Research Article

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Personalized Medicine

Cost–effectiveness of extended *DPYD* testing before fluoropyrimidine chemotherapy in metastatic breast cancer in the UK

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The aim of this study was to evaluate the cost–effectiveness of ToxNav©, a multivariant genetic test, to screen for *DPYD* followed by personalized chemotherapy dosing for metastatic breast cancer in the UK compared with no testing followed by standard dose, standard of care. In the main analysis, ToxNav was dominant over standard of care, producing 0.19 additional quality-adjusted life years and savings of £78,000 per patient over a lifetime. The mean additional quality-adjusted life years per person from 1000 simulations was 0.23 savings (95% CI: 0.22–0.24) at £99,000 (95% CI: £95–102,000). Varying input parameters independently by range of 20% was unlikely to change the results in the main analysis. The probabilistic sensitivity analysis showed ~97% probability of the ToxNav strategy to be dominant.

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Breast cancer is the second most common cause of cancer-related deaths in women worldwide [1]. Each year, 5–10% of newly diagnosed cases are detected at an advanced or metastatic stage. At this stage, breast cancer is often terminal because many patients cannot be cured and are amenable only to palliative care [2]. Different treatment regimens, including chemotherapy, are given to try to contain disease progression in terms of lesion growth and lesion spread to other parts of the body and to prolong survival. Fluorpyrimidine-based drugs, including 5-fluorouracil (5FU), tegafur and capecitabine, are chemotherapy regimens offered to most patients with metastatic breast cancer as they have demonstrated clinical benefit in terms of improved progression-free and overall survival [3–6]. Despite the proven benefit, ~20% of patients receiving these chemotherapies develop mild to severe adverse reactions because they carry specific genetic mutations [7–9].

Dihydropyrimidine dehydrogenase (*DPYD*) variants, which are genetic mutations in the *DPYD*-encoding gene, can cause variability in the activity of the enzyme that is responsible for metabolizing up to 90% of fluoropyrimidine-based chemotherapies. Germline *DPYD* variants are found in 3 to 5% of the general population [10]. Patients with *DPYD* variants that cause slow drug metabolism have a higher risk of severe toxicity when they receive standard-dose fluoropyrimidine therapy. Toxicities include hand–foot syndrome (HFS), mucositis, diarrhea, skin toxicity, tiredness, myelosuppression and multiorgan failure. Severe toxicities are usually managed in inpatient settings and involve dose moderation or treatment discontinuation [11–14].

The Clinical Pharmacogenetics Implementation Consortium (CPIC) 2017 guidelines recommend testing for four SNPs in the *DPYD* gene [15]. However, there are more than 160 identified *DPYD* variants that are clinically

relevant [16]. Also, there is emerging evidence of differences in variant frequency across populations of different ethnic descent [10]. In addition, at least 50% of patients that experience severe toxicity to 5FU or capecitabine are not carriers of the four most common *DPYD* variants [17]. In response, a new extended panel *DPYD* genetic test, ToxNav©, was developed to allow for testing of additional variants that have demonstrated correlation with 5FU and capecitabine toxicities. These include three of the four *DPYD* alleles recommended for testing by the CPIC (excluding rs56038477/rs75017182 HAPB3), 15 additional variants associated with *DPYD* function and one allele of the *ENOSF1* gene [17].

Metastatic breast cancer patients assigned to 5FU or capecitabine chemotherapy could potentially benefit from upfront *DPYD* genotyping with ToxNav followed by their treatment dosing being personalized based on the genotyping results. Specifically, identifying poor metabolizers before receiving therapy would allow for dose modification that could potentially avoid severe toxicities. However, despite upfront *DPYD* testing having been recommended by international regulatory agencies [18] and professional bodies [19,20], it has not been universally and uniformly (i.e., different variants are tested) implemented into routine clinical care [21] in the UK. There is limited evidence on the costs and cost–effectiveness of *DPYD* testing in the UK, and in metastatic breast cancer in particular, making it difficult to determine whether it provides good value for money for the healthcare system [22–28]. Therefore, the aim of this study was to perform a cost–effectiveness analysis of routine upfront *DPYD* testing with ToxNav to personalize fluoropyrimidine-based chemotherapy for metastatic breast cancer patients in the UK.

Methods

This cost–effectiveness analysis adhered to the published guidance for the harmonization and improvement of economic evaluations of personalized medicine [29], the National Institute for Health and Care Excellence guidance for technology appraisal in the UK [30] and the Consolidated Health Economic Evaluation Reporting Standards 2022 statement [31].

Intervention & comparator

The intervention was an extended panel *DPYD* genetic test, ToxNav, accompanied with a recommendation for personalization of capecitabine/5FU dosing. The test results were defined as 'standard' risk if there was no variant found, 'HFS' risk if variants related to HFS were found and 'high' risk for variants related to high toxicity [17]. The comparator was standard of care (SoC), which is receiving capecitabine/5FU chemotherapy without prior *DPYD* genetic testing followed by usual dosing. Currently, according to the CPIC guidelines, cancer patients who are homozygous carriers of the variants rs3918290/rs3918290, rs3918290/intermediate and rs55886062/rs55886062 have a predicted *DYPD* enzyme activity ranging from 0 to 50%, and are therefore classified as critical risk [17]. In these patients, treatment with capecitabine/5FU should be avoided [17]. Heterozygous carriers of the variants rs3918290/+ and rs55886062/+ are also classified as critical risk, but their predicted *DYPD* enzyme activity is approximately 50%, and thus they should be subjected to cautious dosing of capecitabine/5FU ranging from 25 to 50% of standard dose [17]. Homozygous carriers of the variants rs67376798/rs67376798 are classified as high risk with a predicted *DYPD* enzyme activity of 50% and are recommended 50% of standard dose of capecitabine/5FU [17]. Heterozygous carriers of the variants rs67376798/+ are classified as high risk with a predicted *DYPD* enzyme activity of 75% and are recommended 50% of standard dose of capecitabine/5FU and titration [17]. Patients found to be heterozygotes on variants rs12132152/+ and rs2612091/+ are classified as HFS risk with a predicted *DYPD* enzyme activity of 80% and are recommended 100% of standard dosing of capecitabine/5FU [17]. Wild-type carriers classified as bearing standard risk should be given 100% of standard dosing of capecitabine/5FU [17].

Study population

The target population in the analysis comprised women with metastatic breast cancer who were prescribed capecitabine and 5FU chemotherapy regimens in the UK. The mean age of the simulated cohort at the time they entered the Markov model was 60 years. The site of the distant relapse (i.e., lung, bone, liver, brain and/or axillary lymph nodes) and the receptor status of the cancer (i.e., HEGF receptor 2, estrogen or progesterone) were not taken into account in the analysis, as they would not influence capecitabine/5FU dosing or toxicity levels.

