The impact of chemotherapeutic regimens on the cost-utility analysis of Oncotype DX® assay

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Background:

An emerging issue in regards to adjuvant treatment decisions for women with estrogen receptor positive (ER +), HER2 negative (HER2-) early breast cancer (EBC) is how to personalise the adjuvant treatment; whether patients need chemotherapy (CT) with sequential endocrine therapy (ET) or can they be spared from unnecessary CT and treated with adjuvant ET alone.

- Current decision models are based on specific pathological and clinical parameters: tumor size, nodal status, hormone receptor status, HER2 status, histological grade, proliferation activity (e.g. Ki67%), perivascular invasion, and patient preference. (1)

- The Oncotype DX breast cancer multigene expression assay can predict the risk of distant recurrence and the likelihood of chemotherapy benefit for early-stage breast cancer patients treated with a variety of different chemotherapies. (2-3)
  - The assay is intended for pre- and post-menopausal women with early-stage (stage I or II), node-negative, estrogen receptor-positive (ER+), HER2 negative (HER2-) and post-menopausal women with node-positive, hormone receptor-positive, HER2- invasive breast cancers who will be treated with hormone therapy.

- To date, Oncotype DX is the only multi-gene assay included in the published ASCO® and NCCN® guidelines for assessing prognosis and predictive chemotherapy benefit. (4-5) The ODX is the only multi-gene assay that is recognised as being predictive of CT benefit for eligible patients in the latest St. Gallen guidelines and incorporated in the ESMO guidelines. (6-7)

- The use of Oncotype DX in ER+ patients generally results in a reduction in chemotherapy recommendation and utilization.
  - Approximately a third of patients' treatment recommendations are changed after use of the Oncotype DX Recurrence Score® (RS) result; the majority of these recommendations are from CT+ET to ET alone. (8-10)

- Recent datas showed, that the use of ODX generates a decline in net CT usage (-25-46%, ER+,N0 pts; -18.9% ER+, N+ pts). (11-15; 27)

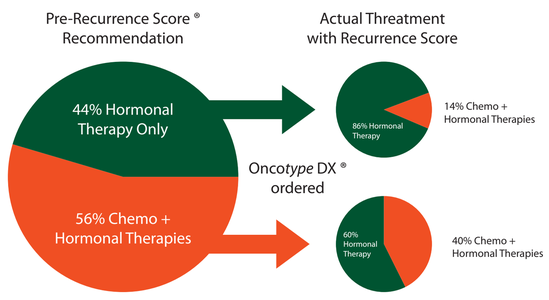

Figure 1. Total net change in CT in Israel, N-pts. Source: (11)

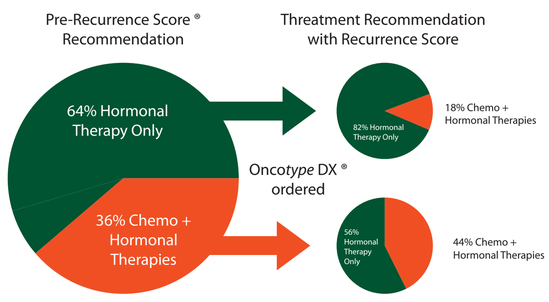

Figure 2. Total net change in CT in Spain, N-pts. Source: (12)

Patients	N	Overall Change Rate Pre- to Post-Oncotype DX ®	CHT to HT	HT to CHT	Other
All evaluable	366	121 33.1% (95% CI 28.3 - 38.1)	79 21.6%	39 10.7%	3 0.8%
Node-negative	244	74 30.3% (95% CI 24.6 - 36.5)	45 18.4%	28 11.5%	1* 0.4%
Node-positive	122	47 38.5% (95% CI 29.9 - 47.8)	34 27.9%	11 9.0%	2** 1.6%

95% confidence intervals calculated using Clopper - Pearson method
* Observation to CHT
** Observation to HT, CT to CHT

Figure 3. Total net change in CT in N-+ pts. Source: (27)

- Published studies have demonstrated the health economical impact of incorporating Oncotype DX ® in clinical practice. (11, 16-23)

