



Original Research

A cost analysis of upfront *DPYD* genotype–guided dose individualisation in fluoropyrimidine-based anticancer therapy



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Abstract Background: Fluoropyrimidine therapy including capecitabine or 5-fluorouracil can result in severe treatment-related toxicity in up to 30% of patients. Toxicity is often related to reduced activity of dihydropyrimidine dehydrogenase, the main metabolic fluoropyrimidine enzyme, primarily caused by genetic *DPYD* polymorphisms. In a large prospective study, it was concluded that upfront *DPYD*-guided dose individualisation is able to improve safety of fluoropyrimidine-based therapy. In our current analysis, we evaluated whether this strategy is cost saving.

Methods: A cost-minimisation analysis from a health-care payer perspective was performed as part of the prospective clinical trial (NCT02324452) in which patients prior to start of fluoropyrimidine-based therapy were screened for the *DPYD* variants *DPYD**2A, c.2846A>T, c.1679T>G and c.1236G>A and received an initial dose reduction of 25% (c.2846A>T, c.1236G>A) or 50% (*DPYD**2A, c.1679T>G). Data on treatment, toxicity, hospitalisation and other toxicity-related interventions were collected. The model compared prospective screening for these *DPYD* variants with no *DPYD* screening. One-way and probabilistic sensitivity analyses were also performed.

Results: Expected total costs of the screening strategy were €2599 per patient compared with €2650 for non-screening, resulting in a net cost saving of €51 per patient. Results of the probabilistic sensitivity and one-way sensitivity analysis demonstrated that the screening strategy was very likely to be cost saving or worst case cost-neutral.

Conclusions: Upfront *DPYD*-guided dose individualisation, improving patient safety, is cost saving or cost-neutral but is not expected to yield additional costs. These results endorse implementing *DPYD* screening before start of fluoropyrimidine treatment as standard of care.

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1. Introduction

The class of fluoropyrimidine anticancer drugs includes 5-fluorouracil (5-FU) and its oral prodrug capecitabine. These drugs are used by approximately two million patients yearly worldwide [1] and are the cornerstone of chemotherapeutic treatment for several solid tumour types, including colorectal, breast, gastric and head and neck cancers. While fluoropyrimidine drugs are highly valuable treatment options, severe and potential fatal fluoropyrimidine-related toxicity remains a major

clinical limitation. Around 15–30% of the patients develop severe treatment-related toxicity [2,3], usually associated with interruption or discontinuation of therapy and often hospitalisation, resulting in increased health-care costs.

During the last decades, it has become clear that safety of patients treated with fluoropyrimidine-based anticancer therapy is strongly affected by interindividual variability in the enzyme dihydropyrimidine dehydrogenase (DPD), which is the main metabolic enzyme of fluoropyrimidines. The DPD enzyme is present in the

liver and inactivates over 80% of 5-FU [4]. DPD enzyme activity varies widely between patients, with an estimated 3–8% of the population having a reduced DPD activity [5,6]. DPD deficiency results in reduced 5-FU clearance, and as a direct consequence, highly increased risk of severe treatment-related toxicity when DPD-deficient patients are treated with standard doses of a fluoropyrimidine drug [7].

DPD deficiency can be caused by genetic polymorphisms in *DPYD*, the gene encoding DPD. Currently, four *DPYD* variants are considered as being clinically relevant, and dosing recommendations are provided for these variants: *DPYD**2A, c.1679T>G, c.2846A>T and c.1236G>A [8,9]. Upfront genotyping followed by a fluoropyrimidine dose reduction in carriers in any of these four variants has proven a useful strategy to improve patient safety [10,11]. However, this strategy has not yet been universally implemented in daily clinical care.