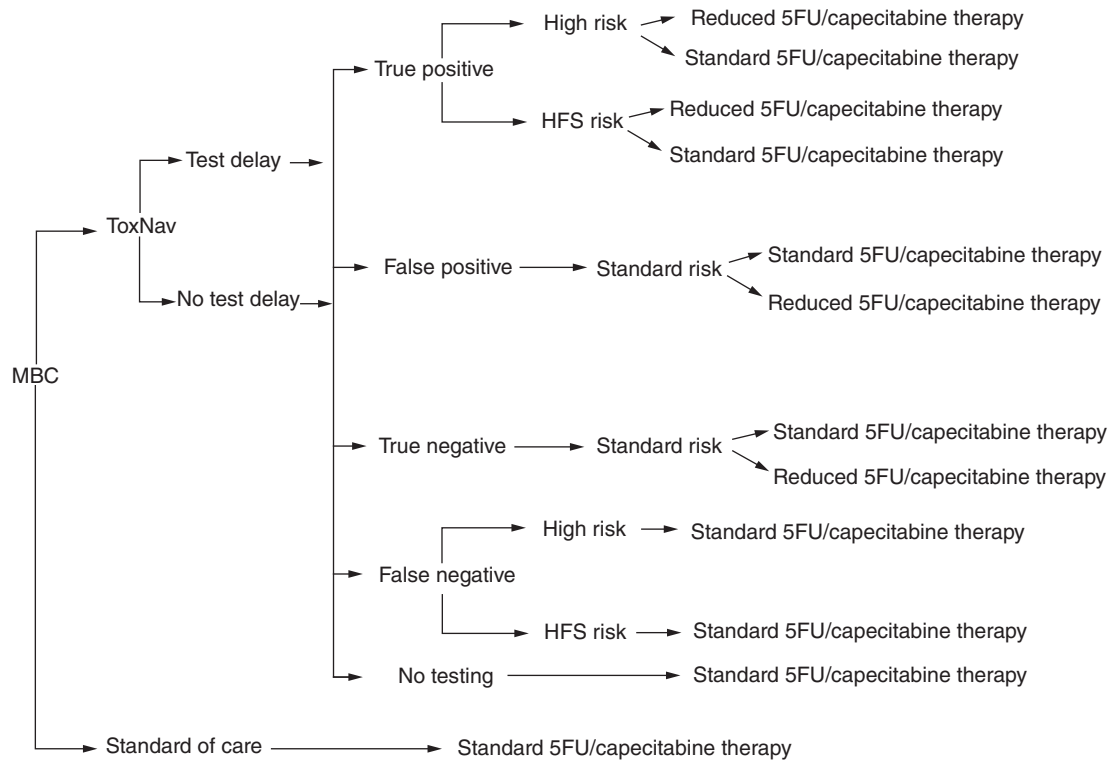

Figure 1. Structure of the decision tree.
5FU: 5-fluorouracil; HFS: Hand–foot syndrome; MBC: Metastatic breast cancer.

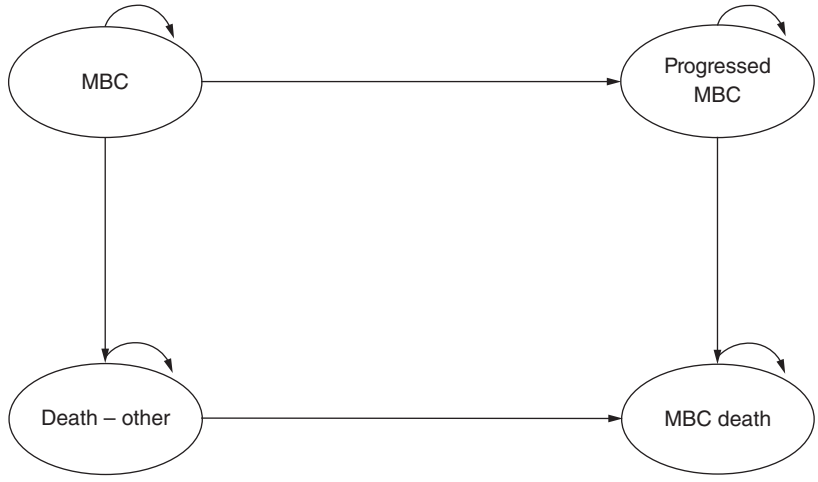

Figure 2. Structure of the Markov model.
MBC: Metastatic breast cancer.

Model structure

A model was developed in Microsoft Excel (Microsoft Corporation, Redmond, Washington) that consisted of two parts; a decision tree (Figure 1) followed by a cohort Markov model (Figure 2). A cohort of 10,000 women with metastatic breast cancer was simulated, starting from testing in the ToxNav arm or the onset of capecitabine/5FU treatment in the SoC arm, to disease progression and death from breast cancer or other causes.

Decision tree

The ToxNav strategy in the decision tree represented the period from testing with ToxNav until start of chemotherapy with a personalized dose. Patients may experience delay of testing, which was reflected in the decision tree branches of the ToxNav strategy. The predictive value of ToxNav – that is, the probability of having a true or false positive or a negative test result – was also incorporated. After receiving the genetic test, patients were distributed into the true positive, false positive, true negative and false negative branches of the tree. The probabilities of being assigned to each branch were calculated on the basis of the sensitivity and specificity of the ToxNav test [16,26], and the prevalence of the *DPYD* mutation [10]. In the SoC branch, patients were directly assigned to standard dose of chemotherapy without undergoing genetic testing.

Markov model

The Markov model incorporated four states: stable metastatic breast cancer (MBC), progressive metastatic breast cancer (progressed MBC), death from disease (MBC death) and death from other causes (death – other). All patients entered the Markov model in the stable metastatic breast cancer state and transitioned to progressive disease and death from disease or other cause according to progression and survival transition probabilities. The Markov model had a lifetime horizon and a cycle length of 2 months. Half cycle correction was implemented by estimating the average of correcting only the first and the last cycle and each two consecutive cycles (trapezoidal rule) [32].

Model parameters

Input parameters that were used to populate the model are presented in Table 1 and described in detail hereafter.

Propensity score matching analysis

To estimate the impact of ToxNav on hospital costs related to toxicity from the chemotherapy, the guidelines of the Medical Research Council in the UK on performing natural experiments were followed and propensity score matching (PSM) was performed to observational data from 466 patients tested with ToxNav during the period 1 June 2019 – 1 September 2020 and 1556 patients from a historical cohort (1 June 2017 – 31 May 2019) who did not receive testing to reduce observed confounding between the two cohorts. The two cohorts consisted of patients diagnosed with upper gastrointestinal, lower gastrointestinal, breast and other cancers, treated with capecitabine or 5FU chemotherapy as standalone or combination therapies at the Oxford University Hospitals (OUH) NHS Trust in the UK. Thereafter, we refer to this study as the OUH study [17]. The trust has implemented upfront *DPYD* testing for all cancer patients assigned to fluoropyrimidine chemotherapy in their clinical practice since June 2019 due to patient safety concerns. Approximately 600 patients are treated per year with capecitabine/5FU at the OUH NHS Trust, and 25% of them are breast cancer patients [17]. Datasets that were collected routinely by the hospital and included patient demographics, diagnosis, tumor characteristics, treatment and adverse events were linked together. The historic and the ToxNav cohorts were matched by sociodemographic characteristics, diagnosis code, treatment, duration of follow-up and estimated survival based on all other observed confounders. Means, standard deviations (SD) and frequencies were calculated to show differences in patient characteristics. Differences were then tested by a two sample t-test and Mann–Whitney test for continuous variables and χ^2 test for categorical variables. Generalized linear regression models combined with PSM were used to perform regression analysis. The results from the OUH study related to the detection of risk variants in the *DPYD* gene in the ToxNav cohort were used to estimate the probabilities that a true-positive patient would be classified as 'standard' risk, 'HFS' risk and 'high' risk. To assess the association of ToxNav with hospital costs during the follow-up period a generalized linear regression models with gamma distribution and log link were used to estimate the cost per cycle. These costs included outpatient care, day care, diagnostics, chemotherapy, radiotherapy, critical and emergency care, elective and non-elective hospital care, equipment, rehabilitation and other. Generalized linear regression models with binomial distribution and logit link were used to estimate the odds ratios of experiencing adverse events from chemotherapy per cycle. For each adverse event, the percentage of each grade (signifying the level of severity) out of all observations per patient was calculated, and the percentage was included as a dependent variable in the regressions. Standard errors were calculated in all regression models. It was possible to perform a complete case analysis because there were only a few missing observations in the dataset [17]. The probabilities for being classified into the risk variants, the costs and the adverse event rates per cycle were based on the whole ToxNav cohort because these were demonstrated to be similar for patients irrespective of their cancers.

Table 1. Model input parameters.

