Cost-effectiveness of pharmacogenomics in clinical practice: a case study of thiopurine methyltransferase genotyping in acute lymphoblastic leukemia in Europe

M Elske van den Akker-van Marle[1], David Gurwitz[2,3], Symone B Detmar[1], Christine M Enzing[1], Michael M Hopkins[4], Emma Gutierrez de Mesa[2] & Dolores Ibarreta[2†]

†Author for correspondence
[1]TNO (Netherlands Organization for Applied Scientific Research), Quality of Life, Leiden/Delft, The Netherlands
[2]Institute for Prospective Technological Studies (IPTS), European Commission Joint Research Center, Seville, Spain
[3]Tel-Aviv University, Faculty of Medicine, Tel-Aviv, Israel
[4]University of Sussex, SPRU: Science and Technology Policy Research, The Freeman Centre, Brighton, UK

Only a few studies have addressed the cost-effectiveness of pharmacogenetics interventions in healthcare. Lack of health economics data on aspects of pharmacogenetics is perceived as one of the barriers hindering its implementation for improving drug safety. Thus, a recent Institute for Prospective Technological Studies (IPTS) study, entitled 'Pharmacogenetics and pharmacogenomics: State-of-the-art and potential socio-economic impact in the EU' included an explorative cost-effectiveness review for a pharmacogenetic treatment strategy compared with traditional medical practice. The selected case study examined the cost-effectiveness of thiopurine methyltransferase (*TMPT*) genotyping prior to thiopurine treatment in children with acute lymphoblastic leukemia (ALL). Information for the cost-effectiveness model parameters was collected from literature surveys and interviews with experts from four European countries (Germany, Ireland, the Netherlands and the UK). The model has established that *TPMT* testing in ALL patients has a favorable cost-effectiveness ratio. This conclusion was based on parameters collected for *TPMT* genotyping costs, estimates for frequency of TMPT deficiency, rates of thiopurine-mediated myelosuppression in TPMT-deficient individuals, and myelosuppression-related hospitalization costs in each of the four countries studied. The mean calculated cost per life-year gained by *TPMT* genotyping in ALL patients in the four study countries was €2100 (or €4800 after 3% discount) based on genotyping costs of €150 per patient. Cost per life-year gained is expected to further improve following the introduction of the wider use of *TMPT* genotyping and the availability of lower cost genotyping methods. Our analysis indicates that *TPMT* genotyping should be seriously considered as an integral part of healthcare prior to the initiation of therapy with thiopurine drugs.

Advances in pharmacogenetics and pharmacogenomics (collectively termed PGx) could positively impact the pharmaceutical and healthcare sectors facilitating drug development and a system of medical care where drugs could be used in a safer and more effective manner. However, many expectations surrounding the clinical application of PGx remain unfulfilled due to several barriers, including:

- The slow development of the evidence base for genotype-phenotype correlations for many genes related to drug pharmacokinetics and pharmacodynamics
- A lack of physician awareness and education in molecular genetics and PGx
- A lack of incentives to facilitate the development of PGx diagnostics for drugs that have already been licensed [1–4]

Only a limited number of PGx applications have reached clinical practice. The potential impact of PGx on healthcare quality and its socio-economic implications are still uncertain. Clarifying the economic aspects of using pharmacogenomic knowledge in drug treatment strategies may facilitate their implementation. Other topics, such as ethical and legal aspects, have to be studied in addition, before a well-considered decision about implementation can be made [5–7]. However economic considerations are likely to play a key role as resources for improving healthcare are limited and must be decided upon in a prudent manner.

With the aim of gaining knowledge on global trends in PGx translational research in academia and the private sector, and diminishing some of these socio-economic uncertainties, the Institute for Prospective Technological Studies (IPTS) [101] of the European Commission Joint Research Centre (JRC) has recently completed a prospective study of the PGx field, entitled 'Pharmacogenetics and pharmacogenomics: State-of-the-art and potential socio-economic impact in the EU' [8,102]. Notably, few studies into the economic implications of PGx have been

Keywords: 6-mercaptopurine, acute lymphoblastic leukemia, adverse drug reactions, cost-effectiveness analysis, drug-metabolizing enzymes, Germany, Ireland, Netherlands, pharmacogenetics, thiopurine drugs, thiopurine methyltransferase (TMPT), United Kingdom

future medicine

undertaken. A recent systematic review of cost-effectiveness analyses of pharmacogenomic interventions in the medical literature published by Phillips and Van Bebber [9] identified only 11 studies that met the inclusion criteria for a cost-effectiveness analysis, with most of these being performed in the USA. A PubMed search carried out in April 2006, based on the criteria of Phillips and Van Bebber, resulted in only one additional cost-effectiveness analysis published since 2004 [10]. One of the aims of the IPTS study was therefore to undertake cost-effectiveness studies for PGx in the European clinical setting, which has distinct features when compared with USA healthcare, and to assess the feasibility of incorporating PGx diagnostic tests into European healthcare systems. In order to provide wide-ranging conclusions for policy makers, these case studies were performed in parallel in four EU member states: Germany, Ireland, the Netherlands and the UK. Other aspects of the study, including market size, reimbursement, quality assurance and professional education related to *TPMT* testing, as well as additional societal, legal, and regulatory and licensing considerations of PGx products in general, are included in the study report available on the IPTS web site [102].

