Economic Evaluation of Genomic Test–Directed Chemotherapy for Early-Stage Lymph Node–Positive Breast Cancer

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Background

Multi-parameter genomic tests identify patients with early-stage breast cancer who are likely to derive little benefit from adjuvant chemotherapy. These tests can potentially spare patients the morbidity from unnecessary chemotherapy and reduce costs. However, the costs of the test must be balanced against the health benefits and cost savings produced. This economic evaluation compared genomic test–directed chemotherapy using the Oncotype DX 21-gene assay with chemotherapy for all eligible patients with lymph node–positive, estrogen receptor–positive early-stage breast cancer.

Methods

We performed a cost–utility analysis using a state transition model to calculate expected costs and benefits over the lifetime of a cohort of women with estrogen receptor–positive lymph node–positive breast cancer from a UK perspective. Recurrence rates for Oncotype DX–selected risk groups were derived from parametric survival models fitted to data from the Southwest Oncology Group 8814 trial. The primary outcome was the incremental cost-effectiveness ratio, expressed as the cost (in 2011 GBP) per quality-adjusted life-year (QALY). Confidence in the incremental cost-effectiveness ratio was expressed as a probability of cost-effectiveness and was calculated using Monte Carlo simulation. Model parameters were varied deterministically and probabilistically in sensitivity analysis. Value of information analysis was used to rank priorities for further research.

Results

The incremental cost-effectiveness ratio for Oncotype DX–directed chemotherapy using a recurrence score cutoff of 18 was £5529 (US $8852) per QALY. The probability that test-directed chemotherapy is cost-effective was 0.61 at a willingness-to-pay threshold of £30 000 per QALY. Results were sensitive to the recurrence rate, long-term anthracycline-related cardiac toxicity, quality of life, test cost, and the time horizon. The highest priority for further research identified by value of information analysis is the recurrence rate in test-selected subgroups.

Conclusions

There is substantial uncertainty regarding the cost-effectiveness of Oncotype DX–directed chemotherapy. It is particularly important that future research studies to inform cost-effectiveness–based decisions collect long-term outcome data.

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There is increasing interest in the use of multi-parameter genomic testing for selecting which patients will and will not benefit from adjuvant chemotherapy after surgical treatment for early-stage breast cancer. Oncotype DX (Genomic Health Inc, Redwood City, CA) is one such commercially available test that produces a recurrence score based on a 21-gene signature. This test has been validated as a prognostic tool for estrogen receptor (ER)–positive lymph node–negative breast cancer (1). It may also predict benefit from chemotherapy in this setting (2). According to National Institute for Health and Clinical Excellence (NICE) guidelines, the current accepted practice in the United Kingdom is to offer chemotherapy to lymph node–positive patients where possible (3). There is emerging evidence that Oncotype DX may provide prognostic and predictive information for breast cancer patients with ER-positive lymph node–positive tumors: The Southwest Oncology Group (SWOG) 8814 trial compared chemotherapy plus hormone therapy with hormone therapy alone in this patient group (4). The investigators conducted a retrospective analysis to explore the contribution of Oncotype DX to clinical decision making (5). The results suggested that the recurrence score derived from Oncotype DX could identify a proportion of patients who would derive little benefit from chemotherapy and could be safely spared this treatment.

The implications of sparing patients chemotherapy are substantial because of the potential to avoid short-term toxicity and the reduced quality of life that are associated with treatment. In addition, the substantial costs of the drugs, their administration, and resulting complications can also be avoided, providing benefits to the individual cancer patient and the population for which the health service provides care. In addition, the underrecognized risk
of long-term toxicity from chemotherapy has the potential to reduce life expectancy. In other cancer types, genomic testing has improved the selection of patients for treatment and has been shown to be cost-effective. An example is the introduction of KRAS mutation testing to select patients with advanced colorectal cancer who may be spared cetuximab (6–8).

In this study, we incorporated clinical outcomes from the SWOG 8814 trial in a model-based cost–utility analysis of Oncotype DX recurrence score–directed chemotherapy. There is evidence that clinicians are increasingly starting to think about cost-effectiveness when defining the optimal package of care for their patients (9). The aim of this study was, therefore, to provide a current estimate of the cost-effectiveness of recurrence score–guided chemotherapy assignment compared with chemotherapy for all patients with ER-positive, lymph node–positive early-stage breast cancer in the United Kingdom. In contrast to previous studies (10–13) supporting Oncotype DX in node-negative patients, we focused on patients who are currently treated with chemotherapy and for whom Oncotype DX may identify those who would derive little benefit. In an additional analysis, we used novel methods in Bayesian decision theory (14) to identify the magnitude of the uncertainties in the evidence base and the priorities for future research to address those uncertainties.

