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Value of information analysis of multi-parameter tests for chemotherapy in early breast cancer: the OPTIMA-prelim trial

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ABSTRACT

Background: Precision medicine is heralded as offering more effective treatments to smaller targeted patient populations. In breast cancer, adjuvant chemotherapy is standard for patients considered high risk after surgery. Molecular tests may identify patients that can safely avoid chemotherapy. We used economic analysis prior to a large scale clinicl trial of molecular testing to confirm the value of the trial and help prioritise between candidate tests as randomised comparators.

Methods: Women with surgically treated breast cancer (ER positive and lymph node positive or tumour size >=30mm) were randomised to standard care (chemotherapy for all) or test-directed care using Oncotype DX. Additional testing was undertaken using alternative tests: MammaPrint™, PAM-50 (Prosigna™), MammaTyper™, IHC4 and IHC4-AQUA™ (NexCourse Breast™). A probabilistic decision model assessed cost-effectiveness of all tests from a UK perspective. Value of information analysis (VoI) determined the most efficient publically funded ongoing trial design in the UK.

Results: There was an 86% probability of molecular testing being cost-effective, with most tests producing cost savings (range -£1,892 to +£195) and QALY gains (range 0.17 to 0.20). There were only small differences in costs and QALYs between tests. Uncertainty was driven by long-term outcomes. VoI demonstrated value of further research into all tests, with ProSigna currently highest priority for further research.

Conclusion: Molecular tests are likely to be cost-effective, but an optimal test is yet to be identified. Health economic modelling to inform the design of an RCT looking at diagnostic technology has been demonstrated feasible as a method for improving research efficiency.

HIGHLIGHTS

Multi-parameter and genomic tests in breast cancer are undergoing rapid development and implementation in lymph node negative breast cancer. There remains substantial uncertainty about the efficacy and cost-effectiveness of such tests when used in higher risk patients. There are major challenges in undertaking meaningful research to inform reimbursement and adoption decisions for these diagnostic tests and for personalised medicine technologies in general.

In this context, we describe how the use of value of information analysis as the primary outcome of a randomised controlled feasibility trial, in the presence of multiple competing technologies, has led to the setup of a major national study which is directly designed to inform an estimate of the cost-effectiveness of a personalised treatment strategy in clinically high risk early breast cancer.

BACKGROUND

There is increasing concern in developed nations that health care costs are increasing at an unsustainable rate. Precision medicine has been heralded as a solution by providing more effective treatments to smaller targeted patient populations. In the context of breast cancer, adjuvant chemotherapy is offered to most women with invasive breast cancer involving the axillary lymph nodes or with otherwise clinically high risk disease.[1–4] As a universal recommendation chemotherapy is, however, not strongly supported by randomised clinical evidence in women who are post-menopausal, of older age and who have oestrogen receptor (ER) positive HER2 negative cancer.[5] It is therefore likely that many women with ER positive breast cancer are being offered chemotherapy with only limited benefit and substantial risk of harm.[6–8] Diagnostic tests that help identify which women can safely avoid chemotherapy could improve health outcomes as well as ease the pressure on strained health system budgets.

Molecular tests may select patients who can safely be spared chemotherapy under the rationale that the sensitivity of tumours to chemotherapy is dependent on underlying cancer biology, not just clinical and pathological factors. Such new technologies are evolving rapidly with an increasing number of commercial and academic institutions offering solutions. Different tests contain different combinations of molecular markers and identify different patients as at high or low risk of recurrence, but their comparative diagnostic properties remains largely unknown.[Ref – not all tests are equal] The maturity of evidence for these tests is very variable and traditional methods for generating level one evidence may lack efficiency. There is a risk that technologies entering the market first will be adopted, thereby stifling the development of evidence for alternative tests that are currently less well

developed but which may emerge as better tests for widespread implementation in the future.

A prospective randomised controlled trial is necessary to measure the clinical utility and cost-effectiveness of molecular testing in this patient population. Such a trial requires large numbers of patients with at least 5 years of follow-up to capture relevant outcomes. The randomised comparison of multiple tests in this context is likely to be prohibitive in terms of scale and cost. Realistically there are only enough resources available to study one test in an adequately powered trial. It is essential that a test chosen to be to focus of such a trial is that which has the highest likely long term societal return on that research investment.

OPTIMA prelim (ISRCTN42400492)[9] was established as a feasibility trial prior to an adequately powered phase three randomised controlled trial of molecular testing in early breast cancer in the UK (Figure Supplementary 1). The objectives were: (i) to evaluate the performance and health-economics of alternative molecular tests to determine which technology(s) are to be evaluated in a subsequent main trial; (ii) to establish the acceptability to patients and clinicians of randomisation to test-directed treatment assignment; and (iii) to establish efficient and timely sample collection and analysis essential to the delivery of molecular tests driven treatment. We report here the results of the health-economic analysis and value of information analysis designed to inform the selection of a test for study in the subsequent OPTIMA trial.

METHODS

The OPTIMAprelim trial

The design of OPTIMA prelim is described in the protocol available to download on the funder's website (http://www.nets.nihr.ac.uk/projects/hta/103401). Eligible patients were women aged ≥40 with ER positive, HER2 negative clinically high risk (1-9 axillary lymph nodes involved, or node negative with a tumour ≥30mm) surgically treated early invasive breast cancer. Women were randomised (1:1) to standard treatment (chemotherapy followed by endocrine therapy) or to test guided therapy (endocrine therapy alone if low risk, standard treatment if high risk). Oncotype DX was used to direct therapy with a cut-point of >25. Chemotherapy was selected from regimens commonly used in the NHS.

Molecular tests

Additional molecular tests were conducted on all patients with available samples to enable a comparison of the allocation of participants into high or low-risk groups by each test. Several alternative tests were considered: Oncotype DX™ (Genomic Health), MammaPrint™/BluePrint™/TargetPrint™ (Agendia, Irvine, California), Prosigna™ Subtype and Prosigna™ ROR_PT, MammaTyper™ (Stratifyer/BioNTech Diagnostics, Mainz, Germany), NexCourse™ Breast by Aqua (Genoptix Medical Laboratories, Carlsbad, California – hereafter referred to as IHC4 AQUA) and IHC4 performed by conventional pathology techniques (HER2 testing by ISH and ER, PgR and Ki67 by quantitative image analysis (Ariol) using standard immunohistochemistry). Tests were performed by the vendor (Oncotype DX, MammaPrint/ BluePrint, MammaTyper, NexCourse Breast by Aqua or in the Ontario Institute of Cancer Research (IHC4, Prosigna using equipment and reagents supplied by the vendor). Tumours were categorised according to the tests pre-defined cut-points into low/intermediate risk

(termed low risk) or mid/high risk (termed high risk); for the purpose of this study, the Oncotype DX RS cut-point of 25 was used to define a high versus low risk test result.

Economic modelling method

The methods for the economic analysis followed the guidelines and reference case of the UK National Institute of Health and Care Excellence (NICE).[10] A simulation model representing the clinical pathway estimated expected costs and quality-adjusted life-years (QALYs) for a cohort of women with high risk ER positive HER2 negative early breast cancer. The analysis was conducted from a UK NHS perspective, uses a lifetime horizon truncated at age 100 and 1 year cycle lengths. Costs are reported in 2012/13 GBP (£) and future costs and benefits are discounted at an annual rate of 3.5%. The model was analysed using the statistical package R.[11]

The model structure was based on a previously published model,[12] and consists of an initial decision-tree (Figure 1a) followed by a seven health-state time-dependent discrete-state transition (modified Markov) cohort model (Figure 1b). The model structure was validated through consultation with clinical experts within the trial management group.

Figure 1a.

Decision Tree – Patients are assigned "chemotherapy for all" or "test-directed chemotherapy."

