chromosomal strand from Golden Path.
[a]Nomenclature as determined by TPMT nomenclature committee (48) (www.imh.liu.se/tpmtalleles). Allele names in parentheses represent old naming system.
[b]Note that these base changes are reported on the positive chromosomal strand for consistency with the other alleles in this table, while the reference sequence NM_000367.2 is on the other strand (alleles are flipped).

Supplemental Table S2. Association between allelic variants[1] and TPMT enzyme activity (49-59)	
Functional Status	**Alleles**
Functional / normal activity/ wild-type[2]	*1, *1S
Non-functional, variant, or mutant / no activity	*2, *3A, *3B, *3C, *4
Probable Reduced-function / decreased activity (most of these alleles are very rare	*5, *6, *8, *9, *10, *11, *12, *13, *16, *17, *18

and most have shown reduced rather than absent activity)	
Unknown/Unclear/Conflicting data	*7, *14, *15, *19, *20, *21, *22, *23, *24, *25, *26, *27, *28, *29, *30, *31

[1]: see www.pharmgkb.org for updates on *TPMT* allelic variants and nomenclature. Allele nomenclature as determined by the TPMT nomenclature committee (48) (www.imh.liu.se/tpmtalleles).

[2]: an important caveat for all genotyping tests is that the decision to assign an allele a "wild-type" status is based upon a genotyping test that interrogates only the most common and already-proven sites of functional variation. In human DNA, it is always possible that a new, previously undiscovered (and therefore un-interrogated) site of variation may confer loss-of- function in an individual, and thus lead to the rare possibility of a non-functional allele being erroneously called as "wild-type"

Supplemental Table S3. Frequencies[1] of alleles in major race/ethnic groups[2]

Allele	Caucasian	Mediter-ranean	South American	African	Middle Eastern	Mexican	Asian	South West Asian
*1	**0.95726**	**0.96081**	**0.95233**	**0.93901**	**0.96987**	**0.92500**	**0.98347**	**0.97837**
*2	0.00190	0.00408	0.00876	0.000792	0.00749	0.00592	0	0.00250
*3A	0.0356	0.0254	0.0287	0.00198	0.0114	0.0533	0.000118	0.00583
*3B	0.000461	0.00426	0.000486	0	0.00562	0.00690	0	0
*3C	0.004205	0.00545	0.00924	0.0495	0.00562	0.00888	0.0157	0.0133
*4-*26	0.0000576 (*7) 0.0002304 (*9) 0.0000576 (*11) 0.0000576 (*12) 0.0000576 (*16) 0.0000576 (*17) 0.0000576 (*18)	N/A	0.000486 (*4)	0.00872 (*8)	N/A	N/A	0.000706 (*6)	N/A

[1]Average frequencies are reported based on the average from the actual numbers of subjects with each allele reported in multiple studies. See Supplemental Table S4 for details and references.
[2]Race/ethnic group designations correspond to those indicated in Supplemental Table S4