Parameter	Value	Range	Distribution	Ref.
Decision tree				
Number of patients	10,000	n/a	n/a	n/a
Sensitivity of ToxNav© test	100%	± 20%	Beta	[44]
Specificity of ToxNav test	98%			[44]
Probability of having test delay	0%			[17]
Prevalence of the *DPYD* mutation	5%			[10]
Cost of ToxNav test	£200			Expert judgement
Probability of a true positive patient to be classified as HFS risk	95%			[17]
Probability of a true positive patient to be classified as high risk	5%			
Probability of a false positive patient to be classified as HFS risk	95%			
Probability of a false positive patient to be classified as high risk	5%			
Physicians' adherence to ToxNav results for high-risk patients to receive reduced capecitabine/5FU	82%			
Physicians' adherence to ToxNav results for HFS-risk patients to receive standard capecitabine/5FU	84%			
Physicians' adherence to ToxNav results for standard-risk patients to receive standard capecitabine/5FU	85%			
Physicians' adherence to testing with ToxNav	96%			
Patients' adherence to testing with ToxNav	100%			
Patients' adherence to treatment	100%			
Markov model				
Survival probabilities				
Lambda PFS	0.0981	± 20%	Gamma	[33]
Lambda OS	0.0142			
Gamma PFS	1.3412			
Gamma OS	1.3591			
Utility weights				
Metastatic breast cancer	0.715	(0.484–0.935)	Beta	[36,37]
Progressed metastatic breast cancer	0.443	(0.258–0.460)		
Utility decrements for adverse events				
Neutrophil count grade 1–2	0.100	± 20%	Beta	[23]
Neutrophil count grade 3–4	0.120	± 20%		[23]
Hemoglobin grade 1–2	0.1714	(-0.1522 – -0.1905)		[23,38]
Hemoglobin grade 3–4	0.1914	(0.1722–0.2105)		[38]
White cell count grade 1–2	0.100	± 20%		[23]
White cell count grade 3–4	0.120	± 20%		[23]
Temperature grade 1–2	0.130	± 20%		[23,36]
Temperature grade 3–4	0.150	± 20%		[36]
Annual discount rate (costs/QALYs)	3.5%	n/a	n/a	
Costs per cycle ToxNav strategy				
High-risk patients on reduced dose cap/5FU	£17726,42	± 20%	Gamma	
High-risk patients on standard dose cap/5FU	£3441,78			
HFS-risk patients on reduced dose cap/5FU	£4479,60			
HFS-risk patients on standard dose cap/5FU	£5800,67			
Standard-risk patients on reduced dose cap/5FU	£4883,06			
Standard-risk patients on standard dose cap/5FU	£5370,65			
Costs per cycle routine practice	£12299,02	± 20%	Gamma	
Adverse events rates	**Mean**	**SD**		
ToxNav strategy				

5FU: 5-fluorouracil; HFS: Hand–foot syndrome; n/a: Not applicable; OS: Overall survival; PFS: Progression-free survival; QALY: Quality-adjusted life years.

Table 1. Model input parameters (cont.).

Parameter	Value	Range	Distribution	Ref.
High-risk patients on reduced cap/5FU				
Neutrophil count grade 1–2	0,07	0,09	Beta	[17]
Neutrophil count grade 3–4	0,04	0,08		
Hemoglobin grade 1–2	0,62	0,26		
Hemoglobin grade 3–4	0,01	0,01		
White cell count grade 1–2	0,12	0,16		
White cell count grade 3–4	0,04	0,09		
Temperature grade 1–2	0,03	0,04		
Temperature grade 3–4	0,00	0,00		
High-risk patients on standard cap/5FU				
Neutrophil count grade 1–2	0,08	0,09	Beta	[17]
Neutrophil count grade 3–4	0,02	0,03		
Hemoglobin grade 1–2	0,52	0,40		
Hemoglobin grade 3–4	0,01	0,03		
White cell count grade 1–2	0,07	0,07		
White cell count grade 3–4	0,01	0,02		
Temperature grade 1–2	0,11	0,13		
Temperature grade 3–4	0,00	0,00		
HFS-risk patients on reduced cap/5FU				
Neutrophil count grade 1–2	0,04	0,06	Beta	[17]
Neutrophil count grade 3–4	0,00	0,02		
Hemoglobin grade 1–2	0,59	0,25		
Hemoglobin grade 3–4	0,03	0,07		
White cell count grade 1–2	0,05	0,08		
White cell count grade 3–4	0,00	0,01		
Temperature grade 1–2	0,03	0,07		
Temperature grade 3–4	0,00	0,00		
HFS-risk patients on standard cap/5FU				
Neutrophil count grade 1–2	0,07	0,13	Beta	[17]
Neutrophil count grade 3–4	0,02	0,04		
Hemoglobin grade 1–2	0,50	0,31		
Hemoglobin grade 3–4	0,02	0,06		
White cell count grade 1–2	0,10	0,16		
White cell count grade 3–4	0,01	0,04		
Temperature grade 1–2	0,02	0,04		
Temperature grade 3–4	0,00	0,00		
Standard-risk patients on reduced cap/5FU				
Neutrophil count grade 1–2	0,06	0,11	Beta	[17]
Neutrophil count grade 3–4	0,02	0,05		
Hemoglobin grade 1–2	0,52	0,33		
Hemoglobin grade 3–4	0,02	0,07		
White cell count grade 1–2	0,09	0,15		
White cell count grade 3–4	0,01	0,02		
Temperature grade 1–2	0,01	0,03		
Temperature grade 3–4	0,00	0,00		
Standard-risk patients on standard cap/5FU				
Neutrophil count grade 1–2	0,06	0,07	Beta	[17]
Neutrophil count grade 3–4	0,03	0,06		
Hemoglobin grade 1–2	0,55	0,31		
Hemoglobin grade 3–4	0,00	0,04		
White cell count grade 1–2	0,09	0,12		
White cell count grade 3–4	0,01	0,04		

5FU: 5-fluorouracil; HFS: Hand–foot syndrome; n/a: Not applicable; OS: Overall survival; PFS: Progression-free survival; QALY: Quality-adjusted life years.

Table 1. Model input parameters (cont.).

Parameter	Value	Range	Distribution	Ref.
Temperature grade 1–2	0,02	0,03		
Temperature grade 3–4	0,00	0,00		
Routine practice				
Neutrophil count grade 1–2	0,06	0,11	Beta	[17]
Neutrophil count grade 3–4	0,02	0,05		
Hemoglobin grade 1–2	0,59	0,33		
Hemoglobin grade 3–4	0,04	0,11		
White cell count grade 1–2	0,11	0,18		
White cell count grade 3–4	0,01	0,04		
Temperature grade 1–2	0,02	0,04		
Temperature grade 3–4	0,00	0,00		

5FU: 5-fluorouracil; HFS: Hand–foot syndrome; n/a: Not applicable; OS: Overall survival; PFS: Progression-free survival; QALY: Quality-adjusted life years.

Decision tree

The probability of patients to experience test delays was built into the ToxNav strategy because test delays could affect the survival in cancer and quality of life due to potential delay in starting treatment. However, the duration of the testing period was 5.6 days (SD 13.8 days) [17], which was not considered a clinically relevant delay (i.e., having an impact on patients' prognosis) by oncologists involved in the OUH study. Therefore, it was assumed that patients in the decision tree were not affected by declines in survival or quality of life, and the probability of test delay was set at 0.

Patients' and clinicians' compliance to the ToxNav testing protocol were incorporated into the decision tree in two ways. First, we included the uptake of testing by patients. That is, although the test may be available to all eligible patients, the actual number taking the test depends on the patients' and clinicians' compliance. The probability of eligible patients actually taking the test was derived from the OUH study [17]. Second, we included clinicians' adherence to dosing recommendations resulting from ToxNav test results. Discrepancies between standardized dosing recommendations and clinicians' behavior were also derived from the OUH study [17]. Patients that did not undergo testing because of non-compliance were assumed to receive a standard dose of capecitabine or 5FU. Also, in the false negative arm of the decision tree all patients received standard dosing.

Markov model

Adverse events rates were based on the PSM and regression analysis described in previous sections [17]. The estimated rate of adverse events was based on data for all cancer patients treated with capecitabine or 5FU, as similar toxicity and *DPYD* variant distribution was observed between different types of cancer [17]. Adverse events were related to hemoglobin, neutrophil count (NC), white cell count (WCC) and temperature. Adverse events were graded according to the Common Terminology Criteria for Adverse Events (v6.0) grading system with severity ranging from 1 (mildest) to 4 (most severe). The adverse events rates by type and grade were combined into two groups: mild events that were graded 1 and 2, and severe events that were graded 3 and 4. Adverse event rates were assumed to be the same in the stable and the progressive disease states.

Costs per cycle were also based on the PSM and regression analysis and covered the costs of treating metastatic breast cancer disease and the costs of treating adverse events, including chemotherapy as a standalone or combination therapy, day care, outpatient, diagnostics, critical and emergency care, elective and non-elective hospitalizations, equipment and rehabilitation. Average two-monthly costs were estimated for the entire SoC arm and subgroups of patients in the ToxNav arm on the basis of patients' risk classification (i.e., high, HFS and standard) and the dosing of capecitabine and 5FU (i.e., reduced or standard) . Cost data were obtained from the financial information system of the OUH NHS Trust. Costs were inflated to 2020–2021 values using the NHS Cost Inflation Index.

