Assessment of Thiopurine Methyltransferase Activity in Patients Prescribed Azathioprine or Other Thiopurine-based Drugs

Evidence Report No. 196

Addendum—Updating the Report and Reanalysis

Search Update

We updated the search to December 2010 restricting to MEDLINE (1950 to December Week 3 2010), the Cochrane Library (2010 4), EMBASE (1980 to 2010 Week 52), and Ovid Healthstar (1966 to December 2010). Title and abstract of 100 new records were screened per protocol. Thirteen records passed to full text screening level. Four records were excluded because they were editorial or reviews, and five because of miscellaneous reasons [6107, 6147, 6152, 6250, 6168, 6154, 6008, 6011, 6136]. Of the four new studies included, one lacked analyzable data [6167]. Two studies contributed to KQ1a and 1b [6017, 6140], and one fair quality cohort contributed to KQ3c [6151].

Methods

As the data were sparse, we made the following modifications to the previous methodology to examine robustness of conclusions.

- for both diagnostic accuracy (KQ1c) and investigation of genotypic association (KQ3c), we undertook additional (**post hoc**) meta-analyses in which all studies were pooled as long as they genotyped at the very least for all ethnicity specific mutations with known prevalence >1%. That is, TPMT*3A for Caucasians, and TPMT*3C for Asians—there were zero studies on participants of African descent.
- When appropriate, sensitivity and specificity estimates were pooled by first transforming proportions into the Freeman-Tukey variant of the arcsine square root transformed proportion [6256]. The pooled proportion was calculated as the back-transformation of the weighted mean of the transformed proportions. Data were pooled using a fixed effects inverse variance weighted average. We revised previous primary meta-analyses and conducted additional meta-analyses where applicable.
- We pooled odds ratios using the fixed effects Mantel-Haenszel method without continuity correction [6254].

Results

KQ 1a and 1b

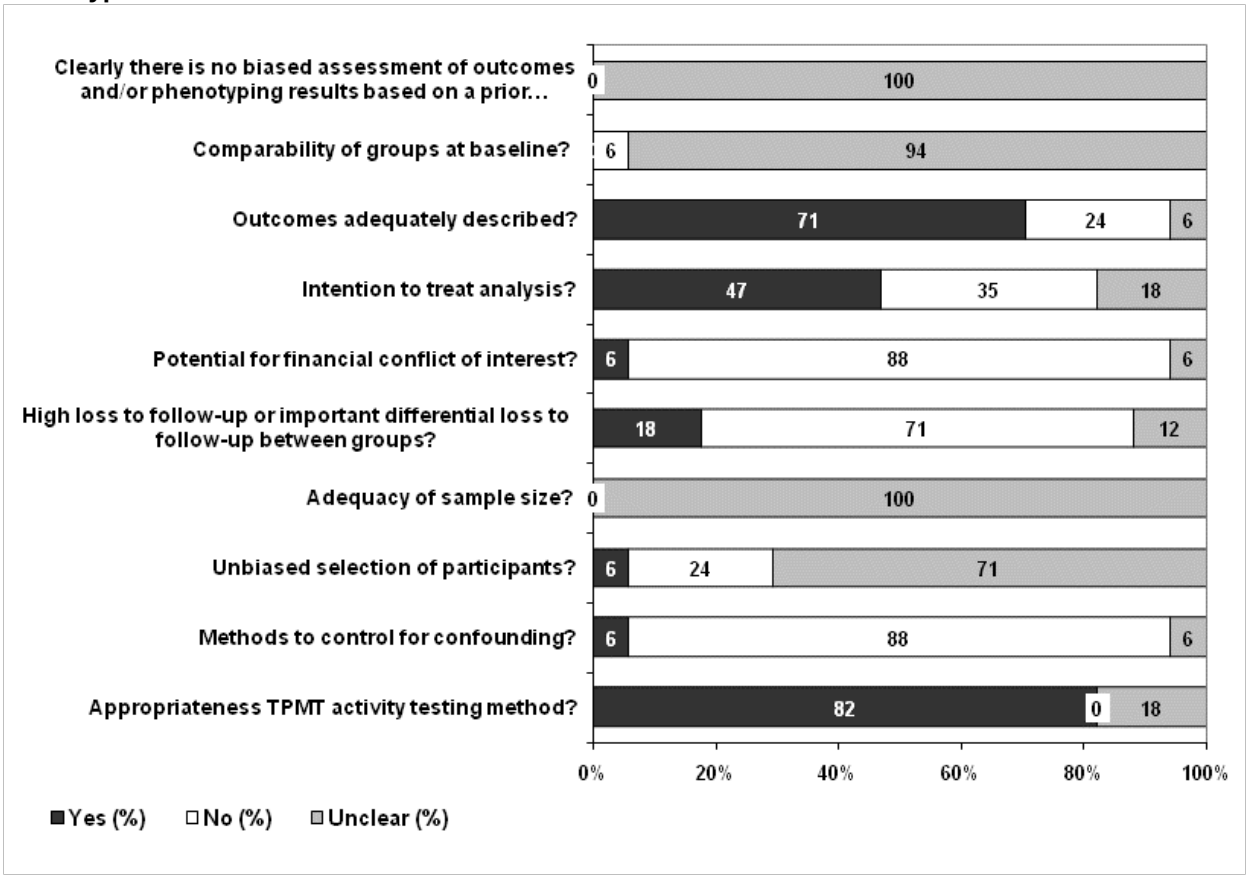
There was no noteworthy change to the results. Conclusions remained unchanged.