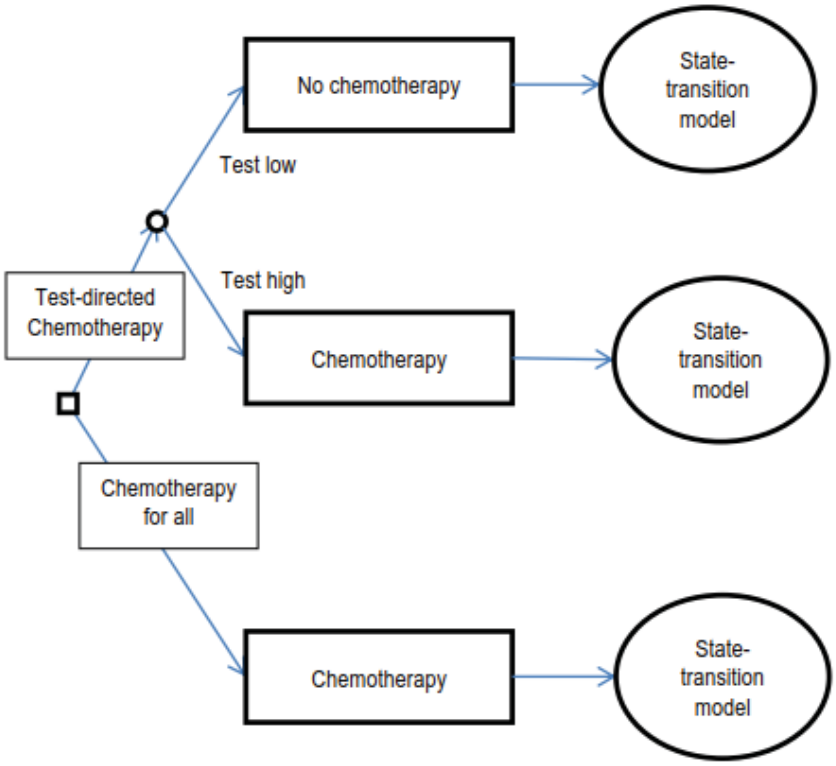
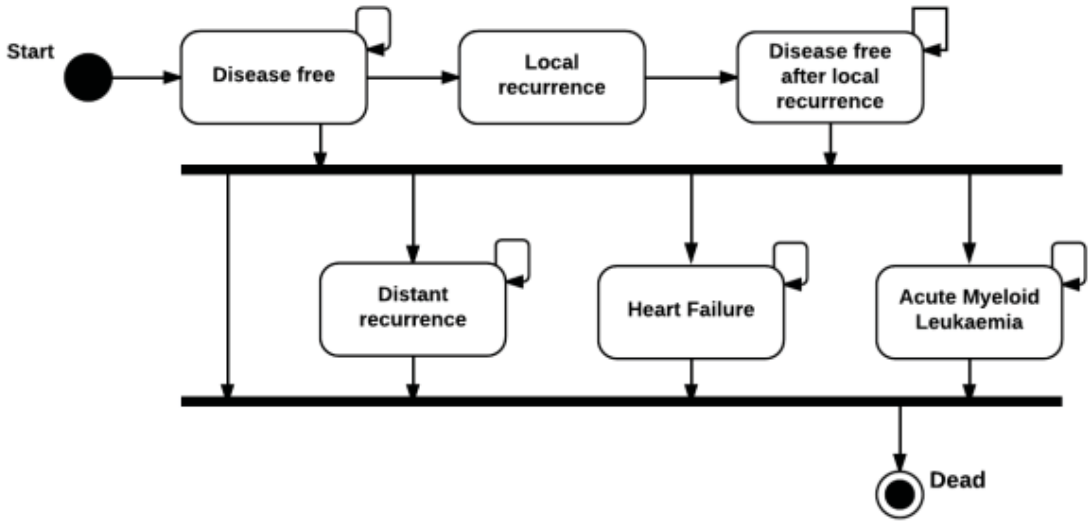


Figure 1b.

State transition model



Model Parameters

Full details of how the model parameters were defined are provided in the supplementary material (Table S3). Briefly, the allocation of patients into high- and low-risk groups was based

on the OPTIMA prelim study. Cancer recurrence rates for the OPTIMA-prelim patients were estimated using 10 year forecasts from Adjuvant! Online.[13] The effect of chemotherapy on recurrence free survival dependent on test score was taken from the SWOG 8814 trial by modelling the log hazard ratio for 10 year recurrence free survival as a linear function of the Oncotype DX Recurrence Score (RS).[14] For other tests, representative uncertainty was introduced into the model using an uncertain prior distribution for the predictive effect from which weighted sampling depended on the degree of discordance between the test and Oncotype DX seen in OPTIMA prelim.

Healthcare costs and quality of life

The cost of tests was determined by using the current public list price (Oncotype DX, MammaPrint, IHC4 AQUA) or, in the absence of a public list price, by communication with the manufacturer (Prosigna) or by best estimate by the analyst following discussion with the manufacturer (MammaTyper). For locally performed tests (MammaTyper, Prosigna and IHC4) the capital costs and per-patient costs to the NHS were estimated by consultation with NHS service managers, pathologists and manufacturers. Where uncertainty existed about the costs, this was represented by a distribution in the probabilistic analysis.

Chemotherapy procurement, delivery and toxicity costs were taken from the British National Formulary, the NHS Commercial Medicines Unit and NHS Reference costs.[15–17] The proportions, case-mix and test selection of patients treated with anthracycline plus taxane, anthracycline alone, or taxane alone were modelled directly from the OPTIMA prelim data. Costs of cancer recurrence and long term toxicities were taken from a bespoke costing study of NHS patients and the published literature.[18] Quality of life (utility) values were extracted from a previously published study and assigned to each model health state, including a decrement for chemotherapy toxicity.[19]

Sensitivity analyses

Probabilistic sensitivity analysis was conducted using Monte Carlo simulation to sample from distributions assigned to model input parameters. In addition, two alternative model specifications were analysed to explore key structural uncertainties:

1. *Sensitivity analysis on the chemotherapy effect*. The assumption of a predictive treatment effect was challenged in a sensitivity analysis that assumed constant relative benefit from chemotherapy across all risk groups based on the Oxford Overview meta-analysis applied over a 5-year period.[20]
2. *Sensitivity analysis on survival after recurrence* - in the base-case analysis the survival after distant recurrence was assumed to be constant across groups. In a sensitivity analysis, survival after recurrence was assumed to depend on whether patients had previously received adjuvant chemotherapy.

Value of Information analysis

Value of information analysis is a powerful method for assigning a value to future planned research.[21–23] It relies on the theory that if the evidence for the effectiveness or cost-effectiveness of a new technology is uncertain then we risk making a sub-optimal decision about which to adopt for use in a population of patients. Making a suboptimal adoption decision has the consequence of lost health or lost resources compared to an optimal decision. The reduction in decision uncertainty therefore has quantifiable value. The results of the value of information analysis were presented using the following statistics:

- *Expected Net Health Benefit* is the central measure of cost-effectiveness expressed in terms of QALYs, assuming a societal willingness to pay threshold value of £20,000 per QALY.

- *Expected value of perfect information* (EVPI) represents the ceiling value of future research. It represents the maximum cost the healthcare funder should be willing to spend on future research.
- *Expected value of perfect parameter information* (EVPPI) measures the ceiling value of future research for a particular model parameter. It represents the maximum cost the healthcare funder should be willing to spend on future research for that particular parameter.
- *Expected value of sample information* (EVSI) measures the actual value of future research of a specified design.

For further information on value of information analysis and its application in health technology appraisal please refer to the published literature. EVPPI was calculated using a non-parametric regression-based approach.[24] EVSI was calculated using nested Monte-Carlo simulation.[25]

The EVPPI was calculated for the five-year recurrence free survival parameters and other parameters that would be informed by the proposed OPTIMA trial (choice of chemotherapy regimen, benefit from chemotherapy, the proportion allocated to high risk by each test, short term chemotherapy toxicity and costs). This represents a ceiling on the value of research in the context of a randomised controlled trial with 5 years of follow up. Each EVPPI calculation is the EVPPI for a comparison between chemotherapy for all and chemotherapy directed by a single alternative test. Tests with higher EVPPI therefore have a higher societal priority for inclusion in further randomised research which has five-year recurrence free survival as an outcome.

RESULTS

The OPTIMA prelim trial recruited 313 patients between October 2012 and June 2014 in 31 UK centres of whom 302 had samples available for molecular testing. The mean age was 58, 68% of patients were post-menopausal and 64% had 1-3 nodes involved (Table 1). The proportion of patients considered as low-risk by each test and therefore potentially spared chemotherapy ranged from 0.82 (Oncotype DX) to 0.55 (IHC4-AQUA) (Table 2). Based on the intended chemotherapy regimen for each patient and the proportion allocated to high or low risk by each test, the expected mean costs of chemotherapy ranged from £3,611 per patient (all patients treated with chemotherapy) to £2,102 per patient (Prosigna-ROR). The correlation coefficients between 10 year predicted recurrence free survival and test scores (where continuous readout available) were 0.24, 0.36, 0.17 and 0.14 for Oncotype DX, Prosigna ROR, IHC4 and IHC4-AQUA respectively.

Table 1. Patient characteristics

CHARACTERISTIC	TOTAL	
	n	%
No. of patients	302	
Age years (Median(Range))	58 (40-78)	
Menopausal status of participant		
Pre/peri-menopausal	97	32
Post-menopausal	205	68
Number of involved nodes		
None	57	19
1-3	192	64
4-9	42	13
+ve sentinel node biopsy without clearance surgery	11	4
Intended chemotherapy regimen		
Anthracycline – non-taxane	116	39
FEC75-80	86	29
FEC90-100	15	5
E-CMF	15	5
Taxane – non-anthracycline (TC)	34	11
Anthracycline – taxane	152	50
FEC-T	149	49
FEC-Pw	3	1
Histological grade		
1	19	6
2	201	67
3	82	27
Largest tumour size in mm (Median(Range))	28 (2-170)	
<=30mm	172	57
>30mm	130	43
Adjuvant! Online 10 year RFS (hormone therapy only)	60.5 (22.0-82.1)	

Table 2. Costs of each testing strategy, proportion allocation to high risk group and expected chemotherapy costs in OPTIMA prelim.