Thiopurine drugs & TPMT phenotype & genotype measurements

Acute lymphoblastic leukemia (ALL) is the most common malignancy of childhood, accounting for approximately 78% of all childhood cancers, with a reported annual incidence rate in the UK of 30–35 per 1 million among children aged 0–14 years, and showing a recent trend for a 0.7% annual increase in incidence [11]. Most of these children are treated with thiopurine drugs which have helped to dramatically improved the ALL cure rate [12]. In 1953, the purine drug 6-mercaptopurine (6-MP) was launched in the USA, and soon thereafter in Europe, under the brand name Purinethol®. The drug inhibits DNA synthesis by blocking the production of guanosine, and thus has therapeutic applications in the treatment of cancer and autoimmune diseases. The expectations of 6-MP were high, and indeed it proved effective in curing many children of leukemia. However, soon thereafter researchers discovered that the drug could be extremely toxic for some patients due to severe myelosuppression [13]. The same scenario occurred with another thiopurine drug, azothioprine, marketed in Europe and the USA since 1968 as Imuran®, where toxicity and fatal sepsis were reported in transplant patients [14].

In the 1990s it became evident that such toxic reactions to thiopurine drugs involve an inherited deficiency in the enzyme thiopurine methyl transferase (TMPT), the key catabolic enzyme of thiopurines [15–18]. Polymorphisms in the *TPMT* gene are responsible for large interindividual differences observed in the activity of the TPMT enzyme. Individuals with two defective copies of the *TPMT* gene – approximately 0.3% of Caucasians – are at increased risk of thiopurine-induced toxicity [19,20]. Evidence was also obtained that approximately 10% of patients have intermediate TPMT activities, representing a heterozygous deficiency, in whom severe toxicity was less likely, but who were also at increased risk of myelosuppression from standard doses of thiopurine drugs [20].

Thus, it is prudent to identify a patient's TPMT activity level before starting therapy, and chose lower thiopurine dosage or alternative drug for patients with intermediate TPMT levels or deficient metabolizers. Phenotypic TPMT assays, performed using the patient's red blood cells as the source of the enzyme, have also been developed [21]. However, the phenotypic assay is labor-intensive, requires qualified knowledge and expensive instrumentation, and is impractical in patients receiving blood transfusions [22].

Genotype assays for *TPMT* may circumvent some or all of these drawbacks, and comparative studies of genotyping and phenotyping for *TPMT* testing are underway. The basic molecular genetic testing methodology developed in the mid 1990s for the detection of mutations associated with TPMT deficiency utilizes polymerase chain reaction (PCR) combined with restriction enzyme digests to detect the presence or absence of specific DNA sequences at a known loci [16]. However, as patents for thiopurine drugs are long since expired, there has been little commercial interest from pharmaceutical companies to develop tests for identifying TPMT-deficient individuals who are at increased risk of suffering myelosuppression. In the 1990s, commercial DNA tests to predict thiopurine drug toxicity became available in the USA. Several companies (for example, Prometheus Laboratories, CA, USA [103]) have developed tests for *TPMT* genotype or phenotype screening which they offer as a service.

Cost-effectiveness analysis of using pharmacogenomics in clinical practice

Analyzing the cost-effectiveness of a PGx strategy in healthcare involves the comparison of the cost and effects of the PGx assay compared with

conventional clinical practice of not using PGx information for pharmacotherapy decisions. When drug safety issues related to polymorphic drug-metabolizing enzymes (DMEs) are considered, key factors in the cost-effectiveness comparison include the polymorphic genotypes of interest and their incidence in the relevant population, the genomic test, the disease state, the treatment and its potential adverse drug reactions (ADRs). A PGx-based treatment strategy is likely to be more cost-effective when:

- The relevant genetic polymorphism is prevalent in the population and has a high degree of penetrance (that is, being highly correlated with a corresponding phenotype)
- The available genetic test is highly sensitive, specific and inexpensive
- The disease state involves outcomes with significant morbidity or mortality if left untreated
- The pharmacotherapy involves a drug with a narrow therapeutic index, and therefore significant and costly ADRs that can be avoided to a significant degree by genotype-individualized therapy [23].

Cost-effectiveness analysis is a widely-used tool to assess the value of new healthcare interventions. Only a few published articles introduce this kind of analysis to the field of pharmacogenomics (for example, [24–29]).

Studies on the cost-effectiveness of *TPMT* genotyping have concentrated on azathioprine treatment in adults [27–29]. All these studies favor the introduction of PCR testing to identify *TPMT* polymorphisms prior to azathioprine treatment. In the present study, the cost-effectiveness of the use of *TPMT* testing in combination with treatment with 6-MP in children with ALL is explored. Cost-effectiveness analyses reported in the scientific literature very seldom include comparisons across different countries. In the present study, information for costs of treating thiopurine-related ADRs, costs of *TPMT* genotyping, and other parameters were collected from experts in four European countries: Germany, Ireland, the Netherlands, and the UK.

Data collection & analysis

A model was developed for the comparison of the costs and effects of the *TPMT* genotyping-based thiopurine treatment strategy in ALL as compared with the traditional medical practice without *TPMT* genotyping, and the model parameters were identified. The model parameters concern economic, genetic and clinical data. Information on model parameters was collected from literature and from expert opinions in the different participating countries (Germany, Ireland, the Netherlands and the UK). In general, not much information on the parameters for the *TPMT* model was specifically available for children with ALL. Therefore, estimates from pharmacoeconomic studies on other thiopurine drugs are frequently used [27–29]. Further details on expert interviews and literature searches are available in the recently published IPTS report [102].

