Tumour profiling tests to guide adjuvant chemotherapy decisions in people with breast cancer (update of DG10).

Erratum to the EAG Diagnostic Assessment Report

Produced by: Sheffield University School of Health and Related Research Health Technology Assessment Group

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[redacted] and [redacted] data marked.

In response to the DAR consultation responses collated by NICE and sent to the EAG on 13th November 2017, the EAG provide the following erratum to the report. None of the amendments changed the overall conclusions of the report.

NB: this document of errata only contains changes that affected one page of the report. Where changes affected multiple pages, corrections were made in an addendum to the report also dated 28th November 2017.

Page 17: In response to Agendia comment #4, the EAG corrected the description of the MINDACT study results from:

"The MINDACT randomised controlled trial (RCT) for MammaPrint reported that for patients who were high-mAOL, low-MammaPrint risk, chemotherapy gave an absolute benefit of 1.5% in 5 year DRFI. This raises the possibility of avoiding chemotherapy in these patients."

To:

"The MINDACT randomised controlled trial (RCT) for MammaPrint reported that for patients who were high-mAOL, low-MammaPrint risk, chemotherapy gave a non-significant absolute benefit of 1.5% in 5 year DMFS (p=0.267). This met the primary objective in that the lower bound of the 95% CI for 5-year DMFS in the no-chemotherapy group was at least 92%. This finding was interpreted by the authors as implying that patients who were high-clinical but low-MammaPrint risk could potentially avoid chemotherapy."

Page 35: In response to Myriad Genetics comment #2, the EAG corrected the description of the EndoPredict Clinical (EPclin) score from:

"From the EPclin score, the probability of metastasis formation within 10 years is estimated, assuming 5 years of hormonal treatment. If the EPclin 10-year risk is less than 10%, the patient is classed as low-risk for metastases recurring in the next 10 years. If the EPClin 10-year risk is 10% or greater the patient is classed as high-risk for metastases recurring in the next 10 years."

To:

"The EP score is a number on a scale between 0 and 15. The EP score is the molecular score only and is not the final test result. An EP score of less than 5 indicates low-risk of distant disease recurrence reoccurring in the next 10 years. An EP score of 5 or more indicates a high-risk of distant disease recurrence in the next 10 years. The EPClin score is calculated by adding clinical data about tumour size and nodal status to the EP score. From the EPClin score, the probability of metastasis formation within 10 years is estimated, assuming 5 years of hormonal treatment. The EPclin score (cut-off 3.3) provides a single low/high risk cut-off; the threshold was set such that women with a low-risk result (EPclin <3.3.) have a lower than 10% risk of developing distant metastases over the next 10 years."

Page 36: In response to Agendia comment #10, the EAG corrected the description of Mammaprint as assessing the risk of distant metastatsis at 5 years to 5 and 10 years.

Page 62: In response to Agendia comment #26, the EAG corrected the description of the results from MINDACT to include the words "non-statistical" and "(p=0.267)", to read:

"For patients who were high-clinical, low-MammaPrint risk, 5-year DMFS was 95.9% with chemotherapy and 94.4% without chemotherapy, a non-significant absolute difference of 1.5% (p=0.267)."

Page 248: In response to Agendia comment #14, the EAG corrected the description of ABCSG6 and ABCSG8 as recruiting only LN0 patients to read:

"Data from other cohorts also have limitations: ABCSG6+857-59 only evaluated Prosigna for a proportion of patients (ABCSG-8);…"

Page 266: In response to Agendia comment #79, the EAG added to the description of the Oncotype DX analyses that the comparisons were between low/intermediate versus high risk groups:

"A further study180 reported increases in likelihood ratio χ^2 for Oncotype DX (low-/intermediate-risk group versus high-risk group) over MammaPrint and vice versa (see Table 84).

Page 355: Table 123 includes two rows which refer to clinical high-risk. The lower column should refer to clinical low-risk. This is a typographical error; the model calculations are not affected.

Page 370: Table 131 of the EAG report refers to the impact of AEs as a "disutility" – this should have stated that the parameter is applied in the model as a QALY loss (hence it reflects a full year impact, but is applied in the first cycle).

Page 409: Two changes were made on this page. The first was in response to Agendia's comment #103; DRFI was changed to DMFS, and the word "non-significant" was added to read:

"The MINDACT randomised controlled trial (RCT) for MammaPrint reported that for patients who were high-mAOL, low-MammaPrint risk, chemotherapy gave a non-significant absolute benefit of 1.5% in 5 year DMFS."

