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

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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 declare that they do not have any conflicts of interest.

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Introduction

Personalized medicine can avert life-threatening adverse events by modulating drug dosages based on the genetic profile of individual patients.[1] This is accomplished through use of enzymatic assays or genetic tests which identify deficiencies in drug metabolism.[2] Clinical guidance is needed to assist physicians in the appropriate use of testing to guide drug dosing. This requires statements, protocols, or care maps that are based on systematic reviews of evidence, assessments of clinical utility, and evaluations of drug-specific dosing recommendations.[3]

A common application of personalized medicine is testing for deficiency in thiopurine S-methyltransferase (TPMT), the enzyme that metabolizes thiopurines.[4] Thiopurines are immunosuppressive and chemotherapeutic drugs widely used to treat chronic inflammatory conditions including inflammatory bowel disease (IBD), autoimmune hepatitis (AIH), idiopathic arthritis, and a number of dermatologic conditions. Thiopurines are also used as maintenance therapy in acute lymphoblastic leukemia (ALL) and to prevent post-transplant organ transplant rejection.[5,6]

Key Messages

- Personalized medicine provides a more tailored approach to patient care, considering a patient's genetic profile when choosing drug therapy and dosage.
- Both a laboratory test and a genetic test are available to determine a patient's TPMT status which predicts their ability to metabolize thiopurines, a class of drugs used in many serious chronic conditions in adults and children.
- Twenty different guidelines for TPMT testing have been produced from 17 clinical organizations.
- Guidelines vary widely in their recommendations regarding which type of TPMT test to use, when to test, and how to adjust thiopurine dosage.
- The quality of guidelines also varied widely with poor quality guidelines failing to adhere to rigorous methods for use of evidence to support recommendations.
- The most rigorous and high quality guidelines came from the National Institute for Health and Clinical Excellence (2012), Cincinnati Children's Hospital Medical Center (2007), British Health Professionals in Rheumatology (2008) and British Association of Dermatologists (2011).
- Interdisciplinary collaboration between experts in genetics, pharmacology and the clinical disciplines would enhance the clinical utility of TPMT testing.

Approximately 89% of Caucasians have 'normal' (i.e. fully functional) TPMT activity, 11% have genetic variants that result in reduced activity, and 0.3% have genetic variants resulting in undetectable enzyme activity.[7,8] Patients with reduced or undetectable TPMT activity treated with standard doses of thiopurines are at risk of serious life-threatening adverse events including myelosuppression, anemia, bleeding, leukopenia, and severe infection.[9] These adverse drug events can result in lengthy hospital admissions and substantial morbidity and reduced quality of life for patients already coping with a serious illness.[10,11] It is therefore important to identify the presence of TPMT deficiencies in patients prescribed thiopurine drugs.

There are two approaches to testing for TPMT status. The most common is a phenotype test that measures the level of TPMT enzyme activity. Unfortunately, results of the enzymatic assay can be confounded by concomitant medications or blood transfusions.[12] Genotype tests that detect the presence of variants of genes responsible for expressing the TPMT enzyme are more versatile, but most commercially available tests capture only a proportion of known genetic variants.[13] It remains uncertain whether the enzymatic assay (phenotype) or genotype test is the most appropriate strategy for clinical practice. Nonetheless, TPMT testing is an application of personalized medicine that been cited as having significant clinical uptake and is used in children.[14,15]

Rationale

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 common application of personalized medicine is testing for TPMT status prior to treatment with thiopurine drugs, which are used to treat a number of auto-immune conditions and paediatric cancer. Numerous documents have been issued to provide guidance to clinicians regarding TPMT testing.

Objectives

The objective 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 and their testing and dosing recommendations.

Methods

Documents including guidelines, clinical protocols and care pathways from all medical and laboratory disciplines were eligible if they included a recommendation statement regarding testing for TPMT status. Electronic citation databases, 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 phenotype). Guidance documents were compared within common therapeutic areas. A quality appraisal was carried out by three independent appraisers using the AGREE-II instrument.[16] 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

Of 350 guidance documents reviewed, 20 were eligible for inclusion, 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. The guidance documents are summarized in Table 1.

Table 1: Characteristics of guidelines that include recommendations for TPMT testing

Identifier, year	Organization	Guidance type	Focus	Target audience	Target condition/field
Inflammatory bowel disease					
ECCO[17]	European Crohn's and Colitis Organization*	CPG	Uni-disciplinary	Gastroenterologists (paediatric)	Paediatric ulcerative colitis
NICE, 2012[18]	National Institute for Health and Clinical Excellence	CPG	Uni-disciplinary	Gastroenterologists	Crohn's disease
APAG, 2010[19]	Asian Pacific Association of Gastroenterology	Consensus statement	Uni-disciplinary	Gastroenterologists	Inflammatory bowel disease
BSG, 2010[20]	British Society of Gastroenterology	CPG	Uni-disciplinary	Gastroenterologists	Inflammatory bowel disease
WGO, 2010[21]	World Gastroenterology Organization	CPG	Uni-disciplinary	Gastroenterologists	Inflammatory bowel disease
BSPGHN, 2008[22]	British Society of Paediatric Gastroenterology Hepatology and Nutrition	CPG	Uni-disciplinary	Gastroenterologists (paediatric)	Paediatric inflammatory bowel disease
CCHMC, 2007[23]	Cincinnati Children's Hospital Medical Center	CPG + algorithm	Uni-disciplinary	Gastroenterologists (paediatric)	Paediatric inflammatory bowel disease
AGA, 2006[24]	American Gastroenterological Association	Medical Position Statement	Uni-disciplinary	Gastroenterologists	Inflammatory bowel disease
Inflammatory skin disorders					
BAD, 2011[25]	British Association of Dermatologists	CPG	Uni-disciplinary	Dermatologists	Inflammatory dermatoses
BAD, 2004[26]	British Association of Dermatologists	CPG	Uni-disciplinary	Dermatologists	Inflammatory dermatoses
AAD, 2009[27]	American Academy of Dermatology	CPG	Uni-disciplinary	Dermatologists	Psoriasis

