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Research Article

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Personalized Medicine

Budget impact and transferability of cost–effectiveness of *DPYD* testing in metastatic breast cancer in three health systems

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The cost–effectiveness and budget impact of introducing extended *DPYD* testing prior to fluoropyrimidine-based chemotherapy in metastatic breast cancer patients in the UK, The Netherlands and Hungary were examined. *DPYD* testing with ToxNav© was cost-effective in all three countries. In the UK and The Netherlands, the ToxNav strategy led to more quality-adjusted life years and fewer costs to the health systems compared with no genetic testing and standard dosing of capecitabine/5-fluorouracil. In Hungary, the ToxNav strategy produced more quality-adjusted life years at a higher cost compared with no testing and standard dose. The ToxNav strategy was found to offer budget savings in the UK and in The Netherlands, while in Hungary it resulted in additional budget costs.

Tweetable abstract: The cost–effectiveness and budget impact of extended *DPYD* testing with ToxNav prior to capecitabine/5-fluorouracil in metastatic breast cancer in the UK, The Netherlands and Hungary were examined. ToxNav was cost-effective in all three countries and budget-saving in the UK and The Netherlands.

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Breast cancer is a leading cause of morbidity and mortality worldwide. In Europe, the healthcare costs to treat the disease are among the highest [1], regardless of the type of healthcare system. In England and Wales, it is the most common cancer diagnosed in women, with over 40,000 new cases and more than 10,000 deaths recorded each year [2]. In The Netherlands, breast cancer is the most commonly detected cancer in women and the second leading cause of cancer deaths [3]. In Hungary, it is the second most frequent cancer diagnosed in the female population and contributes to over 2000 deaths annually [4,5]. Around 6–7% of new cases are diagnosed at an advanced stage, most often at stage IV, which is also referred to as metastatic breast cancer [6]. Another 10% of new cases will eventually develop into an advanced stage in the 5 years following initial diagnosis [7].

Fluoropyrimidine-based chemotherapy regimens, including capecitabine and 5-fluorouracil (5FU), have been widely used in European countries for treating solid tumors, including primary and secondary breast cancers. NICE in England recommends using capecitabine and 5FU for the treatment of locally advanced or metastatic breast cancer [2]. Similar clinical guidance is in place in The Netherlands and Hungary. These guidelines are based on the

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proven benefit of capecitabine and 5FU in terms of improved progression-free and overall survival of cancer patients. However, 10–20% of treated patients experience mild toxicities, and around 1–5% of patients experience severe or life-threatening toxicities that are due to the significantly impaired function of the dihydropyrimidine dehydrogenase (DPYD*)* enzyme that metabolizes these drugs [8–10].

Establishing the *DPYD* status of all patients prior to receiving capecitabine and 5FU could help identify patients at higher risk of severe toxicity and adjust the chemotherapy dose accordingly. Therefore, several European countries have already adopted or are about to adopt *DPYD* genetic testing prior to administering fluoropyrimidine-based chemotherapy. However, there is no uniformity in adopting *DPYD* testing across European countries. In Hungary, upfront *DPYD* testing is not routinely performed. In The Netherlands, *DPYD* testing is part of routine care and targets only four SNPs in the *DPYD* gene. Testing for four SNPs is currently recommended in the guidelines of the Clinical Pharmacogenetics Implementation Consortium (CPIC), 2017 [11–13]. In England, *DPYD* testing is about to become part of routine care in the NHS. There are ongoing discussions about how many and what variants to target. This is because when testing for the four CPIC variants and adjusting dosing accordingly, at least 40–50% of patients still experience severe toxicities following capecitabine and 5FU therapy. This suggests that there are other pathogenic variants in addition to the four SNPs [13]. In addition, the prevalence of different variants may vary across ethnic backgrounds [10].

To further improve the dosing of fluoropyrimidine-based chemotherapy, an extended gene panel (ToxNav©) was developed. The ToxNav test includes three of the four alleles (excluding rs56038477/rs75017182 HAPB3) recommended by CPIC, 15 additional variants associated with *DPYD* function and one allele of the *ENOSF1* gene [14]. ToxNav has been piloted in several hospitals in England. In the Oxford University Hospitals (OUH) NHS Trust, all cancer patients assigned to fluoropyrimidine-based chemotherapy have been tested since June 2019 [15]. In a previous study, thereafter called the OUH study, ToxNav reduced the risk of toxicity-related side effects and hospital costs [15]. In a follow-up economic evaluation, it was estimated that testing metastatic breast cancer patients with ToxNav prior to fluoropyrimidine-based chemotherapy saved the NHS £78,000 and produced 0.19 additional quality-adjusted life years (QALY) per patient over a lifetime compared with standard of care ([SoC]; i.e., no *DPYD* testing) [14]. The transferability of these results to other types of healthcare systems could inform the adoption (i.e., in Hungary) and adaptation (i.e., in The Netherlands) of *DPYD* testing. Therefore, adapting the UK economic model to other settings and investigating the budget impact of testing with ToxNav is an important next step toward the universal adoption of *DPYD* testing in Europe. The aim of this paper was to adapt the UK economic model to assess the cost and effects of upfront *DPYD* testing followed by personalized dosing of fluoropyrimidine-based chemotherapy for patients diagnosed with metastatic breast cancer in The Netherlands and Hungary. In addition, a budget-impact analysis was performed to estimate the expected changes in spending after the introduction of the ToxNav test into the health systems in the UK, The Netherlands and Hungary.

Methods

Overview of UK economic model

The UK economic model was described in detail in a previous publication [14]. In brief, the model compared a strategy including testing with a multipanel gene test (ToxNav) followed by personalized capecitabine/5FU dosing to a strategy of no genetic testing followed by a standard dose of chemotherapy. It consisted of a decision tree and a Markov model built in Microsoft Excel (Microsoft Corporation, WA, USA; Figure 1). The decision tree simulated a cohort of 10,000 women aged 60 years with metastatic breast cancer assigned to chemotherapy. The ToxNav arm includes genetic testing for *DPYD* followed by personalized dosing of capecitabine/5FU. The ToxNav branch (Figure 1) incorporated the potential delay of testing, test sensitivity and specificity and the prevalence of the *DPYD* mutation. The no-genetic-testing arm represented the start of treatment with a standard dose of chemotherapy (Figure 1). The dose of capecitabine or 5FU recommended by the ToxNav manufacturer was based on the results of the test. Patients with a critical-risk variant or high-risk variant for toxicity were recommended a 50% reduced dose. Patients who carried hand-foot-syndrome (HFS) risk or standard risk (no variants detected) were recommended a standard 100% dose. The Markov model simulated the cohort from stable metastatic breast cancer to progressive metastatic breast cancer and death from disease or death from other causes based on progression and survival transition probabilities. The progression and death from disease transition probabilities were obtained from a cost–effectiveness analysis of capecitabine in the UK, while overall survival was taken from UK lifetables (Figure 1). The Markov model ran in 2-month cycles for patients' lifetimes and estimated the costs and effects of the two strategies [14].

