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Avoiding adverse drug reactions by pharmacogenetic testing: A systematic review of the economic evidence in the case of TPMT and AZA-induced side effects

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Objectives: The study aims at evaluating the economic evidence related to testing for genetic variants of the drug-metabolizing enzyme, TPMT. Detecting TPMT genetic variants before the administration of azathioprine (AZA) has the potential to prevent serious and costly adverse drug reactions (ADRs), such as neutropenia. In particular, our analysis concentrated on assessing the reliability of data on costs of neutropenia and performing the tests, the two main cost categories that could inform an economic evaluation of TPMT pharmacogenetic testing.
Methods: A systematic literature review was performed to gather evidence on the costs of testing and neutropenia. Articles were critically appraised for their comprehensiveness and quality. To better estimate costs of TPMT tests, a small-scale survey of European diagnostic laboratories was conducted.
Results: Only seven articles were retrieved specifying the costs associated with the management and treatment of AZA-induced neutropenia. Most of these studies are based on theoretical modeling reconstructed with key-informants or on very few cases of ADRs, and either the methodology for cost calculation is not specified or costs are based on national cost databases and tariffs. After critical appraisal of these studies, we considered €2,116 as the most reliable estimate for the cost of a case of neutropenia. Literature review accompanied by the survey of several diagnostic laboratories also provided an estimate (€68) for TPMT testing. Based on these values, the net cost per prevented case of neutropenia equals to €5,300.

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Conclusions: Solid economic considerations related to TPMT pharmacogenetic testing are still limited by underreporting of ADRs and high level of approximation related to cost data. Ad hoc observational studies and the ADR recording process embedded in pharmacovigilance systems, established across Europe, should represent more reliable sources of cost data in the future.

Keywords: Pharmacogenetic testing, Drug metabolism, AZA-induced adverse drug reactions, TPMT deficiency, Neutropenia

The detection and mapping of genetic variations among individuals (also called polymorphisms), prompted by the sequencing of the human genome, have started a whole new era of research aimed at finding the significance of these variants. Pharmacogenetics (PGx), in particular, is the discipline that identifies and studies those genetic variations in drug-metabolising enzymes (DMEs) that are thought to contribute to the differential pharmacological response of individuals to drugs (11). As DMEs are responsible for the conversion of drugs into inactive principles, people whose genetic make-up renders their DME inefficient and, consequently, "poor" metabolizers might be more prone to develop adverse drug reactions (ADRs), defined by WHO as "any noxious, unintended, and undesired effect of a drug that occurs at doses used in humans for prophylaxis, diagnosis, or therapy"(29). ADRs, whose severity may vary from simple discomfort to fatality, are a relevant issue in healthcare not only because they importantly contribute to levels of mortality and morbidity, but also lead to increased hospital lengths of stay, utilization of healthcare services and therapies and, as such, to a higher consumption of healthcare resources (32). Being able to predict, through a pharmacogenetic test based on the genetic profile of an individual, her/his predisposition to undergoing an ADR has the potential to change medical treatment dramatically (16). The patient could be given a totally different drug or, in absence of alternatives, the dose might be preventively adjusted and accompanied by careful monitoring of side-effects. The objective of giving "the right drug at the right dose for the right patient" could be closer. There is a long-standing debate as to whether the diffusion of pharmacogenetic testing and introduction into clinical practice should be encouraged.