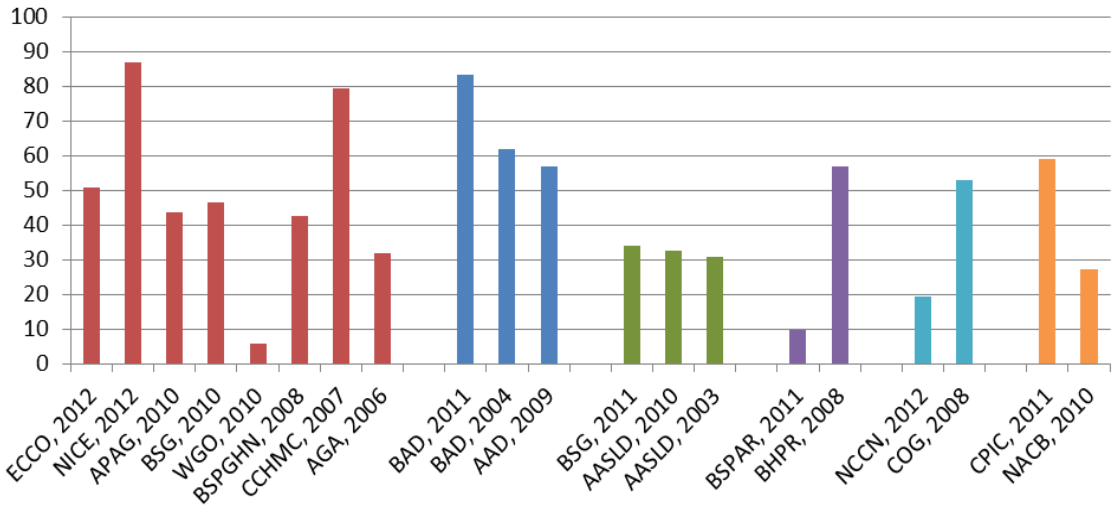
Autoimmune hepatitis					
BSG, 2011[28]	British Society of Gastroenterology	CPG	Uni-disciplinary	Gastroenterologists	Autoimmune hepatitis
AASLD, 2010[29]	American Association for the Study of Liver Diseases	CPG	Uni-disciplinary	Gastroenterologists	Autoimmune hepatitis
AASLD, 2003[30]	American Association for the Study of Liver Diseases	CPG	Uni-disciplinary	Gastroenterologists	Autoimmune hepatitis
Rheumatic diseases					
BSPAR, 2011[31]	The British Society for Paediatric and Adolescent Rheumatology	Medical Position Statement	Uni-disciplinary	Gastroenterologists	Paediatric rheumatology
BHPR, 2008[32]	British Health Professionals in Rheumatology	CPG	Multi-disciplinary	Healthcare professionals, health service managers, patients, national societies	Rheumatic and dermatological conditions
Acute lymphoblastic leukemia					
NCCN, 2012[33]	National Comprehensive Cancer Network	CPG	Uni-disciplinary	Oncologists (paediatric)	Acute lymphoblastic leukemia
COG, 2008[34]	Children's Oncology Group	Clinical Protocol	Uni-disciplinary	Oncologists (paediatric)	Acute lymphoblastic leukemia
General pharmacogenetic testing					
CPIC, 2011[35]	Clinical Pharmacogenetics Implementation Consortium	CPG	Multi-disciplinary	Clinicians	TPMT genotyping and dosing
NACB, 2010[36]	The National Academy of Clinical Biochemistry	CPG	Multi-disciplinary	Medical practitioners (physicians, nurses, pharmacists, clinical researchers)	Pharmacogenetic testing

Note: The ECCO guideline[17] was also endorsed by the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition. The British Health Professionals in Rheumatology guideline[32] was also endorsed by the British Society for Rheumatology.

CPG = clinical practice guideline

Results from the quality appraisal showed great variation in the quality of the included guidance documents across all AGREE domains. For rigor of development, the highest quality guidance documents were the IBD guidelines produced by NICE[18] and Cincinnati Children's Hospital[37] as well as the 2011 guidelines produced by the BAD[25] (see Figure 1). In general, guidance documents assigned a low score failed to use appropriate systematic methods in their development of recommendation statements. In cases where systematic reviews were carried out, very few documents provided sufficient evidence to support recommendations or failed to link recommendations with supporting evidence.

Figure 1: AGREE-II results for rigor of development



Five of the guidance documents made recommendations for genotype testing[25,33-36] and four made recommendations for phenotype testing.[19,20,27,34] 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). A total of 5 guidelines included dose adjustments based on TPMT status, including a recommended adjusted dose or a percentage of the normal dose for each of the TPMT genotypes or phenotypes.[23,25,26,34,35] 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 TMPT 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.

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