Personalised medicine of fluoropyrimidines using DPYD pharmacogenetics

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CHAPTER 6

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

Eur J Cancer. 2018;107:60-7

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Abstract
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 (DPD), the main metabolic fluoropyrimidine enzyme, primarily caused by genetic *DPYD* polymorphisms. In a large prospective study, it was concluded that upfront *DPYD*-guided dose individualization is able to improve safety of fluoropyrimidine-based therapy. In our current analysis, we evaluated whether this strategy is cost-saving.

A cost-minimization 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, hospitalization 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.

Expected total costs of the screening strategy were €2,599 per patient, compared to €2,650 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.

Upfront *DPYD*-guided dose individualization, 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.

Acknowledgements
All 17 participating centers are acknowledged for their contribution to patient inclusion. We thank dr. Maarten Deenen for providing his previously developed cost model (Deenen *et al.* J Clin Oncol 2016) and his input to the study.

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 tumor types, including colorectal, breast, gastric and head- and neck cancer. 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 hospitalization, 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 inter-individual 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 to 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 €2,772 per patient and therefore lower than the non-screening arm, for which the average total medical costs were €2,817 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 individualization in heterozygous carriers of a *DPYD* variant, therefore evaluating the net cost effects of this expanded *DPYD* genotyping strategy.

Patients and methods

Study design and participants

The cost analysis was performed as part of a recently published clinical trial.[11] This was a multicenter study in which 17 hospitals in the Netherlands participated (NCT02324452). Study approval was obtained by 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 centers. 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 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 above mentioned *DPYD* variants were considered wild-type patients in this study, and were treated according to existing standard of care.

Toxicity was graded by participating centers according to the National Cancer Institute common terminology criteria for adverse events (CTC-AE),[14] and severe toxicity was defined as grade 3 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 hospitalization 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 endpoints of the prospective study included a cost analysis of individualized dosing based on upfront genotypic assessment, and pharmacokinetics of capecitabine and 5-FU in *DPYD* variant allele carriers.

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-minimization 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 Figure 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 hospitalization due to 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 ±20% of the baseline value. In the probabilistic sensitivity analysis, all parameters were varied simultaneously by running 1,000 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.