The level of uncertainty about the clinical utility and predictive value of the related tests is high and the barriers to their clinical uptake are many (22). There is, still, incomplete scientific evidence about the correlation between a certain polymorphism or genetic variant and the occurrence of ADRs (19). In other words, which proportion of ADRs would we be able to prevent by screening for those DME genetic polymorphisms? In addition, most countries have yet to establish solid regulatory frameworks around the approval and use of these tests (9;19). There are very few frameworks for evaluating a pharmacogenetic test that would allow to develop some recommendations on their use. One of these frameworks, the ACCE model (8), considers four dimensions: analytical validity, clinical validity, clinical utility, and ethical, legal and social implications of the test, including economic considerations. Conducting complete cost-effectiveness and cost-utility (CEA, CUA) studies of pharmacogenetic testing, on the other hand, presents several difficulties, among which the lack of randomized controlled trials showing the tests' clinical utility and the general underreporting of many ADRs (15). In addition, ADRs might not always have a strong effect on survival (5) or, if the impact is mainly on patients' quality of life, studies identifying quality weights might be completely lacking. Alternatively, as ADRs are often brief events lasting days or weeks, loss in QALY might be negligible. For these reasons, it might be difficult or premature to calculate cost-effectiveness or cost-utility ratios. In the absence of solid CEA/CUA studies, the ACCE framework suggests answering, first, a simpler question: what is the net cost of testing to prevent one adverse event and, consequently: (i) what are the economic benefits associated with actions resulting from testing? and (ii) what are the financial costs associated with testing?

THE CASE STUDY

In this study, we wanted to verify if, based on the existing literature, the questions posed above could be answered for an emblematic case, in which data about ADRs and the scientific evidence supporting the contribution of genetic variations to drug response appeared rather consolidated. The analysis concentrated on the treatment with thiopurine drugs—azathiopurine (AZA) and 6-mercaptopurine (6-MP)—of rheumatoid arthritis (RA) and inflammatory bowel disease (IBD) patients. This pharmacological therapy often leads to ADRs such as myelosuppression or neutropenia, hepatoxicity, pancreatitis, nausea, skin rash, whose reported frequency ranges from 10 percent to 40 percent of treated cases (25). Of all the ADRs listed above, neutropenia is the most life-threatening and, for this reason, AZA treatment is accompanied by regular monitoring of blood cell counts. The frequency of AZA-associated neutropenia is still not well determined. Based on the analysis of seven studies, Winter at al. (31) consider 3.2 percent as a good estimate of the percentage of IBD patients undergoing severe neutropenia, leading to treatment interruption, but the range is rather broad (2 to 8 percent) and the number of patients observed in these retrospective studies is highly variable. Needless to say

the probability of neutropenia occurrence is a fundamental piece of information that might dramatically change clinical and economic conclusions drawn for this case. The uncertainty that still affects this piece of data probably reflects the general lack of comprehensive ADR registries, of standardized procedures for ADR reporting and, in this specific case, of a consistent definition of neutropenia across studies. The DME thiopurine methyltransferase (TPMT), is responsible for AZA metabolism. Patients homozygous for polymorphisms that reduce TPMT activity (poor metabolizers) are more likely to present severe myelosuppression and toxicity effects and to discontinue AZA treatment at standard dosage (23;28). Deficient TPMT activity is not the sole cause of myelosuppression and might account for roughly one-third of all events, as shown in the largest study—41 IBD patients—correlating TPMT polymorphisms with AZA-induced neutropenia (1). The precise quantitative link between TPMT genotype and neutropenia occurrence is still ill-defined and based only on few studies with a rather limited number of patients. There are important barriers to determining this correlation with greater confidence among which organizing large prospective studies and having access to patients' DNA samples. For other side-effects, the evidence of a correlation between TPMT genotype and ADR occurrence is even more limited (7) and, therefore, in this study we focused only on neutropenia. The causal relationship between severe neutropenia and lethality is also rather weak. There are only two reports of mortality associated with thiopurine-induced myelosuppression. In the first case (21), the patient died but was, after a heart transplant, in a highly vulnerable situation; in the second case (2), of 739 IBD patients treated with AZA, 2 died of sepsis after 3 and 132 months, respectively, from treatment initiation. This late onset of side-effects makes factors other than TPMT deficient activity likely causes for the occurrence of neutropenia. In our opinion, linking TPMT testing to the prevention of AZA-induced mortality would require stronger evidence and much broader ADR databases to be conclusive. The impact of AZA-induced neutropenia on quality of life has been estimated only by Priest et al. (18) eliciting opinions from clinicians. The authors conclude that the "QALYs lost through patients developing neutropenia are small."