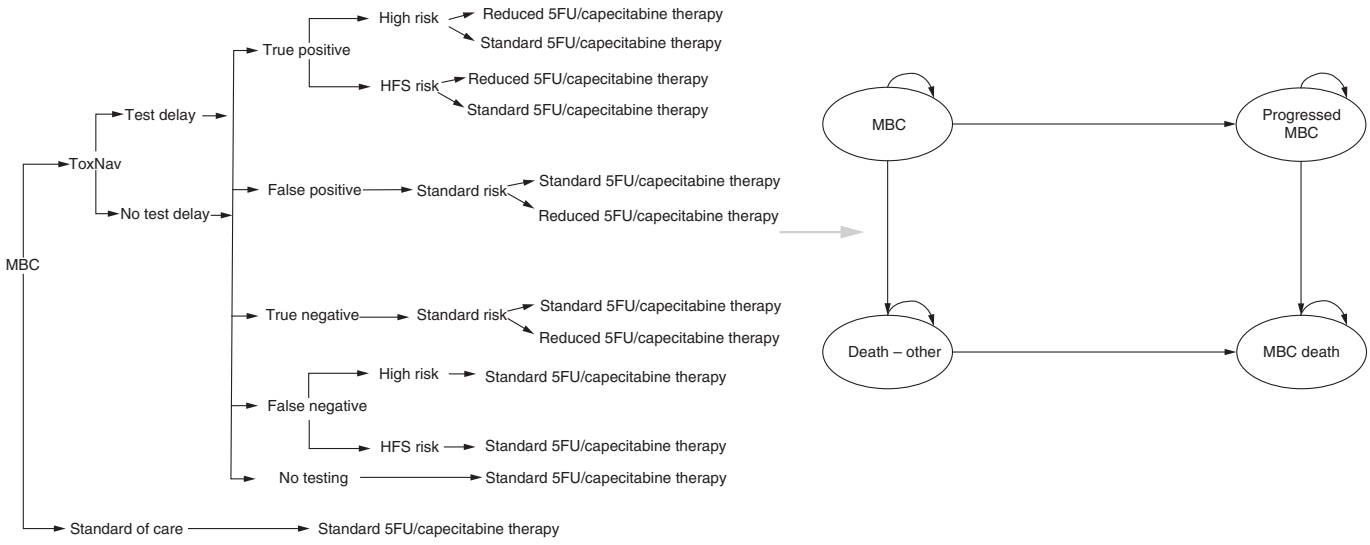

Figure 1. Structure of the decision tree and the Markov model.
5FU: 5-fluorouracil; HFS: Hand-foot-syndrome; MBC: Metastatic breast cancer.

Table 1. Country-specific model input parameters.

Country-specific parameters	Value	Range	Distribution	Ref.
Utility weights				
MBC HU	0.715	(0.484–0.935)	Beta	[24,25]
Progressed MBC HU	0.443	(0.258–0.460)	Beta	[24,25]
MBC NL	0.660	20%	Beta	[20]
Progressed MBC NL	0.550	20%	Beta	[20]
Discount rates				
Annual discount rate (costs/QALYs) HU	3.7%	n/a	n/a	[28]
Annual discount rate (costs/QALYs) NL	4.0/1.5%	n/a	n/a	[27]
Costs				
Cost of ToxNav© test HU/NL	Int €197.64		Gamma	Expert opinion
Costs per cycle: ToxNav strategy–reduced cap/5FU HU	Int €1039.90	±20%	Gamma	Expert opinion
Costs per cycle: ToxNav strategy–standard cap/5FU HU	Int €1039.90	±20%	Gamma	Expert opinion
Costs per cycle: ToxNav strategy–reduced cap/5FU NL	Int €1162.84	±20%	Gamma	[16,19]
Costs per cycle: ToxNav strategy–standard cap/5FU NL	Int €1362.90	±20%	Gamma	[16,19]
Costs per cycle: no genetic testing HU	Int €1039.90	±20%	Gamma	[16,19]
Costs per cycle: no genetic testing NL	Int €1362.90	±20%	Gamma	[16,19]
Cost of terminal disease NL	Int 5931.11	±20%	Gamma	[16,19]

5FU: 5-fluorouracil; HU: Hungary; int €: International euros using purchasing power parity; MBC: Metastatic breast cancer; n/a: Not applicable; NL: The Netherlands; QALY: Quality-adjusted life years.

The input parameters in the decision tree and the Markov model were estimated in the OUH study [15] or derived from the literature (Table 1 & Supplementary Table 1). The parameters that were estimated on the basis of data from the OUH study and fed into the decision tree included the probability of experiencing test delay, patients' and clinicians' compliance to testing and ToxNav manufacturer's dosing recommendations as well as discrepancies between dosing recommendations and actual dosage. In the Markov model, data from the OUH study was used to estimate adverse event rates related to hemoglobin, neutrophil count, white cell count and temperature and costs of therapy and treatment for adverse events per cycle of 2 months [14,15].

The input parameters derived from the literature include the sensitivity and the specificity of the ToxNav test and the prevalence of the *DPYD* mutation that fed into the decision tree [14]. In the Markov model, survival data

for metastatic breast cancer patients, general mortality for the UK and utilities for disease states and disutilities for adverse events were also obtained from the literature [14].

Country adaptations for The Netherlands & Hungary

The parameters for which data were obtained to adapt the UK economic model were grouped into costs: cost of a 2-month cycle of reduced and full-dose capecitabine and 5FU, which included the mean costs of drugs and adverse event treatment; a one-off cost of terminal disease; cost of *DPYD* genetic testing; probabilities: general mortality rates for the female population from the age of 60 years onward; proportion of *DPYD* mutation carriers that are classified as having alleles of HFS risk; utilities: country-specific utilities for the metastatic breast cancer and the progressive metastatic breast cancer disease states; and discounting: discount rates for costs and outcomes. For the remainder input parameters, the data that fed into the UK economic model were used [14].

