The Hospital for Sick Children

Technology Assessment at SickKids (TASK)

THIOPURINE S-METHYLTRANSFERASE TESTING FOR AVERTING DRUG TOXICITY IN PATIENTS RECEIVING THIOPURINES: A SYSTEMATIC REVIEW AND QUALITY APPRAISAL

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REPORT HIGHLIGHTS

The Report Highlights consists of a summary of the full report with the same name and should be evaluated in conjunction with the full report and its appendices. Full documents are available for download at:

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Conflicts of interest

The authors have no conflicts of interest to disclose.

Introduction

Thiopurine S-methyltransferase (TPMT) is an enzyme that metabolizes thiopurine drugs. Thiopurine drugs are commonly used in maintenance treatment for childhood leukemias, as well as, less commonly, for inflammatory bowel disease (IBD), transplant recipients, and dermatological conditions. The absence or a deficiency of TPMT can significantly increase the risk of adverse drug event (ADE) in persons receiving thiopurine therapy as they are unable to metabolize the drug.

Rationale

Phenotype testing for TPMT activity has traditionally been the test of choice to assess TPMT deficiency, however, the recent increase in capacity and use of genotype testing to assist in disease treatment has evoked questions about which method of testing is optimal.

Objectives

The objectives were to systematically review the evidence on the performance characteristics of phenotype and genotype testing for TPMT deficiency,

Key Messages

- Along with traditional phenotype testing, there is a growing use of personalized medicine applications such as pharmacogenomics in clinical diagnostics and clinical decision-making for selection of drug treatment and dose.
- Thiopurine s-methyltransferase (TPMT) testing can use either phenotype or genotype methods. Both tests have limitations, and sensitivity and specificity vary depending on the choice of test and the test methods.
- The quality of studies assessing diagnostic test accuracy in TPMT testing was mixed, with thirty of fifty five studies categorized as high quality based on the quality appraisal.
- The low prevalence of patients with deficient TPMT activity or homogeneous TPMT mutations, the rarest mutations, made estimates of sensitivity of the tests for these mutations uncertain.
- The accuracy of genotyping is affected by the range of polymorphisms included in the test.
- Consistent testing protocols are needed to generate high quality evidence of clinical validity and clinical utility of TPMT genotyping technologies to ensure appropriate and consistent use in patient populations who would benefit from this testing.

and to appraise the quality of the evidence to identify the characteristics of high quality studies.

Target Population

This study sought to include evidence from all patient populations, age groups and clinical indications for which TPMT testing may be pursued.

Methods

Systematic review

The literature was systematically searched using eleven prominent electronic databases and a comprehensive list of grey literature sources. The detailed search strategy used did not limit to language or date, and included both methods of TPMT testing. Results of the search were reviewed to identify relevant studies meeting all inclusion criteria.

Quality appraisal

The Quality Assessment Tool for Diagnostic Accuracy Studies (QUADAS-2) was used to assess quality of the included studies. Data were extracted from each study included basic study design characteristics, study results, diagnostic test performance characteristics, and raw data to populate 2x2 and 3x3 contingency tables to calculate sensitivity, specificity, positive predictive value, negative predictive value, and concordance.

Results

Systematic review

The review process is summarized in Figure 1. Sixty-six studies met inclusion criteria and underwent quality appraisal. These 66 studies comprised three categories –phenotype-genotype comparisons, phenotype-phenotype comparisons and genotype-genotype comparisons.

Quality appraisal

In total, 30/55 phenotype-genotype comparisons were designated as high quality by the quality appraisal, and 6/11 phenotype-phenotype or genotype-genotype comparisons were designated as high quality. The appraisal characteristics for phenotype-genotype comparisons are presented in Table 1 and for phenotype-phenotype or genotype-genotype comparisons are presented in Table 2.

Studies considered of low quality generally contained unclear information relating to the quality components of the appraisal, as opposed to obvious bias or concerns for applicability. Thirteen of 30 high quality studies had low bias and low concern for applicability, while the remaining high quality studies had at least one domain with unclear or high risk associated with it. All of the high quality studies were published between 1997 and 2013, and examined a range of genotype and phenotype test methods.

Based on available data from 15 studies, the calculated sensitivity for genotyping to identify a homozygous mutation ranged from 0.0% to 100.0%. Based on data available from 26 studies, calculated specificity ranged from 97.8% to 100.0%. Based on available data from 25 studies, the calculated sensitivity to detect a homozygous or heterozygous mutation ranged from 13.4 to 100.0% and calculated specificity ranged from 90.9 to 100.0% using data from 26 studies.