TPMT pharmacogenetic testing before AZA treatment is not the only available method to detect whether a patient's TPMT activity is deficient. A biochemical approach, called phenotyping, is in use but has important limitations as blood transfusions interfere with the results. Only one study (18), indirectly compares these alternatives from an economic perspective. The authors state that phenotyping is likely more cost-effective than genotyping as it implies "lower assay costs" and "a greater likelihood of pre-empting neutropenia" (18). In conclusion, due to a high level of uncertainty in epidemiological and clinical data, we considered premature calculating a cost-effectiveness/cost-utility ratio and focused, instead, on estimating the net cost of TPMT genotyping per averted case of neutropenia. For this purpose, as indicated by the ACCE framework, we derived from the published literature two cost categories (costs of ADRs after treatment with AZA and costs of performing TPMT pharmacogenetic testing) and assessed their comprehensiveness and quality.

METHODS

In March 2007, a systematic literature review was conducted by searching Medline and Embase databases. Searches were based initially on the combination of several terms that refer to three main categories: "adverse drug reactions," "costs," and the drug under consideration, azathioprine. For sake of brevity, term combinations are not listed here but are available upon request. The algorithm, although rather comprehensive, allowed retrieving only very few studies. To be certain of the comprehensiveness of our search, we broadened the review to cost of illness and cost-effectiveness studies related either to the specific disease or the drug under examination. Reference lists of all articles of interest have been examined to retrieve several additional publications. The databases of Health Technology Assessment studies and agencies were manually searched for further references. To determine the costs of performing TPMT pharmacogenetic tests we: (i) retrieved data from the literature (systematic review described above); (ii) retrieved prices of commercially available kits through interviews with main producers and analysis of the gray literature; (iii) retrieved costs through interviews with European diagnostic laboratories (total thirty-five). Interviews were based on predefined questions about the type of technology used, the number of tests performed per year, price charged or, alternatively, reimbursed tariffs and estimates of the costs incurred while performing the tests.

Costs obtained from the scientific literature were inflated to the year 2006 by using Eurostat general inflation rates per year for European countries and the U.S. and Canadian inflation rates per period provided by other calculators. In addition, inflated costs were converted to €2007 by using the universal currency converter-exchange rate calculator.

RESULTS

Costs of AZA-induced Adverse Drug Reactions in RA and IBD Patients

The systematic review of the scientific literature identified 3,597 potentially relevant papers. At a closer inspection, only fifty-five were considered of interest. Among these, several were reviews or commentaries without any empirical data and none of the retrieved cost of illness studies quantified the contribution of ADRs to the economic impact of RA or IBD.

Finally, only seven articles (Table 1) provided data on costs of AZA- induced ADRs, with five of them concentrating only on neutropenia. Two of the retrieved studies (26;27) did not refer to RA or IBD but were still appraised in this analysis, due to the scarcity of retrieved papers.

Table 1. Articles Retrieved by Systematic Literature Review: Costs of ADRs

Authors	Type of article	Currency	Source of cost data	One-time costs of ADRs	Converted to €2007 (inflation and conversion rate)	Final appraisal of evidence
Prashker and Meenan (1995) *Arthritis Rheum* **38**: 318-25	Cost analysis based on modeling of RA treatment and management of ADRs	US$ (1995)	Accounting data of three U.S. hospitals	802–2407[1]	**793-2,380**	++
Tavadia et al. (2000) *J Am Acad Dermatol* **42**: 628-32	Cost analysis based on observation of one case	CAN$ (1999)	Unclear but derived from Sunnybrook & Women's College Health Science Centre, Toronto, Canada	7,048	**5,505**	+
Marra et al. (2002) *J Rheumatol* **29**: 2507-12	Cost-effectiveness analysis	CAN$ (1999)	Canadian Provincial Guide to Medical Fees	1,734	**1,329**	+++
Winter et al. (2004) *Aliment Pharmacol Ther* **20**: 593-9	Cost-effectiveness analysis	GBP (2003)	Information and Statistics Division of the Common Services Agency in Scotland	1,367	**2,116**	+++
Oh et al. (2004) *Rheumatology* **43**: 156-163	Cost-effectiveness analysis	US $ (2002)	Average of 4 cases of AZA-induced neutropenia collected in the Hanyang University Hospital in Seoul, Korea	2,051	**1,887**	++
Priest et al. (2006) *Pharmacoeconomics* **24**: 767-781	Cost-effectiveness analysis	US $ (2004)	Local public hospital data (New Zealand)	5,010[2]	**3,725**	++
Van den Akker-van Merle et al. (2006) *Pharmacogenomics* **7**: 783-792	Cost analysis	Euro (2006)	Literature review and interviews with key informants in 4 European countries	1,000	**1,000**	+