Costs

The cost of a 2-month cycle in the Dutch adaptation of the model included the average costs of capecitabine and 5FU (50% capecitabine and 50% 5FU), and treatment of adverse events. The recommended dose of capecitabine (1250 mg tablets per square meter of body surface per 12 h) [16,17] was applied to calculate the average cost of treatment with the drug. The cost of treatment with 5FU was based on the average costs of combination treatments containing 5FU (i.e., cyclofosfamide, methotrexate and 5FU); 5FU, epirubicine and cyclofosfamide; 5FU, doxorubicine and cyclofosfamide [18,19] and the average cost of a hospital day during which intravenous chemotherapy was given based on the tariffs for eight different hospitals in The Netherlands. The costs of treating adverse events included oncology consultation with or without blood transfusion, average costs of antibiotics (penicillin) and paracetamol multiplied by the rates at which these events occurred. For the one-off cost of terminal disease, the costs for the full final year prior to death reported by Schneider *et al.* were used and the costs of the last 2 months were calculated by summing the cost of the final and the second final months and inflating the costs to 2020 Euros [20].

The cost of a 2-month cycle in the Hungarian adaptation of the model was based on claims submitted to the health insurance fund in Hungary and included the cost of therapy with a standard or reduced dose of capecitabine/5FU and the cost of treatment of adverse events. As dose reduction did not modify the reimbursement coding of the inpatient care the costs of treatment with standard and reduced dose were assumed to be equal. As the care of patients in a terminal state can be financed as part of primary care, hospice service or inpatient care, the determination of the cost of terminal disease was not feasible and this parameter was kept at 0.

The cost for *DPYD* testing with a multipanel genetic test could not be determined for either The Netherlands or Hungary, therefore, the cost was assumed to be the same as in the UK and the ToxNav test cost of £200 was converted into international euros (int €197.64) using purchasing power parity (PPP) [21]. All other costs described previously were also expressed in international Euros using PPP.

Probabilities

General population mortality rates were obtained from published data for the Dutch and Hungarian populations. General mortality calculations for The Netherlands were based on data from the Dutch Bureau of Statistics [3]. The mortality per age group from the ages of 60 to 95 and older in 5-year intervals was obtained and the mortality attributable to breast cancer was subtracted. The Hungarian mortality data were based on published lifetables [22], however, the general mortality rates were not corrected with mortality from malignant neoplasm of the breast due to lack of detailed data. Data for the prevalence of high-risk and HFS-risk patients in The Netherlands could not be found, therefore, the parameters used in the UK analysis were applied [14]. For Hungary, these parameters were reported by experts to be less than 5%, therefore, in the main analysis, a value of 4% was assumed for these parameters.

Utilities

The utilities for the stable metastatic breast cancer and progressive metastatic breast cancer states in the Markov model were obtained from a Dutch study of quality of life in metastatic breast cancer [23], while in the Hungarian adaptation, the utilities were assumed to be the same as the UK ones due to a lack of local data [14,24,25].

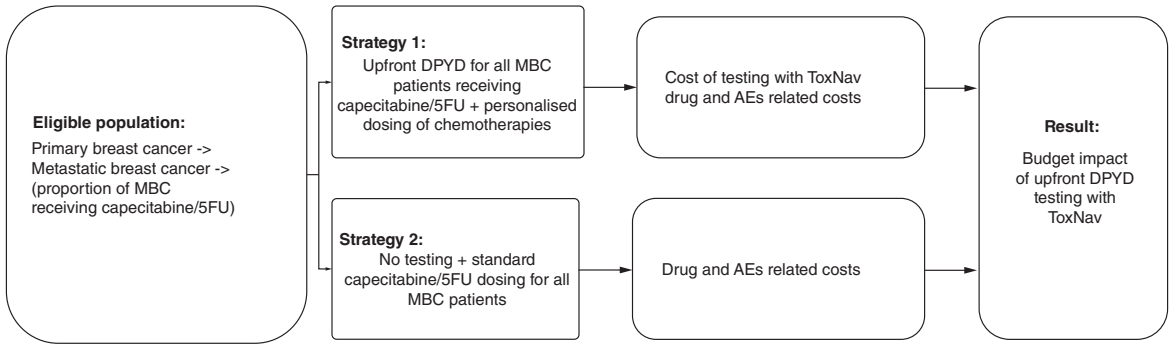

Figure 2. Budget impact model structure.
5FU: 5-fluorouracil; AE: Adverse events; DPYD: Dihydropyrimidine dehydrogenase enzyme; MBC: Metastatic breast cancer.

Discounting

The recommendations of the published guidance for the harmonization and improvement of economic evaluations of personalized medicine were followed [26] and discount rates for costs and outcomes recommended by local guidelines were applied [27,28]. As in The Netherlands costs and outcomes were depreciated differently, a discount rate of 4% was applied to costs and 1.5% to effects [27]. In Hungary, according to local health technology assessment guidelines, costs and outcomes should be discounted at 3.7% [28].

Analyses

The main analysis presented the cost–effectiveness of extended *DPYD* testing prior to fluoropyrimidine-based chemotherapy in metastatic breast cancer patients in The Netherlands and Hungary as an incremental cost–effectiveness ratio (ICER) of costs expressed in international Euros per quality-adjusted life years (QALY) and compared it to the results of the UK economic model that were also converted into international Euros. Univariate and probabilistic sensitivity analyses were performed to test the robustness of model results. In the univariate analysis, the baseline values of input parameters were varied by applying a range of 20%. In the probabilistic sensitivity analysis, all input parameters were simultaneously varied by applying Gamma distribution to the shape and the scale of the survival function of metastatic breast cancer disease, and costs of the bimonthly cycle and the ToxNav test, and Beta distribution to disease state utilities, rates of adverse events and resulting disutilities and the input parameters in the decision tree.

Budget impact analysis

Model structure

In order to see the likely impact of the cost–effectiveness results for the relevant populations, a budget-impact model (BIM) was developed based on the UK economic model. The clinician's compliance with testing was assumed to be 100% (i.e., there were no patients not tested with ToxNav prior to fluoropyrimidine-based chemotherapy initiation). This assumption was based on the current NICE clinical guidance that recommends fluoropyrimidine-based chemotherapy in all patients with advanced breast cancer [2]. The BIM had a time horizon of 5 years. Similar to the UK economic model, the BIM had also a cycle length of 2 months and adopted a healthcare perspective that only considered direct medical costs of testing and treatment in the three countries. The general structure of the BIM is presented in Figure 2.