One of the potential barriers that can make physicians reluctant to implement upfront *DPYD* screening as a routine test is uncertainty on the cost-effectiveness of a *DPYD* screening strategy [12]. Deenen et al. previously showed that upfront screening for one *DPYD* variant, *DPYD**2A, is cost saving, as average total medical costs in the screening arm were €2772 per patient and therefore lower than the non-screening arm, for which the average total medical costs were €2817 per patient. This shows that the reduction in toxicity-related costs outweighs the screening costs. [10] In our current study, we aimed to investigate the medical costs associated with upfront screening for the four *DPYD* variants currently considered clinically relevant and dose individualisation in heterozygous carriers of a *DPYD* variant, therefore evaluating the net cost effects of this expanded *DPYD* genotyping strategy.

2. Patients and methods

2.1. Study design and participants

The cost analysis was performed as part of a recently published clinical trial [11]. This was a multicentre study in which 17 hospitals in the Netherlands participated (NCT02324452). The study approval was obtained from the institutional review board of The Netherlands Cancer Institute, Amsterdam, the Netherlands, and approval from the board of directors of each individual hospital was obtained for all participating centres. All patients provided written informed consent before inclusion in the study.

The study population consisted of patients treated with a fluoropyrimidine-based anticancer therapy, either as single agent or in combination with other chemotherapeutic agents and/or radiotherapy. Prior chemotherapy was allowed, except for prior use of

fluoropyrimidines. Before the start of fluoropyrimidine therapy, patients were genotyped for four *DPYD* variants (*DPYD**2A, c.1679T>G, c.2846A>T and c.1236G>A). Heterozygous *DPYD* variant allele carriers received an initial dose reduction of either 25% (for c.2846A>T and c.1236G>A) or 50% (for *DPYD**2A and c.1679T>G), in line with current recommendations from Dutch and international pharmacogenomic guidelines [9,13]. To achieve maximal safe exposure, dose escalation was allowed after the first two cycles provided that treatment was well tolerated and was left at the discretion of the physician. The dose of other chemotherapeutic agents or radiotherapy was left unchanged at the start of treatment. Homozygous or compound heterozygous *DPYD* variant allele carriers were not included in the study. Non-carriers of the abovementioned *DPYD* variants were considered wild-type patients in this study and were treated according to existing standard of care.

Toxicity was graded by participating centres according to the National Cancer Institute Common Terminology Criteria for Adverse Events [14], and severe toxicity was defined as grade three or higher. Patients were followed for toxicity during the entire treatment period. Toxicity defined as possibly, probably or definitely related to fluoropyrimidine-treatment was considered treatment-related toxicity. Toxicity-related hospitalisation and treatment discontinuation due to adverse events were also investigated.

The primary end-point of the prospective study was the frequency of severe overall fluoropyrimidine-related toxicity across the entire treatment duration. A comparison was made between *DPYD* variant allele carriers treated with reduced dose and wild-type patients treated with standard dose in this study and also with *DPYD* variant allele carriers treated with full dose in a historical cohort derived from a previously published meta-analysis [8]. Secondary end-points of the prospective study included a cost analysis of individualised dosing based on upfront genotypic assessment and pharmacokinetics of capecitabine and 5-FU in *DPYD* variant allele carriers.

2.2. Cost analysis

To compare the prospective screening for four *DPYD* variants (screening strategy) with no *DPYD* screening (non-screening strategy), a cost analysis model was composed. This analysis consisted of a cost-minimisation analysis using a decision analytical model from a health-care payer perspective.

A previously published model by Deenen et al. [10] was used and updated with data from the current study and current prices. Estimated parameters incorporated in the model were derived from data of the present trial and relevant data from literature [15,16]. Interventions for treatment-related toxicity were

prospectively collected for all patients during the trial. An overview of the decision tree is depicted in Fig. 1. In the model, a comparison between the screening strategy (prospective screening for four *DPYD* variants and dose adjustments in heterozygous *DPYD* variant allele carriers) and the non-screening strategy was made. Expected differences in costs of both strategies were calculated.

Costs included were restricted to direct medical costs only and included costs for genotyping, fluoropyrimidine drug therapy including visits to the medical doctor and day care, costs for treatment of adverse events (e.g. extra medication, extra doctor visits, extra assessments) and costs for hospitalisation because of adverse events. Costs for other anticancer drugs than the fluoropyrimidine drugs were not included in the model as they were expected to be equal in both arms. Cost saving was calculated as the difference between the net direct costs of the *DPYD* screening strategy versus the non-screening strategy.