The analyses were performed from the societal perspective, meaning that all medical costs and effects are included regardless of who incurs the costs and who obtains the effects [25]. Indirect costs were not included, such as lost working time for parents of children with ALL in cases of ADRs necessitating hospitalization or additional clinic visits. Costs are shown in 2004 Euros (€). When costs were from other years, the effect of price inflation was removed by using the harmonized annual average price indices of the different case study countries to inflate the data to the year 2004.

In the calculation of the cost-effectiveness ratios, both costs and effects were discounted at a rate of 3% to convert future costs and health effects to their present value (i.e., US dollars expended or health effects experienced n years in the future are discounted at a factor of $1/[1.03]^n$), as recommended by the Panel on Cost Effectiveness in Health and Medicine [30].

TPMT activity in the general population

The distribution of TPMT activity in the population differs with respect to ethnicity. For this study we used the distribution as found in Caucasians. The majority of the individuals (approximately 89%) have high TPMT activity, corresponding to the homozygous wild-type genotype. Approximately 11% of the population are heterozygote at the *TPMT* gene locus and have intermediate TPMT activity. Homozygotes with two *TPMT* mutant alleles have deficient TPMT activity and account for 0.3% of the Caucasian population [16]. Similar levels of TPMT deficiency were reported in Asian [31] and African populations [32], although in some African populations TPMT deficiency might be slightly more frequent c

ompared with Caucasians [32].

Adverse events

Myelosuppression (leucopenia) is the most severe and life-threatening ADR associated with thiopurines. Even when treated successfully, myelo-

suppression is still associated with prolonged hospitalizations and with patient suffering. Sanderson and colleagues reported a frequency of myelosuppression of between 1.4–5% of thiopurine-treated patients [33]. Winter and colleagues [28] assumed the frequency of leucopenia in adults with inflammatory bowel disease treated with thiopurine drugs to be 3.2%, based on the results of seven studies. For patients with rheumatological conditions treated with azathioprine, Marra and colleagues [27] assumed a higher probability of hematological cytopenia of 9%. Other adverse events include allergic reactions (2.3%), nausea, vomiting, lack of appetite, diarrhea (1.4–5%), pancreatitis (1.4–5%), and infections (7%). These adverse events were not included in the analysis, as their costs are assumed to be minor by comparison. Thus, for the current analysis we considered only medical costs related to myelosuppression, and employed the more conservative base value of 3% as probability of myelosuppression in thiopurine-treated individuals based on the studies of Winter and colleagues [28] and Sanderson and colleagues [33].

However, prospective evaluation of TPMT activity or gene status will not eliminate all cases of myelosuppression. Marra and colleagues [27] assumed that approximately 50% of the cases of hematological toxicity could be eliminated by screening for *TPMT* and dosage reduction. Sanderson and colleagues [33] suggest 29% of the adverse reactions to be the result of overdosing 6-MP, based on the study of Colombel and colleagues [34]. Based on the studies [34–36] cited by Winter and colleagues [28], they assume an association of leucopenia with TPMT deficiency of 32%. That is, only one in three cases of myelosuppression during thiopurine therapy is likely to be the result TPMT deficiency. The latter value was therefore used as base value for the analysis, and a conservative value of 20% and the value of 50% used by Marra and colleagues [27] were used for the sensitivity analysis.

Myelosuppression may lead to death. Winter and colleagues [28] assumed that in case of *TPMT* screening of 1000 patients treated with a thiopurine drug, one death may be avoided. We have used this as our base value. As no data exists to support this assumption, we varied this assumption in our sensitivity analysis considerably from a conservative assumption of one death avoided in 10,000 patients to the assumption of avoiding three deaths per 1000 patients. There is a strong trend of improved life expectancy for children with ALL [37]. The difference of the life expectancy of children with ALL with the average EU life expectancy even seems to be closing. In this study we assumed the average EU life expectancy of 75 years for children with ALL. In the sensitivity analysis a life expectancy of 64 years is used as found by Viscomi and colleagues for the period 1987–1991 [37]. Using our base case assumption of avoiding one death in case of TPMT screening of 1000 patients and a mean life expectancy of 75 years indicates that when we perform our analysis for children that are on average 8 years old, screening of 1000 patients will result in 67 life years gained, or with a discount of 3%, 29.6 life-years gained.

PCR test sensitivity & specificity

Oh and colleagues [29] assumed the sensitivity and specificity of PCR genotyping for *TPMT* type **2*, **3A*, **3B* and **3C*, to be 96.3 and 100%, respectively. Marra and colleagues [27] used slightly different estimates for the sensitivity and specificity of the PCR genotyping for type **2* and **3A*, of 95.2 and 100%, respectively. We conservatively used 95.2% as our base value for the sensitivity.

TPMT *genotyping costs*

Large differences were found in the costs of the PCR test, consisting of the material and personnel cost of performing the PCR test, reported by the different countries. Experts in the UK reported an amount of £20–30 (€29–44). In Germany, a wide range from €32–300 was reported. For the Netherlands, the cost of PCR testing were taken to be €175, based on national tariffs. In Ireland, experts estimated the cost per test as €250. In previous cost-effectiveness analyses, amounts of CAD$100 (€72 price level 2004, [27]) and £30 (€44 price level 2004, [28]) were reported for *TMPT* genotyping. We have used the PCR cost of €150 as base value, and the values of €30 and €300 as lower and upper cost values, respectively, for the sensitivity analysis.

