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

EAG Addendum following request from NICE after the 3rd committee meeting (13th June 2018)

Following the 3rd Committee Meeting on 13th June, NICE requested the following additional work from the EAG:

A. Repeating the sensitivity analysis which varied the relative risk of distant recurrence (0.76 in the base case) between 0.6 and 0.9 with the confidential access proposal test costs included (Oncotype DX, EndoPredict, Prosigna)
B. Summarising what data TAILORx does and doesn't provide in terms of the current EAG model
C. An exploratory analysis of Oncotype DX incorporating predictive benefit of chemotherapy using relative risks of recurrence informed by TAILORx
D. Summarise whether key studies in the DAR included or excluded patients with micrometastatic disease.

A: Sensitivity analyses around the relative risk of distant metastases for EPClin and Prosigna

(i) Additional analyses for EPClin – alternative sensitivity analyses around relative risk of distant metastases including access proposals

Table 1 presents the results of additional sensitivity analyses around the relative risk of distant metastases for chemotherapy versus no chemotherapy for EPClin (including the access proposals) versus usual practice.

Table 1: EPClin additional analyses – sensitivity analyses around relative risk of distant metastases, including access proposals

EPClin access proposal (central testing), test = [redacted]									
	LN0, NPI≤3.4			**LN0, NPI>3.4**			**LN+(1-3 nodes)**		
Relative risk	**Inc. QALYs**	**Inc. costs**	**ICER**	**Inc. QALYs**	**Inc. costs**	**ICER**	**Inc. QALYs**	**Inc. costs**	**ICER**
0.76 (base case)	0.01	[redacted]	[redacted]	0.03	[redacted]	[redacted]	0.06	[redacted]	[redacted]
0.60	0.02	[redacted]	[redacted]	0.05	[redacted]	[redacted]	0.09	[redacted]	[redacted]
0.70	0.02	[redacted]	[redacted]	0.04	[redacted]	[redacted]	0.07	[redacted]	[redacted]
0.80	0.01	[redacted]	[redacted]	0.03	[redacted]	[redacted]	0.05	[redacted]	[redacted]
0.90	0.00	[redacted]	[redacted]	0.01	[redacted]	[redacted]	0.03	[redacted]	[redacted]
EPClin access proposal (local testing, 2 samples), test= [redacted] **, labour=** [redacted] **, total cost=** [redacted]									
	LN0, NPI≤3.4			**LN0, NPI>3.4**			**LN+(1-3 nodes)**		
Relative risk	**Inc. QALYs**	**Inc. costs**	**ICER**	**Inc. QALYs**	**Inc. costs**	**ICER**	**Inc. QALYs**	**Inc. costs**	**ICER**
0.76 (base case)	0.01	[redacted]	[redacted]	0.03	[redacted]	[redacted]	0.06	[redacted]	[redacted]
0.60	0.02	[redacted]	[redacted]	0.05	[redacted]	[redacted]	0.09	[redacted]	[redacted]
0.70	0.02	[redacted]	[redacted]	0.04	[redacted]	[redacted]	0.07	[redacted]	[redacted]

0.80	0.01	[redacted]		0.03	[redacted]		0.05	[redacted]	
0.90	0.00	[redacted]		0.01	[redacted]		0.03	[redacted]	
EPClin access proposal (local testing, 6 samples), test= [redacted], labour= [redacted], total cost= [redacted]									
	LN0, NPI≤3.4			**LN0, NPI>3.4**			**LN+(1-3 nodes)**		
Relative risk	**Inc. QALYs**	**Inc. costs**	**ICER**	**Inc. QALYs**	**Inc. costs**	**ICER**	**Inc. QALYs**	**Inc. costs**	**ICER**
0.76 (base case)	0.01	[redacted]		0.03	[redacted]		0.06	[redacted]	
0.60	0.02	[redacted]		0.05	[redacted]		0.09	[redacted]	
0.70	0.02	[redacted]		0.04	[redacted]		0.07	[redacted]	
0.80	0.01	[redacted]		0.03	[redacted]		0.05	[redacted]	
0.90	0.00	[redacted]		0.01	[redacted]		0.03	[redacted]	
EPClin access proposal (local testing, 12 samples), test= [redacted], labour= [redacted], total cost= [redacted]									
	LN0, NPI≤3.4			**LN0, NPI>3.4**			**LN+(1-3 nodes)**		
Relative risk	**Inc. QALYs**	**Inc. costs**	**ICER**	**Inc. QALYs**	**Inc. costs**	**ICER**	**Inc. QALYs**	**Inc. costs**	**ICER**
0.76 (base case)	0.01	[redacted]		0.03	[redacted]		0.06	[redacted]	
0.60	0.02	[redacted]		0.05	[redacted]		0.09	[redacted]	
0.70	0.02	[redacted]		0.04	[redacted]		0.07	[redacted]	
0.80	0.01	[redacted]		0.03	[redacted]		0.05	[redacted]	
0.90	0.00	[redacted]		0.01	[redacted]		0.03	[redacted]	