To examine the effects on variations in parameter values, one-way and probabilistic sensitivity analyses were performed. In the one-way sensitivity analysis, each parameter was varied individually at $\pm 20\%$ of the baseline value. In the probabilistic sensitivity analysis, all parameters were varied simultaneously by running 1000 simulations (Monte Carlo). Since the parameter values of the wild-type patients for both the screening and the non-screening arm are identical, these parameters remained fixed in the probabilistic sensitivity analysis.

3. Results

3.1. Patient characteristics and toxicity incidence

The study was open for inclusion between April 30th, 2015 and December 21st, 2017. In this period, a total of 1103 evaluable patients were enrolled in this study, of whom 85 were heterozygous *DPYD* variant allele carriers (7.7%) and 1018 wild-type patients (92.3%). The group of *DPYD* variant allele carriers included 51 c.1236G>A carriers, 17 c.2846A>T carriers, 16 *DPYD**2A carriers and one c.1679T>G carrier. Details on patient characteristics, treatment and toxicity incidence are published separately [11]. In short, 33 out of 85 *DPYD* variant allele carriers (39%) experienced grade ≥ 3 treatment-related toxicity, while this was significantly lower in the group of wild-type patients with 231 out of 1018 patients (23%) experiencing severe toxicity ($P = 0.001$). Compared with the historical cohort of *DPYD* variant allele carriers treated with full dose, *DPYD* genotype-guided dosing markedly decreased the risk of severe fluoropyrimidine-related toxicity for three out of four variants (*DPYD**2A, c.1679T>G and c.2846A>T; Fig. 2). No reduction in severe treatment-related toxicity was shown for c.1236G>A.

3.2. Cost analysis

All parameter estimates used in the model are provided in Table 1. In the cost analysis, the expected total costs for the screening strategy were €2599 per patient