Discussion

The choice of technologies available for the diagnosis of TPMT deficiency is varied. This review revealed a diverse and large body of literature assessing both phenotype and genotype technologies for TPMT testing across several disease states. There are limitations to both genotype testing and phenotype testing, and neither test can be referred to as the ‘gold standard’ for identifying TPMT deficiency.

The quality appraisal revealed that inadequate reporting of count data, descriptive information of index tests, reference tests, and recruitment methods, and study populations largely contributed to the exclusion of studies due to quality. Lack of reporting of diagnostic test accuracy indicates a need for guidance on reporting of test performance characteristics for diagnostic technologies. Thirty high quality studies comparing phenotype and genotype technologies were included in this

review. The number of polymorphisms included in genotype tests ranged from two to nine, with most studies including TPMT*2 and TPMT*3, the most common genetic variants in persons with deficient TPMT activity. Among the fifteen studies for which both sensitivity and specificity of genotyping could be calculated, ten demonstrated perfect (100%) sensitivity and specificity. The inference of perfect values is misleading, however. The low prevalence of homozygous mutations (0.3%) made it difficult for some study authors to generate sample sizes that were large enough for a stable rate of detection of homozygous mutations. The variation in sensitivity and specificity observed in the present review may also be related to the disease context. The tolerance for the risk of serious ADEs, and consequently values for sensitivity and specificity, may be different for chronic disease such as IBD and dermatological conditions versus life-threatening disease such as ALL.

Routine testing for all possible polymorphisms is more costly and unlikely to be feasible for health care institutions. Although current tests may become less costly in the future, there may also be mutations that have not yet been identified with current methods. Consideration also needs to be given to oversight and regulation, the applicability of pharmacogenetic discoveries in ethnically diverse populations and special populations (children, elderly), and to the anticipated shift from diagnostic pharmacogenetic testing to screening. Clinical and institutional decision-makers require high quality evidence of clinical validity and clinical utility of TPMT genotyping technologies to ensure appropriate and consistent use in patient populations who would benefit from this testing.