The cost of the ToxNav test was assumed to be £200 based on the expert judgment of the oncologists involved in the OUH study [17] (personal communication with prof. A. Bassim Hassan, April 2022).

Survival & utility parameters – Markov model

The transition probabilities for disease progression and death from breast cancer in the Markov model were based on a cost–effectiveness analysis of capecitabine in the UK, with a Weibull distribution fitted to survival data to obtain estimates of progression free and overall survival [33]. General population mortality rates were used to estimate transition probabilities for death from other causes. They were obtained from the Office of National Statistics lifetables for England and were adjusted for mortality from malignant neoplasm of the breast by subtracting the breast cancer mortality per year [34]. Disease progression and survival probabilities, as well as effectiveness of capecitabine and 5FU, were assumed to be the same in the ToxNav and SoC arms. This assumption is justified by a previous matched-pair analysis, which reported that reduced doses did not negatively affect overall and progression-free survival of the patients and the risk of severe chemotherapy toxicity with reduced dose was comparable [35].

The utilities for the stable metastatic breast cancer and progressive metastatic breast cancer state in the Markov model were obtained from a UK study of quality of life in metastatic breast cancer [36,37]. The same study was used to derive disutilities for the adverse events [36,37] alongside other published cost–effectiveness analyses for *DPYD* testing and metastatic breast cancer [23,36,38].

Analyses

Main analysis

The main analysis presented the cost–effectiveness of extended *DPYD* testing prior to fluoropyrimidine-based chemotherapy in metastatic breast cancer in the UK, expressed as an incremental cost–effectiveness ratio (ICER) of costs per quality-adjusted life years (QALY). The analysis was performed taking the NHS and Personal Social Services perspective and a discount rate of 3.5% applied to both effects and costs. The time horizon of the analysis was patients' lifetime (the majority of patients would have died by the end of year 7).

Scenario analysis

In a scenario analysis we tested whether a shorter duration of the ToxNav's effect on modifying chemotherapy ceased to exist after the first 12 months. Effectively, this scenario assumes that all patients had no chemotherapy with capecitabine or 5FU after the first 12 months from their diagnosis with metastatic breast cancer. As a result the disutitlities and associated costs of adverse effects of chemotherapy were set to 0 in the model after the 6th cycle (i.e., 12 months). We also performed a probabilistic sensitivity analysis for this scenario.

Univariate & probabilistic sensitivity analyses

Univariate sensitivity analyses and probabilistic sensitivity analysis (PSA) were performed to test the robustness of the results in the main analysis. The univariate sensitivity analyses examined independently the variation of costs, adverse events rates and disutilities, utilities of disease states, clinicians' compliance to testing and dosing guidance, ToxNav test sensitivity and specificity, *DPYD* mutation prevalence, probability of high-risk mutation by a range of 20% increase and decrease of the parameters from their baseline values. In case that the 20% increase in the sensitivity analysis was exceeding the maximum possible value of 1 in some model parameters (i.e. probabilities and proportions), the upper value of the range was set at 1. The probabilistic sensitivity analysis (PSA) was performed by varying simultaneously all input parameters using 1000 iterations. A gamma distribution was applied to the shape and the scale of the Weibull distribution parameters for disease progression and survival, and costs. A beta distribution was applied for disease state utilities as well as rates of adverse events and the associated disutilities. A beta distribution was used for the input parameters in the decision tree with the exception of the cost of ToxNav test for which a gamma distribution was applied. The results were presented in a cost–effectiveness plane and a cost–effectiveness acceptability curve.

Results

Main analysis

The results of the main analysis are presented in Table 2. On a patient level, the ToxNav strategy led to 4.5 QALYs gained per patient for a cohort of 10,000 simulated women compared with SoC at a lower cost, £66,000 (the mean QALYs per patient from the 1000 simulations was 5.69, SD: 3.05, 95% CI: 5.50–5.88 at mean cost per patient of £83,000, SD: £46,000, 95% CI: £80,000–86,000). The costs and QALYs per patient in the SoC were £144,500 and 4.3, respectively, (the mean QALYs per patient from the 1000 simulations was 5.46, SD: 2.99, 95%

Table 2. Main analysis results per 10,000 simulated women for lifetime horizon, cost year 2020–2021.

Strategy	Costs, £ (disc)	QALYs (disc)	Incremental costs, £	Incremental QALYs	ICER
ToxNav© strategy	331.0 mln	22,670.8	–	–	Dominant
Standard of care	722.9 mln	21,740.0	-391.9 mln	930.8	–
	Costs, £ (undisc)	**QALYs (undisc)**	**Incremental costs, £**	**Incremental QALYs**	**ICER**
ToxNav strategy	340.5 mln	23,227.6	–	–	Dominant
Standard of care	743.8 mln	22,269.8	-403.3 mln	957.8	–

Disc: Discounted; ICER: Incremental cost–effectiveness ratio; mln: Million; QALY: Quality-adjusted life years; Undisc: Undiscounted.

Table 3. Scenario analysis results per 10,000 simulated women for lifetime horizon, cost year 2020–2021.

Strategy	Costs, £ (disc)	QALYs (disc)	Incremental costs, £	Incremental QALYs	ICER
ToxNav© strategy	501.7 mln	26,065.4	–	–	Dominant
Standard of care	700.2 mln	25,593.0	-198.4 mln	472.3	–
	Costs, £ (undisc)	**QALYs (undisc)**	**Incremental costs, £**	**Incremental QALYs**	**ICER**
ToxNav strategy	522.3 mln	26,821.5	–	–	Dominant
Standard of care	720.7 mln	26,349.2	-198.4 mln	472.3	–

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

CI: 5.28–5.65 at mean cost per patient of £182,000, SD: £100,000, 95% CI: £175,000–188,000). This resulted in 0.19 additional QALYs and cost savings of £78,000 per patient over a lifetime (the mean additional QALYs per patient from the 1000 simulations was 0.23, SD: 0.21, 95% CI: 0.22–0.24 at mean cost savings per patient of £99,000, SD: £57,000, 95% CI: £95,000–102,000). For the whole cohort of simulated patients, the QALYs and cost outcomes were 22,670 QALYs and £331 mln for the ToxNav strategy, and 21,740 QALYs and £722 mln for SoC. The ToxNav strategy was considered the dominant one because it produced more incremental QALYs than the SoC strategy at a lower cost.

Scenario analysis

The results of the scenario analysis are presented in Table 3 and show that ToxNav was still the dominant strategy with 0.08 QALYs gained (SD: 0.06, 95% CI: 0.08–0.09) and £37,000 (SD: £15,000, 95% CI: £36,000–£38,000) less cost per patient.

Sensitivity analyses

The results from the univariate sensitivity analyses suggested that varying independently the input parameters by a range of 20% is not likely to change the results in the main analysis and change the dominance of the ToxNav strategy (Figure 3).

The results from the 1000 simulations for the PSA of the main and the scenario analysis are presented in the cost–effectiveness planes (Figure 4A & B) with the majority of the points found to lie in the southeastern quadrant. The uncertainty in the PSA is attributable mostly to the potential gains in QALYs and cost savings for these simulations that lie in the southwestern quadrant of the plane (Figure 4A & B). The PSA for the main analysis showed that ToxNav was cost-effective at any threshold value compared with SoC (Figure 5A & B), with a probability of 97% to be dominant.

Discussion

This study examined the costs and health effects of introducing extended *DPYD* testing before fluoropyrimidine-based chemotherapy in metastatic breast cancer patients in the UK. The results from the main analysis demonstrated that *DPYD* testing with ToxNav for metastatic breast cancer patients before treatment initiation with capecitabine and 5FU is highly cost effective because it leads to more QALYs and less costs to the NHS compared with the current SoC, which consists of no genetic testing and standard dosing of capecitabine and 5FU. The cost savings in the ToxNav strategy resulted from potentially avoiding unnecessary chemotherapy and adverse events from treatment. The uncertainty in the sensitivity analyses is mainly due to the potential gains in QALYs and savings in costs.

