Tumour profiling tests to guide adjuvant chemotherapy decisions in early breast cancer:

EAG Addendum to responses to Comments on DCD2 (5 June 2018)

This document provides the EAG's responses to key themes in the Consultation Comments for the Diagnostics Consultation Document 2 (DCD2, April 2018) produced by NICE following the Diagnostics Appraisal Committee meeting on 14 March 2018.

1. Micrometastases

Some commentators questioned whether the tests might be useful in patients with micrometastases. Data relating to patients with micrometastases were very limited within the evidence base. Two studies relating to Oncotype DX(1-4) were identified that reported micrometastases subgroups, whilst the EAG identified no studies relating to the other tests that reported micrometastases data on its own.

Oncotype DX

The EAG identified two observational studies where patients were treated according to Oncotype DX score and local clinical practice.

1) Clalit Health Services study(1, 2) – reported 5 year DRFI and BCSS, for different cut points (11-25 and 18-30). [redacted]

At the cut point 18-30, Clalit Health reported DRFI for the subgroups LN0-1mic, LN1mic and LN1mic-LN3. Analyses were unadjusted and confounded by treatment with chemotherapy, which was lesser in the LN0-1mic group than in the LN1mic-LN3 group in RS<18 and RS18-30 risk groups, and similar in the RS>30 risk group (see column 5 in Summary

The data is uncertain due to high risk of confounding. LNmic patient outcomes were more similar to LN0 or LN0-1mic patients than to LN1mic-LN3 patients in RS<18 groups, more similar to LN1mic-LN3 patients in RS>30 groups, and variable in RS18-30.

Table 1). It is unclear how much chemotherapy LNmic patients received. DRFI in LN1mic-LN3 patients is likely to be improved by the greater use of chemotherapy, narrowing the difference between LN0-1mic and LNmic-LN3 groups.

However, it can be seen that LNmic low risk patients have DRFI similar to low risk LN0-mic patients, whilst LNmic intermediate and high risk patients have DRFI similar to LN1-3 high risk patients. Surprisingly, LNmic patients had worse DRFI than LN1mic-LN3 at intermediate and high RS scores, perhaps suggesting under-treatment of these patients.

2) SEER registry(3, 4) only reported BCSS using cut points 18-30, and had less than 5 years follow-up.

In the SEER registry analysis, which considers BCSS, the same problems are evident in terms of a lack of adjustment and differential chemotherapy use in LN0 versus LNmic-LN3 patients which mean the data is at high risk of confounding. In addition, the LN0 group is limited to ages 40-84 whereas the LN1mic-LN3 patients are not limited by age.

BCSS was similar in RS<18 and RS 18-30 groups for LN0, LN1mic and LNmic-LN3 groups, but LN1mic was more similar to LN1mic-LN3 in the RS>30 groups than to LN0.

Summary

The data is uncertain due to high risk of confounding. LNmic patient outcomes were more similar to LN0 or LN0-1mic patients than to LN1mic-LN3 patients in RS<18 groups, more similar to LN1mic-LN3 patients in RS>30 groups, and variable in RS18-30.