As noted in the EAG addendum prepared after the second appraisal committee meeting, the use of alternative sources for post-test chemotherapy use for EPClin (Cusumano *et al* or Penault-Llorca *et al* rather than Bloomfield *et al*) results in lower ICERs for EPClin compared with the EAG base case. This analysis is reproduced in Table 2.

Table 2: Further analyses of EPClin access proposals using alternative chemotherapy use sources (assuming relative risk of distant metastases = 0.76)

Source of post-test chemotherapy use probabilities	**ICER (EPClin versus usual practice)**			
	Centralised testing (test cost= [redacted])	**Local testing (test cost= [redacted])**	**Local testing (test cost= [redacted])**	**Local testing (test cost= [redacted])**
LN0, NPI≤3.4				
Bloomfield *et al*	[redacted]	[redacted]	[redacted]	[redacted]
Penault-Llorca *et al*	[redacted]	[redacted]	[redacted]	[redacted]
Cusumano *et al*	[redacted]	[redacted]	[redacted]	[redacted]
LN0, NPI>3.4				
Bloomfield *et al*	[redacted]	[redacted]	[redacted]	[redacted]
Penault-Llorca *et al*	[redacted]	[redacted]	[redacted]	[redacted]
Cusumano *et al*	[redacted]	[redacted]	[redacted]	[redacted]
LN+ (1-4 nodes)				
Bloomfield *et al*	[redacted]	[redacted]	[redacted]	[redacted]
Penault-Llorca *et al*	[redacted]	[redacted]	[redacted]	[redacted]
Cusumano *et al*	[redacted]	[redacted]	[redacted]	[redacted]

(ii) Additional sensitivity analyses for Prosigna – relative risk of distant metastases including access proposals

Table 3 presents the results of sensitivity analyses around the relative risk of distant metastases for chemotherapy versus no chemotherapy for Prosigna (including the access proposals) versus usual practice. Scenario 1 relates to arrangements for labs that have a rental agreement with NanoString for the nCounter system. Scenario 2 is for labs that have existing instrumentation and do not need the rental part of the agreement.

Table 3: Prosigna additional analyses – sensitivity analyses around relative risk of distant metastases, including access proposals

Prosigna Access Scheme, Scenario 1 - test = [redacted], instrument rental fee= [redacted], labour=£240, total cost= [redacted]									
	LN0, NPI≤3.4			**LN0, NPI>3.4**			**LN+(1-3 nodes)**		
RR	**Inc. QALYs**	**Inc. costs**	**ICER**	**Inc. QALYs**	**Inc. costs**	**ICER**	**Inc. QALYs**	**Inc. costs**	**ICER**
0.76 (base case)	0.02	[redacted]	[redacted]	0.07	[redacted]	[redacted]	0.07	[redacted]	[redacted]
0.60	0.03	[redacted]	[redacted]	0.11	[redacted]	[redacted]	0.12	[redacted]	[redacted]
0.70	0.03	[redacted]	[redacted]	0.08	[redacted]	[redacted]	0.09	[redacted]	[redacted]
0.80	0.02	[redacted]	[redacted]	0.06	[redacted]	[redacted]	0.06	[redacted]	[redacted]
0.90	0.01	[redacted]	[redacted]	0.03	[redacted]	[redacted]	0.02	[redacted]	[redacted]
Prosigna Access Scheme, Scenario 2 - test = [redacted], instrument rental fee= [redacted], labour=£240, total cost= [redacted]									
	LN0, NPI≤3.4			**LN0, NPI>3.4**			**LN+(1-3 nodes)**		
RR	**Inc. QALYs**	**Inc. costs**	**ICER**	**Inc. QALYs**	**Inc. costs**	**ICER**	**Inc. QALYs**	**Inc. costs**	**ICER**
0.76 (base case)	0.02	[redacted]	[redacted]	0.07	[redacted]	[redacted]	0.07	[redacted]	[redacted]
0.60	0.03	[redacted]	[redacted]	0.11	[redacted]	[redacted]	0.12	[redacted]	[redacted]
0.70	0.03	[redacted]	[redacted]	0.08	[redacted]	[redacted]	0.09	[redacted]	[redacted]
0.80	0.02	[redacted]	[redacted]	0.06	[redacted]	[redacted]	0.06	[redacted]	[redacted]
0.90	0.01	[redacted]	[redacted]	0.03	[redacted]	[redacted]	0.02	[redacted]	[redacted]