Costs of adverse events

The costs of adverse events were based on hospital days and outpatient visits, as other medical costs are minor by comparison. A Dutch expert estimated that 10% of the patients with a serious ADR require in-patient treatment for at least 7 days. In the Netherlands, this amounts to €2549, price level 2004 [38]. According to this estimate, the other 90% of the patients having serious ADRs are managed as out-patients. As they already have frequent outpatient visits, the expert esti-

mated that this will not result in additional costs. The average healthcare cost per patient with an adverse reaction to thiopurine drug treatment for the Dutch situation can thus be estimated at €255.

Winter and colleagues [28] assumed that in the UK, two-thirds of patients suffering significant leucopenia could be managed as out-patients, requiring two additional visits at £115 (€168). The remaining patients would require hospital admission due to infective complications. Assuming them to stay for 10 days in a hematology ward at £402/day, results in a total amount of £4020 (€5863) for these patients. The average cost per patient in the UK can thus be calculated to be €2178.

Tavadia and colleagues [26] reported Canadian costs of adverse events of CAD$7757 (€5578) per case. Marra and colleagues [27] assumed that 50% of the patients with adverse events would need to be hospitalized, for an average duration of 10 days amounting to CAD$ 2679 (€1925). For the 50% of the patients able to be managed as outpatients the costs were assumed to be CAD$ 790 (€568). The average cost per patient amount was €1247. The interim value of €1000 per myelosuppression event was therefore used on the cost-effectiveness analysis (**Table 1**), and the range of €250–2200 (**Table 2**) was used for the sensitivity analysis.

Base case analysis

Table 1 presents the base values of the model parameters used in the case model. The values are based on the values for the parameters found in literature and reported by experts as described above. The base case values are in between the range described for a model parameter.

Sensitivity analysis

In the sensitivity analysis the values of the model parameters are varied, in order to determine the degree of influence each parameter has on cost-effectiveness. The lower and upper values are based on the values for the parameters found in the literature and reported by experts as described above (**Table 1**).

Results

Base case analysis

The cost-effectiveness analysis was performed for a hypothetical cohort of 100,000 children with ALL using the base case values shown in **Table 1**. Of these 100,000 children, 3000 will experience myelosuppression, of which 960 cases are directly related to TPMT deficiency. Assuming a sensitivity of the PCR test of 95.2% indicates that 914 of the 960 ADRs directly due to TPMT deficiency may be prevented by screening for *TPMT* prior to initiation of 6-MP treatment.

The cost of PCR tests for 100,000 children with ALL, using the mean cost of €150 per test, amount to €15 million. The direct healthcare cost savings due to the prevention of hospitalizations of 914 ALL children with adverse events, when using the base values from **Table 1**, amount to approximately €932,000.

However, the costs saved by prevention of ADR-associated hospitalizations following thiopurine therapy in children with ALL are a minor consideration compared with the potential for saving lives. If we were to avoid one death per 1000 children screened, as explained above, we save 100 children from this hypothetical cohort, that is, we save 6700 life-years by screening 100,000 children. Since screening the cohort for *TMPT* genotypes costs €15 million, following deduction of the costs saved for hospitalizations it would cost €14,068,000 to save these 100 children from the hypothetical cohort. Thus, assuming a life expectancy of 67 additional years per 8-year old child saved, it would cost €2100 per life-year gained, or €4800 after 3% discounting.

Sensitivity analysis

For a univariate sensitivity analysis we varied one variable at a time (**Table 2**). Using the lower values for each of the variables, probability of myelosuppression, adverse events associated with TPMT, mortality prevented per person screened for *TPMT*, life expectancy for children with ALL, sensitivity of the PCR test and the costs of myelosuppression leads to slightly higher costs per life-year gained, hence less favorable cost-effectiveness ratios. However, the changes in the cost-effectiveness ratio when changing most parameters were very small. Only when changing the value of mortality prevented per person screened for *TPMT*, from one in 1000 to one in 10,000s, did the costs per life-year gained increase considerably, to €47,600. In contrast with the other parameters, lowering the costs of the PCR test to the minimum value of €30 (**Table 1**), leads to a more favorable cost-effectiveness ratio of €700 per life-year saved. Using the upper values of the parameters had the opposite effect.

In a multivariate sensitivity analyses, we varied all model parameters included in the sensitivity analysis (**Table 2**) together to arrive at the best and worst cost-effectiveness ratios (as cost per life-year

Table 1. Base case value parameters TPMT model, and lower and upper values for parameters included in the sensitivity analysis.