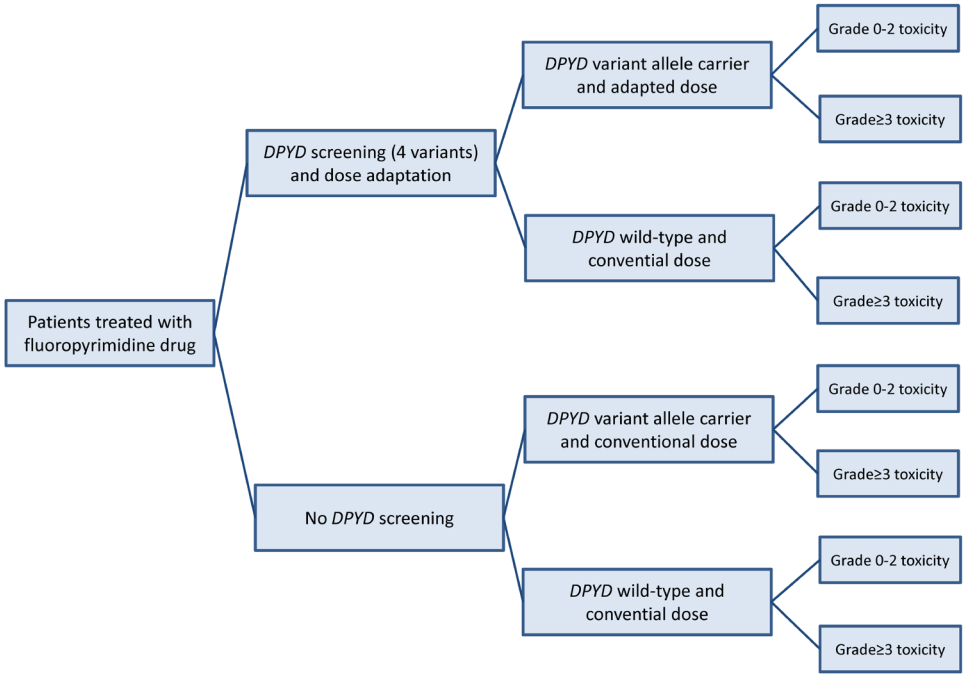

Figure 1. Decision tree for cost analysis

Results

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 1,103 evaluable patients were enrolled in this study, of whom 85 heterozygous *DPYD* variant allele carriers (7.7%) and 1,018 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 1,018 patients (23%) experiencing severe toxicity (p=0.001). Compared to 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; Figure 2). No reduction in severe treatment-related toxicity was shown for c.1236G>A.

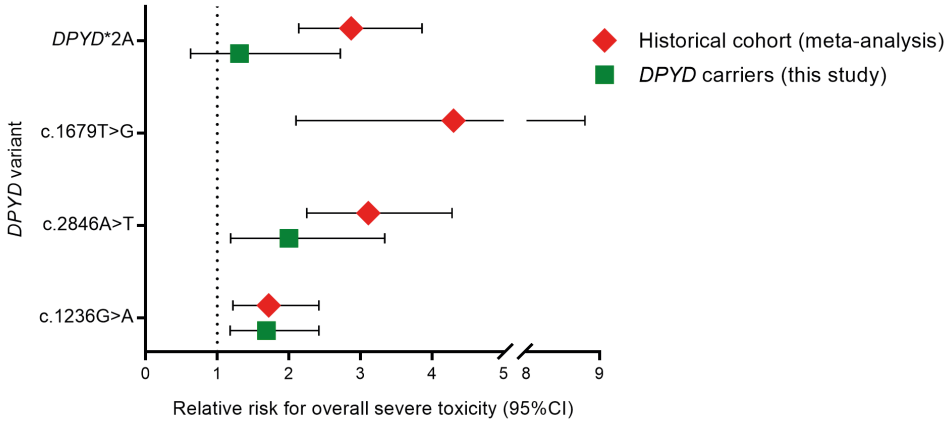

Figure 2. Relative risk for severe treatment-related toxicity of *DPYD* variant allele carriers receiving dose-reduction (this study) and *DPYD* variant allele carriers treated with full dose (historical cohort)
The relative risk for overall grade ≥3 fluoropyrimidine-related toxicity compared to non-carriers 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.
Abbreviations: 95%CI: 95% confidence interval.

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 €2,599 per patient, compared to €2,650 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 Figure 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 hospitalization 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 Figure 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.

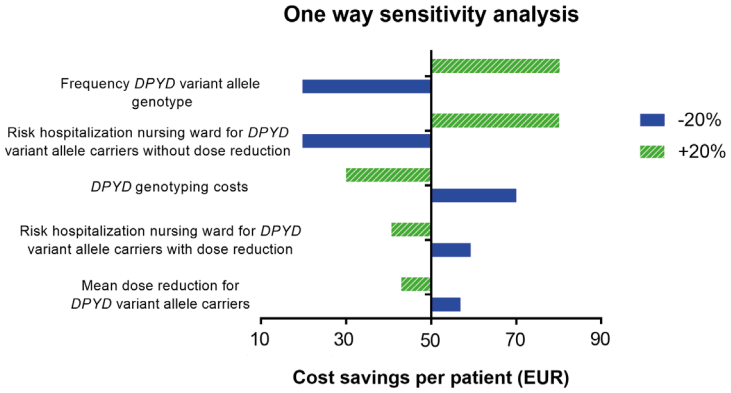

Figure 3. One-way sensitivity analysis of upfront *DPYD* genotyping versus non-screening

All parameters were individually varied by ±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.