Figure 1. PRISMA flowchart

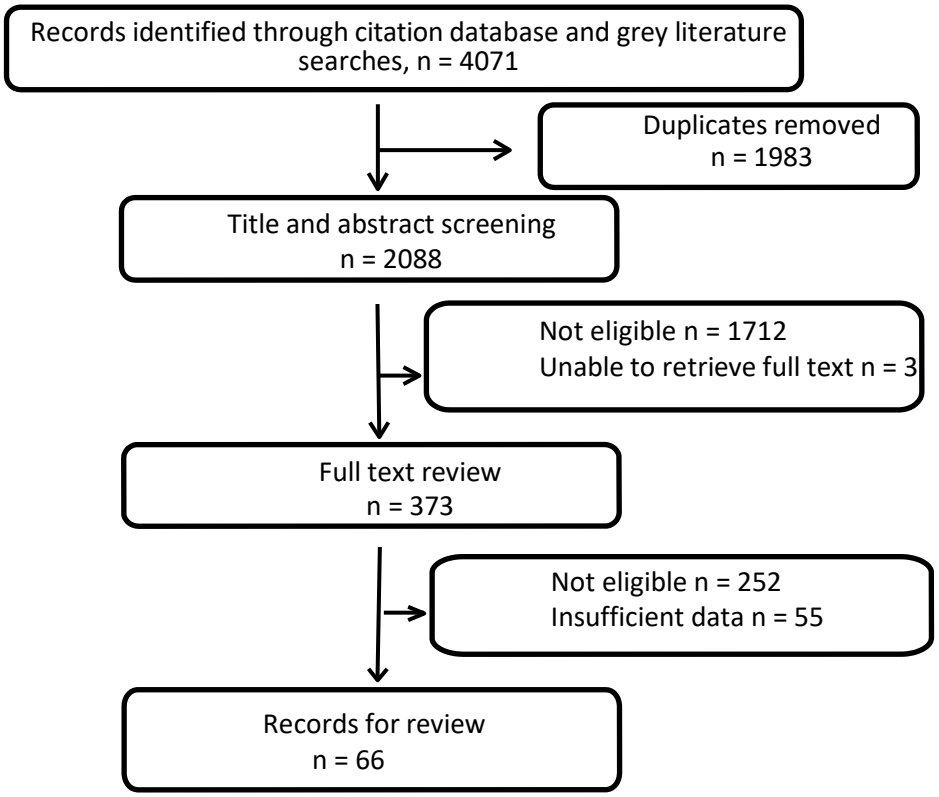

Table 1. QUADAS-2 results for high quality phenotype-genotype studies

Author	Year	Domain 1 - Patient Selection		Domain 2 - Index Test		Domain 3 - Reference test		Domain 4 - Flow and Timing	Domain 5 - Genomics
		Risk of bias	Concern for applicability	Risk of bias	Concern for applicability	Risk of bias	Concern for applicability	Risk of bias	Risk of bias
Ben Salah [1]	2013	Low	Low	Low	Low	Unclear	Low	Low	Low
Fakhoury [2]	2007	Low	Low	Low	Low	Low	Low	Low	Low
Fangbin [3]	2012	Low	Low	Low	Low	High	Low	Low	Low
Ford [4]	2006	Low	Low	Low	Low	High	Low	Low	Low
Ford [5]	2009	Low	Low	Low	Low	Low	Low	Unclear	Low
Ganiere-Monteil [6]	2004	Low	Low	Low	Low	High	Low	Low	Low
Gazouli [7]	2012	Low	Low	Low	Low	Low	Low	Low	Low
Hindorf [8]	2012	Low	Low	Low	Low	Unclear	Low	Low	Low
Jorquera [9]	2012	Low	Low	Low	Low	Low	Low	Low	Low
Langley [10]	2002	Low	Low	High	Low	Low	Low	Low	Low
Larussa [11]	2012	Low	Low	Low	Low	Low	Low	Low	Low
Lennard [12]	2012	Low	Low	Low	Low	Low	Low	Low	Low
Liang [13]	2013	Low	Low	Low	Low	Low	Low	Low	Low
Loennechen [14]	2001	Low	Low	Low	Low	Low	Low	Low	Low
Ma [15]	2006	Low	Low	Low	Low	Unclear	Low	Low	Low
Marinaki [16]	2003	Low	Low	Low	Low	Unclear	Unclear	Low	Low
Milek [17]	2006	Low	Low	Low	Low	Low	Low	Low	Low
Oselin [18]	2006	Low	Low	Low	Low	High	Low	Low	Low

Author	Year	Domain 1 - Patient Selection		Domain 2 - Index Test		Domain 3 - Reference test		Domain 4 - Flow and Timing	Domain 5 - Genomics
		Risk of bias	Concern for applicability	Risk of bias	Concern for applicability	Risk of bias	Concern for applicability	Risk of bias	Risk of bias
Schaeffeler [19]	2004	Low	Low	Low	Low	Low	Low	Low	Low
Schwab [20]	2002	Low	Low	Low	Low	Low	Low	Low	Low
Serpe [21]	2009	Low	Low	Low	Low	Unclear	Low	Low	Low
Spire-Vayron de la Moureyre [22]	1998	Unclear	Low	Low	Low	Low	Low	Low	Low
Spire-Vayron de la Moureyre [23]	1998	Unclear	Low	Low	Low	Low	Low	Low	Low
von Ahsen [24]	2005	Low	Low	Low	Unclear	Unclear	Low	Low	Low
Wennerstrand [25]	2013	Low	Low	Low	Low	Low	Low	Low	Low
Winter [26]	2007	Low	Low	Low	Low	Low	Low	Low	Low
Wusk [27]	2004	Low	Low	Low	Low	High	Low	Low	Low
Xin [28]	2009	Low	Low	Low	Low	Low	Low	Low	Low
Yates [29]	1997	Low	Low	Low	Low	Low	Low	Low	High
Zhang [30]	2007	Low	Low	Low	Low	Unclear	Low	Low	Low

Table 2. QUADAS-2 results for high quality phenotype-phenotype or genotype-genotype studies

Author	Year	Domain 1 - Patient Selection		Domain 2 - Index Test		Domain 3 - Reference test		Domain 4 - Flow and Timing	Domain 5 - Genomics
		Risk of bias	Concern for applicability	Risk of bias	Concern for applicability	Risk of bias	Concern for applicability	Risk of bias	Risk of bias
Chowdury [31]	2007	Unclear	Low	Low	Low	Low	Low	Low	Low
Kim [32]	2013	Unclear	Low	Low	Low	Low	Low	Low	Low
Lu [33]	2005	Low	Low	Low	Low	Unclear	Low	Low	Low
Ma [34]	2003	Low	Low	Low	Low	Low	Low	Low	Unclear
Roman [35]	2012	Unclear	Low	Low	Low	Low	Low	Low	Low
Schaeffeler [36]	2008	Low	Low	Low	Low	Low	Low	Low	Low

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