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Original Article

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Genotype-Guided Thiopurine Dosing Does not Lead to Additional Costs in Patients With Inflammatory Bowel Disease

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Abstract

Background and Aims: Decreased thiopurine *S*-methyltransferase [TPMT] enzyme activity increases the risk of haematological adverse drug reactions [ADRs] in patients treated with thiopurines. Clinical studies have shown that in patients with inflammatory bowel disease [IBD], pharmacogenetic *TPMT*-guided thiopurine treatment reduces this risk of ADRs. The aim of this study was to investigate whether this intervention impacts on healthcare costs and/or quality of life.
Methods: An a priori defined cost-effectiveness analysis was conducted in the Thiopurine response Optimization by Pharmacogenetic testing in Inflammatory bowel disease Clinics [TOPIC] trial, a randomized controlled trial performed in 30 Dutch hospitals. Patients diagnosed with IBD [age ≥18 years] were randomly assigned to the intervention [i.e. pre-treatment genotyping] or control group. Total costs in terms of volumes of care, and effects in quality-adjusted life years [QALYs], based on EuroQol-5D3L utility scores, were measured for 20 weeks. Mean incremental cost savings and QALYs with confidence intervals were calculated using non-parametric bootstrapping with 1000 replications.
Results: The intervention group consisted of 381 patients and the control group 347 patients. The mean incremental cost savings were €52 per patient [95% percentiles –682, 569]. Mean incremental QALYs were 0.001 [95% percentiles –0.009, 0.010]. Sensitivity analysis showed that the results were robust for potential change in costs of screening, costs of biologicals and costs associated with productivity loss.

Conclusions: Genotype-guided thiopurine treatment in IBD patients reduced the risk of ADRs among patients carrying a *TPMT* variant, without increasing overall healthcare costs and resulting in comparable quality of life, as compared to standard treatment.

Key Words: Inflammatory bowel disease; thiopurines; health economics

1. Introduction

Treatment of inflammatory bowel disease (IBD; Crohn's disease [CD] and ulcerative colitis [UC]) with thiopurines is very effective in maintaining remission in the majority of patients.[1] However, approximately 20% of the patients develop adverse drug reactions [ADRs], which may lead to early treatment withdrawal.[2,3]

Thiopurine *S*-methyltransferase [TPMT] is a key enzyme in the conversion of thiopurines to the active metabolite 6-thioguanine.[4,5] Different studies have shown that patients with a decreased TPMT enzyme activity are prone to developing haematological ADRs while being treated with thiopurines.[5] Some of these haematological ADRs can be prevented by personalized thiopurine dosing based on [predicted] TPMT enzyme activity. This activity can be predicted prior to treatment by a pharmacogenetic test or can be determined by direct enzyme activity measurement or by metabolite measurements during treatment.[1,6] A clinical study showed that personalized thiopurine dosing based on pharmacogenetic *TPMT* testing reduces the occurrence of haematological ADRs. Our randomized controlled trial, the Thiopurine response Optimization by Pharmacogenetic testing in Inflammatory bowel disease Clinics [TOPIC] trial, showed that there was no overall difference in the proportions of patients with a haematological ADR between the intervention [7.2%] and control group [7.8%]. However, the small group of patients with a genetic variant in *TPMT* receiving a specified reduced thiopurine starting dose had a 10-fold reduction in haematological ADRs [2.6%], compared to variant carriers, who did not receive dose reduction [22.9%].[7] To treat patients according to their *TPMT* genotype, every individual patient starting thiopurine treatment needs to be genetically tested, generating additional costs, compared to no genotyping. On the other hand, personalized dosing reduces the risk of haematological ADRs and might thus reduce healthcare costs related to hospitalization, patient contacts and overall medication use, as well as societal costs in the form of productivity loss. An earlier prospective cost-effectiveness analysis, the TARGET-study, investigateda range of inflammatory diseases the majority being IBD patients [85%]) and performed the analysis from a healthcare perspective [only healthcare-related costs were included].[8,9] This study showed that genotyping could be a cost-effective strategy, although this was not statistically significant. Other cost-effectiveness studies of pharmacogenetic *TPMT* testing before thiopurine treatment made use of cost-effectiveness modelling, but nonetheless indicated that this intervention could be cost-effective or resulted in cost savings.[10–12] However, because in our TOPIC trial only the small group of patients with the *TPMT* variant showed a reduction in haematological ADRs, the question remained regarding whether pharmacogenetic testing was truly cost-effective.

