Supplementary File 1: Comparison of TransATAC data to other study data (risk classification and prognosis)

TransATAC is an important study since it evaluates four of five in-scope tests; this study is used in the health economic analysis (see Chapter 3). The EAG were provided with an analysis[1] from the TransATAC team, largely based on Sestak 2016a,[2] in ER+, HER2-, LN0 patients. The TransATAC analysis[1] reported two analysis sets: a full set of patients (N=1,048 Oncotype DX; N=693 Oncotype RSPC; N=1,005 IHC4+C; N=855 ROR46; N=878 EPClin), and a reduced set of patients who had received all four of the tests, N=774 (Oncotype RSPC in LN0 patients only, N=693).

The sample does have limitations in that: (a) it is also the derivation cohort for the IHC4 score, so some overfitting (leading to overestimation of prognostic performance) can be expected, (b) it only recruited post-menopausal women who did not receive chemotherapy, (c) it did not recruit PR+ patients and (d) patients with small tumours are likely to be be underrepresented. A similar analysis has subsequently been published.[3]

Some concerns were expressed during the NICE consulation about the suitability and comparability of the TransATAC bespoke analysis to other sources of data. Given these concerns and the limitations listed above, it is important to examine whether TransATAC results are consistent with those of other studies. Four comparisons are presented: i) a comparison of the proportion of patients categorised as low, intermediate or high risk for studies reporting DRFS/DRFI in patients treated with endocrine monotherapy; ii) 10-year DRFS/DRFI in TransATAC and other RCT re-analyses for Oncotype DX; iii) 10-year DRFS/DRFI by clinical risk and Oncotype DX RS; iv) comparison of Oncotpye DX 5 year distant recurrence between TransATAC and observational studies

i) Overall, for the proportion of patients in each risk category, TransATAC did not appear to differ more than other studies when compared to each other, except for Oncotype DX risk categories in LN0 patients where more patients are classified as low risk than in other cohorts (see Table 1).

ii) Rates are fairly consistent across trials, with TransATAC differing less than the two NSABP trials differ from each other (see

Table **2**).

iii) commentators on the EAG report to NICE expressed concerns that the TransATAC recurrence data looked abnormally high in Oncotpye DX low risk patients, with a recurrence rate of 15% at 10 years. The EAG prepared the comparison in ii) to show that overall rates were very similar, and to make it clear that the 15% recurrence rate was for a subgroup of patients who were at clinical high risk (NPI>3.4), Oncotype DX low risk (see Table 3). We could not identify any other studies subgrouping by NPI score. However, the B14 analysis subgrouped by various other measures of clinical risk: tumour size, grade and Adjuvant! Online (AOL).[4, 5] B14 results appeared consistent with TransATAC, with similar 10-year distant recurrence-free rates for Oncotype DX low-risk, clinically intermediate-risk patients (tumour >4cm, 87%; grade poor-differentiated, 86%; AOL intermediate-risk, 86.6%, AOL high-risk, 95.0%). Outcomes for other Oncotype DX risk groups sub-grouped by clinical status were also consistent across studies.

iv) Outcomes at 5 years were similar between TransATAC and observational studies of Oncotype DX. It should be noted that some patients in the observational studies received chemotherapy; this may have improved observed outcomes (see Table 4).

Table 1: Risk categorisation in TransATAC versus other studies reporting DRFS/DRFI for endocrine monotherapy patients

Test	Non-TransATAC studies	% patients					
		low-risk		int-risk		high risk	
		Others*	Trans-ATAC	Others*	Trans-ATAC	Others*	Trans-ATAC
LN0, all ET, no CT							
Oncotype DX	N=2 NSABP B-14;[4 6] Toi 2010[7]	51%, 48%	64%	22%, 20%	27%	27%, 33%	9%
ROR-PT	N=2 ABCSG-8; [8 9] DBCG[10]	48%, NR	55%	32%, NR	30%	20%, NR	15%
EPClin	N=1 ABCSG-6+8[11-13]	[redacted AIC]	73%	-	-	[redacted AIC]	27%
IHC4+C	N=0	-	70%	-	21%	-	9%
LN+, all ET, no CT							
Oncotype DX	N=0	-	57%	-	32%	-	11%
ROR-PT	N= 2 ABCSG-8; [8 9] DBCG[10]	4%; 25%	8%	34%; 27%	32%	62%; 48%	60%
EPClin	N=1 [1, 11-13]	[redacted AIC]	24%	-	-	[redacted AIC]	76%
IHC4+C	N=0	-	28%	-	34%	-	38%

CT, chemotherapy; DRFS/I, distant recurrence-free survival/interval; ET, endocrine therapy; LN, number of positive nodes; AIC, Academic in confidence.