Methods
This analysis was performed within a Bayesian decision analytic framework. The economic model comprises a time-dependent discrete-state transition model (modified Markov model). A detailed explanation of these methods is provided by Sonnenberg and Beck (15). This model was used to estimate mean differences in clinical effects and costs for a hypothetical cohort of women with ER-positive lymph node–positive breast cancer.

Model Structure and Assumptions
The structure of the model was developed by consensus among clinical experts, health economists, and medical statisticians for the purpose of contributing to the design of a proposed UK clinical trial aiming to test the effectiveness and cost-effectiveness of predictive tests in this setting (ie, women with ER-positive lymph node–positive breast cancer). The model was developed from a previously published model (16). The model structure is summarized in Figure 1. The underlying clinical pathway follows NICE guidelines (3) under the assumption that they provide the best available description of current practice in the United Kingdom. Part 1 of the model structure is a decision tree that allocates a patient cohort either to standard care where all patients receive chemotherapy or to a test whereby patients are allocated to high- or low-risk of recurrence groups. The low-risk group is spared chemotherapy. Part 2 of the model structure is a modified Markov model, which is used to calculate mean life-years, quality-adjusted life-years (QALYs), and costs per patient in each group. All patients were assumed to receive identical nonchemotherapeutic adjuvant therapies.

Patients entered the model at the initiation of adjuvant therapy and were assumed to be disease free. The model assumed that patients then moved into a disease-free (follow-up) state, developed a local recurrence (which includes locoregional recurrence) or a distant recurrence, or developed congestive cardiac failure or died. It was assumed that patients remained in the disease-free state until they developed a breast cancer recurrence or cardiac failure or died.

Patients who developed a local recurrence could be treated curatively and move into a separate “disease-free-after-local-recurrence” state, which may carry distinct risks of further distant relapse. For simplicity, we assumed that patients could develop only one local recurrence. Patients were assumed to remain in the distant recurrence state until death from breast cancer or death from other causes. Patients who transitioned to the dead state due to breast cancer incurred additional costs related to terminal care.

Context and Caveats
Prior knowledge
Multigene tests that identify early-stage breast cancer patients who are likely to derive little benefit from adjuvant chemotherapy can potentially spare patients the morbidity from unnecessary chemotherapy and reduce costs. However, the up-front costs of incorporating such tests into clinical practice must be weighed against the clinical benefits and cost savings produced.

Study design
A cost–utility analysis from a UK perspective that compared genomic test–directed chemotherapy using the Oncotype DX 21-gene assay with chemotherapy for all eligible patients with lymph node–positive, estrogen receptor–positive early-stage breast cancer. Recurrence rates for Oncotype DX–selected risk groups were derived from the Southwest Oncology Group 8814 trial data. Simulation analysis was used to examine the probability of cost-effectiveness. Value of information analysis was used to rank priorities for further research to inform cost-effectiveness decisions.

Contribution
The incremental cost-effectiveness ratio of Oncotype DX–directed chemotherapy using a recurrence score cutoff of 18 was £5529 (US $8852) per quality-adjusted life-year. The probability that test-directed chemotherapy is cost-effective was 0.81 at a willingness-to-pay threshold of £30 000 per quality-adjusted life-year. Results were sensitive to the recurrence rate, long-term anthracycline-related cardiac toxicity, quality of life, test cost, and the time horizon. The highest priority for further research identified by value of information analysis is the recurrence rate in test-selected subgroups.

Implications
In the context of the British health system, there is substantial uncertainty regarding the cost-effectiveness of Oncotype DX–directed chemotherapy. Long-term outcome data are needed to inform cost-effectiveness–based decisions.

Limitations
Oncotype DX was not compared with alternative tests designed to select patients for chemotherapy. The possibility that the price of Oncotype DX might change with the introduction of these alternative tests to the market was not considered.

From the Editors
subtracted from the age-adjusted background mortality, which was taken from the UK Office of National Statistics (19). Chemotherapy toxicity rates (National Cancer Institute Common Terminology for Adverse Events grades 3 and 4; http://evs.nci.nih.gov/ftp1/CTCAE/About.html) were estimated from landmark clinical trials (20,21). The lifetime relative risk of congestive cardiac failure after chemotherapy was based on data from the Surveillance, Epidemiology, and End Results database (22). Mortality after onset of congestive cardiac failure was taken from Cowie et al. (23). Additional resource use was estimated from the NICE guidelines, with unit costs calculated from the UK National Health Service (NHS) reference costs and drug costs, which were taken from the 2008 British National Formulary (3,24,25). Specific unit costs that were not available from the reference costs were calculated from reference cost–derived patient bed-days for the most similar type of admission. A detailed breakdown of the chemotherapy costing is presented in Supplementary Tables 2–6 (available online). Costs of breast cancer recurrence, of congestive cardiac failure, and of terminal care were taken from published cost studies (26,27). Quality of life weights (utility values) for all health states except the cardiac failure state were taken from a well-conducted Swedish quality of life study that used the EuroQol EQ-5D questionnaire (28,29). A detailed list of all model parameters, including fitted distributions, is in Supplementary Table 1 (available online).