This study aimed to investigate, from a societal perspective, the differences in costs and quality of life between a personalized thiopurine dosing strategy based on pre-treatment *TPMT* genotyping and based on standard dosing without genotyping.

2. Methods

2.1. Study design and participants

This cost-effectiveness analysis was a priori defined in the study protocol, and data on costs and quality-adjusted life years [QALYs] data were collected as part of the TOPIC trial. The TOPIC trial was a randomized controlled trial (intention to treat [ITT]), including patients with a diagnosis of IBD [age ≥18 years] from 30 Dutch hospitals from October 2007 until December 2010. After written informed consent, patients were randomly assigned to personalized thiopurine dosing based on pre-treatment *TPMT* genotyping for three common genetic variants [intervention], *TPMT*2*, *TPMT*3A* and *TPMT*3C*, or standard dosing with no genotyping [control]. The [block] randomization was based upon a computer-generated schedule per participating centre [block size of four]; patients and gastroenterologists were blinded for this randomization. The study was approved by the local ethics committee [CMO region Arnhem–Nijmegen; protocol number: 13171] and by institutional ethics committees, and registered at clinicaltrials.gov: NCT00521950. More details of the study design and rationale are described elsewhere.[7]

2.2. Procedures

Patients in the control group received standard treatment according to IBD guidelines [2–2.5 mg/kg/day azathioprine or 1–1.5 mg/kg/day 6-mercaptopurine]. Patients in the intervention group with a genetic variant in *TPMT* received 50% [heterozygotes] or 0–10% [homozygotes] of the standard thiopurine dose according to pharmacogenetic dose recommendations of the Dutch Pharmacogenetics Working Group.[13] Patients without a genetic variant received standard treatment as in the control group. For each patient, a letter with a dose advice was sent to the gastroenterologist. If an adverse event occurred, gastroenterologists were allowed to change dose or stop treatment with thiopurines.

2.3. Outcomes

Costs in terms of volumes of care and quality of life are the outcomes of interest for this cost-effectiveness analysis. The primary outcome of the TOPIC trial was the development of haematological ADRs and is reported elsewhere.[7] Standardized case record forms were used to collect data on all [clinical] consultations, diagnostic procedures and hospital admissions. Medication use [type, frequency, dose] was based on patient records, and disease-related absence from work was measured with a patient diary. The Dutch Cost Manual [part of the guideline for economic evaluations] was used to determine standardized cost prices for consultations and productivity losses.[14] Cost prices for medication, diagnostic procedures and hospital admissions were based on Dutch national tariffs.[15,16] Details on the cost prices are summarized in the Supplementary Table 1. The base year for all prices was 2016, and therefore cost prices were updated with Dutch consumer price indices when necessary.[17] Discounting was not applied because of the short time horizon of only 20 weeks for this study.

Quality of life was measured with the EuroQol-5D3L [EQ5D-3L] questionnaire at week 0 and 20, and utilities were calculated with Dutch tariffs for the EQ5D-3L.[18] QALYs were calculated based on the area under the curve between the two time points. If one of the time points of the EQ5D-3L was missing, single imputation of this value was performed. This was done by randomly picking a value from the beta distribution, based on the observed data in the remaining patients at that time point.[19]

2.4. Statistical analysis

Differences between the intervention and control group were evaluated for baseline characteristics and the specific cost components after 20 weeks using Pearson's χ^2 test, Fisher's exact test, Student's *t* test, the Mann–Whitney *U* test or an independent sample Kruskal–Wallis test, as appropriate.