(iii) **Sensitivity analyses for Oncotype DX - relative risk of distant metastases**

Analyses varying the relative risk of distant metastases for chemotherapy versus no chemotherapy for Oncotype DX (assuming no prediction of benefit from chemotherapy) were reported in Table 17 of the EAG's addendum dated 6th March 2018. ICERs ranged from £69,967 to Dominated.

B: Limitations of TAILORx in informing a health economic analysis of Oncotype DX in the LN0 population

Table 4 summarises the available evidence on Oncotype DX RS classification, distant metastases rates on endocrine therapy and relative risks of chemotherapy versus no chemotherapy provided from the TAILORx study.

Table 4: Relevant model inputs available from TAILORx

ODX RS score	% classification	DR rate on ET only	Chemotherapy HR
0-10	✓	✓	✗
11-15*	✓	✓ (only for age ≤50 years)	✓
16-20*	✓	✓ (only for age ≤50 years)	✓
20-25*	✓	✓ (only for age ≤50 years)	✓
26-30	✓	✗	✗
31+	✓	✗	✗

** DR rate for ET for all ages is only available for RS 11-25 as a whole*

The EAG notes that the use of TAILORx in informing a health economic analysis of Oncotype DX within a LN0 patient population who are eligible for chemotherapy according to NCCN guidelines is subject to the following limitations:

(1) TAILORx does not provide any information regarding distant metastases risk for patients receiving endocrine therapy only with an Oncotype DX risk score >25

(2) TAILORx does not provide hazard ratios for chemotherapy versus no chemotherapy for patients with an Oncotype DX risk score of <11 or >25

(3) Around 70% to 75% enrolled in the trial would likely be classified as clinically low-risk and would not be eligible for chemotherapy in the UK. The performance of the test in the population of patients who are eligible for chemotherapy in the UK may be different.

(4) Given the different RS cut-offs applied in TAILORx, this may change the way that clinicians interpret the Oncotype DX RS. Consequently, the NHS England Access Scheme dataset, which is used to inform pre- and post-test chemotherapy probabilities conditional on Oncotype DX risk score, is unlikely to represent clinical decision-making at the cut-offs of 11-25.

As a consequence of these limitations, it is unclear how the results of TAILORx could be used to directly inform a health economic analysis of Oncotype DX.

C: Additional sensitivity analyses for Oncotype DX – assuming zero benefit of chemotherapy for patients with Oncotype DX low-risk

Table 5 presents the results of two sets of analyses:

(1) The first set of analyses present the ICERs for Oncotype DX versus usual practice assuming a predictive benefit based on hazard ratios directly estimated from Paik *et al*, or indirectly estimated from naïve comparisons of B20 versus B14 and B20 versus TransATAC. These analyses were presented in an additional EAG addendum following the second appraisal committee meeting.

(2) The second set of analyses present the ICERs for the same scenario, with the inclusion of an additional assumption of zero chemotherapy benefit for patients in the Oncotype DX low RS category. The EAG notes that this analysis is based on the strong assumption that Oncotype DX not only identifies patients who will not relapse, but also identifies patients who will relapse but will not respond to chemotherapy.