Recurrence rates were derived from the SWOG 8814 trial (4,5). The necessary parameters fitted to individual patient data were kindly provided by the SWOG-8814 trial investigators and are reported in Supplementary Methods and Supplementary Tables 7 and 8 (available online). In the base case analysis, a constant underlying hazard of recurrence was specified for years 1–5 and for years 6–10 for each group of patients. This hazard rate was derived from the Kaplan–Meier survival function and is referred to as method 1; this method is consistent with a step-exponential survival distribution. Survival curves derived from the model using this method are shown in Figure 2. Method 2 was used for sensitivity analysis; this method used Weibull regression to estimate annual recurrence rates. Further details on the parametric survival modeling used in this analysis are described by Collett (30).

Analysis
The cost-effectiveness analysis was conducted according to the specifications of the NICE reference case (31). Outcomes for effects are measured in life-years, which represent the mean number of years of life per patient and are measured by the area under the survival curve. Life-years were weighted by estimates of health-related quality of life, which are represented by utility values, such that death is represented by 0 and 1 is the best possible health, to produce QALYs. Cost outcomes were measured as the mean cost per patient. The final cost-effectiveness outcome measure—the incremental cost-effectiveness ratio (ICER)—is the difference in expected costs for each cohort divided by the difference in expected effects (cost per QALY). According to NICE, the threshold ICER for an intervention to be considered cost-effective in the United Kingdom ranges from £20 000 to £30 000 (31). The analytic perspective was that of the UK NHS; thus, only direct costs to the NHS were considered. The base year for costs was 2011. The starting age of the patient cohort was 60 years,

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**Figure 1.** Model structure. A) Decision tree. The model is evaluated for a control scenario, where all patients receive chemotherapy, or a test-directed scenario, where patients are allocated to chemotherapy or no treatment based on the test results (OncoType DX). The model for the test-directed scenario is evaluated separately for patients with a recurrence score (RS) greater than vs less than or equal to a specified cutoff (<18 in the base case analysis). Test low risk = RS < cutoff; Test high risk = RS > cut-off; Model Test low = the model is run for patients with a low RS; Model Test high = the model is run with for patients with a high RS. B) State transition model. Patients move through mutually exclusive simulated health states. As they do so, they accumulate state-specific quality-adjusted life-years and incur state-specific costs. Open arrows indicate that patients can remain in a state for more than one cycle. Toxicities can be experienced independently from the other states.

**Model Input Parameters**
Estimates for the proportion of patients assigned to high- and low-risk groups and recurrence estimates for each group were from the SWOG 8814 trial (5). Because recurrence-free survival was not available for this study, we used disease-free survival as a proxy for recurrence-free survival, which was justified by the low number of deaths that were likely attributable to treatment (0.36%). The proportions of patients treated with anthracycline and taxane, anthracycline alone, or taxane alone were estimated by consultation with clinical experts in the United Kingdom. The proportion of recurrences that are locoregional was taken from the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial, which included patients in the United Kingdom (17). The mean time from metastatic recurrence to death was estimated from a historical trial in a similar patient group (18). Breast cancer–specific mortality was

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which is consistent with the average age of patients in the majority of trials in ER-positive early-stage breast cancer. The time horizon was the lifetime of the patient cohort where all patients had died by age 100 years. Both costs and benefits were discounted at 3.5% as recommended by the NICE reference case. Mathematical programming was implemented using the R statistical programming language (32). The University of Leeds Advanced Research Computing cluster, which is part of the Yorkshire White Rose High Performance Computing Grid, was used for the analysis.

Sensitivity Analysis. To characterize overall uncertainty in the output measures, we conducted a probabilistic sensitivity analysis by Monte Carlo simulation (33). This method comprises, for repeated model simulations, a random draw from statistical distributions of all model inputs to produce a distribution of model outputs. This distribution allows characterization of uncertainty in the ICER, which, due to the mathematical properties of the ICER, is expressed as a probability of cost-effectiveness rather than confidence intervals (CIs). The distributions from which this random draw was made were fitted to each input parameter using reported means and variance according to methods recommended by the NICE reference case. For example, the beta distribution was used for binomial proportions and utility weights, the Dirichlet distribution was used for multinomial proportions, and the lognormal distribution was used for relative risks, hazard ratios, and costs. A further explanation of probabilistic sensitivity analysis and the simulation techniques used can be found in Briggs et al. (34,35). All analyses were an average of 10 000 simulations.