Model parameter	Base case value	Sensitivity analysis	
		Lower	Upper
Homozygous wild-type	88.7%		
Heterozygous	11.0%		
Homozygous mutant	0.3%		
Probability of myelosuppression	0.03	0.01	0.1
Adverse events associated with TPMT	32%	20%	50%
Mortality prevented per person screened for *TPMT*	0.001	0.0001	0.003
Life expectancy	75 years	64 years‡	
Sensitivity PCR test	95.2%	76.2%*	99.9%*
Specificity PCR test	100%		
Costs PCR test (€ price level 2004)	150	30	300
Costs of myelosuppression (€ price level 2004)	1000	250	2200

‡Based on Viscomi and colleagues [37], assuming 50% boys and 50% girls.
**Marra and colleagues [27].*
PCR: Polymerase chain reaction; TPMT: Thiopurine methyltransferase.

gained). Under the assumption that all of the model parameters mentioned in Table 2 are independent from each other, we can construct a set of extreme parameter values that yield the highest and the lowest cost-effectiveness ratios. To construct the highest (least favorable) cost-effectiveness ratio, we took the lower values for the probability of myelosuppression, the percentage of adverse events directly associated with TPMT deficiency, the mortality prevented by *TPMT* screening and the costs of myelosuppression. For the costs of the PCR test, we used the upper value. This resulted in a cost-effectiveness ratio of €53,500 per life-year saved (€107,900 per life-year gained, with 3% discounting). In contrast, for the lowest (most favorable) cost-effectiveness ratio, taking the upper values for the probability of myelosuppression, the percentage of adverse events directly associated with TPMT deficiency, the mortality prevented by *TPMT* screening and the costs of myelosuppression, and taking the lower value for the costs of the PCR test, resulted in both financial savings (€6.4 million) and a gain in life-years (8900 years, 3% discounting) for a cohort of 100,000 children.

Discussion

The current cost-effectiveness analysis shows that screening for *TPMT* genotypes in children with ALL prior to treatment with thiopurine drugs is highly cost-effective, and thus desired from the socio-economic perspective. This is evident from the cost-effectiveness ratio, defined as the cost per life-year gained, which was calculated as only €2100 (or €4800 after 3% discount) using the base value estimates collected from experts and literature surveys for the four European countries included in the study. This value is by far smaller than the value of US$ 50,000 per life-year gained – often used as a threshold value for indicating a very favorable outcome of cost-effectiveness studies in the USA and £30,000 per quality-adjusted life year (QALY) gained, which is the UK threshold set up by the National Institute for Clinical Excellence (NICE) [104]. It is worth mentioning that there is no agreed European threshold for considering a new technology or treatment as cost-effective. Given that our case studies are set in the UK, Germany, the Netherlands and Ireland, we have reviewed the healthcare technology assessment guidelines for the four mentioned countries. It should be highlighted that only the UK, NICE, sets up the criteria of acceptability for a technology as cost-effective [104]. Thus, an examined medical procedure is typically considered to be cost-effective for society as long as the cost per life-year gained by the procedure remains below this threshold.

Univariate sensitivity analysis was performed by changing each of the base values shown in Table 2 to less or more favorable ones. As shown in Table 2, in most cases this leads to only minimal effect on the calculated cost-effectiveness ratios. Only when the value of mortality prevented per person screened for *TPMT* is changed from the base value of one in 1000 patients to one in 10,000 patients, the costs per life year gained increased considerably

Table 2. Univariate sensitivity analysis: cost-effectiveness ratio, expressed as costs in EUR (price level 2004) per life-year gained (3% discounting).

Model parameter*	Lower value	Upper value
Probability of myelosuppression	5000	4000
Adverse events associated with TPMT	4900	4600
Mortality prevented per person screened for *TPMT*	47,600	1600
Life expectancy	5700	
Sensitivity of PCR test	4800	4700
Costs of PCR test	700	9800
Costs of myelosuppression	5000	4500
Baseline	4800	

**For lower and upper values of model parameters see Table 1.*
PCR: Polymerase chain reaction; TPMT: Thiopurine methyltransferase.

to €47,600. However even this high value is still within the range typically considered as cost-effective. Only the outcome of €101,200 per life-year gained, obtained by constructing a set of extreme parameter values that yield the least favorable cost-effectiveness ratio, appears well above what would have been deemed cost-effective. Only in robust cases, the NICE criteria would accept this figure as "above an incremental cost effectiveness ratio of £30,000/QALY, the case for supporting the technology on these factors has to be increasingly strong" [104]. It could be argued that saving children's' lives by avoiding thiopurine-mediated myelosuppression does make a strong enough case for *TPMT* genotyping. In any case, the most favorable cost-effectiveness ratio resulted in both financial savings and a gain in life-years due to *TPMT* screening. To narrow the uncertainty, further research on the model parameters is warranted. Preferably, the probability of dying due to myelosuppression should be assessed, based on primary data collection. With help of this information the model structure and outcomes can be optimized.

A base value of €150 was employed here for *TPMT* PCR genotyping costs. However, there was a large range of estimates for costs of PCR assays, for example in the range of €32–300 for Germany. This may be caused, in part, by the number of different genotypes assessed. Some centers assay only the most common *TPMT* mutations whereas others perform a "genome scan" which is more expensive but allows a higher sensitivity. Using the low value of €30 for the analysis leads to a fivefold reduction in the cost of life-year gained to only €705 (after 3% discount). In this context, it is important to keep in mind that genotyping costs are expected to decline in the future [39].

The reported costs of adverse advents also varied between the countries participating in this study. This may be due to real cost differences caused by different prices of healthcare services and products between countries, differences in protocols for treatment of the adverse advents, or incomplete estimates of experts. However, the sensitivity analysis showed that these costs have minor consequences for the cost-effectiveness ratio. Of note, the same considerations for better cost-effectiveness of PGx data for reduced genotyping costs may be true for other PGx tests capable of improving drug safety and/or efficacy. At any rate, genotyping costs for each of the drug-metabolizing enzymes (DMEs) tested might be substantially reduced if tests for many DMEs were to be combined in a single DNA-based chip examining them in parallel. Obtaining the full cost-effectiveness advantage from such chip-based multi-DME screening (or DNA sequencing) strategies would require the setting up of reliable electronic-health (e-health) technologies, so that the data gained from a once in a lifetime genotyping would be available for treating physicians (and only to them) throughout the individual's life, possibly even in cases where the health provider and/or country of residence are changed. However, this would require solving crucial ethical and privacy concerns and setting up international agreements for e-health data storage and transfer. Hopefully such barriers would soon be solved, so that the potential of pharmacogenomics, highly related to the consistent nature of genomic data, can be harnessed for improving healthcare quality and equality.