Table 1 Oncotype DX data on micrometastases

Study	Study design	Patients	Subgroup, N	Chemo per group	Cut off	Low-risk: % risk of outcome (95% CI)	Intermediate-risk: % risk of outcome (95% CI)	High-risk: % risk of outcome (95% CI)	Comparison	Adjusted HR (95% CI)
DRFI– 5 year										
Cut off 18-30										
Clalit Health Services Stemmer 2016(1) Stemmer 2016(2)	R	ER+, HER2-, had O-DX test	LN0-1mic N= 1,594(2)	RS<18: 1% RS18-30: 26% RS>30: 89%	18-30	99.5 (98.4, 99.8)	98.8 (97.2, 99.4)	93.1 (87.1, 96.3)	NR	NR
			LN1mic N =270(1)	RS<18: 7% RS18-30: 40% RS>30: 90%	18-30	**99.3** (NR)	**89.2** (NR)	**80.6** (NR)	NR	NR
			LN1mic – LN3 N=627(1)			96.8 (NR)	93.4 (NR)	83.6 (NR)		
Cut off 11-25										
Clalit Health Services Stemmer 2016(1)	R	ER+, HER2-, had O-DX test	**LN1mic** N=270(1)	RS<11: 7% RS11-25: 18% RS >25: 81%	11-25	**97.8** (NR)	**95.9** (NR)	**83.9** (NR)	NR	NR
			LN1mic – LN3 N =627(1)			95.1 (NR)	96.1 (NR)	86.8 (NR)		
BCSS – actuarial 5 year										
Cut off 18-30										
SEER registry Petkov 2016(3) Roberts 2016(4)	R	HR+, HER2-[m]	LN0 40-84 years of age, N =38,568	RS <18: 7% RS 18-30: 34% RS >25: 69%	18-30	99.6 (99.4, 99.7)	98.6 (98.3, 98.9)	95.6 (94.4, 96.6)	Int vs low: HR 3.1 (2.3, 4.3) High vs low: HR 11.0 (7.8, 15.5) All: p<0.001	Int vs low: HR 3.0 (2.1, 4.2) High vs low: HR 7.8 (5.3, 11.6) All: p<0.001
			LNmic N =2820(6)	NR		**98.9** (97.4, 99.6)	**99.1** (97.9, 99.6)	**84** (74.1, 90.4)	NR	NR
			LNmic-LN3 All ages, N =4691	RS <18: 23% RS 18-30: 47% RS >25: 75%		99.0 (98.0, 99.5)[n]	97.7 (95.9, 98.7)	85.7 (76.2, 91.6)	p<0.001	NR

References

1. Stemmer SM, Steiner M, Rizel S, Geffen D, Nisenbaum B, Peretz T, et al. First prospectively-designed outcome study in estrogen receptor (ER)+ breast cancer (BC) patients (pts) with N1mi or 1-3 positive nodes in whom treatment decisions in clinical practice incorporated the 21-gene recurrence score (RS) result. Annals of Oncology Conference: 41st European Society for Medical Oncology Congress, **ESMO**. 2016;27(no pagination).
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3. Petkov VI, Miller DP, Howlader N, Gliner N, Howe W, Schussler N, et al. Breast-cancer-specific mortality in patients treated based on the 21-gene assay: a SEER population-based study. NPJ Breast Cancer. 2016;2:16017.
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6. Roberts MC, Miller DP, Shak S, Petkov VI. Breast cancer-specific survival in patients with lymph node-positive hormone receptor-positive invasive breast cancer and Oncotype DX Recurrence Score results in the SEER database. Breast Cancer Res Treat. 2017;163(2):303-10.

2. Critique of the new Agendia model (MammaPrint versus mAOL)

The EAG has scrutinised the new Agendia model of MammaPrint versus mAOL. This process has led to the identification of a number of important errors in the new model which render the results presented by Agendia invalid. These issues are discussed in the subsequent section.

(a) Errors and other issues identified within the new Agendia model

(1) Unconventional approach to half-cycle correction

The company's approach to half-cycle correction is unconventional and appears to assume that patients can only die if they have previously developed distant metastases. This assumption is not correct. The EAG notes that the company's overall survival estimates are unaffected by this assumption and the predicted survival estimates within each clinical-genomic risk group appear to be correct. However, the QALY gains are impacted. The impact of removing this assumption has not been tested by the EAG.

(2) Patients who have already died in previous cycles contribute to total QALYs in the current cycle

In the clinical low, genomic low group (worksheet "MODEL", cells AL32:AL40), the QALY calculation adds a QALY contribution from patients who have already died during previous cycles, rather than just those new patients who die within the current cycle. This is an error. The other three risk groups (clinical low, genomic high; clinical high, genomic low and clinical high, genomic high) are not affected, but are subject to a further error (see issue #3 below).

(3) The QALY calculations are different between the clinical-genomic risk subgroups

The approach used to calculate per-cycle QALY contributions is not the same between risk groups (e.g. calculations in worksheet "MODEL" column AZ). The calculations in cells AZ40:AZ49 (the mAOL group) draw on the number of new deaths, whilst those in cells AZ21:AZ30 (the MammaPrint group) do not. This appears to be an error. It is unclear what the company intended, although the EAG considers it likely that this approach reflects an inappropriate method for including a half-cycle correction.