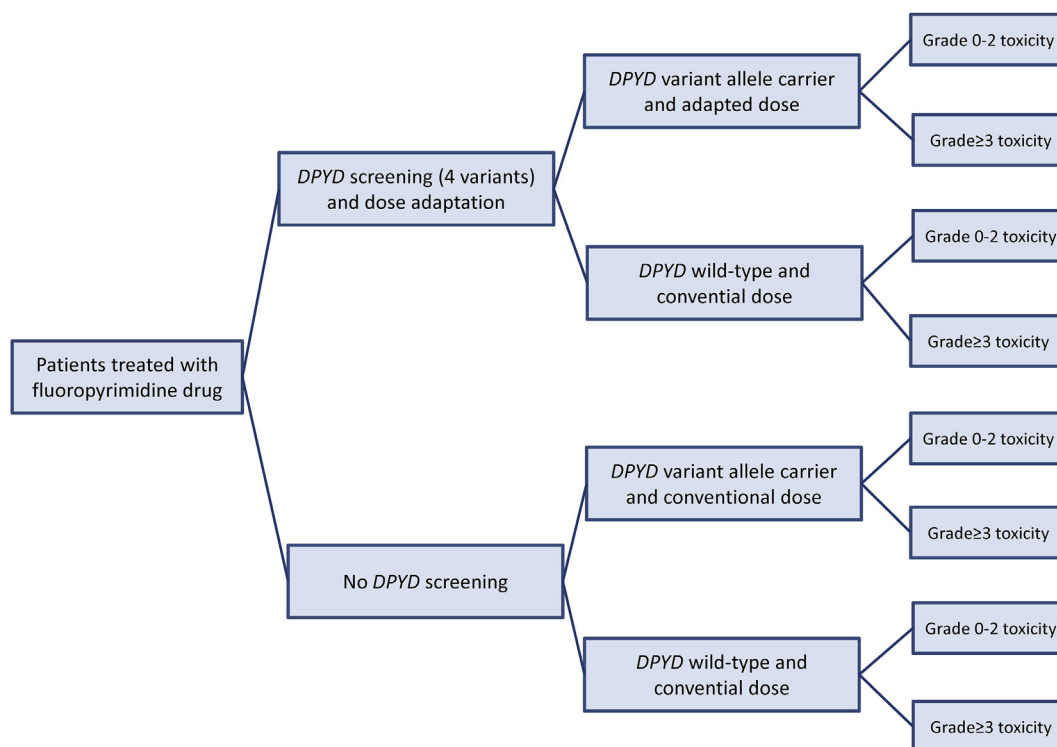


Fig. 1. Decision tree for cost analysis. *DPYD*, gene encoding dihydropyrimidine dehydrogenase.

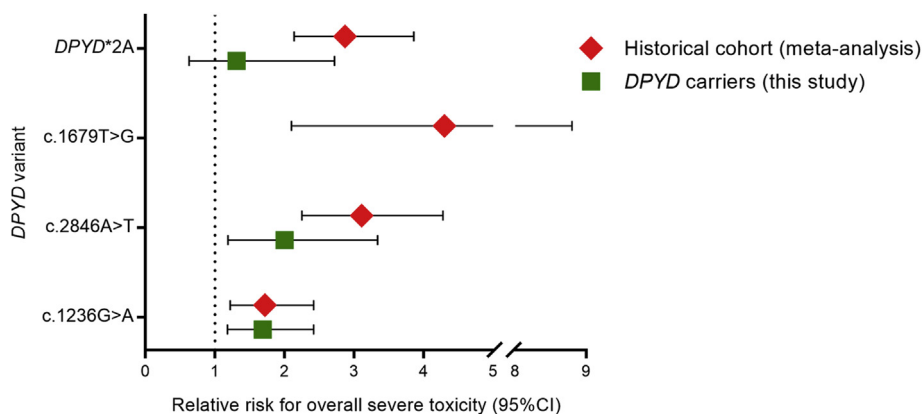


Fig. 2. Relative risk for severe treatment-related toxicity of *DPYD* variant allele carriers receiving dose-reduction (this study) and *DPYD* variant allele carriers treated with full dose (historical cohort). The relative risk for overall grade ≥ 3 fluoropyrimidine-related toxicity compared to non-carriers of this variant was calculated with data from this study [11] and for the historical cohort with data derived from a previously published random-effects meta-analysis [8]. Unadjusted relative risks for the meta-analysis are depicted, as the relative risk in the current study was also calculated as an unadjusted value. For c.1679T>G no relative risk could be calculated in this study, as only one patient who carried c.1679T>G was present. This patient did not experience severe toxicity. 95% CI, 95% confidence interval; *DPYD*, gene encoding dihydropyrimidine dehydrogenase.

compared with €2650 per patient for the non-screening strategy, resulting in a net cost saving of €51 per patient treated.

Results of the one-way sensitivity analysis are depicted in Fig. 3, demonstrating that the frequency of the *DPYD* variant allele genotype had the largest influence on outcome of the cost analysis, followed by the risk of hospitalisation at the nursing ward for *DPYD* variant allele carrier receiving standard dose, and *DPYD* genotyping costs. However, in all cases, the cost saving remained positive.

Results of the simulations for the probabilistic sensitivity analysis are depicted in Fig. 4. Average cost savings from the simulation in the probabilistic sensitivity analysis were €52 per patient (95% interval range -€38 to €176). Average gain in safety was 0.89% (95% interval range -0.04% to 1.79%). This gain in safety represents the difference between the proportion of patients treated without severe toxicity (both wild-type patients and *DPYD* variant allele carriers taken together) in the screening strategy and the non-screening strategy.

4. Discussion

The cost analysis performed in this study showed that prospective *DPYD* screening for these four variants and dose individualisation is cost saving. This confirms that upfront *DPYD* screening does not result in an increase in health-care costs, while it can significantly improve patient safety and prevent toxicity-related deaths, as shown previously [11]. Results of the probabilistic sensitivity analysis and one-way sensitivity demonstrated that even when varying parameters in the model,

the screening strategy is unlikely to result in an increase in costs.