TESTING STRATEGY	PROPORTION LOW RISK (SPARED CHEMOTHERAPY)*	TESTING COST PER-PATIENT (95% CIS)	MEAN CHEMOTHERAPY COST PER-PATIENT**	FORECAST MEAN 10 YEAR RECURRENCE-FREE SURVIVAL(%)††	
				Low risk	High risk
CHEMOTHERAPY FOR ALL	0		£3,611	59.8	
ONCOTYPE DX	0.82	£2,580 (fixed)	£678	60.9	54.6
MAMMAPRINT	0.61	£2,207 (fixed)	£1,409	61.6	57.0
PROSIGNA		£1,672.50 (1,576 - 1,773)			
SUBTYPE	0.59		£1,509	62.4	55.9
ROR	0.65		£1,291	61.8	55.9
MAMMATYPER	0.62	£1,277† (186 - 6,415)	£1,422	61.1	57.5
IHC4-AQUA	0.55	£720 (fixed)	£1,610	60.6	58.7
IHC4	0.61	£152 (61 - 322)	£1,370	60.5	58.5

*Patients with unavailable test results are assumed to be high risk and are treated with chemotherapy.
**Average per-patient procurement and delivery costs, based on prescribing intent and test assignment and not including costs of toxicity.
† Unavailable from manufacturer therefore estimated by analyst
†† Forecast using Adjuvant! Online (treated with hormone therapy but no chemotherapy)

Cost-effectiveness results

In the base case analysis the expected lifetime per-patient cost if all patients receive chemotherapy was £13,961 (95% CI £10,535 - £21,203) and the expected lifetime QALYs was 7.69 (95% CI 5.06 – 9.58). The mean incremental QALYs with each testing strategy were very similar at between 0.17 and 0.20 more than chemotherapy for all, although credible intervals were generally around plus or minus 1 QALY (Table 3). The mean incremental cost per patient was more variable, between an additional cost of £195 (95% CI £-3,206 - £3,430) with MammaPrint to a saving of £1,892 (95% CI -£5,415 - £1,488) with IHC4 in comparison with all patients receiving chemotherapy. The Net Health Benefit from all testing strategies was higher than for standard care, although was of a very similar magnitude between tests.

Uncertainty in the cost-effectiveness of all tests was large (Figure 2a and Figure 2b). The probability that individual tests are more cost-effective than standard care ranged from 75%

(MammaPrint) to 81% (IHC4) in separate two-way comparisons. The incremental analysis, in which all tests compete with each other in a multi-way comparison, demonstrated that the probability that test-directed chemotherapy using any test is more cost-effective than standard care was 86% (Figure 2c).

Table 3. Cost-effectiveness results – incremental analysis in comparison with all patients receiving chemotherapy.

	Oncotype DX	MammaPrint	Prosigna Subtype	Prosigna ROR	MammaTyper	IHC4-AQUA	IHC4
Base case analysis							
Mean incremental QALYs per Person (95% CI)	0.2 (-1.07 – 1.4)	0.18 (-0.87 – 1.1)	0.18 (-0.85 – 1.05)	0.18 (-0.91 – 1.15)	0.18 (-0.95 – 1.15)	0.17 (-0.87 – 1.05)	0.18 (-0.93 – 1.14)
Mean incremental Cost per Person (£) (95% CI)	-108 (-4,610 – 4,292)	195 (-3,206 – 3,430)	-281 (-3,553 – 2,774)	-474 (-4,078 – 2,955)	-944 (-4,481 – 2,380)	-1,115 (-4,373 – 1,943)	-1,892 (-5,415 – 1,488)
ICER (£ per QALY)	DOMINATES*	1,097	DOMINATES*	DOMINATES*	DOMINATES*	DOMINATES*	DOMINATES*
Probability test is cost saving	0.53	0.39	0.62	0.68	0.80	0.84	0.90
Probability test provides more benefit	0.73	0.73	0.74	0.73	0.73	0.73	0.73
Probability that test is cost-effective	0.77	0.75	0.77	0.77	0.78	0.79	0.81
Incremental Net Benefit (QALYs) (95% CI)**	0.21 (-0.87 – 1.21)	0.17 (-0.74 – 0.94)	0.19 (-0.71 – 0.93)	0.21 (-0.76 – 1.01)	0.23 (-0.77 – 1.04)	0.23 (-0.69 – 0.97)	0.27 (-0.69 – 1.08)
Sensitivity analysis: Constant relative chemotherapy effect							
Probability that test is cost-effective	0.33	0.31	0.41	0.35	0.36	0.50	0.43
Incremental Net Benefit versus chemo for all (QALYs) (95% CI)*	-0.09	-0.08	-0.05	-0.05	-0.03	-0.01	-0.02
Sensitivity analysis: Variable survival after recurrence							
Probability that test is cost-effective versus chemo for all	0.97	0.94	0.94	0.94	0.94	0.94	0.95
Incremental Net Benefit versus chemo for all (QALYs) (95% CI)*	0.70	0.54	0.54	0.60	0.61	0.58	0.66

*'Dominates' implies that the test is more effective and less costly than all patients receiving chemotherapy.
**A positive incremental net benefit is necessary for a test to be considered more cost-effective than all patients receiving chemotherapy. The higher the incremental net benefit the more cost-effective the test is expected to be.

FIGURE 2A - SCATTERPLOT ON THE INCREMENTAL COST-EFFECTIVENESS PLANE, COMPARING EACH TEST WITH CHEMOTHERAPY FOR ALL IN THE BASE CASE ANALYSIS

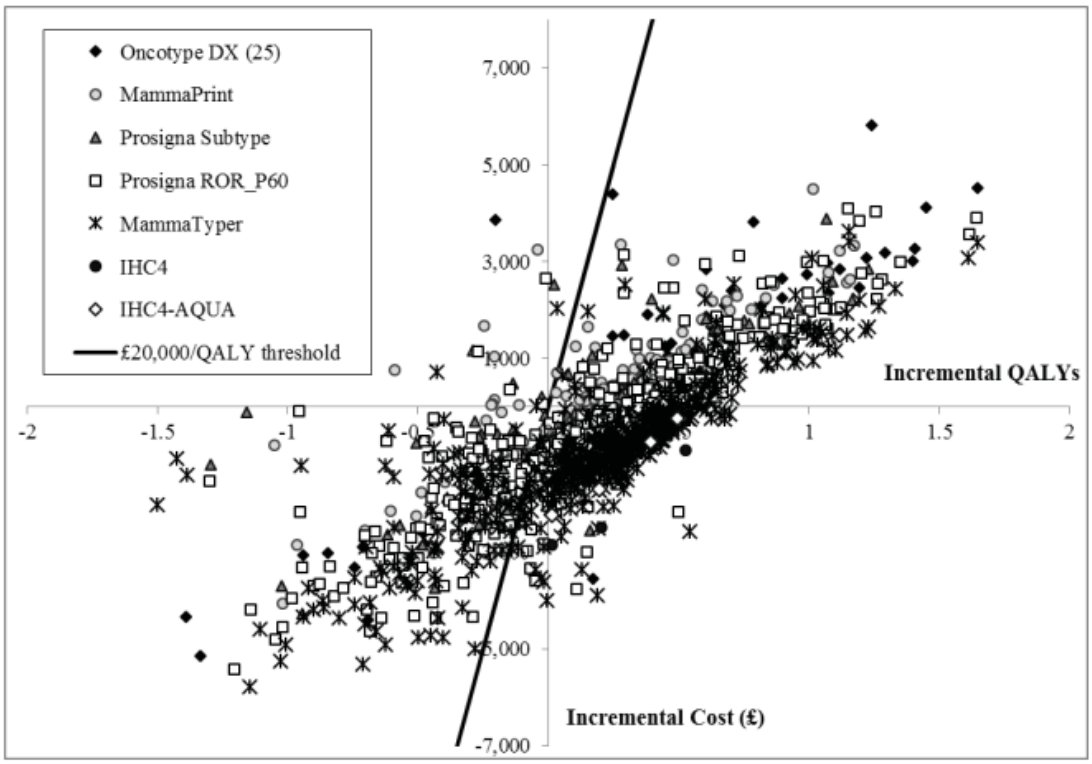


FIGURE 2B - COST-EFFECTIVENESS ACCEPTABILITY CURVES FOR THE BASE CASE ANALYSIS - ALL TESTS COMPARED INDIVIDUALLY WITH CHEMOTHERAPY FOR ALL