Target population

The target population consisted of all patients with metastatic breast cancer in England over 5 years. To estimate the size of the population, the average expected primary breast cancers diagnosed each year were calculated by inflating the average number provided by Cancer Research UK for the period 2016–2018 by 0.09% [6]. National statistics were then used to obtain the numbers of breast cancers diagnosed each year between 1989 and 2020 in The Netherlands [29] and between 2000 and 2018 in Hungary [30]. The disease incidence was assumed to increase at the same pace (i.e., 0.09%) in The Netherlands and Hungary as in the UK. Next, the proportion of advanced disease (i.e., metastatic breast cancer) at initial diagnosis was calculated applying 7% as reported in cancer statistics

for the UK [6] to the number of all newly diagnosed breast cancer patients yearly. Thereafter, 10% of the remainder of breast cancer patients were calculated to develop metastatic disease in the 5 years following initial diagnosis [7]. Using this step-wise approach, the risk of progressing to metastatic breast cancer was calculated to be 33.3% per year in the first 2 years after diagnosis, which then decreased and remained constant at 11.3% per year, thereafter.

Main analysis

The results from the budget impact analysis are presented in terms of costs per year in international Euros for testing and chemotherapy and adverse events treatment for the estimated number of patients with metastatic breast cancer in the three countries. Cost differences for the 5-year period between the two strategies (ToxNav and no genetic testing) are also presented in international Euros.

Scenario analysis

In a scenario analysis, the budget impact of treating half the patients with metastatic breast cancer over 5 years with fluoropyrimidine-based chemotherapy, which also meant providing ToxNav to 50% of patients, was assessed. In another scenario analysis, it was assumed that the cost of the ToxNav test could decrease either due to the introduction of an agreement between the test manufacturer and the health payer (defined as a managed entry agreement) or other *DPYD* genetic tests and a scenario in which the cost of testing was 75% of baseline costs in the fourth and fifth year, respectively, was explored.

Results

Cost–effectiveness analyses

Main analysis

The results of the main analysis are presented in Table 2. The results from the ToxNav strategy in The Netherlands were similar to those in the UK analysis, as more QALYs were generated at a lower cost compared with the strategy involving no genetic testing. In Hungary, the ToxNav© strategy was not cost-saving, yet it was considered cost-effective, given that the ICER in the main analysis was below the lowest threshold of int €31,559 [28] for cost–effectiveness in the country.

On a patient level, the incremental QALYs gained in the Dutch (0.19) and the Hungarian (0.19) analyses were the same as those in the UK (0.19). In terms of incremental costs, in the Dutch adaptation, there were savings of int €150.52 per patient's lifetime in the ToxNav strategy compared with the strategy of no genetic testing (int €77,000 savings per patient in the UK). In the Hungarian adaptation, a cost increase of int €189.74 was spent per patient's lifetime in the ToxNav strategy compared with the strategy of no genetic testing. In the cost–effectiveness analysis for The Netherlands, the ToxNav strategy produced 5.4 QALYs per patient compared with the no genetic testing strategy and the lifetime costs per patient were int €19,882.70. The lifetime costs and QALYs per patient in the no genetic testing strategy were int €20,033.23 and 5.2, respectively. In the analysis for Hungary, the ToxNav strategy produced 4.5 QALYs per patient for a cohort of 10,000 simulated women compared with the no genetic testing strategy, and the lifetime costs per patient were int €12,427.67. The lifetime QALYs and costs per patient in the no genetic testing strategy were 4.4 and int €12,237.93, respectively.

Sensitivity analyses

In the cost–effectiveness analysis for The Netherlands, the mean QALYs per patient from 1000 simulations in the ToxNav arm were 6.72, standard deviation (SD): 4.59, 95% CI: 6.44–7.00 and range: -0.39–31.90 at a mean cost per patient of int €24,242.68, SD: int €11,799.43, 95% CI: int €23,511.34–24,974.02 and range: int €7,361.77–76,898.05. The mean QALYs per patient from 1000 simulations in the no genetic testing arm were 6.49, SD: 4.50, 95% CI: 6.21–6.77, range: -0.77–31.41 at a mean cost per patient of int €24,433.80, SD: int €12,055.83, 95% CI: int €23,686.57–25,181.03 and range: int €7,083.47–77,123.76. In the analysis for Hungary, the mean QALYs per patient from 1000 simulations in the ToxNav arm were 5.59, SD: 2.98, 95% CI: 5.40–5.77 and range: 0.95–18.39 at a mean cost per patient of int €15,622.59, SD: int €8,984.71, 95% CI: int €15,065.71–16,179.46 and range: int €3629.10–59,319.80. The mean QALYs per patient from the 1000 simulations in the no genetic testing arm were 5.37, SD: 2.90, 95% CI: 5.19–5.55 and range: 0.84–18.02 at a mean cost per patient of int €15,365.09, SD: int €9,092.78, 95% CI: int €14,801.52–15,928.67 and range: int €3222.06–58,960.61. The results from the univariate sensitivity analyses suggested that varying parameters by a range of 20% was not likely to

Table 2. Main analysis results per 10,000 simulated women for lifetime horizon (international €, millions; cost year: 2020/2021) in the UK, The Netherlands and Hungary.

Country	Strategy	Costs (disc)	QALYs (disc)	Incremental costs (disc)	Incremental QALYs (disc)	Costs (undisc)	QALYs (undisc)	Incremental costs (undisc)	Incremental QALYs (undisc)	ICER
UK	ToxNav© strategy	€327.1	22,670.8		930.8	€336.5	23,227.6	€-398.5	957.8	Dominant
	No genetic testing	€714.4	21,740.0	–	–	€735.0	22,269.8	–	–	–
The Netherlands	ToxNav© strategy	€99.4	27,121.3	€-0.75	940.5	€103.1	27,444.3	€-0.81	952.3	Dominant
	No genetic testing	€100.2	26,180.8	–	–	€103.9	26,492.0	–	–	–
Hungary	ToxNav© strategy	€62.1	22,694.9	€0.95	931.1	€64.0	23,285.3	€0.95	959.7	Disc/undisc: €1,018.87/€988.58
	No genetic testing	€61.2	21,763.8	–	–	€63.1	22,325.6			–

disc: Discounted; ICER: Incremental cost–effectiveness ratio; QALY: Quality-adjusted life years; undisc: Undiscounted.

change the results in the main analysis and alter the cost–effectiveness of the ToxNav strategy in The Netherlands and Hungary (Figure 3A & B).

The results from 1000 simulations for the probabilistic sensitivity analysis (PSA) are presented in cost–effectiveness planes (Figure 4A & B). In The Netherlands, the simulated ICERs are spread between the northeastern quadrant, where the cost–effectiveness of the ToxNav strategy depends on the cost–effectiveness threshold and the south eastern quadrant where the ToxNav© strategy was considered dominant. At a cost–effectiveness threshold of int €69,666 (80,000 Euros) [27] in The Netherlands, the probability of the ToxNav strategy being cost-effective was 94% (Figure 5A). In the analysis for Hungary, the simulated ICERs were spread over the north and south eastern quadrants. With the cost–effectiveness threshold of int €31,559 (7,294,500 Hungarian forints) [28], the probability of the ToxNav strategy being cost-effective exceeded 90% (Figure 5B). The uncertainty in the PSAs for The Netherlands and Hungary was attributable to both costs of treatment with chemotherapy and adverse events, and gains in quality of life.