However, the net saving for the screening strategy in our cost analysis was with €51 relatively small. One of the determinants for this finding is that in our clinical study, patients carrying a *DPYD* variant were still at increased risk of developing severe treatment-related toxicity compared with wild-type patients (39% versus 23%, $P = 0.001$) [11]. The higher incidence of toxicity in *DPYD* variant allele carriers was mainly driven by carriers of the variants c.1236G>A and c.2846A>T. For these two variants, a 25% dose reduction was applied in the study, which was concluded to be probably insufficient to reduce the incidence of toxicity to the background incidence in wild-type patients.

Our results are in line with four previous studies investigating costs of *DPYD* genotyping and toxicity [10,17]. Deenen et al. previously confirmed that upfront screening for one *DPYD* variant (*DPYD*2A*) is cost saving [10]. Another study, by Cortejoso et al. investigated screening for three variants (*DPYD*2A*, c.2846A>T, c.1679T>G) and compared genotyping costs and costs for treating severe neutropenia in a retrospective analysis. Occurrence of severe neutropenia resulted in average costs of €3044 per patient for treatment of this side-effect (drug and hospitalisation costs). Genotyping costs for the three *DPYD* variants were only €6.40 per patient (approximately sixteen times less expensive than in our study). The authors calculated that *DPYD* genotyping would be cost effective, provided that at least 2.1 cases of severe neutropenia per 1000 treated patients are prevented by upfront genotyping for the three variants [17]. This was, however, not validated in a prospective setting.

Table 1
Cost and probability parameters used in the cost analysis.

| Probabilities and other parameters | | | | |
|---|----------------|-----------------------------|--------------------------------|---------------------------------------|
| Variable | Baseline value | Standard error ^a | Sensitivity range ^b | Reference |
| Frequency <i>DPYD</i> genotype | | | | |
| <i>DPYD</i> wild-type | 0.9229 | 0.0080 | Fixed | This study [11] |
| <i>DPYD</i> variant allele carrier | 0.0771 | 0.0080 | 0.0617–0.0925 | This study [11] |
| Risk severe toxicity | | | | |
| <i>DPYD</i> wild-type | 0.2269 | Fixed | Fixed | This study [11] |
| <i>DPYD</i> variant allele carrier, reduced dose | 0.3882 | 0.0526 | 0.3106–0.4658 | This study [11] |
| <i>DPYD</i> variant allele carrier, standard dose | 0.5015 | 0.0274 | 0.4012–0.6018 | Meta-analysis [8] |
| <i>DPYD</i> wild-type | | | | |
| Hospitalisation nursing ward | 0.1356 | Fixed | Fixed | This study [11] |
| Mean duration (days) | 7.9855 | Fixed | Fixed | This study [11] |
| Hospitalisation ICU | 0.0088 | Fixed | Fixed | This study [11] |
| Mean duration (days) | 3.1111 | Fixed | Fixed | This study [11] |
| <i>DPYD</i> variant allele carrier, reduced dose | | | | |
| Hospitalisation nursing ward | 0.1647 | 0.0400 | 0.1318–0.1976 | This study [11] |
| Mean duration (days) | 5.7857 | 1.3350 | 4.6286–6.9428 | This study [11] |
| Hospitalisation ICU | 0.0235 | 0.0163 | 0.0188–0.0282 | This study [11] |
| Mean duration (days) | 1.0000 | 0.1000 | 0.8000–1.2000 | This study [11] |
| <i>DPYD</i> variant allele carrier, standard dose | | | | |
| Hospitalisation nursing ward | 0.2350 | 0.0422 | 0.1880–0.2820 | Analysis on previous study [10,20] |
| Mean duration (days) | 13.1000 | 3.0000 | 10.4800–15.7200 | Analysis on previous study [10,20] |
| Hospitalisation ICU | 0.0310 | 0.0172 | 0.0248–0.0372 | Analysis on previous study [10,20] |
| Mean duration (days) | 7.0000 | 3.0000 | 5.6000–8.4000 | Analysis on previous study [10,20] |
| Mean number of cycles | | | | |
| Capecitabine | 5.0208 | 0.1567 | 4.0166–6.0250 | This study [11] |
| 5-FU | 5.0426 | 0.3639 | 4.0341–6.0511 | This study [11] |
| Type of fluoropyrimidine drug | | | | |
| Capecitabine | 0.83 | Fixed | Fixed | This study [11] |
| 5-FU | 0.17 | Fixed | Fixed | This study [11] |
| Mean dose intensity for <i>DPYD</i> variant allele carriers | | | | |
| | 0.6910 | 0.0124 | 0.5528–0.8292 | This study [11] |
| Cost parameters (expressed in €) | | | | |
| Variable | Baseline value | Standard error ^a | Sensitivity range ^b | Reference |
| <i>DPYD</i> genotyping costs | | | | |
| <i>DPYD</i> genotyping costs | 100 | Fixed | 80–120 | This study [11] |
| Hospitalisation nursing ward (per day) | 636 | Fixed | Fixed | Guideline [15] |
| Hospitalisation ICU (per day) | 2015 | Fixed | Fixed | Guideline [15] |
| Additional costs for interventions related to toxicity (expect hospitalisation) | | | | |
| Grade 0–2 | 86 | Fixed | Fixed | This study [11] |
| Grade ≥3 | 234 | Fixed | Fixed | This study [11] |
| Treatment costs capecitabine (per cycle) | | | | |
| Capecitabine medication | 144.06 | 30 | Fixed | This study [11]/Price info drugs [16] |
| Medical doctor visit | 132 | Fixed | Fixed | Guideline [15] |
| Treatment costs 5-FU per cycle | | | | |
| 5-FU medication + pharmacy preparation | 59.29 | 20 | Fixed | This study/Price info drugs [16] |
| Administration at day care | 276 | Fixed | Fixed | Guideline [15] |
| Medical doctor visit | 132 | Fixed | Fixed | Guideline [15] |