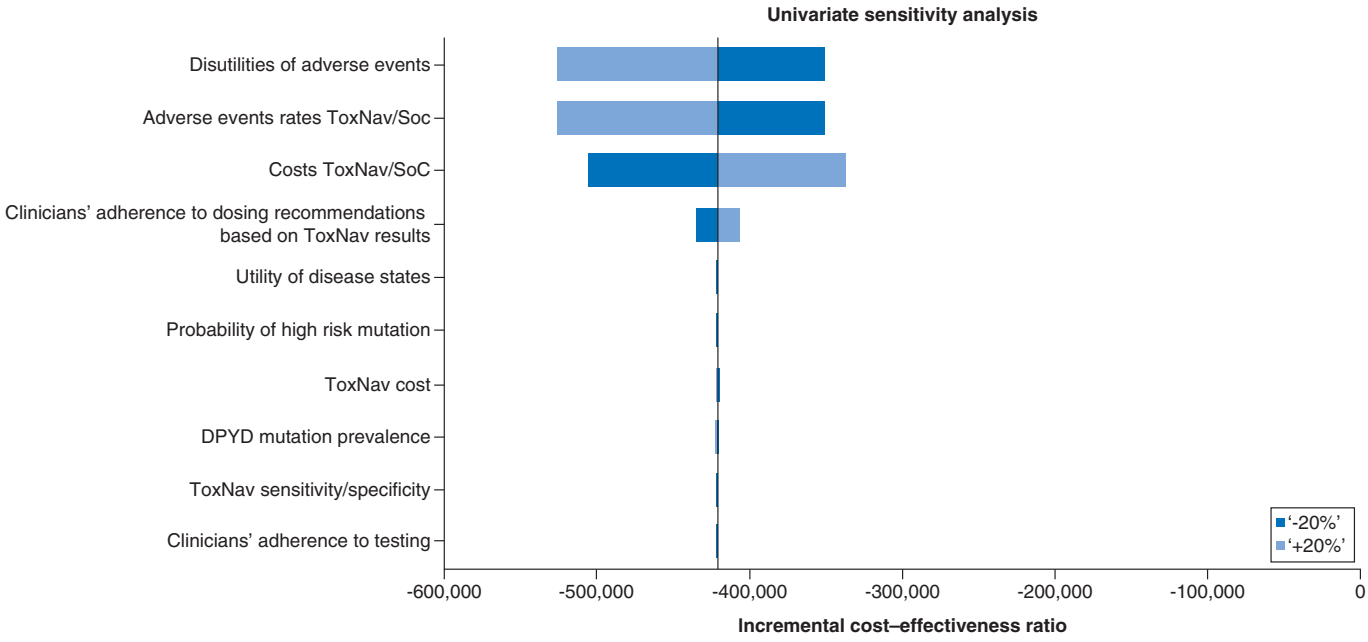

Figure 3. Univariate sensitivity analysis.
DPYD: Dihydropyrimidine dehydrogenase; SOC: Standard of care.

Historically, fluoropyrimidine-based chemotherapy regimens have been the most commonly prescribed anticancer drugs for the treatment of solid tumors, and the toxicities resulting from their use are well known by clinicians and patients alike. Therefore, dose adjustments after experiencing (severe) toxicity have not been uncommon in patients without *DPYD* testing. However, upfront *DPYD* testing before the start of treatment could provide an evidence-based approach to initial dose modification, potentially preventing severe toxicity and, more rarely, deaths due to toxicity; it is therefore increasingly recommended in clinical guidelines [39,40].

In addition, there is a growing body of evidence related to the clinical and cost–effectiveness [22–28,35,41] of modified dosing of fluoropyrimidine-based chemotherapy as a result of prior *DPYD* testing. There are concerns that the foregone benefits of reducing the dose of first-line chemotherapy may outweigh the benefits of the avoided side effects related to high toxicity. However, a published matched-pair analysis reported that reducing the dose of fluoropyrimidine-based chemotherapy in *DPYD* mutation carriers did not result in decreased overall and progression-free survival compared with the patients without a *DPYD* mutation receiving a standard dose of therapy. In addition, the risk of severe chemotherapy toxicity with reduced dose was comparable to the group of patients on standard dose [35]. Furthermore, the OUH study we performed has also shown that the majority of cancer patients without the *DPYD* variant had eventually reduced dose due to decreased toxicity tolerance [17].

Published studies clearly demonstrate that upfront *DPYD* testing followed by dose adjustment is cost-effective [22–28,41]. Our results are in line with previous studies of upfront screening for the *DPYD* variants before start of fluoropyrimidine-based therapy in The Netherlands that reported net cost savings – that is, the costs of *DPYD* screening were outweighed by savings in treatment costs [22,24]. Similar results were found in a study from Ireland reporting that cost savings from reduced hospitalization due to toxicity would be larger than the costs of *DPYD* testing [25]. With regard to improvements in quality of life, our findings are consistent with a previous study from Italy, where greater effectiveness was reported [23], although the estimated quality-of-life gain in the *DPYD* testing strategy was larger in our analysis. A study conducted from the US healthcare perspective reported that stage 3 colon cancer patients who received adjuvant chemotherapy benefited from screening for *DPYD* deficiency to prevent severe and fatal toxicities and that *DPYD* genotyping was cost-effective [28].

Compared with previous economic studies, we report the highest cost savings from *DPYD* testing. Therefore, we tested in a scenario analysis whether assuming shorter time horizon of health disutilitites, related to capecitabine and 5FU, and associated costs will impact the cost–effectiveness results in the main analysis and found that the ToxNav strategy was consistently the dominant one. The main possible reasons for the difference of the