The second was in response to Myriad Genetics comment #1, where a typo was spotted relating to EndoPredict. The sentence was altered to read:

"Microarray studies support conclusions from studies using the commercial versions of the assays in suggesting that Oncotype DX, MammaPrint and EndoPredict can discriminate between high- and low-risk patients regardless of LN status (there were no relevant microarray studies for Prosigna or IHC4)."

Page 434: in response to Agendia comment #123, reference 292 was corrected to read:

“van 't Veer LJ, Yau C, Yu NY, Benz CC, Nordenskjöld B, Fornander T, et al. Tamoxifen therapy benefit for patients with 70-gene signature high and low risk. Breast Cancer Research and Treatment 2017;166(2):593-601.”

The following pages are numbered in accordance with the version of the report sent by NICE for comments.

number as high-risk in LN0 and LN+ groups. However, Oncotype DX categorised more patients as low-risk in LN+ than other tests (57% in Oncotype DX versus 4% to [redacted]% in other tests), but with worse 10-year distant-recurrence free survival/interval (DRFS/DRFI) outcomes (82% in Oncotype DX versus 95% to 100% in other tests).

In terms of prognostic performance, all tests had statistically significant prognostic power in unadjusted analyses in LN0 and LN+ populations. However, recurrence score pathology-clinical (RSPC) was only validated in LN0 patients, and unadjusted analyses using clinical cut-offs were not reported in the validation sets for IHC4 or IHC4+C. All tests provided additional prognostic information over most commonly used clinicopathological factors and over clinical treatment score (CTS) and Nottingham Prognostic Index (NPI) in LN0. Results were more varied in LN+ patients.

There was some evidence of differential chemotherapy benefit between risk groups for Oncotype DX as shown by significant interaction tests between risk group and chemotherapy treatment in unadjusted analyses, but interaction tests sometimes became non-significant when clinicopathological factors were adjusted for. Oncotype DX RSPC (Oncotype DX plus age, tumour size and grade) was prognostic but not statistically significantly predictive for chemotherapy benefit, indicating that the incorporation of CP factors to Oncotype DX may reduce prediction of chemotherapy benefit.

Evidence relating to the ability of MammaPrint to predict benefit from chemotherapy was extremely limited. Although the effect of chemotherapy was significant in high-risk groups and not in low-risk groups, interaction tests between risk groups and chemotherapy treatment were not significant, suggesting no statistically significant difference in effect of chemotherapy between risk groups.

For Oncotype DX and MammaPrint, evidence from observational, non-comparative studies assessing the impact of the test used prospectively in clinical practice suggested that recurrence/survival outcomes in low-risk groups were acceptable even with low rates of chemotherapy. There was no similar evidence relating to the other tests.

The MINDACT randomised controlled trial (RCT) for MammaPrint reported that for patients who were high-mAOL, low-MammaPrint risk, chemotherapy gave a non-significant absolute benefit of 1.5% in 5 year DMFS (p=0.267). This met the primary objective in that the lower bound of the 95% CI for 5-year DMFS in the no-chemotherapy group was at least 92%. This finding was interpreted by the authors as implying that patients who were high-clinical but low-MammaPrint risk could potentially avoid chemotherapy. In patients who were low-mAOL, high-MammaPrint risk, chemotherapy gave an absolute benefit of 0.8%. This could be interpreted to mean MammaPrint would not be a useful test in mAOL low-risk patients, as it would not alter treatment decisions.

EndoPredict (Myriad Genetics)

EndoPredict is a Conformité Européene (CE) marked assay that is designed to assess the risk of distant recurrence within 10 years of initial diagnosis. The test is intended for use in pre- and post-menopausal women with early stage breast cancer with all of the following clinical features:

- ER-positive
- HER2-negative
- lymph node (LN)-negative (no positive nodes) or LN-positive (up to 3 positive nodes).

EndoPredict measures the expression of 12 genes: 3 proliferation associated genes, 5 hormone receptor associated genes, 3 reference (normalisation) genes and 1 control gene.

EndoPredict requires RNA samples extracted from FFPE breast cancer tissue. The test can be performed in a local laboratory using a VERSANT kPCR AD module (Siemens Healthcare Diagnostics). Alternatively, FFPE samples can be submitted to a Myriad Genetics pathology laboratory in Munich that is accredited by the Deutsche Akkreditierungsstelle, a national accreditation body for Germany.