KQ 1c and 3c

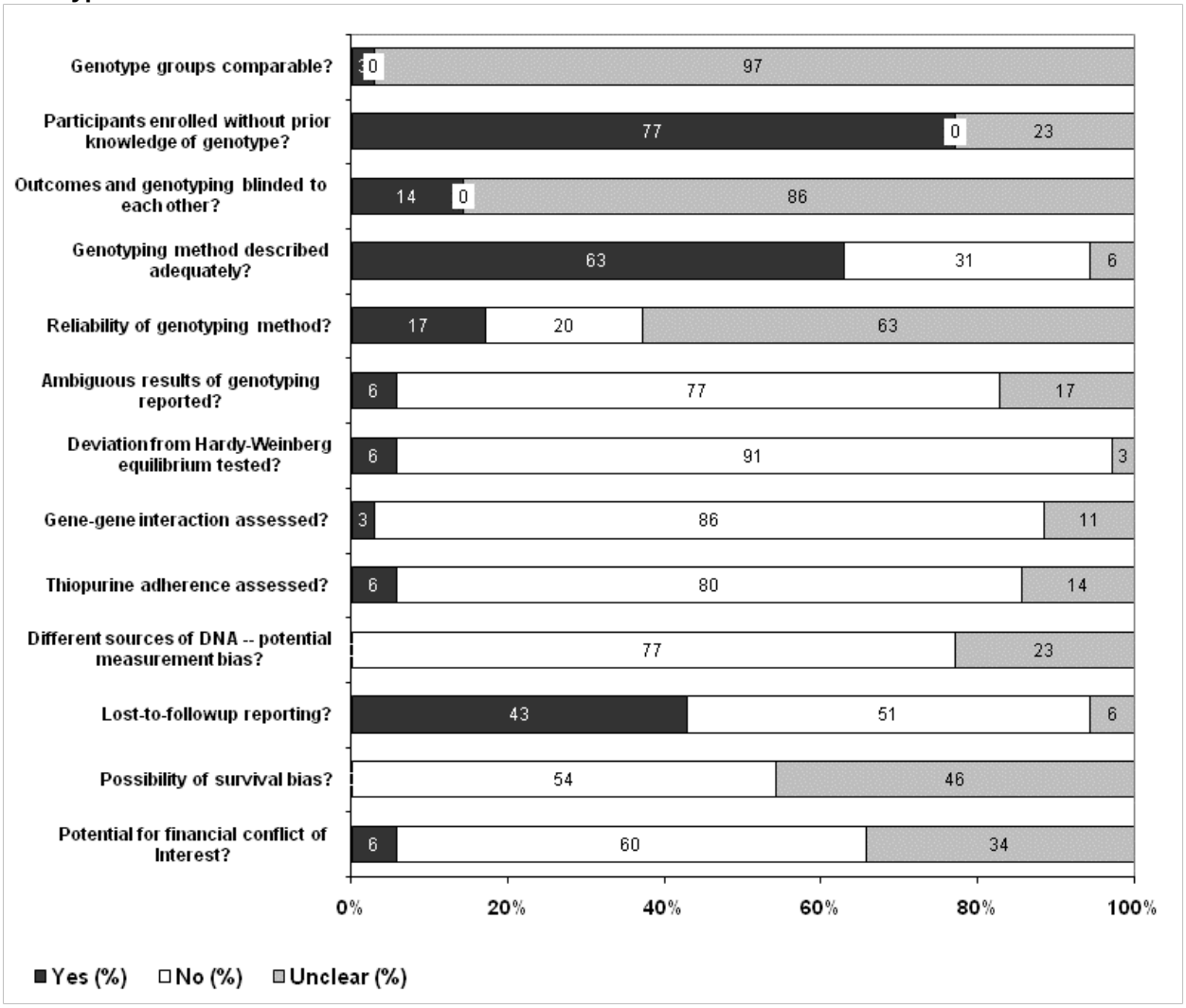
Table Addendum below summarizes new updated quantitative syntheses. No major changes were noted in results as results of modified and post hoc analyses.