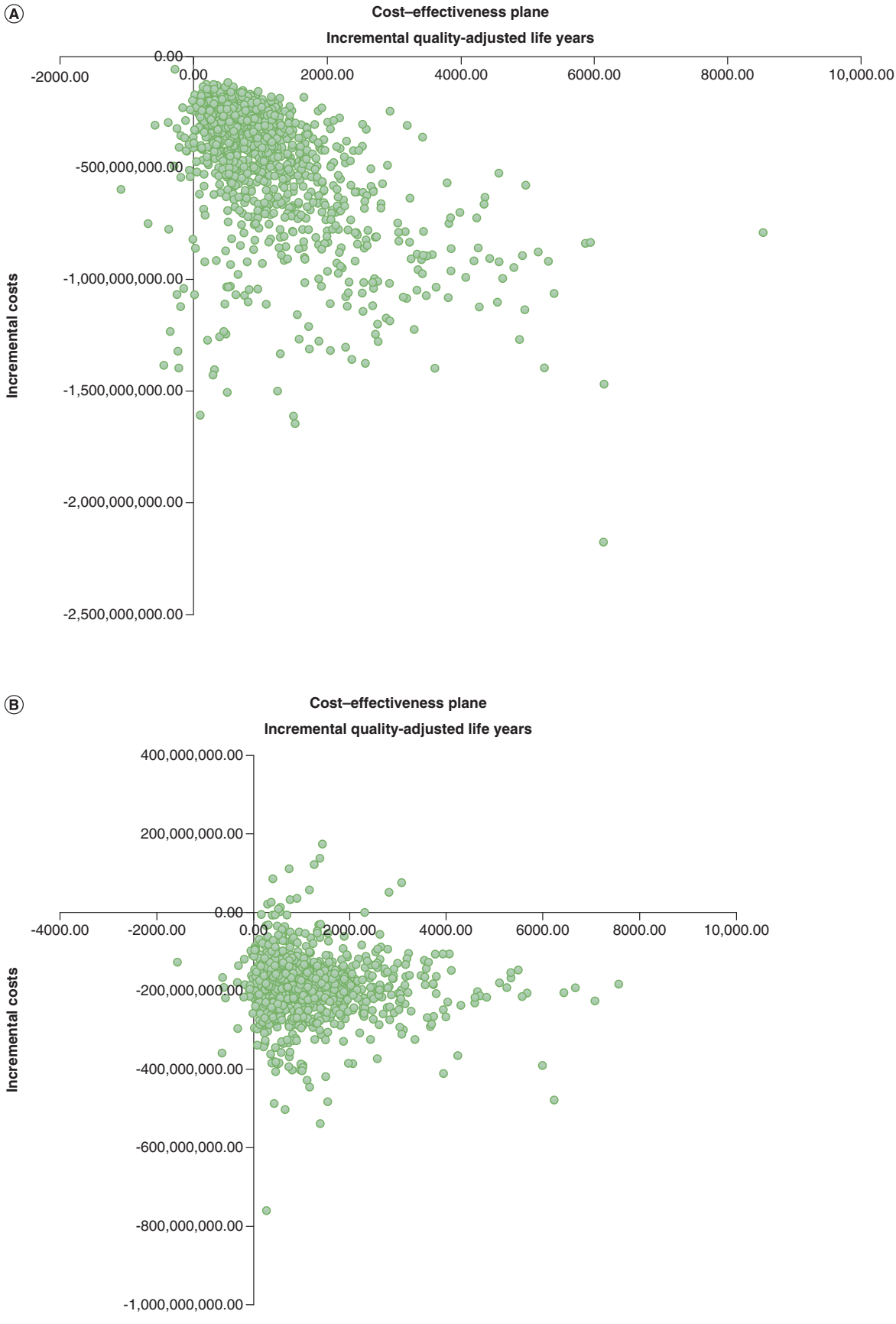

Figure 4. Cost–effectiveness plane of incremental costs and quality-adjusted life years for a cohort of 10,000 patients. (A) Main analysis (ToxNav© vs standard of care). **(B)** Scenario analysis (ToxNav vs standard of care).

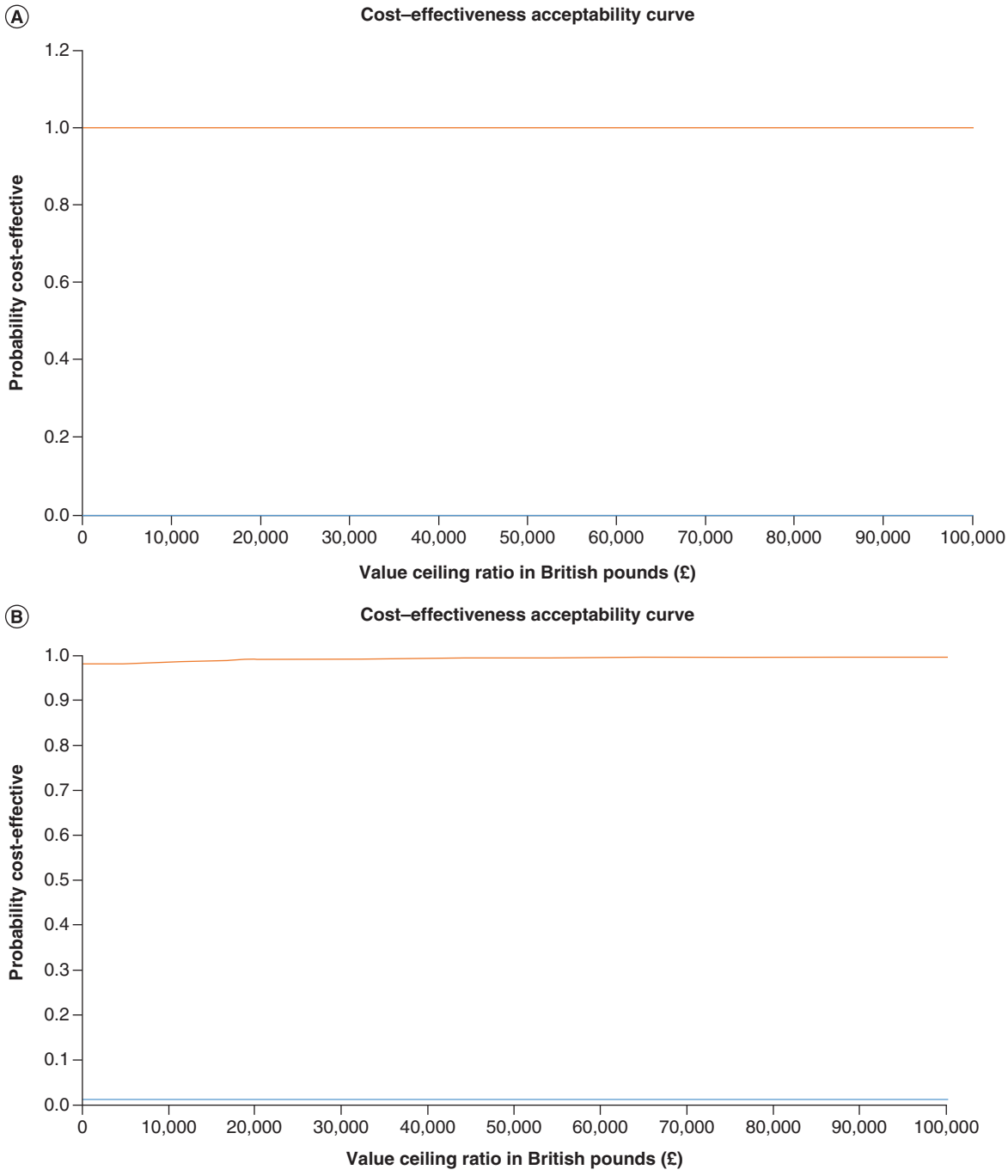

Figure 5. Cost–effectiveness acceptability curve. (A) Main analysis (cost–effectiveness acceptability curve) (ToxNav© strategy vs standard of care). **(B)** Scenario analysis (ToxNav strategy vs standard of care).

reported savings are the comprehensiveness of the cost data in our analysis (which included outpatient care, day care, diagnostics, chemotherapy, radiotherapy, critical and emergency care, elective and non-elective hospital care, equipment and rehabilitation) and the long time horizon (i.e., lifetime). Other studies had a narrow costing scope and only included treating one adverse event (i.e., severe neutropenia and related costs of hospitalization, drugs, tests and analyses) and stated that they underestimated the cost of treating fluoropyrimidine-induced toxicity [41]. There were studies with more detailed costing [24], but it is worth noting that these costs relate to a follow-up period of 168 days at the most, whereas the costs reported in our analysis are lifetime. There were also studies that reported larger hospital costs per treating a patient with toxicity; from a total of 134 analyzed patients treated with

fluoropyrimidines, five were hospitalized, and the total cost of these hospitalizations were €232,061, an average of €46,412 per case [25]. The cost per patient hospitalization in this study is similar to the savings per patient we reported in the scenario analysis, which assumed a shorted time horizon for disutilitites and costs related to adverse events.

Our study has provided a key piece of missing information: evidence on the costs and cost–effectiveness of *DPYD* testing in the UK. The results from our analysis can be used by decision-makers in the UK to guide reimbursement decisions and identify potential areas where additional evidence might be needed. Our study contributes to the growing body of literature that supports the introduction of *DPYD* testing and together with results from previous studies can be used by health payers to make conditional reimbursement decisions for their country regarding piloting *DPYD* testing and collecting relevant local data to assess the risk–benefits. A potential area where additional evidence is worth considering is comparing the effectiveness and cost–effectiveness of testing patients from different ethnic backgrounds and suffering from solid cancers by four *DPYD* variant test versus a multipanel one. Another potential area of additional research is modeling and assessing the effects of dose reductions that happen in real-world settings usually in subsequent rounds of treatment due to reduced toxicity tolerance of patients without *DPYD* variants receiving fluoropyrimidines.

There are currently ongoing initiatives by NHS England to introduce a four-variant *DPYD* testing across the service. A four-variant test may be sufficient to identify mutations prevalent in Caucasian groups; however, it may miss some mutations in other ethnicities. However, it should be noted that a four-variant test may be less expensive than an extended gene panel such as ToxNav and thus make it possible to offer upfront *DPYD* testing to larger number of patients. Therefore, there are important efficiency and equity considerations [42,43] as well as cost–effectiveness considerations to be weighted in by decision-makers when choosing which test should be offered in the NHS. ToxNav is not used routinely in the English NHS; therefore, there are no data on reimbursement fee or the manufacturer's charge for it. Therefore, we informed the test cost parameter in our model using expert judgment, which is not unusual practice in economic modeling when data on parameters are not available. The expert opinion was based on the discussions that the directory of OUH had with the test manufacturer as well as the cost of similar *DPYD* testing found in the scientific literature. For example, the cost of genetic testing for four *DPYD* variants in the papers by Flagoulakis [23] and Hendriks [24] is €100–120 (range €80–120), and in the paper by Brookes [28], it is USA$174.42. In any case, the uncertainty around the cost of ToxNav was addressed in the PSA, which has shown that the ToxNav strategy is consistently a dominant alternative.