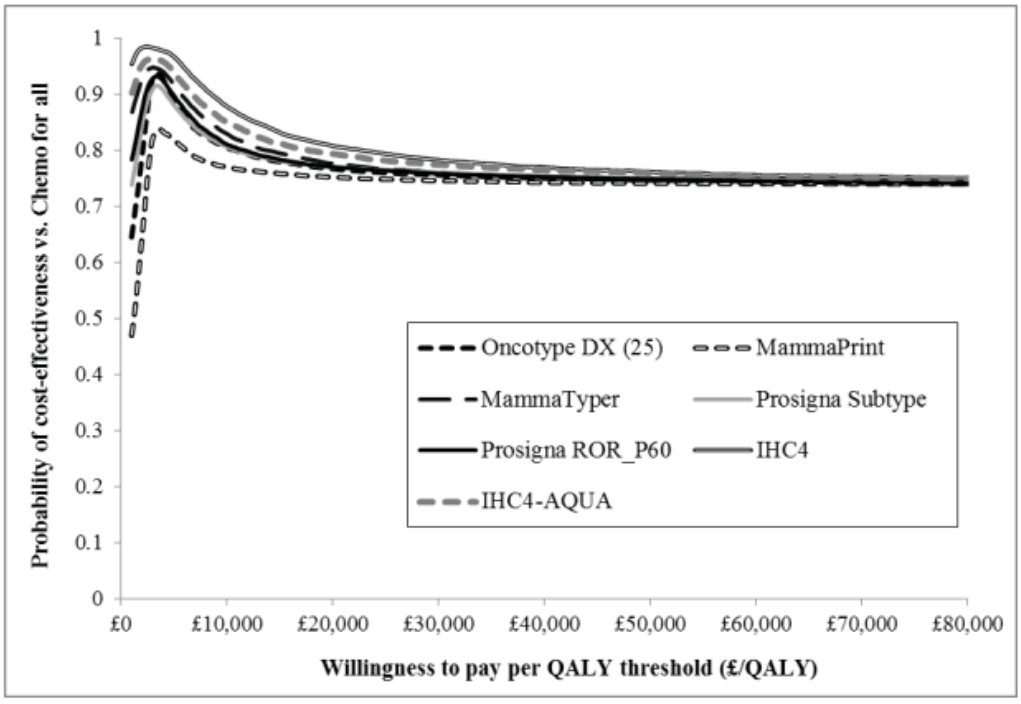
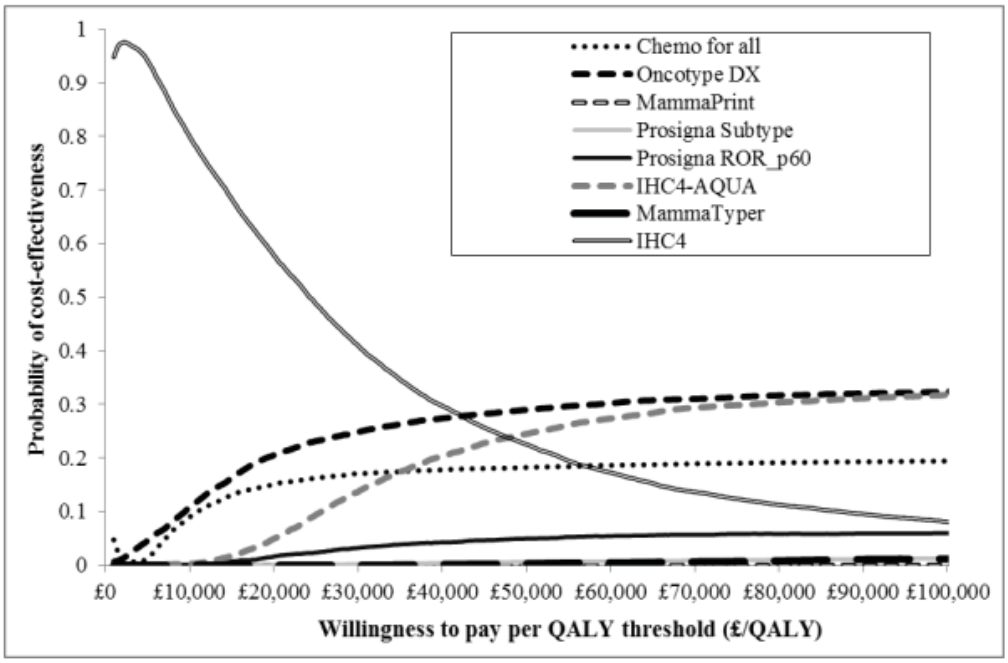


FIGURE 2C - COST-EFFECTIVENESS ACCEPTABILITY CURVES FOR THE BASE CASE ANALYSIS – ALL TESTS INCLUDED AND COMPARED WITH EACH OTHER IN AN 8-WAY COMPARISON

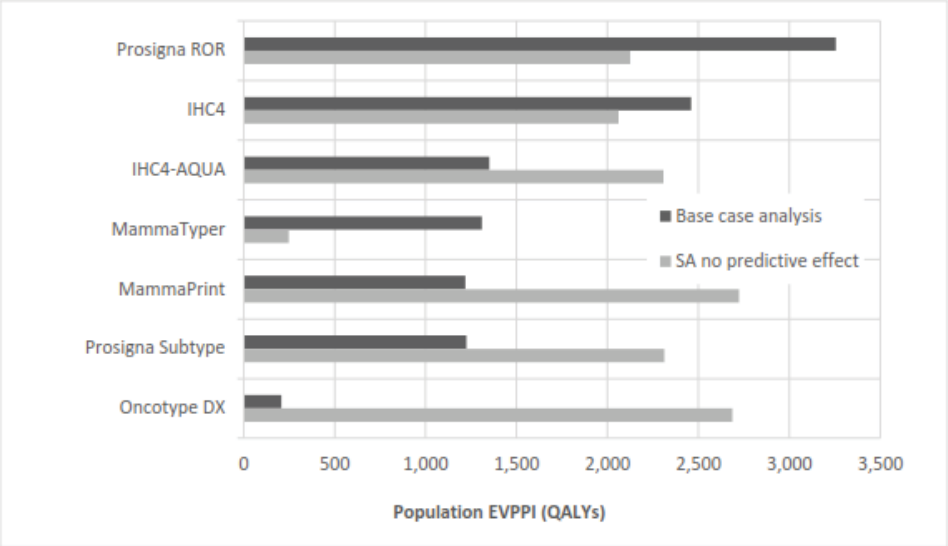


Value of Information Analysis

The expected value of perfect information (EVPI), which represents the expected opportunity cost as a consequence of current decision uncertainty is 0.10 QALYs per patient on the Net Health Benefit scale or 3652 QALYs for the incident population in England over a 10 year time horizon.

The EVPPI was high for all tests included in the base case analysis, suggesting high value in further research into test-directed chemotherapy regardless of which test is the focus of study (Figure 3). The EVPPI favoured Prosigna ROR as the preferred test for inclusion in further research. Ranking of the tests by EVPPI as seen in Figure 3 allows prioritisation between further tests. The Expected Value of Sample Information (EVSI) for an RCT comparing chemotherapy for all with chemotherapy directed by Prosigna ROR with a sample size of 2500 patients per arm was £231 per patient or £8,397,961 for the 10 year incident population. This represents the expected UK health service value of such a trial.

FIGURE 3 - VALUE OF INFORMATION ANALYSIS: EXPECTED VALUE OF PERFECT PARAMETER INFORMATION FOR A RANDOMISED CONTROLLED TRIAL WITH A PRIMARY ENDPOINT OF 5 YEAR RECURRENCE FREE SURVIVAL



Sensitivity analysis – chemotherapy effect

In this analysis treating all patients with chemotherapy was more cost-effective than any of the testing options with a probability of individual tests being cost-effective ranging between 31% and 50% (Table 3). The population EVPI was 4165 QALYs suggesting that further research may be worthwhile even if the chemotherapy effect is thought to be constant. The value of information analysis (Figure 3) shows the ranking of tests for research value which is of a notably different order compared with the base case results, suggesting high value into research on all test apart from MammaTyper.

Sensitivity analysis – survival after recurrence

Here it was assumed that post-recurrence survival is dependent on previous treatment with adjuvant chemotherapy and, by association, test score. Oncotype DX is favoured on the basis of expected cost-effectiveness, with Prosigna ROR falling into second place (Table 3). The population EVPI was 2353 QALYs.