Supplemental Table S4. *TPMT* minor allele frequency

Pooled grouping	Ethnicity	TPMT minor allele frequency (%)					Total patients	TPMT minor alleles observed					Total alleles
		*2	*3A	*3B	*3C	*4–26		*2	*3A	*3B	*3C	*4–26	
Caucasian	British (60)	0.5	4.5	0	0.3	–	199	2	18	0	1	–	398
Caucasian	Bulgarian (61)	0.2	2.2	0	0.2	–	313	1	14	0	1	–	626
Caucasian	Caucasian (62)	0.1	2.9	0	0.3	–	390	1	23	0	2	–	780
Caucasian	Czech (63)	0.1	4.5	0.1	0.9	–	696	2	62	1	12	–	1392
Caucasian	Czech (64)	0	3.4	0	0	–	87	0	6	0	0	–	174
Caucasian	Danish (65)	0	3.3	0	0.3	–	200	0	13	0	1	–	400
Caucasian	Dutch (66)	0	2.6	0.5	0.5		190	0	10	2	2	–	380
Caucasian	Dutch (67)	0	2.1	0	1.4	–	72	0	3	0	2	–	144
Caucasian	Estonian (68)	0.6	4.9	0	0.6	0.3 (*9,*12)	154	2	15	0	2	1 (*9 & *12)	308
Caucasian	European (69)	0.5	5.8	0	0.8	0.3 (*7)	191	2	22	0	3	1 (*7)	382
Caucasian	German (36)	0	2.9	0	0.5	0	105	0	6	0	1	–	210
Caucasian	German (51)	0.2	4.5	0	0.4	0.08 (*9), 0.04 (*16), 0.04 (*17), 0.04 (*18)	1214	6	110	0	9	2 (*9) 1 (*16) 1 (*17) 1 (*18)–	2428
Caucasian	German (52)	0.2	2.9	0	0.6	0.06 (*9) 0.06 (*11)	814	4	48	0	9	1 (*9 &*11)	1628
Caucasian	Greenlandic (65)	0	8.1	0	0	–	142	0	23	0	0	–	284
Caucasian	Irish (70)	0	3.4	0.1	0.4	–	407	0	28	1	3	–	814
Caucasian	Polish (71)	0.4	2.7	0	0.1	–	358	3	19	0	1	–	716
Caucasian	Polish (72)	0.6	4.2	0	0.6	–	180	2	15	0	2	–	360
Caucasian	Polish (73)	–	5.2	0	0.6	–	87	–	9	0	1	–	174
Caucasian	Portuguese (74)	1	2.4	0	0.7	–	143	3	7	0	2	–	286
Caucasian	Portuguese (75)	0	2.8	0	0	–	334	0	19	0	0	–	668
Caucasian	Russian (76)	0.1	2.3	0	0.4	–	995	2	45	0	8	–	1990
Caucasian	Serbian (77)	0.3	3.3	0.5	0	–	200	1	13	2	0	–	400
Caucasian	Swedish (78)	0.1	3.8	0.1	0.4	–	800	1	60	2	7	–	1600
Caucasian	Swedish (79)	0	4.1	0	0.8	–	61	0	5	0	1		122
Caucasian	Swiss (80)	0.2	2.9	0	0.6	–	240	1	14	0	3	–	480
Caucasian	White/Danish (81)	0	5.5	0	0	–	109	0	12	0	0	–	218
Total Caucasian							**8681**	**33**	**619**	**8**	**73**	**1 (*7) 4(*9) 1 (*11) 1 (*12) 1 (*16) 1 (*17) 1 (*18)**	**17362**
Mediterranean	French (82)	0.8	4	0	0.4	–	468	7	28	0	4	–	936
Mediterranean	Greek (83)	3.1	2.6	4.6	1	–	97	6	5	9	2	–	194
Mediterranean	Italian (84)	0.7	2.9	0	0	–	70	1	4	0	0	–	140
Mediterranean	Italian (85)	0.5	3.9	0	1	–	103	1	8	0	2	–	206
Mediterranean	Italian-Caucasian (86)	0	2.2	0.3	0.3	–	943	0	41	6	6	–	1886
Mediterranean	Sardinian (87)	1.7	0.6	0.4	0.8	–	259	9	3	2	4	–	518
Mediterranean	Slovenian (88)	0	4.1	0.3	0.5	–	194	0	16	1	2	–	388
Mediterranean	Slovenian (89)	0	3.4	0	0	–	313	0	21	0	0	–	626
Mediterranean	Spanish (66)	0	2.9	1.2	1.8	–	169	0	10	4	6	–	338
Mediterranean	Spanish (90)	0	2.5	0.7	1	–	216	0	11	3	4	–	432
Mediterranean	Turkish (91)	0	0.9	0	0.9	–	106	0	2	0	2	–	212
Total Mediterranean							**2938**	**24**	**149**	**25**	**32**	**–**	**5876**