[1]The authors do not report how many patients out of the 2,000 considered develop ADRs and calculate an average toxicity cost per patient. To derive the cost of treating ADRs per patient (one-time annual cost) we have assumed that between 10 and 30 percent of patients develop a side-effect that is resolved within the 6 months in which the costs were collected.
[2]Average of costs for life-threatening, severe and moderate neutropenia.

Validity of Reconstructed Clinical Paths in Case of Neutropenia. Before appraising the quality of cost data retrieved from the literature we wanted to verify whether the clinical path for the management and treatment of neutropenia on which the authors based their analyses and calculations could be considered solid and still valid. Through consultation with five rheumatologists and gastroenterologists we concluded that the clinical path followed in the treatment of neutropenia depends on its severity. In summary: (i) If neutrophils are $>1.5 \times 10^9$/L, often the same dose of AZA is maintained (very mild ADR); (ii) If neutropenia is mild (neutrophils between 1.0×10^9/L and 1.5×10^9/L), the dose of AZA is reduced by 50 percent and blood cell counts are monitored weekly. If neutropenia is more severe ($<1.0 \times 10^9$/L), AZA treatment is stopped and ADR is treated. In cases of severe or "clinically significant" neutropenia ($<0.5 \times 10^9$/L), the case is commented with the hematologist and treated with G-CSF (granulocyte-colony stimulating factor). In addition, severe neutropenia might require patient isolation to avoid infections. If the patient with severe neutropenia has no fever, treatment can be carried out in an outpatient setting; otherwise, he/she should be hospitalized to start an antibiotic regimen concomitantly with G-CSF.

Based on the clinical path described above, therefore, we appraised the seven retrieved studies. Van den Akker-van Marle et al. (27) do not present in their study any clinical path. Prashker and Meenan (17) reconstructed the clinical path from medical textbooks and consultation with rheumatologists but it was not possible to deduce from the article whether in 1995 G-CSF was used in the treatment of AZA-induced neutropenia. As clinical trials for the use of G-CSF

in chemotherapy-induced neutropenia were published only in the early 1990s it is possible that this treatment was not included in the above study. This makes the clinical path used in the article and the correspondent cost estimates less applicable to the present context. All the other six studies, instead, clearly mention the use of G-CSF for the treatment of AZA-induced neutropenia. Priest et al. (18) differentiate in moderate, severe and life-threatening neutropenia, but without clear clinical description of these different forms, and for each list the adopted treatments, based on expert opinion. For life-threatening neutropenia, the authors seem to base their clinical path on one case, treated for 7 days in an intensive care unit, that occurred in the local hospital from which cost data are derived. Marra et al. (12) and Winter et al. (31) specify in addition the distribution of patients between in- and outpatient settings (50/50 and 30/70, respectively). Both studies consider an average hospital stay of 10 days.

Quality and Comparability of Cost Data. Concerning the sources of cost data on which the articles are based, the variability is high, making the comparison quite difficult. In Prashker and Meenan (17), cost data were derived from the billing department of the Boston University Medical Center Hospital and compared with data from other two hospitals. Oh et al. (13) and Priest et al. (18) calculated costs based on few cases of AZA-induced neutropenia collected in their respective local hospitals. Costs in Winter et al. (31) were obtained from the Information and Statistics Division of the Common Services Agency in Scotland and are, likely, national averages of costs incurred in that particular year by Scottish hospitals, while in Marra et al. (12) costs are tariffs derived from the Canadian *Provincial Guide to Medical Fees*. Tavadia et al. (24) calculated costs of hospital and outpatient treatments of only one patient, treated with AZA for a dermatological condition, and referred for myelosuppression to the Sunnybrook Women's College Health Science Centre, Toronto. Finally, van den Akker-van Marle et al. (27) derive their cost estimates from the literature and some qualitative interviews with key-informants. Other than Winter et al. (31) and Marra et al. (12), the other articles do not detail costs that were included and the methodology for obtaining the reported total costs.