DISCUSSION

In the adjuvant treatment of early breast cancer, the notable survival gains seen at population level are at the cost of overtreatment and morbidity for many women, as well as unnecessary healthcare expenditure. Molecular testing offers a new era of enhanced risk stratification and may allow the prediction of which patients benefit, and therefore which patients may safely be spared chemotherapy. The potential efficiencies of such a strategy are very apparent, but the challenges of delivering an evidence base adequate to support adoption of this approach are significant and expensive given the large sample sizes required for RCTs of diagnostic tests. By considering the evidence requirements of not only clinical and scientific decision makers, but also health service and reimbursement decision makers earlier than is usual in the research and development process we have been able to optimise research design and research funding decisions within the OPTIMA programme.

The overarching message is that molecular testing has huge potential both from a clinical and a cost-effectiveness perspective; but currently there is equally substantial uncertainty in the evidence base. There is undisputable value in generating robust evidence into molecular testing in our OPTIMA population and a decision to invest in the proposed trial can clearly be made. What is much less certain is which test is best or most cost effective. Based on the information provided by a future RCT primary endpoint of 5-year recurrence free survival, we have been able to rank different tests based on their research value. While it would be desirable to include all tests in a prospective future trial, the resources required for such would be unfeasible. By focussing future research on tests that offer best research value, we are maximising the chances of taking the correct test into practice in the long run.

The key outcome measures of the OPTIMA prelim economic analysis, as qualified by the value of information analysis, remain unfamiliar to many; but we believe they are the correct metric

to answer research questions concerned with the efficient use of limited health care delivery and health research questions. A pitfall that we sought to avoid was the use of statements of effectiveness or cost-effectiveness given the immaturity of much of the data contributing to this analysis. By focussing on decision uncertainty and the risk and consequences of suboptimal decision making we make balanced recommendations about research value, whilst avoiding statements that may prematurely be interpreted as practice-changing. The absence of data directly comparing the clinical validity of tests makes statements about cost-effectiveness difficult to make and is an inevitable limitation of undertaking economic evaluation early in the technology development cycle. The quantification of uncertainties and research value is, however, more valid. This is because uncertainty in the comparative performance is quantitatively inflated in the model as a function of discordance with Oncotype DX. As such the ranking of tests for research value is valid, whereas the ranking of tests for cost-effectiveness is more questionable. To clarify this point, note that ultimately a test which always selects patients in an identical manner to Oncotype DX will perform identically and therefore additional test-specific research will have no value. As with any model, it has limitations due to necessary assumptions; for example, late chemotherapy effects such as cardiac toxicity and second malignancies have not explicitly been modelled, survival distributions are assumed to be exponentially distributed and many of the model parameters including costs and quality of life have been derived from the literature, relying on studies that may not be exactly transferable to the setting under study. We hope that may of these limitations will be addressed within the ongoing OPTIMA research programme.

A particularly important conclusion from this study is drawn from the sensitivity analysis which reveals that molecular tests need to predict chemotherapy effect and that prognostication of baseline risk is not enough for them to be cost-effective.

In conclusion, the economic analyses of the OPTIMA prelim trial have demonstrated that there is significant research value in pursuing a fully powered RCT with a 5-year recurrence free survival primary endpoint in the UK in a clinically high risk ER positive population. The choice of which test to include as the primary determinant of chemotherapy use is much less certain, but Prosigna ROR is currently ranked highest in terms of research value. Health economic modelling to inform a stop-go decision and the adaptation of an RCT looking at a diagnostic technology has been proven feasible as a method for improving research efficiency.

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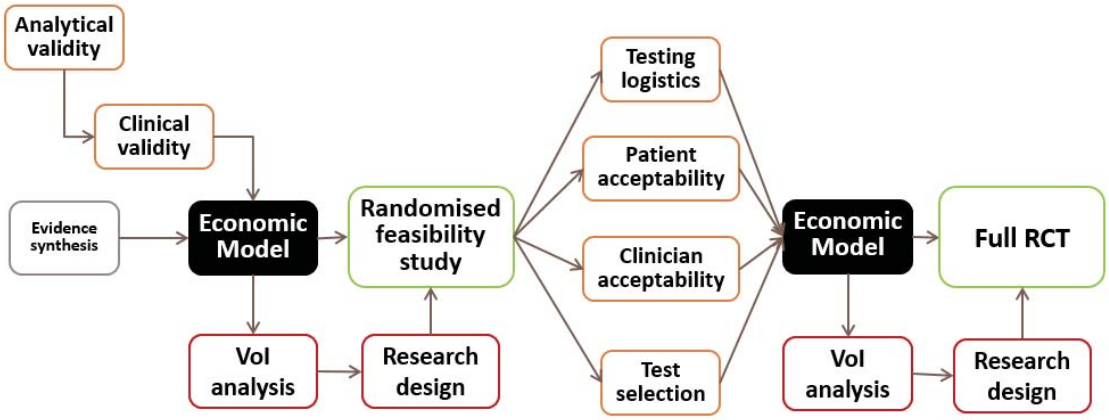
Supplemental Online material for "Economic evaluation of multi-parameter tests for chemotherapy in early breast cancer: the OPTIMA-prelim trial"

Adaptive design with stop-go decision and adaptation points based on economic modelling and feasibility questions



Contents

Section 1: Detailed description of model parameters

Cancer recurrence rates and chemotherapy effect sizes

Forecast recurrence free survival (RFS), assuming no chemotherapy, was derived for the OPTIMA prelim patient population using baseline clinical parameters entered into Adjuvant! Online (www.adjuvantonline.com). Full information on the parameters that underpin Adjuvant! Online has not been made public, therefore, in an attempt to represent likely parameter uncertainty, the sample standard deviation of the Adjuvant! Online RFS estimates was taken as a proxy for the standard error (se) of individual estimates.

The only evidence for a predictive (variable chemotherapy benefit) effect in clinically high risk patients at the time of writing was based on retrospective Oncotype DX testing of patients in the SWOG88-14 trial (*Table S1*). This was represented in the economic model by a linear regression model,

$$logHR = \alpha + \beta RS$$

where logHR = the log hazard ratio for recurrence free survival, alpha = 0.4541 (se 0.03749), beta = -0.0238 (se 0.00418), RS = Recurrence Score and the correlation between alpha and beta is assumed to be -0.5.

The resulting hazard ratio was applied to the no-chemotherapy recurrence rates for all individual patients in the "chemotherapy for all" standard care arm of the model over the first five years. In the "test-directed" arm of the model, the same chemotherapy effect was only applied to patients in the high-risk groups. Where there was no data providing evidence for the predictive ability of alternative tests, extra uncertainty was introduced into the model for these alternative tests depending on the degree of discordance between the test and Oncotype DX. For example, a completely concordant test will have identical predictive ability

and therefore no extra uncertainty is introduced. To achieve adequate representation of extra uncertainty, a suitable prior for the chemotherapy effect of the alternative test was required. In the absence of any informative information this prior treatment effect was represented by a hazard ratio of mean one with a very large standard deviation, assumed to be log-normally distributed. The choice of prior was subject to sensitivity analysis.

In the base case model specification, post-recurrence survival was assumed to be independent of pre-treatment with adjuvant chemotherapy: the annual post-recurrence probability of death was assumed to be constant across groups with a mean of 0.30 (SD 0.22).

Table s1 - Individual patient predicted hazard ratio for chemotherapy vs. no Chemotherapy for five-year disease free survival

Oncotype DX recurrence score	Hazard ratio	Upper 95% CI	Lower 95% CI
10	1.24	0.62	2.48
18	1.03	0.58	1.81
25	0.87	0.53	1.42
31	0.75	0.48	1.18
40	0.61	0.39	0.96

CI, confidence interval.

Chemotherapy treatment and toxicity

The proportions of patients treated with anthracycline plus taxane, anthracycline alone, or taxane alone were estimated from OPTIMA prelim data. Chemotherapy toxicity rates were estimated from landmark chemotherapy clinical trials (Table S2).[2–4] Toxicity rates for FEC100-Pw were assumed to be equivalent to FEC100-T, and toxicity rates for epirubicin (E) were assumed to be equivalent to FEC. Toxicity rates for FEC75 were assumed to be equivalent to two-thirds the rates for FEC100.