South American	Argentinean (92)	0.7	3.1	0	0	0.3 (*4)	147	2	9	0	0	1 (*4)	294
South American	Bolivian (93)	0	6.5	0	0	–	115	0	15	0	0	–	230
South American	Brazil European (94)	0.8	1.6	0	2.1	–	306	5	10	0	13	–	612
South American	Brazilian (95)	2.2	1.5	0.2	1	–	204	9	6	1	4	–	408
South American	Brazilian (96)	0.4	3.9	0	0.9	–	116	1	9	0	2	–	232
South American	Colombian (97)	0.3	3.6	0	0	–	140	1	10	0	0	–	280
Total South American							**1028**	**18**	**59**	**1**	**19**	**1 (*4)**	**2056**
African	Afro-American (98)	0.4	0.8	0	2.4	0.2 (*8)	248	2	4	0	12	1 (*8)	496
African	Black (99)	0	0	0	3.5	–	227	0	0	0	16	–	454
African	Ghanaian (100)	0	0	0	7.6	–	217	0	0	0	33	–	434
African	Ghanaian (8)	0	0	0	6.5	3.4 (*8)	116	0	0	0	15	8 (*8)	232
African	Cabindanian (101)	0	0	0	3.9	2.4 (*8)	103	0	0	0	8	5 (*8)	206
African	Mozambiqueian (102)	0	0.2	0	3.8	1.6 (*8)	250	0	1	0	19	8 (*8)	500
African	Kenyan (103)	0	0	0	10.9	–	101	0	0	0	22	–	202
Total African							**1146**	**2**	**5**	**0**	**125**	**22**	**2524**
Asian	Chinese (104)	0	0	0	1.5	–	462	0	0	0	14	–	924
Asian	Chinese (60)	0	0	0	2.3	–	192	0	0	0	9	–	384
Asian	Chinese (105)	0	0	0	1.4	–	271	0	0	0	15	–	542
Asian	Chinese (106)	0	0.1	0	1	–	701	0	1	0	14	–	1402
Asian	Chinese (107)	0	0	0	1.3	–	278	0	0	0	7	–	556
Asian	Chinese (108)	0	0	0	3.2	–	332	0	0	0	21	–	664
Asian	Chinese (109)	0	0	0	2.3	–	150	0	0	0	7	–	300
Asian	Chinese (110)	0	0	0	1.3	–	225	0	0	0	6	–	450
Asian	Chinese (111)	0	0.3	0	1.6	–	160	0	1	0	5	–	320
Asian	Filipino (112)	0	0	0	1	–	100	0	0	0	2	–	200
Asian	Japanese (113)	0	0	0	0.3	–	151	0	0	0	1	–	302
Asian	Japanese (114)	0	0	0	1.6	–	522	0	0	0	17	–	1044
Asian	Japanese (115)	0	0	0	0.8	–	192	0	0	0	3	–	384
Asian	Japanese (116)	0	0	0	1.4	0.7 (*6)	71	0	0	0	2	1 (*6)	142
Asian	Japanese (117)	0	0	0	1.7	–	242	0	0	0	8	–	484
Asian	Japanese (118)	0	0	0	2.6	–	236	0	0	0	12	–	472
Asian	Japanese (119)	0	0	0	0.5	–	111	0	0	0	1	–	222
Asian	Japanese (120)	0	0	0	0.9	–	279	0	0	0	5	–	558
Asian	Japanese (121)	0	0	0	1	–	147	0	0	0	3	–	294
Asian	Korean (122)	0	0	0	0.9	0.25 (*6)	400	0	0	0	7	2 (*6)	800
Asian	Korean (123)	0	0	0	1.8	0.7 (*6)	342	0	0	0	12	5 (*6)	684
Asian	Korean (124)	0	0	0	1	–	812	0	0	0	17	–	1624
Asian	Korean (125)	0	0	0	1.2	–	286	0	0	0	7	–	572
Asian	Korean (8)	0	0	0	2.5	1.3 (*6)	118	0	0	0	6	3 (*6)	236
Asian	Malay (105)	0	0	0	1.2	0.3 (*6)	217	0	0	0	10	1 (*6)	434
Asian	Taiwanese (112)	0	0	0	0.6	–	249	0	0	0	3	–	498
Asian	Taiwanese (126)	0	0	0	0.4	–	526	0	0	0	4	–	1052
Asian	Thai (112)	0	0	0	1	–	100	0	0	0	2	–	200
Asian	Thai (127)	0	0	0	5.3	–	75	0	0	0	8	–	150
Asian	Thai (128)	–	–	–	3.2	–	139	–	–	–	9	–	278
Asian	Thai (129)	0	0	0	5	–	200	0	0	0	20	–	400
Asian	Tibetan (93)	0	0	0	2	–	50	0	0	0	1	–	100
Asian	Vietnamese (122)	0	0	0	2.8	0 (*6)	159	0	0	0	9	0	318