None of the articles appears to consider any other treatments, and its consequent costs, as one of the possible alternatives followed by clinicians in case of AZA-induced neutropenia. At least two studies (6;30) clearly show how in case of severe neutropenia, clinicians might choose to switch to another thiopurine drug, such as 6-MP, methotrexate or new biological treatment (i.e., infliximab). While methotrexate is in general cheaper than AZA, 6-MP can be twice as expensive as AZA and infliximab even 20 times dearer. These differences in pharmacological treatment costs before and after neutropenia should be taken into consideration as part of the costs of the side-effect. In addition, all the retrieved studies consider only direct medical costs although severe neutropenia may lead to lengthy hospitalizations (median time 10 days) and consequent loss of productivity and absenteeism from work for the patients, who, especially in the case of IBD, are generally young and in employment. If one wanted to appreciate the potential impact of TPMT testing for the overall society it would be probably important to consider also productivity losses due to ADRs and shift the study perspective from that of the third party payer to a societal one.

In two cases (27;31), mortality (1:1,000) was considered as a possible outcome of AZA-induced neutropenia and cost/life-year saved for TPMT testing were calculated. As specified in the introduction the evidence in support to these calculations appears to us too weak to be conclusive. Based on the criteria listed above we ranked these articles for comprehensiveness and quality of the clinical path and cost data, as indicated in Table 1. The estimate of €2,116 per case of AZA-induced neutropenia presented in Winter et al. (31) appeared the most reliable. The cost range is clearly broad, from €800 to €5,500, and a mean of €2,450. Despite the fact that it is unclear whether the costs of chemotherapy-induced and AZA-induced neutropenia can be compared, a recent study (26) shows that inpatient treatment of neutropenia for small-cell lung cancer patients amounts to €3,300, while treatment in an outpatient setting to roughly €980, reinforcing the validity of the estimate considered above.

Costs of Performing TPMT Genotyping Tests

The systematic literature review described above allowed to retrieve studies presenting costs of TPMT pharmacogenetic testing (Table 2). Most of the studies we retrieved refer to the U.S. and Canadian contexts. The only two studies focusing on European countries reached cost estimates of TPMT testing based on interviews with key-informants or retrieved from one diagnostic laboratory. Other than the case of Dubinsky et al. (3), in which the estimate relates to the price of a genotyping service provided by a U.S. private laboratory (Prometheus) and it is, therefore, not comparable, an average cost per TPMT genotyping of €68 (range, €46–84) can be deduced from all the other studies. It is to be noted, nevertheless, that none of the articles clearly specifies what kind of test (which polymorphisms and how many, with or without DNA extraction) correspond to those costs. In addition, cost of testing can be expected to go beyond the costs of the test per se and other cost categories should be taken into consideration as the time of the patient and doctor to carry out the test, any additional counseling service and the pharmacological therapy following positive testing. To verify if the estimates used in the published literature were still valid, we identified thirty-five diagnostic laboratories in Europe performing genetic and molecular biology-based tests. They included hospital-based, stand-alone private laboratories and, in one case, a network of laboratories. Of the labs we could retrieve, twenty-four perform TPMT genetic testing. The number of