Budget impact analyses

Main analysis

The base case estimate of the budget impact of introducing upfront *DPYD* testing as an SoC in the UK and The Netherlands for all metastatic breast cancer patients receiving capecitabine/5FU demonstrated that despite the additional cost of testing, the ToxNav strategy offered budget savings (Table 3). In Hungary, though, introducing upfront *DPYD* testing as an SoC for all metastatic breast cancer patients would incur additional budget costs (Table 3).

Scenario analyses

In the first scenario analysis, the budget impact for treating half of metastatic breast cancer patients with capecitabine/5FU resulted in budget savings for the ToxNav strategy in the UK and The Netherlands (Table 4), while in Hungary there were additional budget costs (Table 4). In the second scenario analysis, the budget impact for introducing upfront *DPYD* testing with reduced cost of the test for the fourth and fifth year for all metastatic breast cancer patients treated with fluoropyrimidine-based chemotherapy the ToxNav strategy was associated with budget savings that were greater than baseline savings in the UK and The Netherlands. In Hungary, there were additional budget costs, though they were smaller as compared with the baseline (Table 5).

Discussion

We provided evidence that upfront *DPYD* testing with a multipanel genetic test (i.e., ToxNav), for metastatic breast cancer patients followed by personalized dosing of fluoropyrimidine-based chemotherapy was likely to be cost-effective compared with no genetic testing and standard dosing of chemotherapy in all three countries, especially in The Netherlands and the UK, where it led to more QALYs gained at lower costs to the health systems. In terms of healthcare budgets, extended *DPYD* testing in metastatic breast cancer patients could lead to int €13,000 savings per patient annually in the UK and int €18 in The Netherlands, while it would require int €40 additional spending per patient per year in Hungary.

A potential explanation for the differences in savings between the UK and The Netherlands could be that, in the analysis for the UK, there were real-world patient data available that allowed the estimation of very granular costs per cycle of drugs and adverse events' treatment for the subgroups of patients in the ToxNav arm. In the Dutch analysis, the costs per cycle for all patients that received full-dose treatment were the same in the ToxNav and the no genetic testing arm, as well as the costs for patients receiving the reduced dose, irrespective of their *DPYD* status. In the Hungarian analysis, there was no difference in costs between full- and reduced-dose drug and adverse events treatment.

This analysis builds upon a growing body of international literature showing that upfront *DPYD* testing is cost-effective in different types of healthcare systems (in The Netherlands, Ireland, Italy, USA) [31–36], that is, tax-based and insurer-based, as well as in systems with different level of resources, as is the case in Hungary. The results of this analysis with regard to the cost–effectiveness of upfront *DPYD* testing prior to initiating treatment with capecitabine and 5FU in cancer patients are in line with previous studies [31–36]. This analysis adds important information to the existing literature by providing the budget impact of introducing *DPYD* testing with an extended gene panel test as an SoC in three European countries. This study is also the first to show that testing an extended panel of *DPYD* mutations is cost-effective in The Netherlands and Hungary, and European countries may consider using

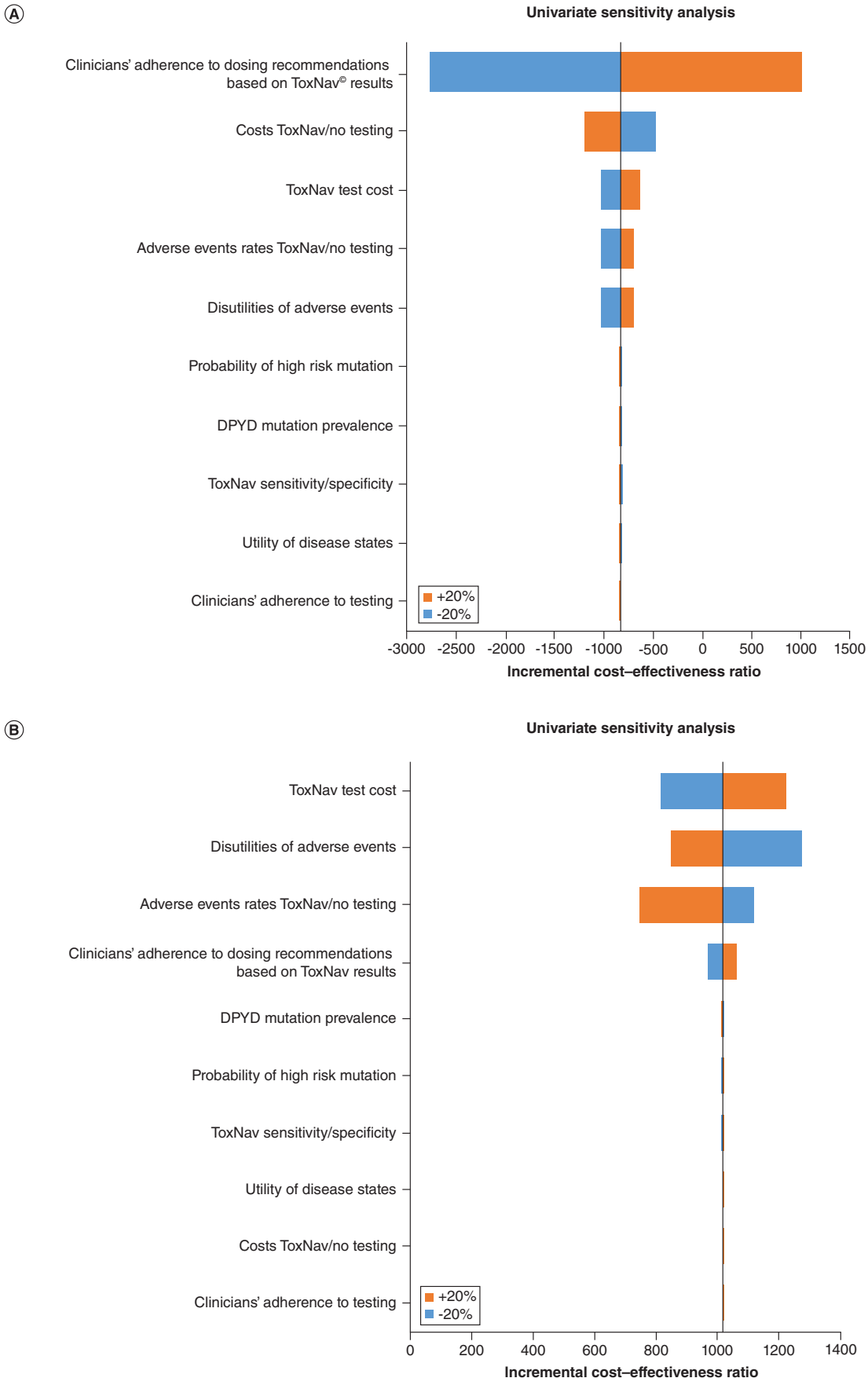

Figure 3. Univariate sensitivity analysis. (A) Univariate sensitivity analysis, The Netherlands. **(B)** Univariate sensitivity analysis, Hungary.
DPYD: Dihydropyrimidine dehydrogenase enzyme.