One-way (deterministic) sensitivity analyses involved holding the parameter of interest fixed and rerunning the probabilistic model 10 000 times. This simulation was repeated for all reasonable values of the parameter of interest as presented in the results. This approach ensures that all parameters are evaluated at their expected value (rather than the mean, which may differ in skewed distributions) and that correlations are preserved.

Value of Information Analysis. Value of information analysis provides a useful framework for setting priorities for further research into cost-effectiveness. The rationale behind this approach relies on the fact that resources that are spent on a new intervention will not be available to spend on alternative interventions. If we invest in a new intervention that is not the most cost-effective option, we stand to lose health (or money) that could have been gained by patients if we had invested in a more cost-effective intervention. Research (ie, the gain of more information), therefore, has value if it reduces the risk of adopting an intervention that is not cost-effective. This value can be quantified as either lost health (measured in QALYs) or lost health-care resources (measured in monetary units) (36,37). An overall maximum value can be calculated (ie, the expected value of perfect information [EVPI]). Alternatively, a maximum value can be attributed to specific types of research (ie, the expected value of perfect parameter information [EVPPPI]). Thus, the EVPI can be thought of as the opportunity cost (lost benefit) associated with the risk of making an incorrect decision about whether to adopt an intervention. The magnitude of this value is related to both the estimated cost-effectiveness and the current level of uncertainty about the cost-effectiveness estimate. It is the value to society of reducing all uncertainty about a decision to zero, and it therefore represents a ceiling on the value of further research. It is useful for determining if further research, including clinical trials and test optimization research, is worthwhile and, if so, the type of research that should be undertaken.

Calculation of value of information in this study used the non-parametric methods that are well described by Briggs et al. (35). The population EVPI estimate is based on a UK annual breast cancer incidence of 45 508 patients per year (38). Of this total population, 86% will have nonmetastatic disease and 75% of those with nonmetastatic disease will have tumors that overexpress ER. Of those with ER-positive nonmetastatic disease, 90% are assumed to have tumors that do not overexpress HER2. We estimate that 30% of the patients with nonmetastatic, ER-positive HER2-negative tumors (n = 7925) will be offered chemotherapy and may therefore benefit from test-guided therapy. An annual discount rate of 3.5% is applied over a 10-year period, assuming that this is the time over which the decision is relevant. Value is expressed as the net monetary benefit (NMB), which is a composite scale that allows financial costs and health benefits to be expressed in common units and relies on the decision rule for cost-effectiveness:

$$\frac{\Delta C}{\Delta B} < \lambda,$$

where $\Delta B$ and $\Delta C$ are the incremental effects and costs, respectively, and $\lambda$ is the willingness-to-pay threshold. This equation is rearranged to give

$$NMB : \lambda \cdot \Delta B - \Delta C > 0.$$
Results

Cost-Effectiveness Analysis

The main results for the base case cost-effectiveness analysis including the mean and incremental costs, life-years, and QALYs are presented in Table 1. The mean ICER for the adoption of Oncotype DX–directed chemotherapy compared with chemotherapy for all was £5529 per QALY gained. The mean incremental cost was £860 per patient (95% CI = −£5224 to £6897), there was a mean incremental QALY per patient of 0.16 (95% CI = 0.44 to 0.74), and there was a mean incremental life-year per patient of 0.15 (95% CI = −0.58 to 0.87). At a willingness-to-pay threshold of £30000 per QALY, the probability that Oncotype DX is cost-effective was 0.61 (Table 1). The mean incremental net monetary benefit associated with use of Oncotype DX was £3808 per patient (95% CI = −£19709 to £26974 per patient) (an intervention can be considered cost-effective if the net monetary benefit is greater than zero). This net monetary benefit is equivalent to a net health benefit of 0.13 QALYs per patient (95% CI = −0.66 to 0.90 QALYs per patient).

Sensitivity analysis consisted of a deterministic analysis, where individual model parameters are varied within a realistic range, and a probabilistic analysis, where results represent simulation from probability distributions fitted to all model parameters. The results of the deterministic and probabilistic sensitivity analyses are shown in Table 2, and the probabilistic results are displayed graphically as an incremental cost-effectiveness plane (Figure 3), as a cost-effectiveness plot in Supplementary Figure 1 (available online), and as a cost-effectiveness acceptability curve (Figure 4). Results from the deterministic analysis are plotted in Figure 5. The probabilistic results presented in Figures 3 and 4 should be considered the valid results from this analysis; deterministic results are presented to allow an appreciation of the sensitivity of results to specific factors. We conducted an additional sensitivity analysis that used a recurrence score cutoff for categorization into high- or low-risk groups of 25 instead of the base case cutoff of 18. This analysis suggested that use of Oncotype DX in this way produced fewer QALYs than treating all patients with chemotherapy and, therefore, had a lower probability of being cost-effective (Table 2). The use of method 2 (Weibull regression) for recurrence rates produced less favorable cost-effectiveness with either cutoff but also higher levels of uncertainty compared with method 1 (constant hazard for recurrence) (Table 2). As expected (assuming that all three chemotherapy regimens had equivalent efficacy), if a higher proportion of patients is treated with a sequential anthracycline and taxane regimen compared with taxane or anthracycline alone, there is a greater probability that Oncotype DX would be cost-effective because patients receiving single-agent regimens experienced less toxicity, and the drug cost savings were greater.