Table 5: Oncotype DX additional analyses – excluding/including predictive benefit and excluding/including assumed hazard ratio for genomic low-risk of 1.0, LN0 NPI>3.4

Estimated HR for chemo vs. no chemo for distant recurrence based on direct/indirect comparisons				
Oncotype DX risk group	**Base case (no predictive effect)**	**B20 (Paik 2006)**	**B20 vs. B14 indirect comparison**	**B20 vs TransATAC indirect comparison**
Low	0.76	1.31	0.64	0.86
Intermediate	0.76	0.61	0.75	0.88
High	0.76	0.26	0.35	0.49
ICER	**Dominated**	**Dominating**	**£24,334**	**£8,150**
Estimated HR for chemo vs. no chemo for distant recurrence based on direct/indirect comparisons, including additional assumption of zero benefit for genomic low-risk patients based on TAILORx				
Oncotype DX risk group	**Base case (no predictive effect)**	**B20 (Paik 2006)**	**B20 vs. B14 indirect comparison**	**B20 vs TransATAC indirect comparison**
Low	0.76	1.00 (assumed from TAILORx)	1.00 (assumed from TAILORx)	1.00 (assumed from TAILORx)
Intermediate	0.76	0.61	0.75	0.88
High	0.76	0.26	0.35	0.49
ICER	**Dominated**	**£1,717**	**£2,425**	**£3,768**

As shown in the table, including an assumption of zero chemotherapy benefit for patients with low RS produces ICERs for Oncotype DX versus usual practice which are consistently less than £4,000 per QALY gained, irrespective of the source of the chemotherapy benefit parameters for the intermediate and high RS groups.

D: Inclusion of Micrometastases in key studies

(i) Oncotype DX

LN mixed: One study only reported data for a mixed population of LN0 and LN+ patients only. (South Florida study by Russell et al. 2016[1]) No information about micrometastases was provided.

LN0: Seven datasets reported data for LN0 patients.

- TransATAC ((data request)[2]Dowsett 2010[3])
- NSABP B-14 (Paik 2004;[4] Wolmark 2016[5])
- NSABP B-20 (Paik 2006[6])
- Sun Yat Sen China study (Gong 2016[7])
- Japanese study (Toi 2010[8])
- Beijing China study (Sun 2011[9])
- E2197 (ECOG tiral) Goldstein 2008 (5 year) ; [10]Sparano 2012[11] (10-year)

None reported whether micrometastases were included or not, apart from TransATAC where micrometastases were not assessed and were treated as LN0 (personal communication). It is unknown how many, if any, patients in the LN0 group had micrometastases in TransATAC. The expert member of the committee judged that the two NSABP B studies would have excluded micrometastases, but the EAG were not able to verify this from the published literature.

LN+: Six datasets reported data for LN+ patients.

- TansATAC ((data request)[2]Dowsett 2010[3 a])
- SWOGG-8814 (Albain 2010[12])
- NSABP B-28 (Wolmark 2016[5]; Mamounas 2012[13])
- PACS01 (Penault-Llorca 2014[14])
- Beijing China study (Sun 2011[9])
- E2197 (ECOG trial) Goldstein 2008 (5 year) ; [10]Sparano 2012[11] (10-year)

None reported whether micrometastases were included or not, apart from TransATAC where micrometastases were not assessed and were treated as LN0 (personal communication).

(ii) EndoPredict

Three reanalyses of RCTs:

- Two LN0 and LN+ (TransATAC[2 15] and ABCSG-6+8[16-18])
- One LN+ only (GEICAM 9906[19 20])

None mentioned micrometastases except TransATAC, where micrometastases were not assessed and were treated as LN0 (personal communication). It is unknown how many, if any, patients in the LN0 group had micrometastases in TransATAC.

(iii) Prosigna

Six reanalyses of RCTs:

- Four LN0 and LN+ (TransATAC,[2 21] ABCSG-8,[22 23] NCIC MA.12,[24] NCIC MA.21[25])
- Two LN+ only (GEICAM 9906,[19 20] CALGB 9741[26]

Two retrospective studies:

- Two LN0 and LN+ (DBCG[27-30] British Columbia[31 32])

None mentioned micrometastases except TransATAC, as above.

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