The main strength of this study is that, to our knowledge, it is the first analysis of the cost–effectiveness of introducing extended *DPYD* testing before fluoropyrimidine-based chemotherapy in metastatic breast cancer patients in the UK. In addition, we used real-world patient-level data to estimate costs and rates of adverse events. Real-world data were also used to inform other model parameters, including probabilities of tested patients to be characterized as bearing standard, high or HFS risk as a result of the ToxNav test, clinicians' and patients' compliance to testing and clinicians' adherence to dosing guidance based on test results.

A limitation of the current study is that the cohort used to estimate the rates of adverse events was predominantly Caucasian, and so the results of our analysis might not be directly applicable to settings where populations are of different ethnicity and the prevalence of various *DPYD* mutations may be different. Had the ToxNav test been applied to a cohort of a more ethnically diverse population, it is likely that it would have detected more variants and, as a result, altered the dosing of chemotherapy drugs, which in turn would affect rates of adverse events and costs. Thus, we may expect that the cost–effectiveness of the test in the current analysis may have been underestimated. In addition, there are equality benefits to be gained by distributing health benefits of genetic testing across all ethnic population groups.

Another limitation is that we did not include reduced survival from cardiac deaths caused by chemotherapy due to lack of data, which potentially underestimated the cost–effectiveness of ToxNav. Furthermore, we assumed equal effectiveness of capecitabine and 5FU in the ToxNav and SoC arms based on the conclusions of a previous matched-pair analysis that reduced doses in slow metabolizers did not negatively affect chemotherapies' effectiveness in terms of overall and progression-free survival [35]. The matched-pair analysis study reported that the risk of severe fluoropyrimidine-related toxicity in *DPYD* carriers who received a reduced dose of the drugs decreased significantly compared with treating them with full dose and was similar to the risk borne by non-carriers [35]. These limitations indicate that the QALYs' gain reported in our analysis is attributable to higher quality of life in the ToxNav arm through the prevention of severe side effects rather than increased survival. Because of the lack of data, we could not consider HFS and diarrhea or enteritis events and the associated impact on quality of life. In addition, we

could not establish the interdependency between blood count events and modeled these independent of each other. Although separate modeling of blood count events has been done in other analyses [23], it should be acknowledged that ideally, blood counts should be modeled as dependent events.

Conclusion

Our cost–effectiveness analysis demonstrated that introducing extended *DPYD* testing before fluoropyrimidine-based chemotherapy in metastatic breast cancer patients in the UK resulted in QALYs gained at lower costs and should, therefore, be recommended for reimbursement. From the perspective of the UK NHS, introducing upfront *DPYD* testing, can potentially generate savings in the healthcare system while improving cancer care.

Executive summary

Introduction

- Fluorpyrimidine-based chemotherapies, including 5-fluorouracil (5FU), tegafur and capecitabine, have demonstrated improved progression-free and overall survival in metastatic breast cancer.
- Mild to severe adverse reactions are develop by ~20% of patients due to specific genetic mutations in the *DPYD*-encoding gene responsible for metabolizing fluoropyrimidine-based chemotherapies. Current Clinical Pharmacogenetics Implementation Consortium guidelines recommend testing for four *DPYD* variants; however, there are more than 160 identified variants, and at least 50% of patients who experience severe toxicity to 5FU or capecitabine are not carriers of the four most common variants. ToxNav©, a multivariant genetic test, was developed to allow for testing of 19 variants that have demonstrated correlation with 5FU and capecitabine toxicities.
- *DPYD* variants carriers are slow drug metabolizers and have a higher risk of severe toxicity when they receive standard-dose fluoropyrimidine therapy; therefore, they could potentially benefit from upfront *DPYD* genotyping with ToxNav followed by personalized dosing based on genotyping results.
- Our aim was to evaluate the cost–effectiveness of ToxNav to screen for *DPYD* variants followed by personalized chemotherapy dosing for metastatic breast cancer in the UK compared with no testing followed by standard dose, referred to as standard of care (SoC).

Methods

- A decision tree and a four state lifetime Markov model were developed to simulate the intervention (ToxNav followed by personalized chemotherapy dosing) versus SoC in women with metastatic breast cancer aged 60 years. The Markov model ran in 2-month cycles; scenario analysis, univariate sensitivity analyses and probabilistic sensitivity analyses were performed to test the robustness of the results in the main analysis.
- Model parameter were populated by using real-world data from the Oxford University Hospitals NHS Trust and published literature.

Results

- The results from the main and the scenario analyses demonstrated that *DPYD* testing with ToxNav for metastatic breast cancer patients before treatment initiation with capecitabine and 5FU is highly cost-effective because it leads to quality-adjusted life years gained and reduced costs compared with the current SoC. The results from the sensitivity analyses showed that ToxNav was cost-effective at any willingness-to-pay threshold with a probability of 97% to be dominant.
- The cost savings in the ToxNav strategy resulted from potentially avoiding unnecessary chemotherapy and adverse events from treatment. The uncertainty in the sensitivity analyses is mainly due to the potential gains in quality-adjusted life years and savings in costs.

Discussion & conclusion

- There are currently ongoing initiatives by the NHS England to introduce a four-variant *DPYD* testing across the service, and it should be noted that there are important efficiency and equity considerations as well as cost–effectiveness considerations to be weighted in by decision-makers when choosing how many variants should be offered for testing in the NHS.
- Our study contributes to the growing body of literature that supports the introduction of *DPYD* testing and together with results from previous studies can be used by health payers to make conditional reimbursement decisions for their country regarding piloting *DPYD* testing and collecting relevant local data to assess the risk–benefits.

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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 is provided in the manuscript.

References

1. Ferlay J, Soerjomataram I, Dikshit R *et al.* Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int. J. Cancer* 136(5), E359–E86 (2015).
2. Cardoso F, Harbeck N, Fallowfield L *et al.* Locally recurrent or metastatic breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 23, vii11–vii9 (2012).
3. Alsaloumi L, Shawagfeh S, Abdi A, Basgut B. Efficacy and safety of capecitabine alone or in combination in advanced metastatic breast cancer patients previously treated with anthracycline and taxane: a systematic review and meta-analysis. *Oncol. Res. Treat.* 43(12), 694–702 (2020).
4. Mauri D, Polyzos NP, Salanti G *et al.* Multiple-treatments meta-analysis of chemotherapy and targeted therapies in advanced breast cancer. *J. Natl. Cancer Inst.* 100(24), 1780–91 (2008).
5. Paracha N, Reyes A, Diéras V *et al.* Evaluating the clinical effectiveness and safety of various HER2-targeted regimens after prior taxane/trastuzumab in patients with previously treated, unresectable, or metastatic HER2-positive breast cancer: a systematic review and network meta-analysis. *Breast Cancer Res. Treat.* 180(3), 597–609 (2020).
6. Zhao Q, Hughes R, Neupane B *et al.* Network meta-analysis of eribulin versus other chemotherapies used as second- or later-line treatment in locally advanced or metastatic breast cancer. *BMC Cancer.* 21(1), 758 (2021).
7. Van Cutsem E, Twelves C, Cassidy J *et al.* Oral capecitabine compared with intravenous fluorouracil plus leucovorin in patients with metastatic colorectal cancer: results of a large phase III study. *J. Clin. Oncol.* 19(21), 4097–106 (2001).
8. Koopman M, Antonini NF, Douma J *et al.* Sequential versus combination chemotherapy with capecitabine, irinotecan, and oxaliplatin in advanced colorectal cancer (CAIRO): a phase III randomised controlled trial. *Lancet.* 370(9582), 135–42 (2007).
9. Hoff PM, Ansari R, Batist G *et al.* Comparison of oral capecitabine versus intravenous fluorouracil plus leucovorin as first-line treatment in 605 patients with metastatic colorectal cancer: results of a randomized phase III study. *J. Clin. Oncol.* 19(8), 2282–92 (2001).
10. Mattison LK, Fourie J, Desmond RA *et al.* Increased prevalence of dihydropyrimidine dehydrogenase deficiency in African-Americans compared with Caucasians. *Clin. Cancer Res.* 12(18), 5491–5 (2006).
11. Saif MW, Ezzeldin H, Vance K *et al.* DPYD*2A mutation: the most common mutation associated with DPD deficiency. *Cancer Chemother. Pharmacol.* 60(4), 503–7 (2007).
12. Largillier R, Etienne-Grimaldi MC, Formento JL *et al.* Pharmacogenetics of capecitabine in advanced breast cancer patients. *Clin. Cancer Res.* 12(18), 5496–502 (2006).
13. Deenen MJ, Tol J, Burylo AM *et al.* Relationship between single nucleotide polymorphisms and haplotypes in DPYD and toxicity and efficacy of capecitabine in advanced colorectal cancer. *Clin. Cancer Res.* 17(10), 3455–68 (2011).
14. Rosmarin D, Palles C, Pagnamenta A *et al.* A candidate gene study of capecitabine-related toxicity in colorectal cancer identifies new toxicity variants at DPYD and a putative role for ENOSF1 rather than TYMS. *Gut.* 64(1), 111–20 (2015).
15. Palles C, Fotheringham S, Chegwidden L *et al.* An evaluation of the diagnostic accuracy of a panel of variants in DPYD and a single variant in ENOSF1 for predicting common capecitabine related toxicities. *Cancers.* 13(7), 1497 (2021).
16. Toffoli G, Giodini L, Buonadonna A *et al.* Clinical validity of a DPYD-based pharmacogenetic test to predict severe toxicity to fluoropyrimidines. *Int. J. Cancer.* 137(12), 2971–80 (2015).