The price of Oncotype DX, the model time horizon, the relative risk of long-term chemotherapy-related congestive heart failure, and the quality of life weight when on chemotherapy had a large influence on the cost-effectiveness of Oncotype DX. Sensitivity analysis of these parameters (Figure 5) suggested that Oncotype DX rapidly lost cost-effectiveness as its price increased above the current market price of £2576. Long-term outcomes to at least 20 years need to be considered before a stable cost-effectiveness estimate close to the final ICER of £5529 per QALY was reached. Increased risk of long-term cardiac toxicity associated with chemotherapy and the more detrimental effect of chemotherapy (vs no chemotherapy) on quality of life also had a moderate influence on the cost-effectiveness results such that Oncotype DX was cost-effective at higher willingness-to-pay thresholds.

The incremental life-years and the incremental QALYs were of a similar magnitude (Table 1), suggesting that the relative contribution of differences in quality of life between standard care and the intervention (which could be considered to be the incremental utility) was small but present. The small size of this difference most likely reflects the relatively short time over which quality of life is likely to differ (ie, the chemotherapy treatment period and immediately afterward) and the relatively small number of patients who are likely to experience long-term cardiac toxicity.

Value of Information Analysis

The value of information analysis illustrates the potential consequences of the uncertainty in the cost-effectiveness estimate. The overall maximum expected health-care resource lost as a consequence of current uncertainty in cost-effectiveness is in excess of £2000 million (this is the population EVPI, calculated from a per-patient EVPI of £3045 at a willingness-to-pay threshold of £30000 per QALY as detailed in the “Methods” section). This EVPI assumes that the decision about whether to adopt Oncotype DX is relevant for the next 10 years and that the market price of the test does not change. The EVPI represents the maximum societal value of further research into all evidence informing the economic model in all patient groups. Results are presented graphically in Figure 6 for a range of willingness-to-pay thresholds and broken down by types of evidence. The EVPPI results presented in Figure 6 suggest that the majority of the uncertainty in the decision to adopt Oncotype DX is due to uncertainty in the recurrence rates in contemporaneous subgroups of patients as selected by the Oncotype DX risk score. This uncertainty in the recurrence rates was at least 10-fold more important compared with other types of evidence contributing to the decision, depending on the willingness-to-pay threshold. By contrast, other types of evidence (such as quality of life data, cost data, type of relapse, or frequency of chemotherapy-related toxicities) were not identified as having such a high priority for further research.

Table 1. Base case cost-effectiveness results*

<table>
<thead>
<tr>
<th>Result</th>
<th>Standard care†</th>
<th>Oncotype DX–directed chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cost, £</td>
<td>22720</td>
<td>23130</td>
</tr>
<tr>
<td>Incremental cost, £</td>
<td>—</td>
<td>860</td>
</tr>
<tr>
<td>Total life-years</td>
<td>13.37</td>
<td>13.52</td>
</tr>
<tr>
<td>Incremental life-years</td>
<td>—</td>
<td>0.15</td>
</tr>
<tr>
<td>Total QALYs</td>
<td>10.16</td>
<td>10.32</td>
</tr>
<tr>
<td>Incremental QALYs</td>
<td>—</td>
<td>0.16</td>
</tr>
<tr>
<td>ICER, £ per QALY</td>
<td>—</td>
<td>5629</td>
</tr>
<tr>
<td>Probability cost-effective</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WTP = £30000 per QALY</td>
<td>—</td>
<td>0.61</td>
</tr>
<tr>
<td>WTP = £20000 per QALY</td>
<td>—</td>
<td>0.58</td>
</tr>
</tbody>
</table>

* ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; WTP = willingness-to-pay threshold; — = not applicable.
† Chemotherapy for all patients.
Immediate Budget Impact