* Individual values are given respectively for studies listed in column 2.

Table 2: 10-year distant recurrence for Oncotype DX (RCT re-analyses; endocrine monotherapy)

Nodal status	Oncotype DX risk group	Percent of patients distant recurrence-free at 10 years (95% CI)		
		TransATAC data request[1] LN0 LN0	B14 (Paik 2004,[4] Tang 2011a)[5] LN0	B20 (Paik 2006[14])
LN0	ODX low	94.9	93.2 (90.4, 96.0)	96.8 (93.7, 99.9)
LN0	ODX int	87.7	85.7 (79.7, 91.7)	90.9 (82.5, 99.4)
LN0	ODX high	77.2	69.5 (62.6, 76.4)	60.5 (46.2, 74.8)

Data from Table 12 in EAG report. No additional RCTs of endocrine monotherapy reported distant recurrence in LN+ patients.

Table 3: 10-year distant recurrence for Oncotype DX by clinical risk group (RCT re-analyses)

Oncotype DX risk group	Clinical risk	TransATAC data request[1] LN0		B14 (Paik 2004,[4] Tang 2011a)[5] LN0	
		Definition of clinical risk	% DRF at 10yr (95% CI)	Definition of clinical risk	% DRF at 10yr
ODX low	Clinical low	NPI≤3.4	98.3 (96.3-99.2)	Tumour <1cm	100
				Grade well-diff	96
				AOL low-risk	94.4
	Clinical intermediate	NPI>3.4	85.4 (77.6-90.7)	Tumour >4cm	87
				Grade poor-diff	86
				AOL int-risk	86.6
				AOL high-risk	95.0
ODX int	Clinical low	NPI≤3.4	93.1 (86.7-96.5)	Tumour <1cm	87
				Grade well-diff	91
				AOL low-risk	90.0
	Clinical intermediate	NPI>3.4	79.8 (69.4-86.9)	Tumour >4cm	88
				Grade poor-diff	76
				AOL int-risk	86.1
				AOL high-risk	76.6
ODX high	Clinical low	NPI≤3.4	83.8 (57.7-94.5)	Tumour <1cm	83
				Grade well-diff	69
				AOL low-risk	81.8
	Clinical intermediate	NPI>3.4	74.9 (59.8-85.1)	Tumour >4cm	47
				Grade poor-diff	60
				AOL int-risk	56.8
				AOL high-risk	68.5

TransATAC data from Table 124 in EAG report. B14 data by size/grade estimated from graphs in Paik 2004.[4] DRF, distant recurrence-free

Table 4: 5-year outcomes for Oncotype DX (RCTs and observational studies; some chemotherapy use)

Oncotype DX risk group			**LN0-mic**						**LN0-3, clin high risk**
	TransATAC data request[1] (LN0) N=829		**CT use in obs. studies**	TAILORx (Sparano 2015[15]) N=1626	MD Anderson (Le Du 2015[16]) N=1030	Clalit (Stemmer 2016[17]) N=1594	Memorial Sloan Kettering (Wen 2017[18]) N=1406	SEER (Petkov 2016,[19] Roberts 2016[20]) N=38,568	WSG PlanB (Nitz 2017 [21-23]) N=2646
	CT use	**DRFI 5yr**		**DRFS 5yr**	**DRFS 5yr**	**DRFI 5yr**	**DRFI 5yr**	**BCSS 5yr**	**IDFS 5yr**
ODX very low (<11/12)	None		0%	99.3 (98.7, 99.6)			99.9%	99.6 (99.4, 99.8)	94.2 (91.2, 97.3)
ODX low (RS<18)	None	99.1	1-12%	-	95.9 (93.0, 97.6)	99.5 (98.4, 99.8)	99.6%	99.6 (99.4, 99.7)	
ODX int (RS 18-30)	None	94.0	26-43%		-	98.8 (97.2, 99.4)		98.6 (98.3, 98.9)	94.3 (92.8, 95.8) **(RS 12-25)**
ODX high (RS >30)	None	88.9	89-90%		76.4 (59.2, 87.1)	93.1 (87.1, 96.3)		95.6 (94.4, 96.6)	84.2 (80.6, 87.8) **(RS ≥25)**

Data from Table 26 in EAG report. CT, chemotherapy; DRFS, distant recurrence-free survival; DRFI, distant recurrence-free interval; IDFS, invasive disease-free survival; BCSS, breast cancer-specific survival

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