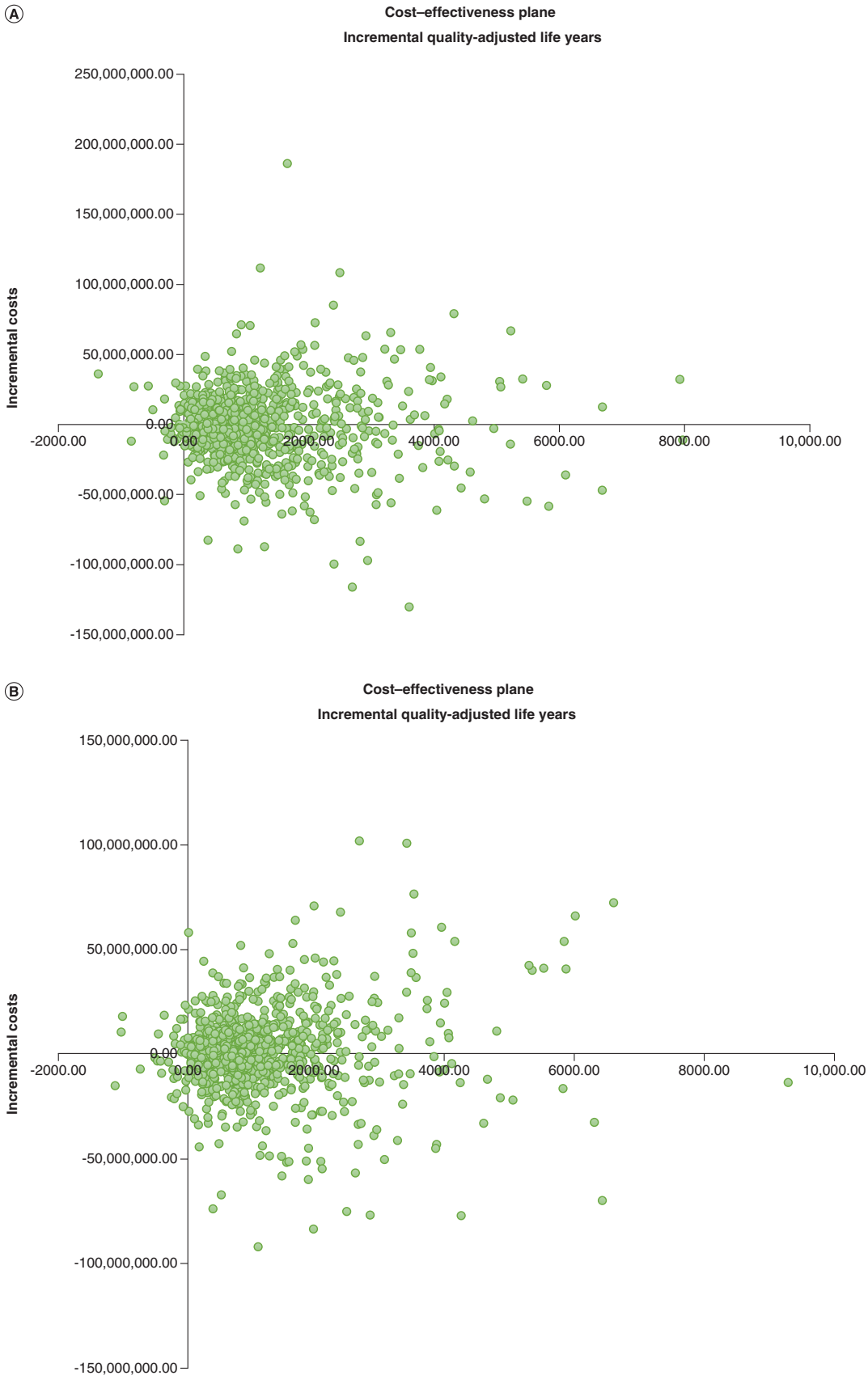

Figure 4. Cost–effectiveness plane of incremental costs and QALYs (ToxNav© strategy vs no genetic testing). (A) Cost–effectiveness plane of incremental costs and QALYs (ToxNav© strategy vs no genetic testing), The Netherlands. **(B)** Cost–effectiveness plane of incremental costs and QALYs (ToxNav© strategy vs no genetic testing), Hungary.
QALY: Quality-adjusted life years.