(4) The QALY gains for patients in some clinical-genomic risk groups are counted 1.5 times each cycle

For some, but not all, of the clinical-genomic risk subgroups, the QALY gains are counted 1.5 times during each cycle. For example, the formula in cell AZ21 is *"=(((AR21*(1-AE_sec_prim))*u_CL_GH_ACT)-(du_CT*AR21)+(AR21*AE_sec_prim*u_AML)+(AS21*u_DM)+(AS21*u_DM*0.5))/(1+oDR)^cycle"*. This formula includes the per-cycle QALY contribution for those with progressed disease (cell AS21) 1.5 times. This is an error which applies to the discordant clinical-genomic risk groups in which chemotherapy is given. It is unclear what the company intended, although the EAG considers it likely that this approach reflects an inappropriate method for including a half-cycle correction.

(5) *The costs for patients in some clinical-genomic risk groups are counted 1.5 times each cycle*

For some, but not all, of the clinical-genomic risk subgroups, the costs are counted 1.5 times during each cycle. For example, the formula in cell AX21 is *"=((AR21*c_monitoring2)+(AR21*((p_ET_CL_GH)*c_ET))+(AR21*AE_CHF*c_CHF)+(AR21*AE_sec_prim*c_AML)+(AS21*c_DM)+(AS21*c_DM*0.5))/(1+cDR)^cycle".* This formula includes the per-cycle cost contribution for those with progressed disease (cell AS21) 1.5 times. This is an error which applies to the discordant clinical-genomic risk groups in which chemotherapy is given. Again, it is unclear what the company intended, although the EAG considers it likely that this approach reflects an inappropriate method for including a half-cycle correction.

(6) Very high per-cycle probability of AML and application of lifetime AML cost each cycle

The new Agendia model includes a per-cycle probability of AML following chemotherapy of 0.012 and applies the lifetime cost of treating AML to these patients during each cycle. According to the new Agendia model, the source used to inform this parameter is the MINDACT trial, although the EAG was unable to locate this value from the Cardoso trial paper or the accompanying supplementary material.[1] Based on the company's new model, this per-cycle AML probability results in around 13% of all patients developing AML by 10-years. The EAG considers this to be very high and notes that it is approximately 25 times higher than the probability applied in the EAG model, based on Wolff *et al*[2] (0.49% develop AML at 10-years). The EAG considers it likely that this value has been miscalculated and that it represents an error. The EAG notes that this value was applied in the company's original model, but was not identified as a major issue by the EAG due to the presence of other serious programming errors which invalidated the model results.

(7) Double counting of the HRQoL impact of chemotherapy-related adverse events

The company's new model includes clinical-genomic subgroup-specific health state utility values for the DMFS state during the first model cycle. The EAG believes that these differences between risk subgroups should account for disutilities associated with chemotherapy-related adverse events. The apparent source of these estimates is the MINDACT trial.[1] During all subsequent cycles, the utility for the DMFS state is based on Lidgren *et al*[3] (the source and value used in the EAG model). As the company also include separate parameters relating to the disutility associated with adjuvant chemotherapy, the EAG considers that simultaneous use of the MINDACT utilities does not make sense and leads to double-counting.

(8) Inconsistent assumptions regarding the magnitude and duration of chemotherapy-related adverse events

The EAG model applies a QALY loss of 0.038 for all patients receiving adjuvant chemotherapy during the first cycle. This estimate was taken from Campbell *et al*[4] and is assumed to relate to the first year

after starting chemotherapy, based on text reported in the paper. The company's new model applies a QALY loss of 0.076 (double the value reported by Campbell *et al*) during the first year and applies a second disutility of 0.038 during the second year. Noting the company's response to the second DCD, which states that the disutility is applied only in the first year (see table of responses to DCD2, comment 47), the EAG considers the disutilities applied in the company's new model to be incorrect.

(9) The cost of the MammaPrint test is partially included in the usual care (no testing) group and only partially accounted for in the MammaPrint group

The company's new model adopts a hybrid decision-tree Markov approach, based on the concordant and discordant clinical-genomic risk subgroups. This approach is different to the original model critiqued within the EAG report. The company's new model now includes parameters relating to the probability that clinical/genomic high-risk patients do/do not receive chemotherapy and that clinical/genomic low-risk patients do/do not receive chemotherapy. For those discordant patients who are assumed not to follow the test in the MammaPrint group, some costs and outcomes from the Markov sub-models of the usual care (no test) group are used. As a consequence of the way the model is programmed, this means that the cost of the MammaPrint test is not included in the MammaPrint group for those patients who are clinical low, genomic high risk but do not get chemotherapy or for those patients who are clinical high, genomic low risk and do get chemotherapy. These reflect errors.