5-FU, 5-fluorouracil; *DPYD*, gene encoding dihydropyrimidine dehydrogenase; ICU, intensive care unit.

^a The standard error was calculated on data of this study or otherwise estimated for parameters not derived from this study. The standard error is used for the probabilistic sensitivity analysis.

^b The sensitivity range is calculated by varying the baseline value $\pm 20\%$. The sensitivity range is used for the one-way sensitivity analysis.

The third study, by Murphy et al., investigated the cost implications for reactive *DPYD* screening (i.e. screening patients for *DPYD* variants after experiencing severe toxicity) versus prospective screening [18]. In a period of 3 years, all patients experiencing severe (grade ≥ 3) fluoropyrimidine-related toxicity in an Irish hospital were screened for four *DPYD* variants (*DPYD**2A, c.2846A>T, c.1679T>G and c.1601G>A). Genotyping costs, if prospective *DPYD* screening for all patients would have been performed, were calculated. Total costs

of hospitalisation for five *DPYD* variant allele carriers (identified after experiencing severe toxicity) were €232,061, while prospectively testing would have cost in total €23,718 for the 134 included patients (€177 per patient), showing that hospitalisation costs are significantly higher than costs for prospective *DPYD* screening [18]. The main difference between their study and our study was that the study by Murphy et al. did not collect data on the prospective *DPYD* screening strategy but only on reactive *DPYD* screening.