Currently, in the NHS, the default position is to recommend chemotherapy for the majority of patients considered fit enough with lymph node-positive, ER-positive early-stage breast cancer. We conducted an additional analysis to assess the short-term implications if the NHS adopted Oncotype DX for decision making in these patients. A detailed calculation of chemotherapy cost savings during the treatment period only is presented in Supplementary Table 9 (available online). In summary, if the cost of chemotherapy is £6243 per patient, then the NHS would spend £49 million on chemotherapy per year without Oncotype DX. Assuming that the use of Oncotype DX removed the need for chemotherapy in 70% of patients, the saving in chemotherapy costs translates to £35 million per year because fewer patients will receive chemotherapy. Balancing this saving is the additional cost of Oncotype DX, which is £20 million if the test costs £2576 per patient tested. The net savings to the NHS would therefore be £14 million per year. As a consequence of these chemotherapy-related cost savings, Oncotype DX would be cost saving over the chemotherapy treatment period provided that the proportion

### Sensitivity Analysis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Incremental cost (£)</th>
<th>Incremental QALYs</th>
<th>ICER (£/QALY)</th>
<th>Probability cost-effective†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Method 1 for recurrence rates</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RS cutoff ≤18</td>
<td>860</td>
<td>0.16</td>
<td>5529</td>
<td>0.61</td>
</tr>
<tr>
<td>RS cutoff ≤25</td>
<td>790</td>
<td>−0.20</td>
<td>Test dominated</td>
<td>0.27</td>
</tr>
<tr>
<td><strong>Method 2 for recurrence rates (Weibull)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RS cutoff ≤18</td>
<td>2277</td>
<td>−0.02</td>
<td>Test dominated</td>
<td>0.53</td>
</tr>
<tr>
<td>RS cutoff ≤25</td>
<td>2132</td>
<td>−0.35</td>
<td>Test dominated</td>
<td>0.39</td>
</tr>
<tr>
<td><strong>Type of chemotherapy (all patients)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEC100</td>
<td>1221</td>
<td>0.16</td>
<td>7631</td>
<td>0.61</td>
</tr>
<tr>
<td>FEC100-T</td>
<td>−1336</td>
<td>0.16</td>
<td>Test dominates</td>
<td>0.62</td>
</tr>
<tr>
<td>TC</td>
<td>1450</td>
<td>0.16</td>
<td>9063</td>
<td>0.59</td>
</tr>
<tr>
<td><strong>Proportion of recurrences that are local</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>988</td>
<td>0.15</td>
<td>6712</td>
<td>0.59</td>
</tr>
<tr>
<td>0.5</td>
<td>642</td>
<td>0.17</td>
<td>3859</td>
<td>0.67</td>
</tr>
</tbody>
</table>

* FEC100 = fluorouracil, epirubicin, and cyclophosphamide; FEC100-T = fluorouracil, epirubicin, cyclophosphamide, then docetaxel; ICER = incremental cost-effectiveness ratio; QALY = quality-adjust life-year; RS = recurrence score; TC = docetaxel and cyclophosphamide.
† If the test is dominated, it is more costly and less effective compared with chemotherapy for all patients; if the test dominates, it is less costly and more effective.‡ At a willingness-to-pay threshold of £30 000 per QALY.

**Figure 3.** Incremental cost-effectiveness plane. Uncertainty in the cost-effectiveness estimate is represented here by plotting the difference in costs (incremental costs) against the difference in effects (incremental quality-adjusted life-years [QALYs]) for 1000 simulation outputs from the model. Points plotted in the upper left quadrant suggest that Oncotype DX is less effective and more costly than standard care (therefore not cost-effective), whereas points plotted in the lower right quadrant suggest that Oncotype DX is more effective and less costly (therefore cost-effective). Points in the upper right quadrant are cost-effective if they lie above the diagonal line, which represents a willingness-to-pay threshold of £30 000 per QALY.

**Figure 4.** Cost-effectiveness acceptability curve. The cost-effectiveness acceptability curve presents uncertainty around the cost-effectiveness estimate. It shows the probability that Oncotype DX is cost-effective at a range of willingness-to-pay thresholds (the threshold in the United Kingdom is historically thought to lie between £20 000 and £30 000 per quality-adjusted life-year [QALY]).
of patients tested who are low risk of recurrence was greater than 40%.

**Discussion**

This study suggests that Oncotype DX has the potential to be very cost-effective if adopted by the NHS in the United Kingdom for the selection of women with ER-positive, lymph node-positive early-stage breast cancer. This statement must, however, be interpreted with caution due to the uncertainty in the evidence. There remains a substantial probability that the adoption of Oncotype DX may lead either to more overall costs or less overall health benefit. This risk needs to be reduced by further research before a definitive recommendation to adopt can be made.