For discordant patients in the usual care group who do not follow the chemotherapy decision indicated by their clinical risk level, the model now uses costs and outcomes from the Markov sub-models of the MammaPrint group. As a consequence of the way the model is programmed, this means that the cost of the MammaPrint test is partially included in the usual care group. This can be seen by changing the cost of MammaPrint to any alternative value – erroneously, this changes the total cost for the usual care group. This is an error.

(b) Additional EAG analysis exploring the impact of correcting errors in the new Agendia model

The EAG has attempted to rectify as many errors as possible in order to generate more reliable estimates of the cost-effectiveness of MammaPrint using the company's new model. The following analyses were undertaken:

(1) The QALY contribution of previously dead patients was removed and changed to reflect QALY contributions of those patients dying in the current cycle.
(2) The cost of the test was applied fully to the MammaPrint group and was removed from the usual care group.
(3) The probability of developing AML was divided by 25, thereby approximately reflecting the estimate applied in the EAG model.

(4) The half-cycle correction attempted by the company was removed. The EAG notes that it is better to exclude the half-cycle correction altogether than to include an adjustment which is known to be incorrect.
(5) The clinical-genomic risk group-specific utility values for the DMFS state in the first cycle were replaced with the utility value for DMFS (0.824).
(6) The disutility associated with chemotherapy in year 1 was set equal to 0.038. The disutility associated with chemotherapy in year 2 was set equal to zero.
(7) Analyses (1)-(6) were combined.

The results of the EAG's corrections are shown in Table 2. Each row of the table shows each individual correction; the final row shows the impact of all corrections combined. As shown in the table, the EAG's corrections to the new Agendia model suggest that MammaPrint is dominated by usual care in both the overall MINDACT population and the clinical high-risk subgroup.

Table 2: Results of the EAG's corrections to the new Agendia model

Scenario number	Scenario description	MINDACT ITT population			Clinical high-risk subgroup (based on mAOL)		
		Incremental QALYs	**Incremental costs**	**Incremental cost per QALY gained**	**Incremental QALYs**	**Incremental costs**	**Incremental cost per QALY gained**
-	Agendia new base case	0.0054	£687	**£126,104**	0.0198	-£928	**Dominating**
1	Remove QALY contribution of previously dead	0.0054	£687	£126,104	0.0198	-£928	Dominating
2	Apply MammaPrint cost fully to MammaPrint group, remove test cost from usual care	0.0054	£1,018	£186,893	0.0198	-£618	Dominating
3	Divide per-cycle AML probably by 25	-0.0014	£812	Dominated	0.0033	-£625	Dominating
4	Remove half-cycle correction	0.0121	£953	£78,805	0.0340	-£373	Dominating
5	All DMFS utilities=0.824 for all risk subgroups	0.0040	£687	£170,646	0.0169	-£928	Dominating
6	Apply chemotherapy-related AE QALY loss of 0.038 in first year only	-0.0038	£687	Dominated	-0.0025	-£928	Dominated
7	All EAG corrections combined	-0.0054	£1,410	**Dominated**	-0.0076	£240	**Dominated**

References

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2. Wolff AC, Blackford AL, Visvanathan K, Rugo HS, Moy B, Goldstein LJ. Risk of marrow neoplasms after adjuvant breast cancer therapy: the National Comprehensive Cancer Network experience. *Journal of Clinical Oncology* 2015;33:340-9.
3. Lidgren M, Wilking N, Jonsson B, Rehnberg C. Health related quality of life in different states of breast cancer. *Quality of Life Research* 2007;16:1073-81.
4. Campbell HE, Epstein D, Bloomfield D, Griffin S, Manca A, Yarnold J*, et al.* The cost-effectiveness of adjuvant chemotherapy for early breast cancer: A comparison of no chemotherapy and first, second, and third generation regimens for patients with differing prognoses. *European Journal of Cancer* 2011;47:2517-30.