Since one new study was added to KQ3c syntheses, risk of bias charts for genotypic and phenotypic association studies were revised:

Phenotypic Association



Genotypic Association



Revised Conclusions

There is a dearth of good quality primary research addressing the comparative effectiveness of TPMT pretesting and test performance of TPMT genotyping with respect to enzymatic activity testing.

Evidence of limited quality indicates that the estimates of sensitivity of genotyping are imprecise, despite near perfect specificity, to identify subnormal enzymatic activities. There is currently insufficient evidence addressing the utility of TPMT testing prior to commencement of thiopurine therapy in comparison with routine blood count monitoring. It also remains unclear whether pre-testing guides appropriate prescribing. Indirect evidence confirms previously known strong associations between low levels of TPMT enzymatic activity and the presence of TPMT allelic polymorphisms status with thiopurine related leukopenia. This was reflected in significant associations between low levels of enzymatic activity and myelotoxicity.

Table Addendum

DIAGNOSTIC ACCURACY OF TPMT GENOTYPING					
		Meta-analysis 1		Meta-analysis 2	
Genotypes Tested	***N of studies***	***Sensitivity (95% CI)***	***Specificity (95% CI)***	***Sensitivity (95% CI)***	***Specificity (95% CI)***
TPMT *2, *3A & *3C	3	86.15 (70.88, 96.33)	98.71 (96.45, 99.85)	n/a	99.63 (98.28, 99.99)
TPMT *2, *3A, *3B, & *3C	7	70.33 (61.45, 78.50)	99.71 (99.15, 99.97)	50.00 (8.48, 91.52) Studies pooled = 2	99.81 (99.36, 99.99)
TPMT *3A, *3B, & *3C	3	70.69 (54.52, 84.54)	98.04 (95.76, 99.46)	0.00 (0.00, 97.50) Singe study estimate	99.81 (98.89, 99.96)
TPMT *3A, *3B, & *3C with Snow et al (sensitivity analysis)[739]	2	75.50 (61.17, 87.40)	98.12 (96.01, 99.46)	0.00 (0.00, 97.50) Singe study estimate	99.76 (98.84, 99.99)
TPMT *3A, *3B, *3C, *3D	1	100.00 (47.82, 100.00)	100.00 (92.89, 100.00)	100.00 (2.50, 10.00)	100.00 (93.39, 100.00)
TPMT *2, *3A, *3B, *3C, *3D	1	100.00 (47.82, 100.00)	96.59 (90.36, 99.29)	100.00 (2.50, 10.00)	100.00 (96.07, 100.00)
TPMT*2, *3A, *3B, *3C, *3D, *4, *5, *6, *7, *8	1	100.00 (83.89, 100.00)	100.00 (66.37, 100.00)	75.00 (34.91, 96.81)	100.00 (84.56, 100.00)
TPMT *2, *3A, *3B, *3C, *3D, *4, *5, *6, *7, *8, 10, *14, *15	3	81.59 (69.64, 91.07)	98.29 (96.52, 99.45)	94.44 (71.36, 99.22) Studies pooled = 2	99.80 (99.05, 99.99)
TPMT *2, *3A, *3B, & *3C and *2, *3A, & *3C[$]	10	73.80 (66.11, 80.82)	99.56 (98.99, 99.89)	50.00 (8.48, 91.52) Studies pooled = 2	99.77 (99.37, 99.97)
Additional analysis	19	79.90 (74.81, 84.55)	99.03 (98.47, 99.46)	76.44 (59.29, 90.01)	99.76 (99.45, 99.94)