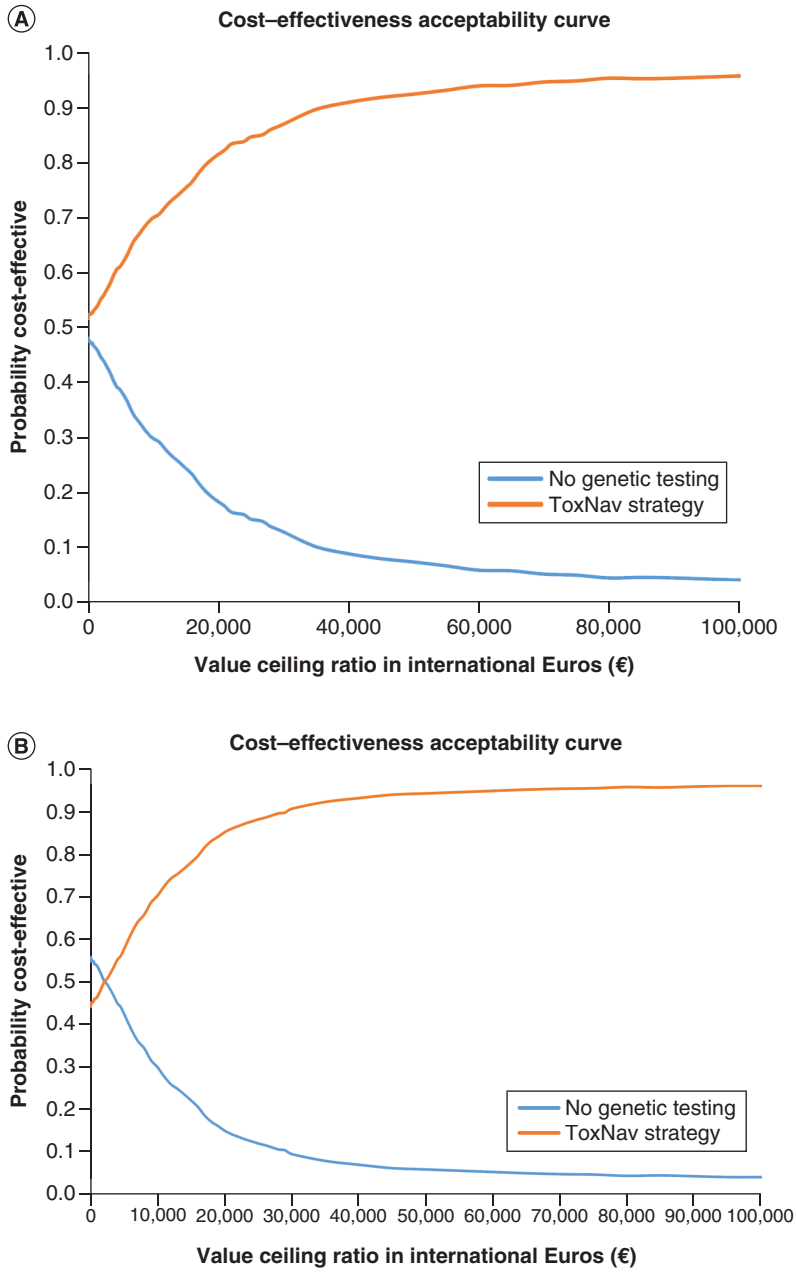

Figure 5. Cost–effectiveness acceptability curve (ToxNav© strategy vs no genetic testing). (A) Cost–effectiveness acceptability curve (ToxNav strategy vs no genetic testing), The Netherlands. **(B)** Cost–effectiveness acceptability curve (ToxNav strategy vs no genetic testing), Hungary.

such tests to reduce potential race inequalities in cancer treatment with fluoropyrimidine-based chemotherapy. These results, together with results from previous analyses, can guide decision-makers in countries where there is not yet an economic analysis of upfront *DPYD* testing on the type of data required. In addition, it could be used to consider conditional reimbursement while local evidence is collected and analyzed.

Performing country adaptations of economic evaluations may be hampered by the unavailability of local data regarding costs and outcomes [37]. In this analysis, data regarding the cost of multipanel *DPYD* genetic testing was not readily available for The Netherlands (where only a four-variant *DPYD* test is used) and Hungary. Therefore, we had to assume that the price of the *DPYD* test was the same as in the UK and convert it to international Euros. This assumption could potentially explain the additional health budget required in Hungary to establish upfront

Table 3. Budget impact analysis results: base case analysis for UK, The Netherlands and Hungary in million international Euros.

	Year 1			Year 2			Year 3			Year 4			Year 5		
Strategy 1: ToxNav© strategy	UK	NL	HU	UK	NL	HU	UK	NL	HU	UK	NL	HU	UK	NL	HU
ToxNav test costs	1.8	0.59	0.27	1.8	0.59	0.27	1.8	0.59	0.27	1.8	0.59	0.27	1.8	0.59	0.27
Drug and AEs treatment costs	264.7	21.6	7.8	427.5	34.8	12.7	506.6	41.2	15.0	540.9	44.0	16.1	554.7	45.1	16.5
Total costs	266.5	22.2	8.1	429.3	35.4	12.9	508.4	41.8	15.3	542.7	44.5	16.3	556.5	45.7	16.7
Strategy 2: No genetic testing strategy															
Drug and AEs treatment costs†	610.2	22.1	7.8	985.3	35.6	12.7	1167.6	42.1	15.0	1246.7	45.0	16.1	1278.4	46.1	16.5
Budget impact															
Testing budget impact‡	1.8	0.59	0.27	1.8	0.59	0.27	1.8	0.59	0.27	1.8	0.59	0.27	1.8	0.59	0.27
Drug and AEs treatment impact§	-345.5	-0.5	0	-557.8	-0.8	0	-661.0	-0.9	0	-705.8	-1.0	0	-723.8	-1.0	0
Total budget impact¶	-343.6	0.09	0.27	-556.0	-0.2	0.27	-659.2	-0.4	0.27	-704.0	-0.4	0.27	-722.0	-0.4	0.27

†Equal to total costs for no genetic testing strategy as there are no genetic testing costs.
‡Equal to testing with ToxNav© test per year.
§Estimated as difference in drug and AEs treatment costs between ToxNav and no genetic testing strategy.
¶Estimated as difference in total costs between ToxNav and no genetic testing strategy.
AE: Adverse events; HU: Hungary; NL: The Netherlands.

Table 4. Budget impact analysis results: scenario based on 50% of metastatic breast cancer population in UK, The Netherlands and Hungary in million international Euros.

	Year 1			Year 2			Year 3			Year 4			Year 5		
Strategy 1: ToxNav© strategy	UK	NL	HU	UK	NL	HU	UK	NL	HU	UK	NL	HU	UK	NL	HU
ToxNav test costs	0.9	0.3	0.14	0.9	0.3	0.14	0.9	0.3	0.14	0.9	0.3	0.14	0.9	0.3	0.14
Drug and AEs treatment costs	132.4	10.8	3.9	213.7	17.4	6.3	253.3	20.6	7.5	270.4	22.0	8.0	277.3	22.5	8.2
Total costs	133.3	11.1	4.1	214.6	17.7	6.5	254.2	20.9	7.7	271.3	22.3	8.2	278.2	22.8	8.4
Strategy 2: No genetic testing strategy															
Drug and AEs treatment costs†	305.1	11.0	3.9	492.6	17.8	6.3	583.8	21.1	7.5	623.3	22.5	8.0	639.2	23.0	8.2
Budget impact															
Testing budget impact‡	0.9	0.3	0.14	0.9	0.3	0.14	0.9	0.3	0.14	0.9	0.3	0.14	0.9	0.3	0.14
Drug and AEs treatment impact§	-172.7	-0.25	0	-278.9	-0.4	0	-330.5	-0.5	0	-352.9	-0.5	0	-361.9	-0.5	0
Total budget impact¶	-171.8	0.04	0.14	-278.0	-0.1	0.14	-329.6	-0.2	0.14	-352.0	-0.2	0.14	-361.0	-0.2	0.14

†Equal to total costs for no genetic testing strategy as there are no genetic testing costs.
‡Equal to testing with ToxNav test per year.
§Estimated as difference in drug and AEs treatment costs between ToxNav and no genetic testing strategy.
¶Estimated as difference in total costs between ToxNav and no genetic testing strategy.
AE: Adverse events; HU: Hungary; NL: The Netherlands.