The test process involves using a reverse transcription-quantitative polymerase chain reaction (RT-qPCR), in which target messenger RNAs are reverse transcribed, amplified and simultaneously detected. The raw data are then exported to online evaluation software (EndoPredict Report Generator) which performs a quality check and calculates the EP score and the EPClin score. The EP score is a number on a scale between 0 and 15. The EP score is the molecular score only and is not the final test result. An EP score of less than 5 indicates low-risk of distant disease recurrence reoccurring in the next 10 years. An EP score of 5 or more indicates a high-risk of distant disease recurrence in the next 10 years. The EPClin score is calculated by adding clinical data about tumour size and nodal status to the EP score. From the EPClin score, the probability of metastasis formation within 10 years is estimated, assuming 5 years of hormonal treatment. The EPclin score (cut-off 3.3) provides a single low/high risk cut-off; the threshold was set such that women with a low-risk result (EPclin <3.3.) have a lower than 10% risk of developing distant metastases over the next 10 years. It takes approximately 2 days to obtain the test results if the test is done in-house. If samples are sent away for testing, the turnaround time for the central service is 4 to 5 working days.

MammaPrint (Agendia)

MammaPrint is a CE marked microarray that is designed to assess the risk of distant recurrence within 5 and 10 years and whether a woman would benefit from chemotherapy. The test is intended for use in pre- and post-menopausal women with Stage I or II breast cancer with the following clinical features:

- tumour size less than or equal to 5cm
- LN-negative or LN-positive (up to 3 positive nodes)

The test can be used irrespective of ER and HER2 status, that is, it can be used for tumours that are ER-negative or ER-positive, and HER2-negative or HER2-positive. MammaPrint measures the expression of 70 genes, including genes associated with 7 different parts of the metastatic pathway: (i) growth and proliferation; (ii) angiogenesis; (iii) local invasion; (iv) entering the circulation; (v) survival in the circulation; (vi) entering organs from the circulation, and (vii) adaption to the microenvironment at a secondary site. The MammaPrint test is offered as an off-site service. In Europe, samples are sent for analysis at the Agendia laboratory in Amsterdam, the Netherlands. The test requires a FFPE breast cancer tissue sample from a surgical specimen or core needle biopsy.

The test process involves isolation of RNA from FFPE sample followed by reverse transcription of the RNA to get complementary deoxyribonucleic acid (cDNA). The cDNA is amplified and labelled before being hybridised (bound) to the diagnostic microarray. The microarray is washed and then scanned using an Agilent DNA microarray scanner. The scan file is analysed using Agilent Feature Extraction Software and an algorithm is used to calculate the correlation of the sample profile to a "Low Risk" template profile on a scale of -1.000 to +1.000 with a cut off at 0. The threshold was set such that women with a low-risk result have a 10% risk of developing distant metastases over the next 10 years without any adjuvant hormone or chemotherapy. Test results are available to healthcare professionals within 10 days of submitting the sample.

Oncotype DX Breast Recurrence Score (Genomic Health)

Oncotype DX is designed to assess the risk of distant recurrence within 10 years and predict the likelihood of chemotherapy benefit. The test also reports the underlying tumour biology: ER, PR and HER2 status. The test is intended for use in pre- and post-menopausal women with Stage I or II breast cancer that has the following clinical features:

- LN-negative or LN-positive (up to 3 positive nodes)
- ER-positive
- HER2-negative

DRFS/DRFI/IDFS for LN+ patients, which was 97% (7% received chemotherapy). It was not possible to determine whether patients in intermediate- and high-risk categories had better outcomes than low-risk patients as a result of using Oncotype DX due to the observational nature of the studies.

MammaPrint: Two studies reported evidence relating to the clinical utility of MammaPrint. MINDACT is an RCT of MammaPrint versus clinical practice. This study randomised patients with discordant MammaPrint and mAOL risks to chemotherapy or no chemotherapy. For patients who were high-clinical, low-MammaPrint risk, 5-year DMFS was 95.9% with chemotherapy and 94.4% without chemotherapy, a non-significant absolute difference of 1.5% (p=0.267). This raises the possibility of avoiding chemotherapy in these patients. In patients who were low-clinical, high-MammaPrint risk, 5-year DMFS was 95.8% with chemotherapy and 95.0% without chemotherapy, an absolute difference of 0.8%. This could be interpreted as showing that MammaPrint may not be useful in this group as it would increase chemotherapy rates without improving outcomes. However, the comparator was mAOL, and it is unclear whether the same would be true for other clinical risk scores.