2.5. Cost-effectiveness analysis

Costs and QALYs from a societal perspective [all costs relevant for society, including productivity losses] were calculated for the two groups [intervention and control] for the follow-up period of 20 weeks. Comparing the intervention and control groups, an incremental cost effectiveness ratio [ICER] per patient was calculated by dividing the incremental costs by the incremental QALYs. Confidence intervals around the ICER were calculated by using non-parametric bootstrapping with 1000 replications.[20] A cost-effectiveness [CE] plane was used to graphically present the uncertainty around the cost-effectiveness ratio.

Sensitivity analyses were performed on lower genotyping costs [–33%; €100 instead of €150], as these costs differ between laboratories and are expected to decrease in the coming years. Analyses without cost of biologicals or productivity losses were also performed to evaluate the influence of these variables on the results.

3. Results

3.1. Patients

This analysis included all patients of the TOPIC trial [excluding those with missing data on all costs or on quality of life measurements], resulting in 381 patients in the intervention group and 347 in the control group. There were no statistically significant baseline differences between the two groups, except for the percentage of patients treated with biologicals [Table 1, intervention group, 3.7%; control group, 7.2%; $p = 0.035$]. This is in line with the total patient population [$n = 783$] of the TOPIC trial, as reported previously.[7]

3.2. Costs

The mean costs for [clinical] consultations with, for example, a gastroenterologist or surgeon, diagnostic procedures and hospital admissions, medication use, and indirect costs in the form of productivity losses for each group during the 20-week assessment are shown in Table 2. The outcomes did not show statistically significant differences between the groups, except for medication use between the populations when missing data are excluded [intervention group = €302; control group = €387; $p = 0.047$].

3.3. Cost-effectiveness

The incremental costs and effects on QALYs across both groups resulting from the 1000 bootstrapped replications are presented in Table

Table 1. Baseline patient characteristics

	Intervention [*n* = 381]	Control [*n* = 347]
Male, *n* [%]	173 [45.4]	156 [45.0]
Age, years [SD]	42.4 [15.8][a]	41.1 [15.9][b]
Age of disease onset, years [SD]	37.0 [15.5][a]	35.6 [14.9][c]
Disease duration until treatment start, median [min–max], years	1.4 [0–45.0][a]	1.0 [0–49.7][b]
Medication, *n* [%]		
Azathioprine	245 [64.3][a]	230 [66.3][c]
6-Mercaptopurine	135 [35.4][a]	117 [33.7][c]
None started	1 [0.3][a]	0 [0][c]
Drug dose start, median [min–max], mg/kg		
Azathioprine	2.1 [0–2.7][d]	2.2 [0–3.1][e]
6-Mercaptopurine	1.2 [0.5–1.9][f]	1.2 [0.6–1.6][g]
Drug dose 20 weeks, mg/kg		
Azathioprine	2.1 [0.5–2.7][h]	2.2 [0.6–3.1][i]
6-Mercaptopurine	1.1 [0.3–1.5][j]	1.1 [0.4–1.5][k]
Co-medication, *n* [%]		
Corticosteroids	316 [82.9][a]	283 [81.6][c]
Mesalamine	192 [50.4][a]	176 [50.7][c]
Biologicals	14 [3.7][a]	25 [7.2][c]
TPMT variant, *n* [%]	40 [10.5]	34 [9.8]
Side effects, *n* [%]		
Leukopenia	28 [7.3][a]	26 [7.5][c]
Trombocytopenia	2 [0.5][a]	2 [0.6][c]
Utility start, mean [SD]	0.77 [0.22][l]	0.77 [0.20][m]
Utility 20 weeks, mean [SD]	0.82 [0.21][n]	0.82 [0.22][o]

TPMT, thiopurine *S*-methyltransferase. The table shows means [SD], medians [min–max] or *n* [%] for the different characteristics. There were no statistically significant baseline differences between the two groups [$p < 0.05$], except for biological use [$p = 0.035$]. [a]$n = 381$, [b]$n = 346$, [c]$n = 347$, [d]$n = 247$, [e]$n = 229$, [f]$n = 134$, [g]$n = 118$, [h]$n = 160$, [i]$n = 149$, [j]$n = 98$, [k]$n = 97$, [l]$n = 375$, [m]$n = 335$, [n]$n = 266$, [o]$n = 243$.