17. Tsiachristas A, Vallance G, Koleva-Kolarova R *et al.* Can upfront DPYD extended variant testing reduce toxicity and associated hospital costs of fluoropyrimidine chemotherapy? A propensity score matched analysis of 2022 UK patients. *BMC Cancer.* 22(1), 458 (2022).
18. European Medicines Agency. EMA recommendations on DPD testing prior to treatment with fluorouracil, capecitabine, tegafur and flucytosine (2020). www.ema.europa.eu/en/news/ema-recommendations-dpd-testing-prior-treatment-fluorouracil-capecitabine-tegafur-flucytosine (Accessed 16 June 2022).
19. Van Cutsem E, Cervantes A, Adam R *et al.* ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Ann. Oncol.* 27(8), 1386–422 (2016).
20. Deenen MJ, Meulendijks D. Recommendation on testing for dihydropyrimidine dehydrogenase deficiency in the ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Ann. Oncology.* 28(1), 184 (2017).
21. England NHS. Clinical Commissioning Urgent Policy Statement: pharmacogenomic testing for DPYD polymorphisms with fluoropyrimidine therapies. NHS England, London, UK (2020). www.england.nhs.uk/publication/clinical-commissioning-urgent-policy-statement-pharmacogenomic-testing-for-dpyd-polymorphisms-with-fluoropyrimidine-therapies/.
22. Deenen MJ, Meulendijks D, Cats A *et al.* Upfront genotyping of DPYD*2A to individualize fluoropyrimidine therapy: a safety and cost analysis. *J. Clin. Oncol.* 34(3), 227–34 (2016).
23. Fragoulakis V, Roncato R, Fratte CD *et al.* Estimating the effectiveness of DPYD genotyping in Italian individuals suffering from cancer based on the cost of chemotherapy-induced toxicity. *Am. J. Hum. Genet.* 104(6), 1158–68 (2019).
24. Henricks LM, Lunenburg C, de Man FM *et al.* A cost analysis of upfront DPYD genotype-guided dose individualisation in fluoropyrimidine-based anticancer therapy. *Eur. J. Cancer.* 107, 60–7 (2019).
25. Murphy C, Byrne S, Ahmed G *et al.* Cost implications of reactive versus prospective testing for dihydropyrimidine dehydrogenase deficiency in patients with colorectal cancer: a single-institution experience. *Dose Response.* 16(4), 1559325818803042 (2018).
26. Ontario Health (Quality). DPYD genotyping in patients who have planned cancer treatment with fluoropyrimidines: a health technology assessment. *Ont. Health Technol. Assess. Ser.* 21(14), 1–186 (2021).
27. Toffoli G, Innocenti F, Polesel J *et al.* The genotype for DPYD risk variants in patients with colorectal cancer and the related toxicity management costs in clinical practice. *Clin. Pharm. Ther.* 105(4), 994–1002 (2019).
28. Brooks GA, Tapp S, Daly AT *et al*. Cost–effectiveness of DPYD genotyping prior to fluoropyrimidine-based adjuvant chemotherapy for colon cancer. *Clin. Colorectal Cancer.* 21(3), e189–e195 (2022).
29. Vellekoop H, Huygens S, Versteegh M *et al.* Guidance for the harmonisation and improvement of economic evaluations of personalised medicine. *PharmacoEconomics.* 39(7), 771–88 (2021).
30. National Institute for Health and Care Excellence. NICE health technology evaluations: the manual (2022). www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation (Accessed 26 April 2022).
31. Husereau D, Drummond M, Augustovski F *et al.* Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) Statement: updated reporting guidance for health economic evaluations. *Appl. Health Econ. Health Policy.* 20(2), 213–21 (2022).
32. Elbasha EH, Chhatwal J. Myths and misconceptions of within-cycle correction: a guide for modelers and decision makers. *Pharmacoeconomics.* 34(1), 13–22 (2016).
33. Delea TE, Tappenden P, Sofrygin O *et al.* Cost–effectiveness of lapatinib plus capecitabine in women with HER2+ metastatic breast cancer who have received prior therapy with trastuzumab. *Eur. J. Health Econ.* 13(5), 589–603 (2012).
34. Office of National Statistics. (2021). www.ons.gov.uk/
35. Henricks LM, van Merendonk LN, Meulendijks D *et al.* Effectiveness and safety of reduced-dose fluoropyrimidine therapy in patients carrying the DPYD*2A variant: A matched pair analysis. *Int. J. Cancer.* 144(9), 2347–54 (2019).
36. Lloyd A, Nafees B, Narewska J *et al*. Health state utilities for metastatic breast cancer. *Br J Cancer.* 95(6), 683–90 (2006).
37. Diaby V, Adunlin G, Ali AA, Zeichner SB *et al.* Cost–effectiveness analysis of 1st through 3rd line sequential targeted therapy in HER2-positive metastatic breast cancer in the United States. *Breast Cancer Res. Treat.* 160(1), 187–96 (2016).
38. Beauchemin C, Letarte N, Mathurin K *et al*. A global economic model to assess the cost–effectiveness of new treatments for advanced breast cancer in Canada. *J. Med. Econ.* 19(6), 619–29 (2016).
39. Loriot MA, Ciccolini J, Thomas F *et al.* Dihydropyrimidine déhydrogenase (DPD) deficiency screening and securing of fluoropyrimidine-based chemotherapies: update and recommendations of the French GPCO-Unicancer and RNPGx networks. *Bull Cancer.* 105(4), 397–407 (2018).
40. Lunenburg CATC, van der Wouden CH, Nijenhuis M, Crommentuijn-van Rhenen MH, de Boer-Veger NJ, Buunk AM *et al.* Dutch Pharmacogenetics Working Group (DPWG) guideline for the gene–drug interaction of DPYD and fluoropyrimidines. *Eur. J. Hum. Genetics.* 28(4), 508–17 (2020).
41. Cortejoso L, García-González X, García MI *et al*. Cost–effectiveness of screening for DPYD polymorphisms to prevent neutropenia in cancer patients treated with fluoropyrimidines. *Pharmacogenomics.* 17(9), 979–84 (2016).

42. Manrai AK, Funke BH, Rehm HL *et al.* Genetic misdiagnoses and the potential for health disparities. *New Engl. J. Med.* 375(7), 655–65 (2016).

43. Ben-Eghan C, Sun R, Hleap JS *et al.* Don't ignore genetic data from minority populations. *Nature.* 585(7824), 184–6 (2020).

44. Lee LYW, Starkey T, Sivakumar S *et al.* ToxNav germline genetic testing and PROMinet digital mobile application toxicity monitoring: Results of a prospective single-center clinical utility study-PRECISE study. *Cancer Med.* 8(14), 6305–6314 (2019).