RASTER is a prospective observational study in which patients were treated according to MammaPrint plus usual clinical practice (LN0) or [redacted]. The 5-year DRFI for LN0 patients was 97.0% for low-risk patients (15% had chemotherapy) and 91.7% for high-risk patients (81% received chemotherapy). [redacted] The DRFI rates in the MammaPrint low-risk group may be considered sufficiently low for these patients to avoid chemotherapy. MammaPrint provided additional prognostic information over AOL and NPI, but not over PREDICT plus. Estimates of prognostic performance between risk groups are likely to be affected by the differing rates of chemotherapy per group, and the fact that chemotherapy use was influenced by MammaPrint.

Decision impact

Decision impact studies assess how decisions to use or not use chemotherapy change pre- and post-use of the test. Only decision impact studies from the UK and Europe were included, since other countries may have very different rates of chemotherapy use. The percentage of patients with any change in treatment recommendation or decision (either to or from chemotherapy) among UK studies was 29% to 49% across four Oncotype studies, 37% in one EndoPredict study, and 27% in one IHC4+C study. Ranges across European (non-UK) studies were 5% to 70% for Oncotype, 38% to 41% for EndoPredict, 14% to 41% for Prosigna and 13% to 51% for MammaPrint. The net change in the percentage of patients with a chemotherapy recommendation or decision (patients changing to chemotherapy minus those changing to no chemotherapy) among UK studies was a reduction of 8% to 23% across four Oncotype studies, an increase of 1% in one EndoPredict study, and a reduction of

Multivariable Cox models: Both ABCSG-6+8[57-59] and GEICAM 9906[83, 92] used multivariable analyses and showed that EP was an independent prognostic parameter for 10-year DMFS/DRFS after adjustment for clinical variables (**Error! Reference source not found.**), while ABCSG-8[54] showed a similar finding for Prosigna.

Discussion: Studies assessing multiple tests

Few studies reported data from multiple tests and no study reported all comparisons of interest to the decision problem. Of most relevance to the decision problem was the TransATAC analysis,[43] as this includes patients from the UK, analyses four of the five tests, reports ER+, HER2- LN0-3 patients only, and provides change in likelihood ratios which allows comparisons between tests to be made. However, the TransATAC data also has limitations: it is the derivation set for IHC4 and is therefore likely to be subject to some over-fitting and overestimation of prognostic performance; only menopausal patients were recruited; and MammaPrint was not tested. It is also only a single cohort and ideally all comparisons would be available in multiple independent cohorts. Data from other cohorts also have limitations: ABCSG6+8[57-59] only evaluated Prosigna for a proportion of patients (ABCSG-8);[54, 55] WSG Plan B recruited only high-risk patients, and patients were treated with chemotherapy according to Oncotype DX score;[108, 109, 111] Russell *et al*. 2016[100] was an observational study and reported only very limited study characteristics and analyses, Gong *et al*. 2016[85] used non-standard test methods for Onctoype-DX and IHC4, and was conducted in population of different ethnicity to the decision problem population; and GEICAM 9906[83, 92] included a high proportion of LN>4 patients (36%) and used a non-standard ROR-PT assay.

As the data comparing the tests to each other is limited so are the conclusions that can be drawn. Broad observations include that generally speaking, the more patients are placed in a low-risk category, the poorer the event-free survival for that group. For example, in LN0 patients in TransATAC,[43] EPClin categorised 73% as low-risk and these patients had a 10-year DRFI of 93.4%, whilst Prosigna categorised 54% as low-risk and these patients had a 10-year DRFI of 97%. This effect was more pronounced in LN+ patients in TransATAC, among whom Oncotype DX categorised 57% as low-risk and these patients had a 10-year DRFI of 80.6%, while Prosigna categorised 8% as low-risk and these patients had a 10-year DRFI of 100%. Another broad observation is that the tests generally perform differently in LN+ and LN0 patients. In TransATAC, both EPClin and IHC4+C tests reported lower HRs in the LN0 subgroup than in the LN+ subgroup at 10 years (EPClin LN0 HR 3.88 vs LN+ HR 6.58; IHC4+C LN0 6.06 vs LN+ 9.57), whilst Oncotype DX reported higher HRs in the LN0 subgroup than LN+ subgroup (Oncotype DX LN0 HR 5.83 vs LN+ HR 2.77). Data from other cohorts generally supported these broad observations.