When considering whether to adopt Oncotype DX into routine clinical practice, it is important to note that Oncotype DX, which is a product commercialized by Genomic Health, Inc, has a high list price and is protected by patent. The current absence of equally validated alternatives to Oncotype DX means that the test cost is unlikely to be reduced in the near future. Therefore, it is important to weigh carefully the necessary up-front costs of incorporating this test into clinical practice against the potential for both cost savings and clinical benefits. It is also important to consider the strength of the evidence and the uncertainty regarding any contributory estimates of costs, benefits, and harms. A retrospective analysis of clinical trial data suggested that Oncotype DX can contribute to risk stratification and selection for chemotherapy of patients with ER-positive lymph node–negative breast cancer (1). Researchers in different countries have looked at the cost-effectiveness of Oncotype DX in this setting based on scenario analyses, and most have concluded that it is cost-effective at common willingness-to-pay thresholds in their countries (10–13). However, none has described the uncertainty in these estimates in a meaningful way.

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**Figure 5.** Sensitivity analysis. Model parameters for factors that had an influence on the cost-effectiveness were varied to demonstrate their relative impact on the incremental cost-effectiveness ratio: **A** the price of Oncotype DX, **B** the model time horizon, **C** the relative risk of long-term chemotherapy-related congestive heart failure, and **D** the utility weight (quality of life) when on chemotherapy. QALY = quality-adjusted life-years.
that is, there is a substantial risk that such a decision would reduce effective reimbursement decision based on the current evidence; results puts us at high risk of making the incorrect or non–cost-uncertainty around the mean estimates of all the cost-effectiveness on the basis of current evidence. However, the magnitude of the Oncotype DX be reimbursed by the NHS in the United Kingdom mate for the ICER, then it may be possible to recommend that per QALY gained. If we were highly certain about the mean esti accepted UK threshold for cost-effectiveness of £20 000–£30 000 Oncotype DX is very cost-effective when compared with a generally gained. The implication of this estimate, if accurate, is that at face value, the mean ICER was approximately £6000 per QALY resulted in only small increases in life expectancy (0.15 life-years), Overall, therefore, the change in costs was the dominant factor influencing incremental cost-effectiveness. Taken at face value, the mean ICER was approximately £6000 per QALY gained. The implication of this estimate, if accurate, is that Oncotype DX is very cost-effective when compared with a generally accepted UK threshold for cost-effectiveness of £20 000–£30 000 per QALY gained. If we were highly certain about the mean estimate for the ICER, then it may be possible to recommend that Oncotype DX be reimbursed by the NHS in the United Kingdom on the basis of current evidence. However, the magnitude of the uncertainty around the mean estimates of all the cost-effectiveness results puts us at high risk of making the incorrect or non–cost-effective reimbursement decision based on the current evidence; that is, there is a substantial risk that such a decision would reduce rather than increase the total benefit to the UK population. The plot on the cost-effectiveness plane (Figure 3) showed there is an equally substantial probability that Oncotype DX would either cost more and produce fewer QALYs compared with current prac- tice (ie, it is dominated by current practice) or that it would save money and produce more QALYs (ie, it dominates current prac- tice). Put a different way, if these results were interpreted in the classical framework of predefined statistical significance levels and hypothesis testing, then the confidence intervals around the cost-effectiveness estimate would be sufficiently wide that the result would not be statistically significant. However, that is not to say that Oncotype DX would not be cost-effective.

This study has several limitations. First, in the additional analysis where we considered the short-term impact on the NHS budget should Oncotype DX be adopted, we conducted an analysis of the immediate budget impact to illustrate the financial implications for healthcare providers during the chemotherapy treatment period only. Thus, the budget impact results do not characterize the strength of evidence, and they do not consider the long-term costs of cancer recurrence and treatment toxicity, nor do they consider relative life expectancy and quality of life. They should therefore be interpreted with caution and used only for those look- ing to quantify the implications of adopting Oncotype DX within a health service but should not be used for reimbursement decision making. Second, this study only considered Oncotype DX and did not examine the relative value of Oncotype DX and alternative tests designed to select patients for chemotherapy. Third, this study also did not consider that the price of Oncotype DX might change with the introduction of these alternative tests to the market.

Perhaps the most useful conclusions to be drawn from this study are those that can contribute to the design of prospective research into the cost-effectiveness of test-directed therapy: The results were highly sensitive to the method used to represent the underlying hazard for recurrence in each group. There was a poor model fit (with a recurrence rate that increases over time) in low-risk groups for the Weibull survival models fitted to the SWOG 8814 trial data, which is not surprising given that event numbers were as low as 15 in some groups. This poor model fit is likely to explain poor outcomes in patients spared chemotherapy in the model and the consequent poor cost-effectiveness of test-directed therapy when using this method. It is our belief that a constant hazard rate specified separately for the first 5 years and for years 5–10 is likely to more accurately represent the true recurrence rates. It may also seem counterintuitive that using a recurrence score cutoff of 25, which spared more patients chemotherapy, produced less cost-effective outcomes. This finding may be due to worse outcomes of patients in the SWOG trial with a score between 18 and 25 who were spared chemotherapy, but it may also be due to low patient numbers and poor model fit. Therefore, the most important recommendation for further cost-effectiveness research is for future researchers to collect additional retrospective or prospective information on recurrence rates. Such information should ideally cover at least 5 years (but preferably longer) and should be specific to test-selected risk groups. Indeed, the value of information analysis confirmed that most of the uncertainty around the decision about what is the most cost-effective strategy at common willingness-to-pay thresholds arises from uncertainty.
about the recurrence rates. There is therefore high societal value in research into recurrence rate, which can only reliably be provided by a prospective randomized trial.