TABLE S2 - Chemotherapy toxicity rates from landmark trials

Parameter	Mean	Distribution	Source
TC (USO 9735 trial)	N = 506		Jones et al, 2009
Febrile Neutropenia	0.046	Beta(23,483)	
Anaemia	0.010	Beta(5,501)	
Thrombocytopenia	0.005	Beta(2,504)	
Stomatitis	0.008	Beta(4,502)	
Diarrhoea	0.025	Beta(12,494)	
Nausea and vomiting	0.030	Beta(15,491)	
FEC100 (PACS-01)	N=995		Roche et al, 2006
Febrile Neutropenia	0.084	Beta(84,911)	
Anaemia	0.014	Beta(14,981)	
Thrombocytopenia	0.003	Beta(3,992)	
Stomatitis	0.04	Beta(40,955)	
Diarrhoea	0	Beta(1,996)	
Nausea and vomiting	0.205	Beta(204,791)	
FEC100-T (PACS-01)	N=1001		Roche et al, 2006
Febrile Neutropenia	0.112	Beta(112,889)	
Anaemia	0.007	Beta(7,994)	
Thrombocytopenia	0.004	Beta(4,997)	
Stomatitis	0.059	Beta(59,942)	
Diarrhoea	0	Beta(1,1002)	
Nausea and vomiting	0.112	Beta(112,889)	
E-CMF (TACT2)	N=1029		Cameron et al, 2010
Febrile Neutropenia	0.13	Beta(137,892)	
Anaemia	0.03	Beta(31,998)	
Thrombocytopenia	0.01	Beta(10,1019)	
Stomatitis	0.00	Beta(1,1030)	
Nausea and vomiting	0.04	Beta(46,983)	
Diarrhoea	0.02	Beta(24,1005)	

Late effects

Parameters are included in Table S3 (Table . Population age and gender-specific incidence of congestive heart failure were taken from Office of National Statistics published data as presented by the British Heart Foundation.[5] The lifetime relative risk of congestive cardiac failure after chemotherapy was based on data from the Oxford Overviews and applied to the

population incidence, to provide an estimate of excess congestive heart failure due to chemotherapy.[6] Mortality after onset of congestive cardiac failure was taken from a UK population study.[7]

The age and gender-specific incidence rate of acute myeloid leukaemia was taken from a large UK primary care derived population database.[8] There is evidence for an increased relative risk of acute myeloid leukaemia in patients treated with chemotherapy from a number of published pooled trial-based analyses, but this was difficult to estimate reliably due to the low absolute numbers of observed events.[6,9–12] A relative risk of two was therefore specified in the model, but was assigned a very high standard error to reflect this uncertainty. Survival after a diagnosis of acute myeloid leukaemia was based on UK Cancer Registry statistics, as provided in a report by the Northern and Yorkshire Cancer Registration and Information Service (NYCRIS).[13]

Other transition probabilities and proportions

The mean time from metastatic recurrence to death was estimated from a UK patient level analysis of 1000 consecutive breast cancer patients in a single NHS Trust with a minimum of ten years follow-up.[14] An estimate of the proportion of recurrences that are locoregional was taken from the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial, which included a large number of UK patients with similar characteristics to patients enrolled into OPTIMA prelim.[15] Background age-specific non-breast cancer mortality was estimated by subtracting age-specific breast cancer–specific mortality from the age and gender-specific background mortality, obtained from the UK Office of National Statistics.[16]

Table S3 - Transition probabilities and proportions

Parameter	Mean	se	Distribution	Notes	Source
Proportion locoregional vs distant recurrence	0·31	0.015	Beta	Proportion of recurrences that are local to the original breast cancer primary	Baum et al, 2003
Death after distant recurrence	0·30	0.025	Beta	Annual probability of death after a distant recurrence (ER +ve)	Walkington et al, 2012
Background mortality	Age - specific		fixed	Life tables	Office of National Statistics, 2009
Chemo-associated excess mortality (first year)	0.0024	0.0019	Beta	2.4% age 55-69	EBCTCG, 2012
Background rate CHF	Age-specific		fixed	Annual age-specific female incidence of CHF	Townsend et al, 2012
Relative risk of CHF with anthracycline treatment	1·61	0.31	Log-normal	Applied as a constant lifetime risk	EBCTCG, 2012
Death after CHF	0.6	0.033	Beta	Hillingdon study	Cowie et al, 2000
Background annual rate AML (female, age 60-79)	0.00296	fixed	fixed		Bhayat et al, 2009
Relative risk of AML after chemo	7.6	7.1	Log-normal	NCCN analysis	[12]
Relative 5-year survival for AML (female,age 65+)	0.0383	0.0048	Beta	Assumes constant relative survival, applied to background mortality rate	Oliver et al, 2013

se, standard error; ER, estrogen receptor.

Costs

Costs were adjusted to a base year of 2013-2014 using the Hospital and Community Health Service (HCHS) pay and prices index published by the Personal Social Services Research Unit (PSSRU). In the probabilistic analysis costs were assumed to have a log-normal distribution. The additional expected healthcare costs in patients receiving chemotherapy were derived by combining the expected costs of chemotherapy procurement and delivery with those expected from follow-up. Assumptions were made about routine practice in the UK NHS based on advice from oncologists in London, Edinburgh and Leeds:

- Chemotherapy regimens represented in the economic model are FEC100, FEC100-T, FEC-Pw, TC, and E-CMF.
- Average body surface area 1.7 m^2
- Relative Dose Intensity 92% (all planned cycles completed).
- No vial sharing permitted (remaining drugs in vials assumed to be wasted)
- Standard supportive medication, procurement, laboratory, pharmacy and administration costs are based on eMIT, BNF and NHS reference costs.
- Two medical oncology clinic visits per regimen and one specialist nurse review per cycle.
- Granulocyte colony-stimulating factor (GCSF) (5x doses of filgrastim 300mcg) for 50% of FEC, 100% of FEC-T and 0% of TC and E-CMF cycles.
- Aprepitant is used as a prophylactic anti-emetic for 20% of FEC cycles.
- Grade 3 and 4 acute toxicity rates as per the PACS-01, USO 9735 and TACT2 trials (including febrile neutropenia rates for TC=4.6%, FEC100=8.4%, FEC100-T=11.2% and E-CMF=13%).
- 50% of toxicity-related hospital admissions were assumed to be greater than two days (long stay) and 50% were assumed to be less than two days (short stay)
- 15% of patients have a central line inserted (but associated complications of this are not costed).
- Community healthcare costs, out-of-pocket patient and carer costs, and costs due to future lost-productivity are not included.

- Value Added Tax (VAT) is not included on drug costs.

Unit costs for on-chemotherapy grade 3 and 4 toxicity were taken from the UK NHS reference costs. [17] A full breakdown of chemotherapy costs is given in *Tables S4 to S7*.

Table S4 - Chemotherapy drug costs per cycle

Regimen	Drug	Dose mg/m2	Dose (mg/patient)	Vial size (ml)	Vial strength (mg/ml)	Mg per vial	Price per vial	No vials/ cycle	Drug cost/ cycle
FEC100	Fluorouracil [a]	500	782	10	25	250	£ 3.20	4	£ 12.80
	Epirubicin [b]	100	156.4	100	2	200	£ 27.87	1	£ 27.87
	Cyclophosphamide [a]	500	782			1000	£ 17.06	1	£ 17.06
TC	Docetaxel [b]	75	117.3	7	20	140	£ 35.74	1	£ 35.74
	Cyclophosphamide [a]	600	938.4			1000	£ 17.06	1	£ 17.06
FEC100-T	Fluorouracil [a]	500	782	10	25	250	£ 3.20	4	£ 12.80
	Epirubicin [b]	100	156.4	100	2	200	£ 27.87	1	£ 27.87
	Cyclophosphamide [a]	500	782			1000	£ 17.06	1	£ 17.06
FEC100-T	Docetaxel [b]	100	156.4	8	20	160	£ 44.55	1	£ 44.55
E-CMF	Epirubicin[b]	100	156.4	100	2	200	£ 27.87	1	£ 27.87
	Cyclophosphamide[a]	600	938.4			1000	£ 17.06	2	£ 34.12
	Methotrexate[a]	40	62.56	2	25	50	£ 2.62	4	£ 10.48
	Flourouracil[a]	600	938.4	10	25	250	£ 3.20	8	£ 25.60
FEC75	Flourouracil[a]	500	782	10	25	250	£ 3.20	4	£ 12.80
	Epirubicin[b]	75	117.3	100	2	200	£ 27.87	1	£ 27.87
	Cyclophosphamide[a]	500	782			1000	£ 17.06	1	£ 17.06
FEC100-Pw	Fluorouracil [a]	500	782	10	25	250	£ 3.20	4	£ 12.80
	Epirubicin[b]	100	156.4	100	2	200	£ 27.88	1	£ 27.88
	Cyclophosphamide[a]	500	782			1000	£ 17.06	1	£ 17.06
	Paclitaxel[b]	80	136	25		150	£ 11.26	3	£ 33.78

Assumes average surface area of 1.7m2 and a relative dose intensity of 92%. 1 cycle of Pw = 3 doses given weekly.
[a] British National Formulary 2013
[b] Department of Health Commercial Medicines Unit (CMU) electronic Market Information Tool (eMIT)

