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External Validation of a Thiopurine Monitoring Algorithm on the SONIC Clinical Trial Dataset

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Introduction

Several reports leverage patterns in Electronic Medical Record (EMR) data to create algorithms to optimize outcomes in healthcare.^{1–3} More recently, there has been an increasing call for the use of clinical trial data repositories.⁴ Open clinical trial data sharing has allowed us evaluate the generalizability of algorithms to predict response to thiopurines in patients with inflammatory bowel disease. Yale University Open Data Access (YODA, <http://yoda.yale.edu/>) is a data-sharing platform which provides access to multiple clinical trial datasets. Previously we internally validated machine learning algorithms for both clinical and biological remission among patients on thiopurines.^{2,3} We now sought to externally validate the previously developed algorithm to predict objective remission in the SONIC clinical trial of azathioprine, infliximab, or the combination of azathioprine and infliximab in Crohn's disease using open clinical trial data.

Thiopurines continue to be used as monotherapy or as part of combination therapy for the treatment of inflammatory bowel disease (IBD). Worldwide, thiopurines are frequently used as a monotherapy as they remain a low-cost option for steroid-sparing therapy. Experts in IBD rely on patterns in the complete blood count and differential (CBCD) and

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Conflicts of interest:

The authors disclose the following: The Regents of the University of Michigan, along with authors Peter Higgins, Akbar Waljee and Ji Zhu, have a patent on the application of machine learning to patterns in the complete blood count and differential and the comprehensive chemistry panel to the prediction of clinical response to thiopurines. The patent was granted 2/28/2012. The remaining authors disclose no conflicts of interest.

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comprehensive chemistry panel (COMP) to monitor their patients, as thiopurine metabolites perform poorly in the evaluation of clinical response.⁵ Metabolites have also failed to show benefit in two prospective randomized controlled trials.^{6–7} Patterns in the CBCD and COMP can be successfully used to predict objective remission with high accuracy, and have been internally validated.³

Methods

In order to externally validate this algorithm for objective remission, we used data from the SONIC multicenter, randomized, double-blind controlled trial in patients with moderate-to-severe Crohn's disease, treated in three arms with infliximab plus azathioprine, infliximab, or azathioprine (ClinicalTrials.gov number, NCT00094458). We applied our algorithm to predict objective remission on thiopurine monotherapy in IBD to the SONIC dataset to provide an external validation. We hypothesized that this algorithm would be minimally helpful (AuROC $\approx$ 0.50) for patients in the infliximab alone arm, modestly helpful (AuROC $\approx$ 0.60) for patients in the combination (infliximab + azathioprine) arm, and quite helpful (AuROC $\approx$ 0.75) in the patients treated with azathioprine monotherapy.

The initial trial randomized 508 patients, and details of this study can be found on the ClinicalTrials.gov website and in the corresponding publication.⁸ We selected only those patients who had objective inflammation at entry to the study, defined by a C-reactive protein (CRP) $>$ 6 mg/L or documented endoscopic ulceration (ULCRTN field = Yes). Subjects who did not complete the week 26 visit (withdrawn) or those with no recorded CRP or ULCRTN value at week 26 (missing data) were not included in our analysis. In total, there were 244 inflamed subjects with complete data. Objective remission was defined by the absence of objective inflammation as defined by a CRP $\leq$ 6 AND a response of "No" for the ULCRTN field at week 26. Subjects not in objective remission were defined based on a CRP $>$ 6 mg/L or ULCRTN field = Yes. Of the 244 subjects analyzed, 77 achieved objective remission and 167 did not (Figure 1a).

Independent predictor variables included all of the values from the CBCD, COMP, and the patient's age calculated as the exact number of years.

Results

Using the previously developed algorithm, we externally tested the performance of this algorithm in this dataset.³ The performance of the algorithm was evaluated using the Area under the Receiver Operating Characteristic Curve (AuROC). Using a previously defined³ cut-off of 0.564, we were able to predict which patients achieved objective remission on thiopurine monotherapy with an AuROC of 0.76 (Figure 1b). The performance characteristics of this algorithm were also evaluated for subjects in the combination (infliximab and azathioprine) arm (AuROC = 0.67), and for subjects in the infliximab monotherapy arm (AuROC = 0.60), with diminishing results, as expected.

Discussion

These thiopurine algorithms provide an accurate, rapid, low-cost, and generalizable alternative to thiopurine metabolites to evaluate objective remission in patients with IBD on thiopurine therapy. These algorithms have been implemented and automated in an EPIC™ EMR and standard clinical workflow.

In addition, we are now in the process of engaging other hospitals, predominantly in Taipei and Hong Kong where thiopurine use is more prevalent than in the US, to do a prospective validation study using our algorithms.

It should be noted that there are limitations to our study that include the retrospective nature of evaluating our algorithm, as well as the generalizability. We hope that these issues will be addressed in a prospective study.

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Abbreviations

IBD	Inflammatory bowel disease
COMP	Comprehensive chemistry panel
CBCD	Complete blood count with differential
AuROC	Area under the Receiver Operating Characteristic curve
OR	Objective Remission
EMR	Electronic Medical Record
CRP	C-reactive protein

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Figure 1.

Figure 1a. Consort Diagram for analysis dataset

Figure 1b. ROC curves for different cohorts

Inflamed patients defined by a CRP > 6 mg/L or documented endoscopic ulceration

OR = Objective Remission defined by a CRP ≤ 6 mg/L and no documented endoscopic ulceration at week 26

Figure 1c. Variable Importance Plot identifying the important predictor variables that were used to build the model