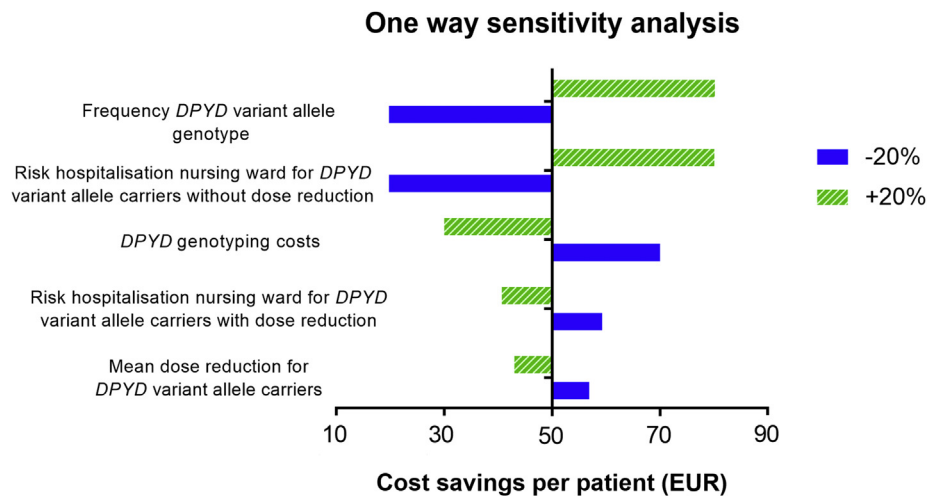


Fig. 3. One-way sensitivity analysis of upfront *DPYD* genotyping versus non-screening. All parameters were individually varied by $\pm 20\%$ (-20% depicted in blue, $+20\%$ depicted in green), effects of which cost savings are indicated by horizontal bars. The vertical line indicates the baseline costs savings of €50. *DPYD*, gene encoding dihydropyrimidine dehydrogenase. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

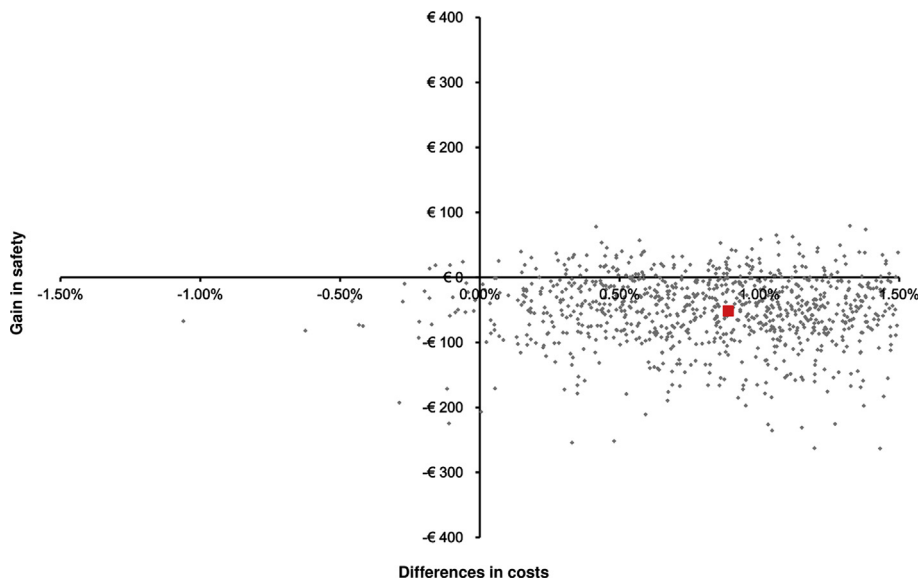


Fig. 4. Probabilistic sensitivity analysis of the cost analysis. For this sensitivity analysis, all parameters were varied simultaneously by running 1000 Monte Carlo simulations. The red square indicates the observed values. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

The fourth study was a retrospective study as well, performed by Toffoli et al. [19] Toxicity-related costs on 550 colorectal cancer patients were investigated, and genotyping for the same four variants as in our study was performed, but this was done retrospectively and not used for dose adjustments. This showed that average costs for treatment of toxicity were higher in *DPYD* variant allele carriers (€2972) than in non-carriers (€825), $P < 0.0001$ [19].

To conclude, in addition to the important finding that upfront *DPYD* genotype-guided dose individualisation is able to markedly increase patient safety, this

study now confirms that this upfront *DPYD* screening strategy does not result in an increase in direct medical costs. This further endorses that *DPYD* genotyping should be implemented as routine clinical care.

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Conflict of interest statement

J.H.M.S. is shareholder of Modra Pharmaceuticals bv, inventor of patents on oral taxanes and consultant to Debiopharm. All other authors have declared no conflicts of interest.

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