When comparing cost-effectiveness of *TPMT* genotyping for pediatric ALL patients in the four case study countries, variables that may affect

Highlights

- Cost-effectiveness of thiopurine methyltransferase (*TPMT*) genotyping in pediatric acute lymphoblastic leukemia (ALL) patients was calculated as €2100 per life-year gained (or €4800 after 3% discounting) for four case study European countries (Germany, Ireland, the Netherlands and the UK).
- According to conventional definitions, these values represent favorable cost-effectiveness for *TMPT* genotyping in pediatric ALL patients.
- Among the four case study European countries, *TPMT* genotyping in pediatric ALL patients appears to have the most favorable cost-effectiveness value in the UK, due to lower genotyping costs and higher hospitalization costs.
- Sensitivity analysis showed that the rate of mortality prevented per person screened and polymerase chain reaction (PCR) costs had the strongest effect on cost-effectiveness of *TMPT* screening. Further research on these model parameters is warranted.
- As genotyping costs are projected to continue decreasing, cost-effectiveness of *TPMT* genotyping prior to thiopurine therapy is likely to keep improving.

country differences are the cost variables, as other factors, including the prevalence of TPMT deficiency, may be assumed to be similar across the mostly Caucasian populations of these countries. Since expert interviewees estimated a much lower cost for PCR costs in the UK, using the low-end UK value yields approximately sixfold more favorable cost-effectiveness for *TPMT* genotyping compared with the base value presented in **Table 2**. Since hospitalization costs calculated for myelosuppression were highest in the UK, this further contributes to the conclusion – according to base values employed here – that among the four studies European countries *TPMT* genotyping in children with ALL is the most cost-effective in the UK. In contrast, the higher PCR costs estimated for Ireland mean that in this country cost-effectiveness is lower than in other study countries. We may assume that in future, due to better availability of *TPMT* genotyping services, *TPMT* genotyping would become less expensive, further improving its cost-effectiveness, and minimizing cost-differentials between countries.

Thiopurine drugs are commonly used for additional indications other than ALL, most notably, for treating rheumatoid arthritis (RA), inflammatory bowl disease (IBD), and other autoimmune diseases and for immune suppression following tissue transplants [40] Life-threatening myelosuppression is a common ADR associated with thiopurine therapy. Estimates for rates of dangerous myelosuppression appear to be similar for pediatric ALL and the other indications (approximately 3% of patients receiving high-dose thiopurine drugs), and *TPMT* genotyping costs, as well as hospitalization costs used in the current study are likely in the same approximate range for the other indications. Therefore, although further studies may be required, it appears from the current study that *TPMT* genotyping might also show favorable cost-effectiveness values for the above mentioned additional indications.

It remains obvious from this study that there is a crucial need for more detailed cost-effectiveness analyses of further examples of the use of pharmacogenetics in the clinic for reducing the alarmingly high rates of ADRs [41], which have been estimated in recent studies to be directly related to over 6% of hospital admissions in the UK [42], as well as in Germany [43]. Hopefully, additional studies yielding data regarding favorable societal cost-effectiveness of PGx testing would assist in its implementation as an integral part of pharmacotherapy decision making for drugs having narrow therapeutic indexes similarly to thiopurines.

In spite of favorable cost-effectiveness values for PGx in the clinic, as reported here and in previous studies [27–29], levels of clinical implementation of PGx remain low, as concluded by the recent IPTS study on 'Pharmacogenetics and pharmacogenomics: State-of-the-art and potential socio-economic impacts in the EU' [102]. As indicated in the IPTS report, this seems to be due, in part, to barriers of physician awareness and education on the potential clinical benefits of genomics and pharmacogenetics [44–46]. We hope that the present findings on the evident cost-effectiveness of *TPMT* genotyping prior to the initiation of pharmacotherapy with thiopurine drugs would stimulate further studies on cost-effectiveness of pharmacogenetics in healthcare, and eventually contribute to its wider implementation in the clinic.

Acknowledgments

This study was funded by the European Commission through the European Science and Technology Observatory network (ESTO). We are grateful for the help and input received from Adam Hedgecoe (University of Sussex), Jim Ryan (CIRCA Group) and Sibylle Gaisser (Frauenhofer Institute Systems and Innovation Research) and would like to especially thank the experts who took the time to participate in the interviews.

The full IPTS study, "Pharmacogenetics and pharmacogenomics: State-of-the-art and potential socio-economic impact in the EU" is available on the internet [102].