Table 2. Costs of consultations, diagnostic procedures and hospital admissions, medication use, and indirect costs for both treatment strategies

Type of costs	Intervention		Control	
	Total population[a]	Population with complete data	Total population[b]	Population with complete data
Consultations	€0 [0–1576]	€114 [33–1576][c]	€0 [0–1836]	€115 [33–1836][d]
Diagnostic procedures and hospital admissions	€31 [0–20 671]	€269 [12–20 671][e]	€41 [0–11 900]	€198 [12–11 900][f]
Medication use	€302 [0–14 180]	€302 [1–14 180][g]	€386 [5–15 034]	€387 [5–15 034][h]
Indirect costs	€0 [0–27 800]	€1633 [70–27 800][i]	€0 [0–27 800]	€1355 [104–27 800][j]

Costs are presented as medians with minimum and maximum values. There were no statistically significant differences between the groups [$p < 0.05$], except for medication use [$p = 0.047$]. [a]$n = 381$, [b]$n = 347$, [c]$n = 118$, [d]$n = 205$, [e]$n = 380$, [f]$n = 95$, [g]$n = 96$, [h]$n = 187$, [i]$n = 345$, [j]$n = 92$.

Table 3. Costs and effects of both treatment strategies based on non-parametric bootstrapping with 1000 replications

Treatment strategy	Costs	Incremental costs	QALYs	Incremental QALYs
Intervention	€2181 [€1822, €2546]	–€52 [–€682, €569]	0.302 [0.295, 0.308]	0.001 [–0.009, 0.010]
Control	€2232 [€1789, €2741]		0.301 [0.294, 0.308]	

Costs and QALYs are presented as means with 95% percentiles resulting from non-parametric bootstrapping with 1000 replications. QALYs, quality-adjusted life years.

3 and Figure 1. The mean incremental costs were –€52 for the intervention, but with wide variability (95% percentiles [–682, 569]); mean incremental QALYs were 0.001 [95% percentiles –0.009, 0.010]. The simulated ICERs were scattered over all four quadrants of the CE-plane. In 57% of the replications, the intervention resulted in QALYs gained through the intervention [north-east and south-east quadrants in Figure 1], of which 32% of the replications also resulted in lower costs ['dominant', south-east quadrant]. In 19% of the replications, the intervention resulted in reduced QALYs and extra costs ['inferior', north-west quadrant]. In the other 24% of the replications, the intervention induced QALY losses in combination with lower costs [south-west quadrant].

Sensitivity analysis with lower genotyping costs of €100 [–33%] showed there was still no statistically significant difference [95% percentiles –€732, €519] between the intervention and control groups [Table 4]. This can also be seen in the CE-plane, which showed slightly more replications in the southern quadrants [63% vs 56% in the base case analysis] [Figure 2A]. Exclusion of the productivity losses also resulted in no statistically significant difference [95% percentiles –€115, €456] between the two groups [Table 4]. This was also reflected in the CE-plane, where 85% of the replications were in the northern quadrants [Figure 2B]. In 37% of these replications, there were also fewer effects ['inferior', north-west quadrant]. The relatively strong effects of productivity loss were mainly due to a few patients [one in the genotyping group, three in the control group] being on sick leave for the whole length of the study. Excluding these patients from the analysis showed almost the same increase in costs as excluding the entire productivity costs from the analysis [see Supplementary Figure 1, Supplementary Table 2].

As biological use at baseline was significantly different between the two strategies, the influence of costs for biologicals on our results was also evaluated. Sensitivity analysis leaving out these costs showed that there was no significant difference [95% percentiles –€531, €632] [Table 4].

4. Discussion

The TOPIC trial showed that there was no overall difference in a haematological ADRs between the intervention and control groups, although this secondary analysis showed that pre-treatment *TPMT* genotyping to determine individualized dosing of thiopurine treatment in IBD patients is still a cost-neutral intervention. In our study, the mean costs in the intervention group were not statistically significant [95% percentiles: –€682, €569]. Sensitivity analysis showed that lowering of the costs for *TPMT* genotyping, excluding biological costs or lack of accounting for productivity losses, did not substantially alter these results. Although productivity costs greatly influenced the final results, this seems a coincidence as baseline characteristics between the two groups were the same. Importantly, we saw no difference in QALYs between the strategies, with a mean difference of 0.001 QALYs [95% percentiles: –0.009, 0.010].