Table 2. Cost of TPMT tests in the literature

Authors	Country	Cost of TPMT test	Converted to €2007 (inflation and conversion rate)	Source of cost data
Tavadia et al. (2000) *J Am Acad Dermatol* **42**: 628-32.	Canada	100 CAN$	**75**	Cost at local lab
Oh et al. (2004) *Rheumatology* **43**: 156-163	Korea	100 US$	**84**	Hanyang University Hospital, Seoul
Marra et al. (2002) *J Rheumatol* **29**: 2507-12.	Canada	100 CAN$	**77**	Authors' estimate based on other PCR-based tests
Winter et al. (2004) *Aliment Pharmacol Ther* **20**: 593-9	UK	30 GBP	**46**	Cost at local lab
Dubinsky et al. (2005) *Am J of Gastroenterology* **100**: 2239-2247	USA	510 US $	**409**	Authors' estimate (use of PRO-Predict Rx® TPMT, patented TPMT test)
Priest et al. (2006) *Pharmacoeconomics* **24**: 767-81	New Zealand	78 US $	**58**	Cost at local lab
Van den Akker-van Merle et al. (2006) *Pharmacogenomics* **7**: 783-792	Germany Ireland Netherlands UK	150 €	**150**[3]	Interviews with key informants

[3]The authors calculated this value as an average of very broad cost ranges across 4 countries. Not to introduce further approximations, we did not consider this value for our calculations.

TPMT genetic tests varied from less than 10 to over 300 cases every year. To better identify the costs of performing TPMT testing we investigated (i) the price of the genotyping kits available on the European market and (ii) the costs of labor, additional reagents, or services that could be connected to performing the tests. Kits for TPMT pharmacogenetic testing are commercially available in Europe as indicated in Table 3, with a price per sample of €20–30. We cannot exclude that there are other small producers we were not able to find. In addition, TPMT has been inserted in broader detection platform (such as TaqMan® Drug Metabolism Genotyping Assays from Applied Biosystems) in which up to 220 DME genes are checked at the same time, whose cost per sample is likely lower.

Still, of all the diagnostic labs we contacted only one stated using a commercial kit while the others have developed their own in-house tests. Labs often stressed how genotyping, in addition to phenotyping, should be considered the default practice and offered the recommendations of the European Commission (4) in support of their opinion. Two of the UK laboratories we contacted, instead, mainly relied on the traditional biochemical approach, considered it superior and limited genetic testing to confirming cases that were unclear by phenotyping or high-risk patients.

As most of the labs have developed their technologies, we enquired about three main cost categories related to performing the tests: DNA extraction from the blood sample, polymerase chain reaction (PCR) and reagents, and technician time. Ten laboratories could provide an estimate that ranged from €20 to €100 and roughly corresponded to what obtained through the literature review. Instead, the tariffs reimbursed by insurances or NHS systems for TPMT genetic testing greatly varied according to the context and ranged between 70 and €400 with an average of €188.

Cost per Averted Case of Neutropenia

In conclusion, if we consider a cohort of 100,000 RA or IBD patients who, before being administered AZA, are screened for TPMT genetic variants we can calculate the net cost per prevented event. Sanderson and colleagues (20) suggest that the frequency of neutropenia occurrence is between 1.4 and 5 percent. Taking 3 percent as an average frequency, 3,000 patients will undergo neutropenia but only one in three cases will likely be due to TPMT deficient activity (Winter et al.; 32 percent, 960 patients) (31). Considering a test sensitivity of 95.2 percent (as in Marra et al.) (12), overall 914 cases of neutropenia could be avoided by TPMT testing, each with a cost of €2,116 (total averted costs: €1,934,000).

Table 3. TPMT Pharmacogenetic Kits Commercially Available in Europe

Purpose	Kit	Producer	Detected gene variants	Price
Clinical	Artus TPMT PCR Kit	QIAGEN (Hamburg, Germany)	TPMT*1, TPMT*2, TPMT*3A, TPMT*3B, TPMT*3C	€33/sample
Clinical and Research	Muta Real®TPMT	ImmunDiagnostik AG (Bensheim, Germany)	TPMT*2, TPMT*3A, TPMT*3B, TPMT*3C	€21/sample

Table 4. Base-Case Analysis and Parameters for Sensitivity Analysis

Parameter	Range 1	Base-case	Range 2	Cost/averted case 1	Cost/averted case base	Cost/averted case 2
Frequency of neutropenia	1.4%	3%	5%	€13,846	€5,324	€2,349
Association TPMT genetic profile and neutropenia	20%	32%	50%	€9,793	€5,324	€2,646
Test sensitivity	92%	95.2%	99%	€5,585	€5,324	€5,042
Cost of averted neutropenia	€800	€2,116	€5,500	€6,640	€5,324	€1,940
Cost of TPMT test	€20	€68	€100	€72	€5,324	€8,825

Taking €68 as the cost of performing a TPMT test, the net cost (€6,800,000–€1,934,000) amounts to roughly €5,300 per prevented case of neutropenia. We performed univariate sensitivity analysis with the values reported in Table 4.