In terms of how much additional prognostic information the tests provide over clinicopathological variables or algorithms (e.g. NPI, AOL, CTS), most data came from TransATAC,[43] where increases in

C-index of 0.844, indicating MammaPrint was able to further discriminate between patients with and without OS events.

A further study[180] reported increases in likelihood ratio χ^2 for Oncotype DX (low-/intermediate- risk group versus high-risk group) over MammaPrint and vice versa (see **Error! Reference source not found.**). This showed that the likelihood ratio χ^2 increased by 14.4 units ($p<0.001$) when Oncotype was added to MammaPrint, and of 9.2 ($p=0.002$) when MammaPrint was added to Oncotype DX, indicating both tests had added prognostic value over the other, but Oncotype DX added a little more.

Oncotype DX and MammaPrint, LN0: Pairs of C-indexes (AUC) for Oncotype DX and MammaPrint were reported in four studies[180, 181, 183, 184] (for 8 cohorts, two of which were pooled analyses). C-indexes for Oncotype DX ranged from 0.608 to 0.71 and for MammaPrint from 0.604 to 0.81. P-values were only reported in one study[184] (5 cohorts) and were not always statistically significant, possibly due to smaller sample sizes in these subgroup analyses compared to the full LN+/- cohorts. Oncotype DX had a higher C-index in five cohorts (Prat *et al*. 2014 and four of the cohorts reported in Yang *et al*. 2014),[180, 184] and MammaPrint had a higher C-index in three (Tobin *et al*. 2014; Xu 2017; GSE19615 from Yang *et al*. 2014).[181, 183, 184]

Oncotype DX and MammaPrint, LN+: One study[180] reported the C-index for LN+ patients. This was 0.64 for Oncotype DX and 0.61 for MammaPrint.

Additional prognostic value in microarray studies

Oncotype DX, MammaPrint and EndoPredict in LN+/-: One study[173] reported a multivariable analysis including Oncotpye-DX and MammaPrint separately alongside ER status, tumour grade, nodal status, age, tumour size and treatment (endocrine therapy, chemotherapy or both) in patients with mixed nodal status (**Error! Reference source not found.**). The cohort used was the derivation cohort for MammaPrint (and there may therefore be some overfitting of the model, resulting in overestimation of the prognostic performance for MammaPrint) and a subgroup of ER+ only patients. Tests were analysed as categorical rather than continuous variables. All high vs. low HRs were statistically significant though the intermediate vs. low analyses (Oncotype DX only) were not. High vs. low HRs were higher for Oncotype DX than for MammaPrint, though this is perhaps to be expected as Oncotype DX high vs. low comparisons do not account for the intermediate patients while MammaPrint has only two categories and the analyses are therefore not comparable.

One study reported a multivariable analysis in Oncotype DX intermediate patients (**Error! Reference source not found.**), and MammaPrint was shown to have additional prognostic value in this subgroup of patients (adjusted for

Prosigna (253)	0.27	0.38	0.35
IHC4+C (279)	0.36	0.38	0.25
EPClin (254)	0.47	-	0.53
LN+ (1-3 nodes)			
Oncotype DX (219)	0.57	0.32	0.11
Prosigna (192)	0.08	0.32	0.60
IHC4+C (213)	0.28	0.34	0.38
EPClin (198)	0.24	-	0.76

* Values may not sum to 1.0 due to rounding errors

Risk classification probabilities - MammaPrint

The evaluation of MammaPrint was based on the MINDACT trial.[134] This study was selected for inclusion in the analysis for three reasons: (a) the trial publication and supplementary material provide sufficient information to estimate risk classification probabilities and DMFS probabilities conditional on risk classification within the same patient populations; (b) it includes a large sample size, and (c) the study allows for the estimation of the benefit of chemotherapy between discordant groups.

Risk classification probabilities for MammaPrint were obtained from the trial publication of the MINDACT trial[134] and the accompanying supplementary material (see Table **1**).