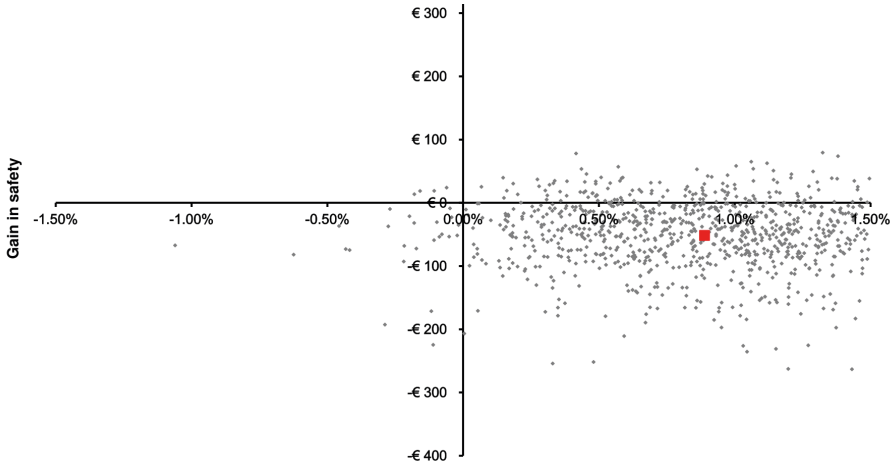

Figure 4. Probabilistic sensitivity analysis of the cost analysis

For this sensitivity analysis, all parameters were varied simultaneously by running 1,000 Monte Carlo simulations. The red square indicates the observed values.

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 *DPYD* genotype				
DPYD wild-type	0.9229	0.0080	Fixed	This study[11]
DPYD variant allele carrier	0.0771	0.0080	0.0617—0.0925	This study[11]
Risk severe toxicity				
DPYD wild-type	0.2269	Fixed	Fixed	This study[11]
DPYD variant allele carrier, reduced dose	0.3882	0.0526	0.3106—0.4658	This study[11]
DPYD variant allele carrier, standard dose	0.5015	0.0274	0.4012—0.6018	Meta-analysis[8]
DPYD wild-type				
Hospitalization nursing ward	0.1356	Fixed	Fixed	This study[11]
Mean duration (days)	7.9855	Fixed	Fixed	This study[11]
Hospitalization ICU	0.0088	Fixed	Fixed	This study[11]
Mean duration (days)	3.1111	Fixed	Fixed	This study[11]
DPYD variant allele carrier, reduced dose				
Hospitalization 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]
Hospitalization 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]
DPYD variant allele carrier, standard dose				
Hospitalization 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]
Hospitalization 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 *DPYD* variant allele carriers	0.6910	0.0124	0.5528—0.8292	This study[11]

table continues

Cost parameters (expressed in €)				
Variable	**Baseline value**	**Standard error[a]**	**Sensitivity range[b]**	**Reference**
DPYD genotyping costs	100	Fixed	80—120	This study[11]
Hospitalization nursing ward (per day)	636	Fixed	Fixed	Guideline[15]
Hospitalization ICU (per day)	2,015	Fixed	Fixed	Guideline[15]
Additional costs for interventions related to toxicity (expect hospitalization)				
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]

[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 ±20%. The sensitivity range is used for the one way sensitivity analysis.
Abbreviations: 5-FU: 5-fluorouracil; *DPYD*: gene encoding dihydropyrimidine dehydrogenase; ICU: intensive care unit.

Discussion

The cost analysis performed in this study showed that prospective *DPYD* screening for these four variants and dose individualization is cost-saving. This confirms that upfront *DPYD* screening does not result in an increase in healthcare 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 to 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 for treatment for this side effect of €3,044 per patient (drug and hospitalization costs). Genotyping costs for the three *DPYD* variants were only €6.40 per patient (approximately 16 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 1,000 treated patients are prevented by upfront genotyping of the three variants.[17] This was, however, not validated in a prospective setting.

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 three 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 hospitalization 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 hospitalization 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.

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 of 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 (€2,972) than in non-carriers (€825), p<0.0001.[19]

To conclude, in addition to the important finding that upfront *DPYD* genotype-guided dose individualization 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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