Bibliography

1. Evans WE, McLeod HL: Pharmacogenomics – drug disposition, drug targets, and side effects. *N. Engl. J. Med.* 348(6), 538–549 (2003).
2. Evans WE, Relling MV: Moving towards individualized medicine with pharmacogenomics. *Nature* 429(6990), 464–468 (2004).
3. Frueh FW, Gurwitz D: From pharmacogenetics to personalized medicine: a vital need for educating health professionals and the community. *Pharmacogenomics* 5(5), 571–579 (2004).
4. Kirchheiner, J, Fuhr U, Brockmoller J: Pharmacogenetics-based therapeutic recommendations – ready for clinical practice? *Nature Rev. Drug Discov.* 4(8), 639–647 (2005).
5. Breckenridge A, Lindpaintner K, Lipton P, McLeod H, Rothstein M, Wallace H: Pharmacogenetics: ethical problems and solutions. *Nature Rev. Genet.* 5(9), 676–680 (2004).
6. Knoppers BM, Chadwick R: Human genetic research: emerging trends in ethics. *Nature Rev. Genet.* 6(1), 75–79 (2005).
7. Lunshof, JE: Personalized medicine: How much can we afford? A bioethics perspective. *Personalized Med.* 2(1), 43–47 (2005).
8. Hopkins MM, Ibarreta D, Gaisser S *et al.*: Putting pharmacogenetics into practice. *Nature Biotechnol.* 24(4), 403–410 (2006).
9. Phillips KA, Van Bebber SL: A systematic review of cost-effectiveness analyses of pharmacogenomic interventions. *Pharmacogenomics* 5(8), 1139–1149 (2004).
10. Perlis RH, Ganz DA, Avorn J *et al.*: Pharmacogenetic testing in the clinical management of schizophrenia: a decision–analytic model. *J. Clin. Psychopharmacol.* 25(5), 427–434 (2005).
11. Kroll ME, Draper GJ, Stiller CA, Murphy MF: Childhood leukemia incidence in Britain, 1974–2000: time trends and possible relation to influenza epidemics. *J. Natl Cancer Inst.* 98(6), 417–420 (2006).
12. Coulthard SA, Matheson EC, Hall AG, Hogarth LA:The clinical impact of thiopurine methyltransferase polymorphisms on thiopurine treatment. *Nucleosides Nucleotides Nucleic Acids* 23(8–9), 1385–1391 (2004).
13. Philips FS, Sternberg SS, Hamilton S, Clarke DA: The toxic effects of 6-mercaptopurine and related compounds. *Ann. NY Acad. Sci.* 60(2), 283–296 (1954).
14. Fulginiti VA, Scribner R, Groth CG *et al.*: Infections in recipients of liver homografts. *N. Engl. J. Med.* 279(12), 619–626 (1968).
15. Lennard L, Gibson BE, Nicole T, Lilleyman JS: Congenital thiopurine methyltransferase deficiency and 6-mercaptopurine toxicity during treatment for acute lymphoblastic leukaemia. *Arch. Dis. Child* 69(5), 577–579 (1993).
16. Krynetski EY, Schuetz JD, Galpin AJ, Pui CH, Relling MV, Evans WE: A single point mutation leading to loss of catalytic activity in human thiopurine *S*-methyltransferase. *Proc. Natl Acad. Sci. USA* 92(4), 949–953 (1995).
17. McLeod HL, Relling MV, Liu Q, Pui CH, Evans WE: Polymorphic thiopurine methyltransferase in erythrocytes is indicative of activity in leukemic blasts from children with acute lymphoblastic leukemia. *Blood* 85(7), 1897–1902 (1995).
18. Andersen JB, Szumlanski C, Weinshilboum RM, Schmiegelow K: Pharmacokinetics, dose adjustments, and 6-mercaptopurine/methotrexate drug interactions in two patients with thiopurine methyltransferase deficiency. *Acta Paediatr.* 87(1), 108–111 (1998).
19. Tai HL, Krynetski EY, Yates CR *et al.*: Thiopurine *S*-methyltransferase deficiency: two nucleotide transitions define the most prevalent mutant allele associated with loss of catalytic activity in Caucasians. *Am. J. Hum. Genet.* 58(4), 694–702 (1996).
20. El-Azhary RA: Azathioprine: current status and future considerations. *Int. J. Dermatol.* 42(5), 335–341 (2003).
21. Ford LT, Cooper SC, Lewis MJ, Berg JD: Reference intervals for thiopurine *S*-methyltransferase activity in red blood cells using 6-thioguanine as substrate and rapid non-extraction liquid chromatography. *Ann. Clin. Biochem.* 41(Pt 4), 303–308 (2004).
22. Cheung ST, Allan RN: Mistaken identity: misclassification of TPMT phenotype following blood transfusion. *Eur. J. Gastroenterol. Hepatol.* 15(11), 1245–1247 (2003).
23. Flowers CR, Veenstra D: The role of cost-effectiveness analysis in the era of pharmacogenomics. *Pharmacoeconomics* 22(8), 481–493 (2004).
24. Veenstra DL, Higashi MK, Phillips KA: Assessing the cost-effectiveness of pharmacogenomics. *AAPS PharmSci.* 2(3), E29 (2000).
25. Phillips KA, Veenstra D, Van Bebber S, Sakowski J: An introduction to cost-effectiveness and cost–benefit analysis of pharmacogenomics. *Pharmacogenomics* 4(3), 231–239 (2003).
26. Tavadia SM, Mydlarski PR, Reis MD *et al.*: Screening for azathioprine toxicity: a pharmacoeconomic analysis based on a target case. *J. Am. Acad. Dermatol.* 42(4), 628–632 (2000).
27. Marra CA, Esdaile JM, Anis AH: Practical pharmacogenetics: the cost effectiveness of screening for thiopurine *S*-methyltransferase polymorphisms in patients with rheumatological conditions treated with azathioprine. *J. Rheumatol.* 29(12), 2507–2512 (2002).
28. Winter J, Walker A, Shapiro D, Gaffney D, Spooner RJ, Mills PR: Cost-effectiveness of thiopurine methyltransferase genotype screening in patients about to commence azathioprine therapy for treatment of inflammatory bowel disease. *Aliment Pharmacol. Ther.* 20(6), 593–599 (2004).
29. Oh KT, Anis AH, Bae SC: Pharmacoeconomic analysis of thiopurine methyltransferase polymorphism screening by polymerase chain reaction for treatment with azathioprine in Korea. *Rheumatology (Oxford)* 43(2), 156–163 (2004).
30. Gold M, Siegel J, Russell L, Weinstein M: Cost-effectiveness in health and medicine. Oxford University Press, New York, NY, USA (1996).
31. Collie-Duguid ES, Pritchard SC, Powrie RH *et al.*: The frequency and distribution of thiopurine methyltransferase alleles in Caucasian and Asian populations. *Pharmacogenetics* 9(1), 37–42 (1999).
32. Ameyaw MM, Collie-Duguid ES, Powrie RH, Ofori-Adjei D, McLeod HL: Thiopurine methyltransferase alleles in British and Ghanaian populations. *Hum. Mol. Genet.* 8(2), 367–370 (1999).
33. Sanderson J, Ansari A, Marinaki T, Duley J: Thiopurine methyltransferase: should it be measured before commencing thiopurine drug therapy? Ann. *Clin. Biochem.* 41(Pt 4), 294–302 (2004).
34. Colombel JF, Ferrari N, Debuysere H *et al.*: Genotypic analysis of thiopurine *S*-methyltransferase in patients with Crohn's disease and severe myelosuppression during azathioprine therapy. *Gastroenterology* 118(6), 1025–1030 (2000).
35. Ansari A, Hassan C, Duley J *et al.*: Thiopurine methyltransferase activity and the use of azathioprine in inflammatory bowel disease. *Aliment Pharmacol. Ther.* 16(10), 1743–1750 (2002).
36. Schwab M, Schaffeler E, Marx C *et al.*: Azathioprine therapy and adverse drug reactions in patients with inflammatory