Table 1: Risk classification probabilities using MammaPrint (MINDACT)

Population	**Proportion of patients with risk classification**	
	MammaPrint low-risk	**MammaPrint high-risk**
MINDACT ITT population (n=6,693)	0.64	0.36
MINDACT mAOL clinical high-risk subgroup (n=3,370)	0.46	0.54
MINDACT mAOL clinical low-risk subgroup (n=3,324)	0.82	0.18

Health utilities associated with other model health states and events

The disutility associated with local recurrence was taken from a published model of first, second, and third generation adjuvant chemotherapy regimens for breast cancer reported by Campbell *et al*.[263] Within this study, the 6-month disutility associated with local recurrence was estimated to be 0.108 (SE=0.04). The HRQoL impact of chemotherapy-related AEs was also taken from Campbell *et al*;[263] the model assumes a disutility of 0.04 (assumed SE=0.004) during the first 6-month model cycle. The health utility associated with AML was assumed to be 0.26 based on a previous economic evaluation.[277]

Health utility estimates applied in the EAG model

Table 2 summarises the health utilities assumed in the EAG's base case analysis.

Table 2: Health utilities applied in the EAG model

Health state / event	Duration applied in model	Mean	Standard error	Source
Recurrence-free	Indefinite	0.824	0.018	Lidgren *et al*[265]
Distant metastases	Indefinite	0.685	0.029	
Disutility distant metastases	Indefinite	-0.14	0.11	Calculated using difference method[289]
Local recurrence	Once-only QALY loss applied on transition to distant recurrence state	-0.108	0.04 (assumed)	Campbell *et al*[263]
Chemotherapy AEs	Once-only QALY loss applied in first cycle	-0.038	0.004 (assumed)	
AML	Indefinite	0.26	0.04 (assumed)	Younis *et al*[277]

Resource use and costs

The model includes the following cost components:

(i) Costs associated with the tumour profiling test

(ii) Costs of adjuvant chemotherapy acquisition and administration (including chemotherapy-related toxicity)

(iii) Costs associated with endocrine therapy

(iv) Costs of routine follow-up visits and tests

(v) Costs of other therapies (zoledronic acid and G-CSF)

(vi) Costs of treating local recurrence (once-only cost)

(vii) Costs associated with treating distant metastases.

For Oncotype DX and MammaPrint, evidence from observational, non-comparative studies assessing the impact of the test used prospectively in clinical practice suggested that recurrence/survival outcomes in low-risk groups were acceptable even with low rates of chemotherapy. There was no similar evidence relating to the other tests.

The MINDACT randomised controlled trial (RCT) for MammaPrint reported that for patients who were high-mAOL, low-MammaPrint risk, chemotherapy gave a non-significant absolute benefit of 1.5% in 5 year DMFS. This raises the possibility of avoiding chemotherapy in these patients. In patients who were low-mAOL, high-MammaPrint risk, chemotherapy gave an absolute benefit of 0.8%. This could be interpreted to mean MammaPrint would not be a useful test in mAOL low-risk patients, as it would not alter treatment decisions.

Decision impact studies from the UK and Europe reported that the percentage of patients with any change in chemotherapy recommendation or decision pre-/post-test ranged from 27% to 49% across UK studies (included Oncotype DX, EndoPredict and IHC4+C) and from 5% to 70% across European studies (included all tests except IHC4). The net change in the percentage of patients with a chemotherapy recommendation or decision pre-/post-test ranged from an increase of 1% to a decrease of 23% among UK studies, and a decrease of 0% to 64% across European studies.

Concordance between tests was not fully reviewed, but one UK study (OPTIMA prelim) which compared Oncotype DX, MammaPrint, Prosigna and IHC4 concluded that whilst tests assigned similar proportions of patients to low/intermediate and high-risk categories, test results for an individual patient could differ markedly depending on which test was used.

Data relating to anxiety and health-related quality of life (HRQoL) was limited as most studies did not include a comparator, instead adopting a pre-test/post-test design. Anxiety generally reduced post-test, but it is unclear if this would occur equally after a treatment decision made according to clinical factors. HRQoL improved in some analyses.

Microarray studies support conclusions from studies using the commercial versions of the assays in suggesting that Oncotype DX, MammaPrint and EndoPredict can discriminate between high- and low-risk patients regardless of LN status (there were no relevant microarray studies for Prosigna or IHC4).

6.1.2 Cost-effectiveness – principal findings

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