Total Asian							**8495**	**0**	**2**	**0**	**267**	**12(*6)**	**16990**
South West Asian	British Asian (130)	0	0.6	0	2.4	–	85	0	1	0	4	–	170
South West Asian	British SW Asian (60)	0	1	0	0	–	99	0	2	0	0	–	198
South West Asian	Indian (131)	2.1	0.7	0	2.1	–	71	3	1	0	3	–	142
South West Asian	Indian (105)	0	0.5	0	0.8	–	200	0	2	0	3	–	400
South West Asian	Indian (132)	0	0.3	0	2.1	–	145	0	1	0	6	–	290
Total South West Asian							**600**	**3**	**7**	**0**	**16**	–	**1200**
Mexican	Mexican adults (133)	1.4	4.4	1.7	1.7	–	147	4	13	5	5	–	294
Mexican	Mexican newborns (134)	0.3	5.7	0.3	0.6	–	360	2	41	2	4	–	720
Total Mexican							**507**	**6**	**54**	**7**	**9**	–	**1014**
Middle Eastern	Egyptian (135)	0	0.3	0	1.3	–	194	0	1	0	5	–	388
Middle Eastern	Iranian (136)	2.2	1.7	1.6	0.5	–	832	36	28	27	9	–	1664
Middle Eastern	Israeli (137)	0	1.2	0	0.4	–	881	0	22	0	6	–	1762
Middle Eastern	Jordanian (138)	0	0.6	0	0.3	–	169	0	2	0	1	–	338
Middle Eastern	Kazak (139)	0	0.3	0	0.9	–	327	0	2	0	6	–	654
Total Middle Eastern							**2403**	**36**	**55**	**27**	**27**	–	**4806**

"-" indicates that an allele frequency was not provided

Supplemental Table S5. Evidence linking genotype with phenotype			
Type of experimental model (in vitro, in vivo preclinical, or clinical)	**Major findings**	**References**	**Level of evidence***
In vitro	MP's catabolism to methylmercaptopurine absent in human erythrocytes, lymphocytes, liver, and kidneys from *TPMT* homozygous deficient individuals	**(56, 140-142)**	High
In vitro	TG's catabolism to methylthioguanine	**(143)**	High
In vitro	Mechanisms of functional inactivation for *TPMT* *2, *3A, *3B, *3C, *4 demonstrated by expression of specific variant alleles	**(59, 144, 145)**	High
In vitro	Heterologous expression of *TPMT* catabolizes mercaptopurine to methylmercaptopurine, thioguanine to methylthioguanine, and TIMP to methylTIMP	**(146, 147)**	High
In vitro	TPMT deficiency could lead to chronic exposure to thiopurine and could be linked to development of brain cancer (astrocytomas).	**(148)**	Low
preclinical	*TPMT* knock-out mice have more morbidity and mortality from thioguanine and mercaptopurine than wild type mice; heterozygotes were at intermediate risk.	**(149)**	High
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	**(150-153)**	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	**(20, 154-167)**	High