Based on several earlier reports[8–12] we expected to find a difference in costs [medical and societal] and QALYs between the two intervention groups.[7,8,21] However, this could not be confirmed with our available data, as there were no differences in the proportions of patients with a haematological ADR between the intervention and control group and due to the low prevalences of both the *TPMT* variants [±10%]. If effect sizes achieved with the intervention do not reach very high values, analyses at the population level will be too insensitive to pick these up,[22,23] especially in a background where disease and the treatment with thiopurines already have considerable impact on the costs [especially productivity losses] and the quality of life in the majority of patients.[24,25] In addition, due to the small number of patients with a genetic variant, we dis not observe a difference in costs and QALYs in patients with or without a variant of *TPMT* [data not shown]. Furthermore, it has been suggested that *TPMT* testing is mainly relevant for patients with no TPMT activity, as these could develop major adverse events. However, the prevalence of these variants is very low [0.1% in the TOPIC trial]. Although on an individual level these will cause lower quality of life and an increase in costs, they will probably cause no significant differences on a population level. Finally, the disease and treatment with thiopurines already have a large impact on the costs [especially productivity losses] and quality of life in the majority of patients.[24,25]

Our study was in line with the results of the only other prospective cost-effectiveness analysis, the TARGET-study.[8,9] These

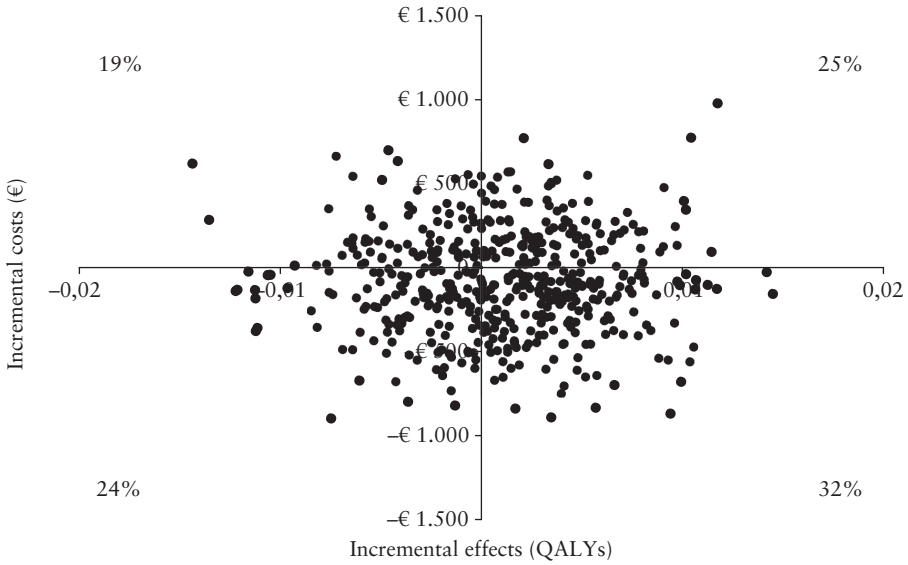

Figure 1. Cost-effectiveness [CE] plane. The CE plane shows the results of the non-parametric bootstrapping with 1000 replications representing the uncertainty surrounding the cost-effectiveness ratio of the initial CE analysis. The percentages indicate the amount of the bootstrapped replications [*n* = 1000] in the corresponding quadrant.