bowel disease: impact of thiopurine *S*-methyltransferase polymorphism. *Pharmacogenetics* 12(6), 429–436 (2002).

37. Viscomi S, Pastore G, Dama E *et al.*: Life expectancy as an indicator of outcome in follow-up of population-based cancer registries: the example of childhood leukemia. *Ann. Oncol.* 17(1), 167–171 (2006).
38. Oostenbrink J, Bouwmans C, Koopmanschap M, Rutten F: *Handbook for Costing Research. Methods and Guideline Prices for Economic Evaluations in Health.* Health Care Insurance Board, Amstelveen, the Netherlands. Actualized version (2004).
39. Church GM: Genomes for all. *Sci. Am.* 294(1), 46–54 (2006).
40. Kurzawski M, Dziewanowski K, Gawronska-Szklarz B, Domanski L, Drozdzik M: The impact of thiopurine *S*-methyltransferase polymorphism on azathioprine-induced myelotoxicity in renal transplant recipients. *Ther. Drug Monit.* 27(4), 435–441 (2005).
41. To Err Is Human. Building a Safer Health System. Committee on Quality of Health Care in America. Institute of Medicine. In: Institute of Medicine Report. Kohn L, Corrigan J, Donaldson M (Eds), National Academy Press, Washington, DC, USA (1999).
42. Pirmohamed M, James S, Meakin S *et al.*: Adverse drug reactions as cause of admission to hospital: prospective analysis of 18,820 patients. *BMJ* 329(7456), 15–19 (2004).
43. Dormann H, Neubert A, Criegee-Rieck M *et al.*: Readmissions and adverse drug reactions in internal medicine: the economic impact. *J. Intern. Med.* 255(6), 653–663 (2004).
44. Gurwitz D, Weizman A, Rehavi M: Education: Teaching pharmacogenomics to prepare future physicians and researchers for personalized medicine. *Trends Pharmacol. Sci.* 24(3), 122–125 (2003).
45. Gurwitz D, Lunshof JE, Dedoussis G *et al.*: Pharmacogenomics education: International Society of Pharmacogenomics recommendations for medical, pharmaceutical, and health schools deans of education. *Pharmacogenomics J.* 5(4), 221–225 (2005).
46. Baars, MJ, Henneman L, Ten Kate LP: Deficiency of knowledge of genetics and genetic tests among general practitioners, gynecologists, and pediatricians: a global problem. *Genet. Med.* 7(9), 605–610 (2005).

Websites

101. Institute for Prospective Technological Studies (IPTS) website. www.jrc.es
102. Institute for Prospective Technological Studies (IPTS) Report. Pharmacogenetics and Pharmacogenomics: State-of-the-art and potential socio-economic impacts in the EU. www.jrc.es/home/pages/detail.cfm?prs=1387
103. Prometheus Laboratories *TPMT* genotyping test. www.prometheuslabs.com/212a.asp?nav=products
104. Guide to the Methods of Technology Appraisal. National Institute for Clinical Excellence (NICE) 2003. www.nice.org.uk/pdf/methodologyconsultationdraftfinal.pdf