Table S5 - Supportive medications

	Unit dose	Unit cost	Units per cycle	% use	Per cycle
Dexamethasone (oral) [a]	2mg	£0.03	20	1	£0.60
Dexamethasone (IV) [a]	3.3mg	£0.40	8	1	£3.20
Ondansetron [a]	8mg	£0.15	1	1	£0.15
Aprepitant (pre-made pack) [b]	1 pack	£47.42	1	0.2	£9.48
Metoclopramide [a]	10mg	£0.01	7	0.5	£0.03
Filgrastim (GCSF) [b, c] *	300mcg	£52.70	5	1*	£263.50

Total cost of supportive medications per cycle	
FEC100+50%GCSF	£ 145.21
FEC100+GCSF	£ 276.96
T+GCSF	£ 267.48
FEC75	£ 13.46
CMF	£ 0.36
TC	£ 3.98
P	£ 0.08
E	£ 0.03

[b] British National Formulary 2013
[a] Commercial Medicines Unit (CMU) electronic Market Information Tool (eMIT)
[c] GCSF is used for 100% of FEC-T cycles, 50% of FEC100 cycles and 0% of TC cycles

Table S6 - On-chemotherapy toxicity costs derived from the NHS reference costs

Parameter	Mean (£)	HRG code
Toxicity (grade 3 & 4) HRG – short stay		
Anaemia	644	PA48B
Febrile neutropenia	877	PA45Z
Nausea	340	PA28B
Diarrhoea	356	PA26B
Thrombocytopenia	540	SA12K
Stomatitis	387	CZ23Y
Toxicity (grade 3 & 4) HRG – long stay		
Anaemia	1,099	PA48B
Febrile neutropenia	3,485	PA45Z
Nausea	856	PA28B
Diarrhoea	1,107	PA26B
Thrombocytopenia	1,311	SA12K
Stomatitis	1,551	CZ23Y

HRG, Healthcare Resource Group

Table S7 - Overall costs per regimen (assuming 50% short stay AND 50% LONG STAY for toxicity)

Drug Regimen (no. cycles)	Central line costs	Drug costs	Delivery costs	Supportive meds	Medical oncology costs	Specialist nurse review	Blood tests	Toxicity costs	Total cost
FEC100 (6)	£18.17	£346.38	£1,284.58	£871.27	£310.81	£613.10	£62.32	£359.53	£3,866.17
FEC100-T (3 + 3)	£18.17	£306.84	£1,284.58	£1,238.07	£450.03	£613.10	£62.32	£378.18	£4,351.30
TC (4)	£18.17	£211.20	£856.39	£15.91	£310.81	£408.74	£41.55	£158.16	£2,020.93
FEC75 (6)	£18.17	£346.38	£1,284.58	£80.77	£310.81	£613.10	£62.32	£239.69	£2,955.82
Epi-CMF (4 + 4)	£18.17	£392.28	£2,569.16	£1.54	£450.03	£817.47	£124.64	£360.10	£4,733.39
FEC100-Pw (3 + 3)	£18.17	£274.53	£2,569.16	£435.89	£450.03	£613.10	£124.64	£378.18	£4,863.70

The mean annual costs of disease-free and cancer recurrence health states were estimated from an updated audit of hospital income recorded (Table S8).[18] These costs are based on the national Payment by Results tariff produced by the UK Department of Health specific to each year in which they were incurred, adjusted for inflation to the base year for the analysis. Patient data was censored at last follow-up contact and the Kaplan-Meier Sample Average cost method was used to adjust for censoring.[19] The annual cost of the disease-free state was based on year two onwards costs under the assumption that this represents the costs of follow-up minus chemotherapy costs.

Table S8 - Disease-free and cancer recurrence health state annual costs

Parameter	Mean (£)	SE
COSTS		
Disease free (annual cost excluding chemo-related costs)	1,000.31	3.83
Disease free after local recurrence (annual, year 2 on)	1,354.17	151
Local recurrence (first year)	6,126.35	517
Distant recurrence (annual)	1,681.53	32

SE, standard error

Test costs

Test costs were calculated on a per sample basis using current list prices and data from manufacturers. Where a list price was not available in the public domain, the manufacturers were asked for an expected UK price. Any anticipated NHS discounts were not considered. Any assumptions used in the cost calculations were based on expert opinion. Costs were converted to 2013 pound sterling (GBP £) using the following exchange rates: GBP to EURO (€) = 0.825, and USD ($) to GBP = 0.60.

All tests were assumed to be exempt from VAT: for tests conducted within the NHS it was assumed that all NHS purchasing was operated under a Managed Service Contract (which excludes VAT); similarly tests conducted by commercial institutions for the NHS are exempt from VAT. For tests conducted within NHS laboratories, labour costs were calculated based on estimates of the overall time to run assay samples, and did not include sectioning time, pathologist time to mark areas for extraction and for reporting.

Oncotype DX: For Oncotype DX, tests are sent to the manufacturer (Genomic Health) to complete and return, with no additional costs to the NHS. The cost for Oncotype DX is based on the manufacturer list price at the time of analysis (£2580).

MammaPrint/BluePrint: Tests are sent to the manufacturer to complete and return, with no additional costs to the NHS. The advertised list price, confirmed by manufacturer at the time of analysis, was 2675 Euro excluding VAT, equivalent to GBP £2,207.

Prosigna: Testing requires the purchase or lease of a nanoString instrument in addition to individual assay kits in order to process samples within the NHS. The cost per test therefore depends upon the machine capital costs (purchase and services), the assay cost, ribonucleic acid (RNA) extraction/ preparation, and the labour costs. These are summarized below.

1) Capital costs:

Machine purchase, lifetime and service costs were communicated by the manufacturer at the time of the analysis:

- Machine purchase – US$ 285,000 = GBP £171,000.
- Machine expected lifetime – 5 years
- Service cost – US$ 15,000/year = $75,000/ 5 years = GBP £45,000/ 5 years
- Total capital cost per site = £216,000 per 5 years

The expected number of tests required is 4376 per year (Cancer Registry data). Assuming five sites within the NHS, then 875 tests are required per year, per site. Capital cost per test (five sites) is therefore £216,000/5/875 = £49.37. There is uncertainty around the number of instruments that would be purchased across England. Assuming three sites we have a lower (25^{th}) quartile value of £29.61 and assuming ten sites we have an upper (75^{th}) quartile value of £98.72.

2) Assay cost:

Prosigna Assay - £1,277 (manufacturer quoted UK cost)

Cartridge sizes – four or ten

Each cartridge pack includes one quality assurance (QA) sample, and an entire cartridge must be used at once; any unused cartridges from the pack are wasted. Thus a pack of four can run a maximum of three samples plus one QA test and a pack of ten can run up to nine samples.

Assuming a five day working week, 52 weeks/year, and excluding Christmas and New Year (three days), there are ~257 ((52x5)-3) working days in a year. Assuming five sites, to complete 875 tests per year requires completing (on average) 3.4 tests per day per site, or 17 per week per site. Assays are assumed to be batched on a weekly basis. Therefore running 17 tests per

week requires two cartridges of size ten, with wastage of one sample. We therefore assume that on average cartridge sizes of size ten are used with one sample wasted.

The expected assay cost is therefore £1,596.25/ test (£1277 x 10/8).

There is uncertainty around the number of samples that would be wasted per cartridge. This is represented in the model using a lognormal distribution with a lower bound of £1,418.89/ test (assuming maximum number of 9 samples run using cartridge size ten i.e. £1277x10/9) and an upper bound of £5108/ test (assuming minimum number of 1 samples run using cartridge size four i.e. £1277x4/1), assuming these bounds are 95% confidence intervals.

3) Labour cost:

Biomedical scientist time: assuming "batching" of tests in groups of 17 (plus two controls) it is estimated that 11 hours of hands-on time are required for the macro-dissection, RNA extraction and assay set up. This equates to 39 minutes of biomedical scientist time per test. Valued at an agenda-for-change grade seven technician hourly rate of £22.98, this equates to £14.94 labour cost.

4) RNA extraction/preparation materials:

USD $500 for 25 isolations using Roche kit (US$ 20/ sample = GBP £12 per sample; communication with manufacturer).

Total cost per Prosigna test: Capital cost per test (£49.37) + assay cost (£1,596.25) + RNA extraction cost (£12) + labour cost (£14.94) = £1672.56.

Incorporating uncertainties around the capital cost, assay cost and labour costs gives a lognormal distribution, with mean £1672.50 and standard deviation £50.94 (mu = 7.422, sigma = 0.030).

MammaTyper: Testing requires the purchase or lease of a Roche LightCycler real-time PCR platform. The cost per test therefore depends upon the machine capital costs (purchase and servicing), the assay cost, RNA extraction, preparation and the labour costs. These are summarized below.