Table 5. Budget impact analysis results: scenario based on reduced cost of ToxNav© test (75% of baseline cost) in years 4 and 5 in UK, The Netherlands and Hungary in million international Euros.

	Year 1			Year 2			Year 3			Year 4			Year 5		
Strategy 1: ToxNav© strategy	UK	NL	HU	UK	NL	HU	UK	NL	HU	UK	NL	HU	UK	NL	HU
ToxNav test costs	1.8	0.59	0.27	1.8	0.59	0.27	1.8	0.59	0.27	1.4	0.44	0.20	1.4	0.44	0.20
Drug and AEs treatment costs	264.7	21.6	7.8	427.5	34.8	12.7	506.6	41.2	15.0	540.9	44.0	16.1	554.7	45.1	16.5
Total costs	266.5	22.2	8.1	429.3	35.4	12.9	508.4	41.8	15.3	542.2	44.4	16.3	556.0	45.5	16.7
Strategy 2: No genetic testing strategy															
Drug and AEs treatment costs†	610.2	22.1	7.8	985.3	35.6	12.7	1167.6	42.1	15.0	1246.7	45.0	16.1	1278.4	46.1	16.5
Budget impact															
Testing budget impact‡	1.8	0.59	0.27	1.8	0.59	0.27	1.8	0.59	0.27	1.4	0.44	0.20	1.4	0.44	0.20
Drug and AEs treatment impact§	-345.5	-0.5	0	-557.8	-0.8	0	-661.0	-0.9	0	-705.8	-1.0	0	-723.8	-1.0	0
Total budget impact¶	-343.6	0.09	0.27	-556.0	-0.2	0.27	-659.2	-0.4	0.27	-704.4	-0.6	0.20	-722.4	-0.6	0.20

†Equal to total costs for no genetic testing strategy as there are no genetic testing costs.
‡Equal to testing with ToxNav test per year.
§Estimated as difference in drug and AEs treatment costs between ToxNav and no genetic testing strategy.
¶Estimated as difference in total costs between ToxNav and no genetic testing strategy.
AE: Adverse events; HU: Hungary; NL: The Netherlands.

DPYD testing as the SoC for metastatic breast cancer patients assigned to fluoropyrimidine-based chemotherapy regimens as costs are in general lower in the Hungarian healthcare system.

Personalized medicine interventions are often associated with high costs. Affordability challenges have been identified as barriers to reimbursement and may prevent access to personalized medicines with proven effectiveness [38]. Therefore, on a European level decision-making authorities should engage in efforts to evenly distribute the benefits of personalized medicine among European countries by negotiating appropriately set prices with the manufacturers. This analysis has demonstrated that a multipanel genetic test for *DPYD* mutations prior to fluoropyrimidine-based chemotherapy for metastatic breast cancer patients can be a cost-effective personalized medicine intervention in both high-income and upper-middle-income European countries.

We have previously argued that appropriate reimbursement of personalized medicines with proven clinical and cost–effectiveness is vital for the clinical uptake of such interventions [38]. Considering the favorable cost–effectiveness of upfront *DPYD* testing for cancer patients that were prescribed capecitabine/5FU as well as the potential budget savings, decision-makers can help realize the full potential of this personalized medicine innovation and avoid delays that would lead to welfare loss by adopting *DPYD* testing as the standard of clinical care.

The limitations of this study mainly relate to limited data availability. Due to a lack of data, we based the costs of multipanel *DPYD* genetic testing in The Netherlands and Hungary on the UK value. Also, the rates of adverse events, which were assumed to be the same in all three analyses, were derived from a UK cohort of a predominantly Caucasian population. As costs and rates of adverse events could impact the estimated cost–effectiveness and quality of life gain, the lack of more detailed data could have potentially biased the estimated cost–effectiveness of the ToxNav strategy in The Netherlands and Hungary. In addition, the exclusion of cardiotoxicity and cardiac deaths related to chemotherapy due to lack of data in all three analyses could have potentially underestimated the impact of ToxNav on quality of life and its cost–effectiveness.

Upfront *DPYD* testing with a four-variant test is currently the SoC for cancer patients in The Netherlands and there are ongoing initiatives by NHS England to introduce a four-variant *DPYD* testing. Although a four-variant test may from a clinical perspective be sufficient to detect mutations prevalent in predominantly Caucasian groups, additional studies would be needed to investigate the cost–effectiveness of the test assessing the four variants recommended by CPIC compared with an extended gene panel test.

Conclusion

This cost–effectiveness analysis showed that introducing extended *DPYD* testing prior to fluoropyrimidine-based chemotherapy in metastatic breast cancer patients in the UK and The Netherlands resulted in more QALYs gained at lower costs, while in Hungary more QALYs were generated at a higher cost, however, the ToxNav© strategy was considered cost-effective in all main analyses. From the perspective of the healthcare payers, introducing upfront *DPYD* testing can potentially generate savings in the healthcare system in the UK and The Netherlands but would increase the health budget needed to provide the service to all metastatic breast cancer patients assigned to capecitabine and 5FU in Hungary. Future research could consider whether similar findings are found in other countries.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/pme-2022-0133

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Executive summary

- The aim of this research was to examine the cost–effectiveness and budget impact of introducing extended *DPYD* testing prior to fluoropyrimidine-based chemotherapy in metastatic breast cancer patients in the UK, The Netherlands and Hungary.

Results

- *DPYD* testing with ToxNav© was cost-effective in the UK, The Netherlands and Hungary.
- In the UK and The Netherlands, the ToxNav strategy led to more quality-adjusted life years and lower costs to the health systems compared with no genetic testing and standard dosing of capecitabine/5-fluorouracil.
- In Hungary, the ToxNav strategy produced more quality-adjusted life years at a higher cost compared with no testing and standard dose.
- The ToxNav strategy was found to offer budget savings in the UK and in The Netherlands, while in Hungary it resulted in additional budget costs.

Discussion

- This study is the first to show that testing an extended panel of *DPYD* mutations is cost-effective in the UK, The Netherlands and Hungary.
- European countries may consider using such tests to reduce potential race inequalities in cancer treatment with fluoropyrimidine-based chemotherapy.

entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

This study did not require approval by a medical ethics committee.

Data sharing statement

All data used to populate the model are provided in the manuscript.

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