Table 4. Costs and effects of sensitivity analysis of both treatment groups based on non-parametric bootstrapping with 1000 replications

Treatment strategy	Costs	Incremental costs	QALYs	Incremental QALYs
Lower genotyping costs of €100 [–33%]				
Intervention	€2133 [€1748; €2565]	–€97[–€732; €519]	0.302 [0.295; 0.308]	0.001 [–0.008; 0.010]
Control	€2229 [€1776; €2713]		0.301 [0.294; 0.308]	
Without productivity losses				
Intervention	€1187 [€985; €1417]	€161 [–€115; €456]	0.302 [0.295; 0.308]	0.001 [–0.009; 0.010]
Control	€1026 [€856; €1219]		0.301 [0.294; 0.307]	
Without biologicals costs				
Intervention	€1994 [€1633; €2348]	€75[–€531; €632]	0.302 [0.295; 0.308]	0.001 [–0.009; 0.010]
Control	€1919 [€1496; €2356]		0.301 [0.294; 0.308]	

Costs and QALYs are presented as means with 95% percentiles resulting from non-parametric bootstrapping with 1000 replications. QALYs, quality-adjusted life years.

authors concluded that there was a probability of 71% that pre-treatment genotyping, at approximately the same price for screening [£150], would be a cost-effective strategy at a willingness to pay [WTP] of £20 000 per QALY. In our study from a societal perspective, a slightly smaller probability of 56% was found at approximately the same WTP [€20 000]. Our study was also in line with other cost-effectiveness studies that have made use of cost-effectiveness modelling.[10–12] Therefore, although not significant in the case of the two prospective studies, all cost-effectiveness studies so far suggest that *TPMT* testing prior to thiopurine treatment in IBD patients could be beneficial, or at least cost-neutral, from an economic perspective.

Our study should be viewed in the context of some strengths and limitations. Clear strengths of the TOPIC study are its prospective randomized design, size of the study and use of validated outcome measures. Another strength is that gastroenterologists made the final decision to start, change dosage or stop thiopurine treatment, and even the advised treatment adjustment based on a patient's genetic profile was not followed in all cases.[7] The study therefore provided a realistic reflection of the clinical treatment procedures in IBD patients.

Our study also had some limitations. The first limitation concerned the relatively short follow-up time of 5 months. Potential long-term costs and effects related to pre-treatment *TPMT* genotyping were therefore not estimated. However, the majority of thiopurine treatment-related haematological ADRs occur within 4 months of treatment initiation, so we are likely to have captured the majority of genotype-related cost differences.[7,8,26] A second limitation could be the testing of only three common *TPMT* variants. Therefore, we could have missed deficient cases at risk of developing leukopenia. In the TOPIC trial, 12 patients without one of the three pre-tested variants had low TPMT enzyme activity [<60 mg 6-methylguanine/mmol haemoglobin/h], and one of these patients developed leukopenia.[7] This confirms that genetic testing cannot explain all cases of decreased enzyme activity, but this is not necessarily harmful. In addition, complete sequencing of the coding region of the *TPMT* gene revealed a known silent variant in four of the patients [*TPMT**1S], indicating that we did not miss any relevant genetic variant. An alternative for genetic testing could be enzyme testing. In the TOPIC trial we showed that patients carrying a genetic variant had a lower TPMT enzyme activity than patients without a variant. This confirmed that enzyme-based testing and genetic testing can