	decreased doses		
clinical	Increased risk of myelosuppression in *TPMT* heterozygotes receiving normal doses of MP	**(20, 89, 150, 156, 158, 168, 169)**	High
clinical	Increased risk of leukopenia in TPMT heterozygotes and homozygotes receiving thiopurines for treatment of chronic inflammatory diseases.	**(170)**	High
clinical	Compared with intermediate or normal TPMT activity, low TPMT enzyme activity significantly associated with myelotoxicity and leukopenia.	**(170)**	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	**(52)**	High
clinical	No change in relapse risk for heterozygous patients with ALL who receive MP doses adjusted downward for TPMT defective patients	**(171, 172)**	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	**(21, 31, 168)**	High
clinical	Increased risk of secondary leukemia in those with low TPMT activity and in those with high thiopurine active metabolites when dosed independently of TPMT status	**(32-34, 173, 174)**	Moderate
clinical	*TPMT* genotyping is useful in predicting myelosuppression and likelihood of clinical response to AZA/6-MP in IBD	**(121, 125, 159-162, 175-179)**	Moderate
clinical	*TPMT* genotyping is useful in predicting myelosuppression and likelihood of clinical response to AZA in CD	**(158, 176, 180-182)**	Moderate

clinical	*TPMT* genotype-based dosing reduced toxicity while maintaining drug efficacy in trial of AZA for moderate-severe atopic eczema	**(183)**	Moderate
clinical	*TPMT* genotyping is useful in predicting myelosuppression from AZA in RA	**(90, 184-186)**	Moderate
clinical	*TPMT* genotyping is useful in predicting myelosuppression from AZA in transplant recipients	**(163-165, 187, 188)**	High
Clinical	No change in clinical outcome for IBD patients who receive AZA based on TPMT activity or TG concentration	**(189)**	Moderate
Clinical	Increased risk of hepatotoxicity to MP in ALL patients with TPMT wild-type genotype and with higher MP metabolite (6-MMPN)	**(190)**	Moderate

Supplemental Material

This supplemental material was updated on November 9, 2012.

Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for thiopurine methyltransferase (*TPMT*) genotype and thiopurine dosing

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CPIC Updates:

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

Literature Review:

We searched the PubMed database (1966 to October 2012 and Ovid MEDLINE (1950 to October 2012) for keywords ((TPMT) OR (thiopurine methyltransferase) OR thiopurine S-methyltransferase) AND (thiopurine OR mercaptopurine OR thioguanine OR azathioprine) for the contribution TPMT genotype had on predicting a thiopurine-related adverse drug event (ADE) or outcome. Definitive reviews (1-5) were relied upon to summarize much of the earlier literature.

To construct a *TPMT* minor allele frequency table (Supplemental Table S3) based on ethnicity, the following search criteria were used: (TPMT) OR (thiopurine) AND ((allele) OR (frequency) OR (genotype)). Studies were considered for inclusion if: (1) the ethnicity of the population was clearly indicated, (2) either allele frequencies or minor allele percentages for *TPMT* genotypes were reported, (3) the method by which *TPMT* was genotyped was reliable and proven (no proof-of-principle experiments), (4) the sample population consisted of at least 50 patients, and (5) the study represented an original publication (no reviews). The combined analysis included 8,676 Caucasians, 2,938 Mediterraneans, 1,028 South Americans, 1,146 Africans, 8,377 Asians, 600 South West Asians, 507 Mexicans, and 2,403 Middle Easterners. A similar search strategy was used to gather the body of evidence related to the use of thiopurines in specific disease states and the relative contribution *TPMT* genotype had on predicting a thiopurine-related adverse drug event (ADE).

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 the rs# for each of the specific genomic nucleotide alterations that define the alleles, are described in Supplemental Table S1.

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 Supplemental Table S2. The most common inactivating allele among Caucasians for TPMT is designated as *3A; other alleles predominate in other ethnic/ancestral groups (Tables S3 and S4). 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: Ala 154 Thr (rs1800460) and Tyr 240 Cys (rs1142345); when the rare genotype is present at these two SNP positions in the heterozygous state, the assumption is that the rare genotypes are 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 (at the frequencies shown in supplemental Tables 3 and 4) 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 homozygote deficient diplotype (*3B/*3C)—a call consistent with homozygous TPMT deficiency. If one assumes that the frequency of the *3B allele is 0.000461, and of the *3C allele is 0.004205 (Table S3), the probability of finding such a compound homozygote 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, (6, 7) 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 distinguish these two genotypes, which 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 (heterozygote) from a very rare *3B/*3C diplotype (homozygous deficient). 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.

