

The Hospital for Sick Children
Technology Assessment at Sick Kids (TASK)

EXECUTIVE SUMMARY

**THIOPURINE DOSING USING THIOPURINE METHYLTRANSFERASE
STATUS: A SYSTEMATIC REVIEW OF CLINICAL GUIDANCE**

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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Introduction

Advances in the understanding of the relationship between genetics and drug metabolism in the field of pharmacogenetics have allowed for drug treatments to become increasingly tailored to individual patients. A considerable number of medications now include information about the contribution of genetic variation in modulating drug metabolism and/or response in product monographs. A common application of personalized medicine is testing for thiopurine S-methyltransferase (TPMT) status prior to treatment with thiopurine drugs, which are used to treat a number of auto-immune conditions and paediatric cancer.

Clinical guidance on the use of pharmacogenetics is required to assist healthcare professionals with decisions regarding which test to order and how test results should be interpreted in order to improve patient care. Systematic reviews of available evidence can be used to identify gaps in the literature which in turn can help inform judgments about the value of a test, as well as set research agendas. The objective of this study was to conduct a systematic review of clinical guidance documents that recommend TPMT testing prior to the administration of thiopurine drugs. The specific aims were to 1) review the breadth of guidance documents and their sources, and 2) critically appraise the quality of the guidance documents by evaluating the quality of evidence used to support the preferential use of one method (genotyping versus phenotyping) over another and used to guide dose adjustments based on TPMT status.

Methods

Guidance documents including guidelines, clinical protocols and care pathways from all medical and laboratory disciplines were eligible if they included a recommendation statement to test for TPMT status. Databases including MEDLINE, EMBASE and CINAHL along with government agency websites and online repositories of clinical guidelines were searched for eligible articles. Data extracted from eligible documents included document characteristics, recommendation statements for TPMT testing, and dosing recommendations based on TPMT status (genotype or phenotypes). Guidance documents were compared within common therapeutic areas. A quality appraisal was carried out by three independent appraisers using the AGREE-II instrument. Scores for each document were recorded for quality domains related to Scope and purpose, Stakeholder involvement, Rigor of development, Clarity of presentation, Applicability and Editorial independence. Guidance documents were ranked according to quality.

Results

A total of 20 guidance documents were included, spanning a wide range of topics including the treatment of inflammatory bowel disease (IBD) (including Crohn's disease and ulcerative colitis) (n=8), inflammatory skin disorders (n=3), autoimmune hepatitis (n=3), rheumatic disease (n=2), ALL (n=2) and general pharmacogenetic testing (n=2). Six of the included guidance documents were focused on the treatment of paediatric patients with thiopurine drugs. Results from the quality appraisal showed great variation in the quality of the included guidance documents across all AGREE domains. Five of the included guidance documents made recommendations for genotype testing and four made recommendations for phenotype testing. The remaining guidance documents included general statements about the need for TPMT status determination, without specifying the test method (genotype or phenotype). A total of 13 guidance documents included dosing recommendations based on TPMT status, with the most common recommendation being to avoid treatment in patients with extremely low or absent TPMT activity (homozygous mutant) and to reduce thiopurine doses in patients with intermediate TPMT activity (heterozygous). Five of the included guidance documents recommended adjustments of a typical dose for each TPMT genotype or phenotype. Guidance documents that included dosing recommendations were of the highest quality in terms of total AGREE-II score and the rigor of development domain.

Conclusions

Clinical guidance on the use of pharmacogenetics is required to assist healthcare professionals with decisions regarding which test to order and how test results should be interpreted in order to improve patient care. Variations in recommendations for TPMT testing reflect the need for clarity in the clinical validity and utility of various TPMT test methods. The variability amongst these guidance documents also illustrates a lack of consistency and rigor in the methods used to develop recommendation statements. The development of high quality guidance for pharmacogenetic testing requires interdisciplinary collaboration between experts in the fields of genetics, pharmacology and the clinical disciplines responsible for administering the test-treatment combinations and careful adherence to methods for evidence-based guideline development. Systematic reviews of available evidence can be used to identify gaps in the literature which in turn can help inform judgments about the value of a test, as well as set research agendas.