It is important to recognize that any model is a simplification of reality, and the model presented here is no exception. The acceptability of such simplifications or assumptions should be judged according to the likelihood that they introduce either substantial bias in the estimate of costs and/or outcomes or an important loss of precision in the estimates of costs and/or outcomes. An important loss of precision or bias is one that, if resolved, would be likely to change a decision. The impact of such assumptions around the parameters of the model was evaluated in the presented sensitivity analyses. The importance of assumptions inherent to the structure of the model was not assessed explicitly in this article. It is our belief that a more complex model structure would produce very similar results, but more research into model structure would be required.

It is important to consider the transferability of data used in our analysis to the UK setting. The data used to inform recurrence rates in this analysis were derived from a historical trial conducted in North America that involved a unique study population and treatments. The transferability or generalizability of these data to the UK setting is not captured in the estimate of uncertainty we report. Therefore, the uncertainty should be considered a minimum estimate. It is credible that taking into account the transferability of data from a US trial into a UK setting would generate additional uncertainty and even introduce bias into the results. If data from other historical trials that compare chemotherapy with no chemotherapy can be obtained, then it may be possible to improve on the accuracy of this analysis, which was based on data from the SWOG trial alone. Examples include the Adjuvant Breast Cancer (39) and the Tamoxifen and Exemestane Adjuvant Multinational (40) trials, both of which would contribute data from a UK or European perspective; however, these data would still represent historical event rates, which may be higher than contemporary rates. The use of decision aids such as Adjuvant Online! was not specifically incorporated into the model; the current variation in reliance Adjuvant Online! among different practitioners would, in our opinion, undermine this analysis if it were included. As the role of such tools expands into lymph node–positive subpopulations, it will be necessary to consider their use in future cost-effectiveness analyses, either for defining the control arm or as an adjunct to Oncotype DX.

Assuming that we are able to measure recurrence rates in test-selected groups, it would be useful if research that informs cost-effectiveness also included assessment of quality of life and long-term cardiac side effects in chemotherapy-treated and non-chemotherapy-treated patients. Some of these data could be collected in a short (ie, 6-month) follow-up study, as could data about the use of health-care resources; although drug costs are easy to find from formulary lists, actual resource use remains speculative in this study because it was based largely on clinical opinion and an assumption of compliance with NICE guidelines. A fully informed analysis from a UK perspective would require dedicated data collection in the United Kingdom. Estimates of long-term costs and quality of life (eg, associated with cancer recurrence or cardiac toxicity) are derived from higher quality evidence than the short-term data sources (eg, costs of toxicity) in this analysis because they rely on previously published dedicated cost and quality of life studies. They are, however, subject to assumptions of data transferability to our patient population and require confirmation in a formal study with long-term follow-up. Confirmation is also needed to ensure that patients do not suffer decrement to their quality of life due to worry associated with not receiving chemotherapy.

For clarification regarding interpretation of these results for individual patients, it should be noted that this analysis presents results for the average patient, aged 60 years, only. As such, input parameters represent the mean value of all patients. Although this is the correct approach when making health-care reimbursement decisions about a defined population, outcomes are likely to be very different for individual patients with characteristics far from the average. For example, younger patients may derive more benefit from chemotherapy but may have a higher risk from late toxicities compared with older patients and will clearly be expected to live much longer. Subgroup analyses will therefore be essential to look at cost-effectiveness by age group and by other risk factors. Inevitably, more data at individual patient level are required for clinical and economic outcomes if subgroup analysis is to be possible. Such analysis will be achievable in future prospective trials.

Given the large potential for Oncotype DX to improve the selection of patients who are likely to benefit from adjuvant chemotherapy, it is not surprising that there has been much interest and early use of this test in many developed nations. This study highlights the uncertainty around the clinical effectiveness (as measured by recurrence rates) and cost-effectiveness of Oncotype DX. The importance of prospective randomized research into Oncotype DX cannot be underestimated. It is therefore important to examine competitors to Oncotype DX, such as PAM50, Mammastrat, IHC4, and MammaPrint (41–44). In the context of the NHS, the decision to adopt and pay for Oncotype DX currently carries a substantial risk of a negative balance of costs and health benefits.

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