The frequencies of phenotypic groups homozygous for one of any of the variant nonfunctional alleles, heterozygous (one wild-type and one variant allele), and homozygous for wild-type alleles that are cited in the CPIC guidelines is based on the assumption that the frequency of the wild-type allele are between 0.925 and 0.984, and the frequency of a nonfunctional allele is between 0.016 and 0.075, depending upon ethnicity/race. Assuming Hardy-Weinberg equilibrium, this leads to the estimates of 1 in 178 to 1 in 3736 being homozygous for a nonfunctional allele (depending upon ethnicity and ancestry), 3% to 14% being heterozygote, and ~ 86-97% being homozygous for wild-type alleles. These estimates of phenotypic group frequencies differ among race/ethnic groups, as per the allele frequency estimates in Tables S3 and S4.

Available Genetic Test Options

Commercially available genetic testing options change over time. Some laboratories offering clinical testing are listed at http://www.pharmgkb.org/resources/forScientificUsers/pharmacogenomic_tests.jsp. Furthermore, 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/conditions/C2720286/.

Many commercially available tests 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.

While there are no specific Current Procedural Terminology (CPT) codes for a *TPMT* genotyping test, the CPT code modifier 9A has been reserved for *TPMT*. Because CPT codes for genetic tests are procedure-based, several codes are currently used to reflect the multiple steps involved in genetic testing. For example, the CPT codes for an individual *TPMT* genotyping test might include: 83891 – Isolation or extraction of highly purified nucleic acid (x1), 83898 – Amplification of patient nucleic acid for three different DNA sequences (x3), 83896 – Nucleic acid probe (x6), and 83912 – Interpretation and report (x1). However, these codes are subject to change and may vary depending on the clinical laboratory procedure used for genetic testing. It should also be noted that while CPT codes are designed to be universal, it is the jurisdiction of the healthcare and service providers and that will determine proper coding. Current coding is not yet well adapted to handle array-based multi-gene platforms.

Several health insurance companies cover testing for *TPMT* genotypic or phenotypic assays but the coverage may be indication-specific. For example, "Aetna considers *TPMT* gene mutation assays (e.g., PRO-Predict^{R} *TPMT*) or TPMT phenotypic assays (TPMT enzymatic activity, e.g., PRO-Predict^{R} EnzAct) medically necessary prior to initiation of 6-mercaptopurine or azathioprine therapy" for inflammatory bowel disease. (9) (9) (9) (9) Some clinical laboratories may provide healthcare professionals with template letters for physician appeal, medical necessity and pre-authorization to assist in obtaining reimbursement for *TPMT* genotyping. However, not all organizations support reimbursement for TPMT testing.

Levels of Evidence linking genotype to phenotype

Multiple grading scales for evidence were evaluated. (10-12) Ultimately, we chose a simple scale of high, moderate, or weak to grade the levels of evidence, based on criteria previously published.(11)

> 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.

We have focused on presenting evidence from well-done studies, and it is the interpretation of the results from these studies that provide the framework for the strength of the dosing recommendations in Table 2.

Strength of Dosing Recommendations

CPIC's dosing recommendations are based on weighting the evidence from a combination of preclinical functional and clinical data (Table S5), as well as on some existing disease-specific consensus guidelines. **(5, 13)** 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 (with thiopurines as substrate), *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 protein stability or enzyme activity.

Overall, the dosing recommendations are simplified to allow rapid interpretation by clinicians. They have been adopted from the rating scale for evidence-based therapeutic recommendations on the use of retroviral agents. (10)

Strong recommendation for the statement
Moderate recommendation for the statement
Optional recommendation for the statement

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. Although there may be some settings in which aminosalicylates affect TPMT activity, other studies clearly show no in vivo drug interactions. (14-18) TPMT may be spuriously altered from baseline if the patient has recently received allogeneic erythrocyte transfusions.(2, 5, 19-22) Furthermore, since 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 a heterozygote 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.