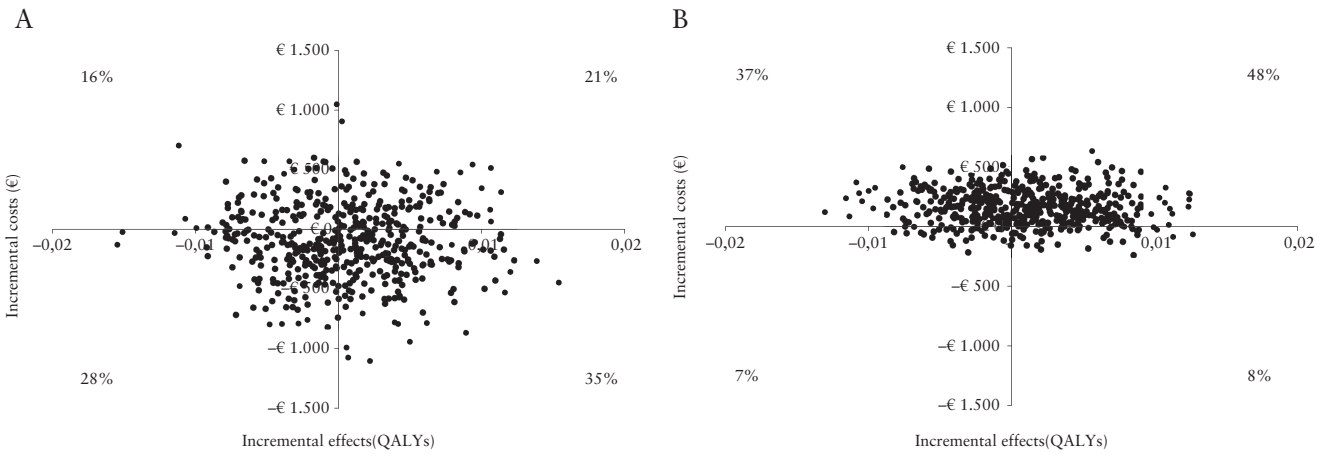

Figure 2. [A] Results of non-parametric bootstrapping, when genotyping costs were lowered by 33%. [B] Results of non-parametric bootstrapping, when productivity losses were not taken into account. The percentages indicate the amount of the bootstrapped replications [$n = 1000$] in the corresponding quadrant.

give comparable results. In addition, the costs of genetic testing and enzyme-based testing are comparable. However, genetic testing is a well-accepted alternative to enzyme-based testing.[27] A third potential limitation was that the study might have been partly unblinded; the gastroenterologist might have identified patients with a genetic variant in the intervention group based on the [lower] dose advice for other patients in the intervention and control groups who all received standard dose advice. This might have resulted in an overestimation of costs in the *TPMT*-variant group, masking any cost savings, if gastroenterologists had treated the intervention group differently from the control group, resulting in more use of healthcare resources in these patients. Missing EQ5D-3L data at one of the two time points [week 0 and/or week 20] had to be imputed, which also represents a potential limitation of the study. However, we saw no difference in the number of missing data or the reason for missing data [e.g. patients did not complete the questionnaire, or pages from the returned questionnaire were missing] between the two groups [data not shown]. Imputation is therefore unlikely to have influenced the observed difference in QALYs. Lastly, the difference in biological use at baseline between the two groups was a limitation. As shown in the outcomes of the different cost components, medication use was also significantly different between the intervention and control groups after 20 weeks. Including these costs, although not related to the intervention of interest, probably resulted in an underestimation of the difference between the intervention and control groups. Sensitivity analysis excluding costs for biologicals still indicated that the intervention was cost-neutral without a change in incremental QALYs compared to no genotyping. We decided not to perform further post-hoc analysis by excluding these patients, because this could have led to baseline imbalance and a lower statistical power.

Recent data have suggested that nudix hydrolase [*NUDT*] mutations may be equally important as *TPMT* mutations in predicting thiopurine-induced myelotoxicity, even in European populations.[28] Pre-treatment genotyping for *NUDT*, with or without *TPMT*, to optimize thiopurine treatment could therefore be an interesting area for future research regarding the effects on preventing haematological ADRs.

Despite the existence of guidelines concerning thiopurine dosing based on TPMT activity and cautions printed on thiopurine drug-labels, the uptake of genetic *TPMT* testing prior to thiopurine treatment has been relatively limited. *TPMT* testing cannot replace haematological monitoring, as leukopenia is not fully predictable by TPMT activity.[29] We believe that *TPMT* testing can be viewed as a good option to optimize dosing at the start of treatment especially for those patients carrying a genetic variant in *TPMT*. Studies have shown that the rate of leukopenia decreases despite intensive haematological monitoring.[7,8]

In conclusion, our study shows that thiopurine dosing based on *TPMT* genotype provides a cost-neutral opportunity to individualize thiopurine treatment in IBD patients, as it prevents haematological ADRs in patients at risk without extra costs to the healthcare system.

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Conflict of Interest

None declared.

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All authors listed were involved in the study design and interpretation of the data for the study. Corine van Marrewijk, Marieke J. H. Coenen, Dirk de Jong collected data. Data analysis was performed by Reinier L. Sluiter, W. Kievit and Marieke J. H. Coenen. Funding was obtained by Barbara Franke, Hans Scheffer and Henk-Jan Guchelaar. The manuscript was written, and edited by all authors, and they gave final approval for publication.

Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

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