1) Capital costs:

Capital costs include a Roche Diagnostics LightCycler real-time PCR machine. Purchase and service costs of the LightCycler machine were communicated by Roche at the time of the analysis:

- LightCycler LC/Z480 (96 well) machine purchase – GBP £23,500.
- Machine expected lifetime – 10 years
- Service cost – 10% of purchase cost from year 2 = £21,150 (to 10 years)
- Total capital cost per site = £44,650 over 10 years

The expected number of tests required is 4376 per year (bespoke analysis by Public Health England Cancer Registry). Assuming five sites within the NHS, then 875 tests are required per year, per site. Capital cost per test (five sites) is therefore (£44650*5)/(4376*10) = £5.102. There is uncertainty around the number of instruments that would be purchased across England. Assuming three sites we have a lower (25^{th}) quartile value of £3.061 and assuming ten sites we have an upper (75^{th}) quartile value of £10.203.

2) Assay cost:

MamaTyper Assay - £1277 (Interquartile range 400 – 1400) (analyst estimated UK price)

MammaTyper tests are purchased in batches of 10 (8 tests + 2 controls).

Two controls need to be included with each rtPCR run. Controls can be reused/thawed up to three times.

Assuming a five day working week, 52 weeks/year, and excluding Christmas and New Year (three days), there are ~257 ((52x5)-3) working days in a year. Assuming five sites, to complete 875 tests per year requires completing (on average) 3.4 tests per day per site, or 17 per week per site. Assays are assumed to be batched on a weekly basis. Therefore running 17 tests per week in a single batch with two controls.

The expected assay cost is therefore £1596 per test (price*10/8) (IQR 500-1750).

3) Labour cost:

Biomedical scientist time: assuming "batching" of tests in groups of 17 (plus two controls) it is estimated that 11 hours of hands-on time are required for the macro-dissection, RNA extraction and assay set up. MammaTyper preparation, set up master mixes, distribute master mixes and set up real time instrument is estimated at 1 hour. This equates to 42 minutes of biomedical scientist time per test. Valued at an agenda-for-change grade seven technician hourly rate of £22.98, this equates to £16.09 labour cost.

4) RNA extraction/preparation materials:

£283 for 50 isolations using Roche kit £12 per sample.

Total cost per MammaTyper test: Capital cost per test (£5.102) + assay cost (£1596) + RNA extraction cost (£12) + labour cost (£16.09) = £1629.192 (Interquartile range 531.15 – 1788.29).

Incorporating uncertainties around the capital cost, assay cost and labour costs gives a lognormal distribution, with mean £1629.19 and standard deviation £1905.11 (mu = 6.991, sigma = 0.899).

IHC4 AQUA: Price provided by the manufacturer in 2014 for in-house/central commercial testing was $1200 (GBP £720).

IHC4: For IHC4 performed using routine staining methods, costs of staining are relatively simple to estimate however, due to the quantitative nature of the IHC4 score additional pathological assessment is required to accurately estimate ER histoscores and PgR and Ki67 percentage positive cells within the narrow bands (30 units or 10%) required.

Within the OPTIMA prelim study IHC4 was performed in a central laboratory, using tissue microarrays and image analysis, which does not reflect routine diagnostic practice (where whole slides are assessed) and precludes accurate assessment of test costs as they would be in an NHS setting. No formal measurement of the time required by individual pathologists to perform the additional quantification required for this test is available to provide a cost estimate was undertaken within OPTIMA prelim. For the purposes of the economic model, the time taken for IHC4 was estimated by consultation with NHS pathologists and laboratory managers.

All IHC4 testing was assumed to be conducted at local hospitals and laboratories, using currently available technology. Block selection and retrieval was not costed as these are already routinely conducted within the NHS. The cost of consultant time was assumed to be £157 per hour based on PSSRU unit costs. The calculation of the IHC4 cost per test was as follows:

ER - £26 (10 mins) extra pathologist time

PR - £15 consumables/lab costs + £26 (10 mins) pathologist time

Ki67 - £20 consumables/lab costs + £52 (20 mins) extra pathologist time

HER2 – no extra cost

Generation of IHC4 report via algorithm - £13 (5 mins of pathologist time)

Total cost per test = **£152**

As there remains uncertainty about this estimate, which is based on expert opinion, therefore it will be represented as an uncertain parameter in the OPTIMA model, with mean £152 and interquartile range £116 - £207 (sd 69) (implying that there is a 50% chance that the true cost lies within this range). Represented in the model by a lognormal distribution with parameters mu=4.93 and sigma=0.429

Utilities

A literature review was carried out to update the relevant health utility values for the OPTIMA model from a previously published relevant systematic review (Table S9).[20] Full details of the search strategy, literature review method and data extraction are available on request.

Table S9 – Utility parameters

Utilities				
	Mean	sd	Distribution	Source
Starting utility	Age group specific 60-64 = 0.81 65-74 = 0.78 75-100 = 0.71	fixed	na	Kind et al 1998 [21]
Disease free (no chemo) [a]	-0.003	0.03	lognormal	Campbell, 2011[22]
Disease free (on chemo) [a]	-0.099	0.033	lognormal	Campbell, 2011[22]
Local recurrence [a]	-0.108	0.04	lognormal	Campbell, 2011 [22]
Distant recurrence [a]	-0.303	0.16	lognormal	Campbell, 2011 [22]
Congestive heart failure	0·528	0.047	beta	Kirsch, 2000 [23]

[a] decrement from age and sex matched controls

Section 2: Parameterisation of Sensitivity Analyses

Sensitivity Analysis 1: Constant benefit from chemotherapy

Chemotherapy benefit from the Oxford Overview meta-analysis was applied to the predicted recurrence-free survival (RFS) over a 5-year period for patients receiving chemotherapy in the model. The hazard ratio for RFS for anthracycline chemotherapy was taken to be 0.69 (SE 0.04) over the first 5 years with an additional benefit from the addition of a taxane of 0.84 (95%CI 0.78-0.91).[6] A limitation of this approach is that it only allows incorporation of uncertainty around the forecast where full information is available about the prognostic model; such information is not available for Adjuvant!. Therefore, in an attempt to represent likely uncertainty, the sample standard deviation of the Adjuvant! RFS estimates was taken as a proxy for the standard error of individual estimates.

Sensitivity Analysis 2: Survival after cancer recurrence varies depending on whether patients received chemotherapy as adjuvant therapy for their early cancer.

It is likely that patients who have received adjuvant chemotherapy will survive for a different length of time after a recurrence compared to those who did not receive adjuvant chemotherapy. In the base-case the annual post-recurrence probability of death was assumed to be 0.30 (SD 0.22). In sensitivity analysis 2 the annual probability of death after recurrence varied depending on whether previous adjuvant chemotherapy had been given. Given that overall survival is available for the SWOG88-14 trial, the post-recurrence survival parameter was derived by calibrating the economic model against this outcome measure. The resulting annual probability of death following recurrence is therefore 0.40 (standard deviation (SD) 0.17) for patients treated with adjuvant chemotherapy and 0.14 (SD 0.17) for patients who did not receive adjuvant chemotherapy and who had a low Oncotype DX RS.

Section 3: Incident population calculations for value of information analysis

There is very little evidence to inform this parameter in the relevant patient populations. Given that overall survival is available for the SWOG88-14 trial, the post-recurrence survival parameter was derived by calibrating the model against this outcome measure. The resulting annual probability of death following recurrence is therefore 0.40 (standard deviation (SD) 0.17) for patients treated with adjuvant chemotherapy and 0.14 (SD 0.17) for patients who did not receive adjuvant chemotherapy and who had a low Oncotype DX RS.

In order to provide an estimate of total value of information an estimate of number of patients for whom the reimbursement decision is pertinent is required. Based on information provided by the West-midlands cancer registration service, the annual incident population of patients eligible for OPTIMA in England alone is around **4376** patients (Table S10). It should be noted that the quality of cancer registration data is higher in the West-midlands region than other regions. The West-Midlands population diagnosed of breast cancer represents 10.9% of the total English population of patients diagnosed with breast cancer. English estimates are therefore based on a multiple of the West-Midlands estimate rather than data for the whole of England. The pertinent time horizon for the decision problem was assumed to be ten years.

Table S10: Annual incident patient population eligible for the OPTIMA trial.

Cohort: women diagnosed with invasive breast cancer in 2010 (calendar year)	Women diagnosed in WEST MIDLANDS region	
	Number	**%**
Number of women diagnosed with at least one invasive (*) breast cancer tumour in 2010	4,456	100%
Criteria		
[Women aged 40 or more]	4,280	96.1%
& [tumour was surgically treated]	3,550	79.7%
& [tumour was ER positive]	2,969	66.6%
& [tumour was HER2 negative]	2,440	54.8%
&([1 to 9 positive axillary lymph nodes] OR [axillary lymph nodes were negative AND invasive tumour size > 30mm])	877	19.7%
& [patient was treated with chemotherapy]	485	10.9%
& [patient was MO or Mx at diagnosis] (i.e no known metastases at diagnosis)	**477**	10.7%

*invasive = excluding micro-invasive tumours

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