The influence of genetic polymorphism in inosine triphosphate pyrophosphatase (*ITPA*) on thiopurine-induced adverse events was recently investigated during combination chemotherapy for acute lymphoblastic leukemia (ALL).(31) The effects of a common *ITPA* nonfunctional variant allele (rs41320251) on mercaptopurine metabolism and toxicity during treatment of children with ALL was significant only in patients whose thiopurine dose had already been adjusted for *TPMT* genotype. In this context, patients with a variant *ITPA* allele had a significantly higher probability of severe febrile neutropenia if their dose had been adjusted for *TPMT* genotype. In patients whose thiopurine is not adjusted for *TPMT* status, then the *TPMT* polymorphism is the dominant determinate of thiopurine toxicity, with ITPA having a negligible effect. This study illustrates that once therapy has been adjusted for a dominant genetic polymorphism (*TPMT*), other genetic polymorphisms may surface as having an influence on treatment response.

One caveat to thiopurine use is that some serious long-term adverse effects (secondary tumors) have been associated with defective TPMT activity (32-35) 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.(36) Veno-occlusive disease and persistent splenomegaly have been associated with low TPMT activity, although not necessarily with *TPMT* genotype, in children receiving thioguanine.(37) Moreover, some adverse reactions to thiopurines, such as pancreatitis and hepatotoxicity, are not related to low TPMT activity. (38)

Hepatic nodular regeneration hyperplasia (NRH) has been reported in patients treated with thiopurines for inflammatory bowel disease (IBD); (39, 40) however, only two studies reported *TPMT* genotype. (41, 42) In both studies NRH was observed in patients who were heterozygous for the *TPMT*3A* mutation. Further studies are needed to confirm the association between NRH and *TPMT* genotype.

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.(43, 44)This interaction is enhanced with increasing levels of the methylated 6-mercaptopurine metabolite, MeTIMP.(44)Additionally, the risk of significant bone-marrow suppression is increased if oral 6-mercaptopurine is co-administered with high dose methotrexate.(45) Patients who are TPMT deficient may experience life-threatening myelosuppression during combination therapy.(46) Thus, reductions in the dose of concurrently given 6-mercaptopurine during high dose methotrexate therapy can significantly reduce the risk of severe myelotoxicity.(43, 47)

*Rating Scheme for Quality of Evidence as per (11)
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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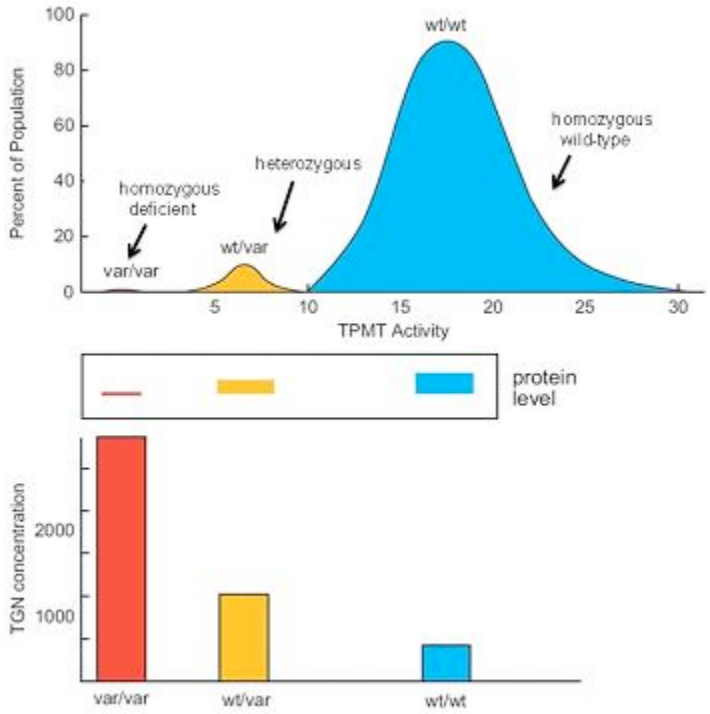

Figure Legend

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.