TPMT PHENOTYPIC AND GENETIC ASSOCIATION WITH THIOPURINE TOXICITY						
Outcomes	**Phenotypic association**			**Genotypic association (primary analysis)**		
Adverse Event	***I vs. N***	***L vs. I***	***L vs. N***	***Heterozygotes vs. noncarriers***	***Homozygotes vs. noncarriers***	***Heterozygotes vs. homozygotes***
Mortality, hospitalization, SAE and HQoL	-	-	-	-	-	-
Infection	-	-	-	0.07 (0.00, 118.75) 3 studies, 154 patients	-	-
Withdrawal due to adverse event(s)	1.81 (0.89 – 3.67) 4 studies, 425 patients	-	-	3.44 (0.78, 15.21) 3 studies, 150 patients	-	-
Myelotoxicity	1.58 (0.72, 3.50) 5 studies, 902 patients	**14.53** (2.78, 76.01) 3 studies, 92 patients	**19.12** (4.56, 80.24) 3 studies, 403 patients	0.37 (0.08, 1.66) 4 studies, 187 patients	1.36 (0.30, 6.16) 2 studies, 55 patients	-

Table Addendum (continued)

TPMT PHENOTYPIC AND GENETIC ASSOCIATION WITH THIOPURINE TOXICITY (continued)						
Outcomes	**Phenotypic association**			**Genotypic association (primary analysis)**		
Adverse Event	***I vs. N***	***L vs. I***	***L vs. N***	***Heterozygotes vs. noncarriers***	***Homozygotes vs. noncarriers***	***Heterozygotes vs. homozygotes***
Leukopenia	1.12 (0.70, 1.78)*	**2.74** (1.54, 4.86)	**2.56** (1.41, 4.67)	**4.29** (2.67, 6.89)	**20.84** (3.42, 126.89)	2.26 (0.26, 19.91)
	8 studies, 762 patients	4 studies, 257 patients$^{\infty}$	4 studies, 397 patients$^{\Omega}$	18 studies, 1825 patients	5 studies, 482 patients	4 studies, 42 patients
Neutropenia	-	-	-	-	-	-
Anemia	1.66 (0.36, 7.64)	-	-	1.27 (0.30 - 5.45)	-	-
	2 studies, 246 patients	-	-	2 studies, 110 patients	-	-
Thrombocytopenia	-	-	-	2.00 (0.34, 11.71)	-	-
	-	-	-	3 studies, 253 patients	-	-
Hepatotoxicity	1.62 (0.75 - 3.51)	1.19 (0.13, 11.11)	2.17 (0.26, 18.29)	0.43 (0.14, 1.34)	2.89 (0.52, 16.02)	-
	7 studies, 775 patients	2 studies, 68 patients	2 studies, 433 patients	11 studies, 1032 patients	3 studies, 218 patients	
Pancreatitis	1.15 (0.38, 3.47)	1.92 (0.19, 19.72)	N/A	0.40 (0.12, 1.32)	0.80 (0.14, 4.57)	-
	6 studies, 1117 patients	2 studies, 68 patients		10 studies, 807 patients	4 studies, 288 patients	
				Additional analysis Inconclusive results for all outcomes, except: • withdrawal due to adverse events – heterozygotes versus noncarriers **5.55** (2.26, 13.63)) • leukopenia -- heterozygotes versus noncarriers, **4.87** (3.34, 7.09) • leukopenia -- homozygotes versus noncarriers, **49.24** (10.23, 236.99) • leukopenia -- homozygotes versus heterozygotes, **7.54** (1.15, 49.57) • hepatotoxicity – homozygotes versus heterozygotes **29.00** (1.40, 600.54)		

*Estimates that lost statistical significance in the modified analysis; ∞ = I2 57%, and p-value >0.05; Ω = I2 79%, and p-value <0.05
I= intermediate activity; L = low activity