CONCLUSIONS

Our analysis, based on a systematic review of the literature and a small-scale survey of European diagnostic labs, has allowed us to make an estimation of the net cost of performing TPMT testing to avert one case of neutropenia (~€5,300/averted case). Comparisons are difficult as the economic evidence related to other pharmacogenetic tests is still rather limited. Considering the case of warfarin and its DME, CYP2C9, for instance, studies have shown costs of US$5,778 (year 2001) and US$5,900 (year 2003) per averted bleeding event (10). These costs are rather comparable to what obtained for TPMT genotyping. Sensitivity analysis shows that the net cost of TPMT genotyping is particularly sensitive to the prevalence of ADR and to the degree of association between ADR and TPMT genetic profile. These uncertainties can only be reduced by studies with more numerous cases of neutropenia and by the possibility to correlate their occurrence with the TPMT genetic profile of the patients. This clearly requires solid ADR databases and reporting, and the possibility to collect DNA samples of individuals. In the United States, the PharmGKB database collects genetic and clinical information about people that have participated in studies through the NIH Pharmacogenetics Research Network (15). A similar initiative could be also helpful in the European context to gather enough evidence about the correlation between genotypes, frequencies of different DME genetic variants and clinical outcomes/ADRs. The results provided in the present study are also sensitive to the costs of TPMT testing and to those of neutropenia. It is hard to evaluate whether the costs of TPMT tests, as they have been estimated in the literature, are actually not exaggerated. We have, for instance, found it difficult to elicit the real costs of reagents and procedures from the diagnostic laboratories we have interviewed. In the future, costs of TPMT tests are supposed to decrease based on the newest technological platforms but these considerations presume the ready up-take of pharmacogenetic tests by diagnostic laboratories and their willingness to invest in this type of rather sophisticated and high-throughput testing. Regarding costs of neutropenia, it is evident how the precise description of its management and treatment and related cost data are rather uncommon both in cost-effectiveness and cost-of-illness studies. This paucity of economic data has already been underlined in other studies (9;15), together with the consequent difficulty in deriving robust conclusions on the impact on ADR incidence of pharmacogenetic tests and their potential cost-effectiveness. In addition, productivity losses due to neutropenia are never considered although it may lead to lengthy hospitalizations and affect young people in employment. Inclusion of indirect costs will be fundamental to fully appreciate the societal value that these technologies might have. Limitations in the quality of the existing cost data are also evident as, in many cases, cost estimates are not the result of observational studies but of theoretical modelling, and rely on national tariffs and cost databases rather than on accounting data of healthcare organizations or "bottom-up" costing approaches. To improve cost data and estimates there is a clear need for well-designed prospective studies in which costs of ADRs are systematically collected and evaluated both in their direct and indirect components. In the UK, for the first time, the Department of Health has funded a trial that aims at evaluating the clinical benefit and the cost-effectiveness of TPMT genotyping for AZA treatment in RA patients, in comparison to the traditional biochemical methodology (14). The trial is on-going and precious information will derive, in this sense, from this initiative.

Adverse drug reactions are also monitored in Europe through the EMEA and a network of pharmacovigilance units within the national medicines agencies. It would be important that data on ADRs collected through these means could be available not only for clinical and safety purposes but also used as the basis for economic studies. For instance, few simple questions about the treatments followed in case of ADR could be easily introduced in the reporting form filled in by clinicians. It is worth noting the recent European Commission's strategy on pharmacovigilance that aims, among other things, to simplify the procedures for ADR reporting. Despite these opportunities for improvement, whether societies are willing to pay this amount of money to prevent an ADR is still to be understood.

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