Publicaion	Reported Findings (Cost per QALY gained with Oncotype DX ®)	Country Treshold (Willingness to pay for 1 QALY [$])	Country	Comment
Klang et al. 2010	USD 10,700	USD 35,000	Israel	Cost Effective
Tsoi et al. 2010	USD 63,421	USD 75,000	Canada	Cost Effective
Paulden et al. 2011	> USD 29,000	USD 75,000	Canada	Cost Effective
Kondo et al. 2010	USD 3,848	USD 50,000	Japan	Cost Effective
Madaras et al. 2011	USD 14,110	USD 20,000	Hungary	Cost Effective
O' Leary et al. 2010	AUS 9,986	AUS 18,000	Australia	Cost Effective
de Lima Lopez et al. 2011	Improved outcomes (QALYs), reduced costs		Singapore	Cost Savings
Hornberger et al. 2005			USA	Cost Savings
Lyman et al. 2007			USA	Cost Savings

Figure 5: Cost-effectiveness of ODX againts individual country thresholds.

Study Objects:

1. To estimate the cost-effectiveness of using Oncotype DX® for recommended patients in a single-center Hungarian hospital.
2. To estimate the impact of using the various CT regimens on the cost-effectiveness of Oncotype DX®.

Methods:

- Between October 1, 2009 and October 1, 2010, 410 consecutive patients were identified from the National Institute of Oncology cancer registry as women with stage I-II, ER+, HER2- breast cancer who had received adjuvant therapy:
  - Patients were divided into two subgroups by nodal status: node-negative and 1-3 nodes positive.
  - Patients received one of four chemotherapy regimens: CMF/MMM, TE/TEC, FAC/FEC, or AC/EC.

- A Markov model was developed to assess the cost and outcomes (measured in QALYs) associated with using Oncotype DX® in the Hungarian clinical practice, from the perspective of the Hungarian National Health Insurance. The structure of this model is described in figure 6.

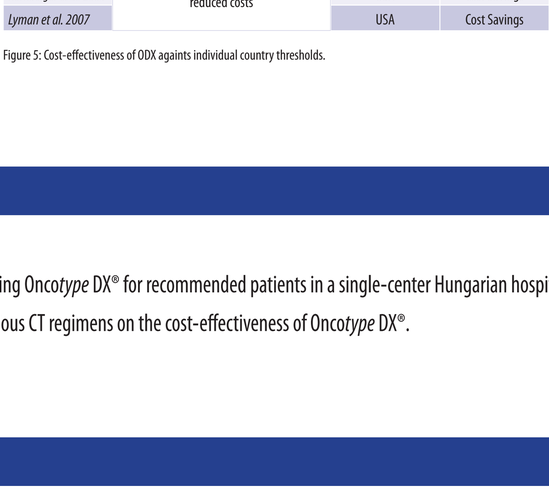

Figure 6: Model structure

- The model used an expected change in chemotherapy use after the integration of the Oncotype DX® assay of -22.8% for node-negative patients and -18.9% for node-positive patients. (The expected net change for node negative patients is based on the weighted average of Klang et al. 2011 and Albanell et al. 2011 The decrease in CT usage after ODX was -30.3%. But if the RS was high they registered an +7.5% increase an average. For node positive patients – based on Rezai et al 2011 – the decrease was -27.9%, while the increase because of high RS was +9.0%) (11,12,27)

- The utility scores associated with each of the health states were collected from literature. (25)

- Costs of chemotherapy and recurrence were extracted from the official cost database in Hungary (26). These cost only reflected the direct medical costs associated with CT (i.e. drugs, supportive care and adverse events). Monitoring, administration and indirect costs were not included.

- The time horizon was 30 years; costs were discounted at a rate of 3%. We estimated the impact of the choice of CT on the cost-utility of ODX using two different scenarios:
  - The current clinical practice from the hospital (actual scenario).
  - The administation of the currently most effective CT regimen to all aligible patients (hypothetical scenario) In the hypothetical calculation more pts. were treated with CT+ET and in these cases all N0 pts recieved FE(100)C, and all N+ pts. recieved TEC regimens (regardless of clinical scenario and stage).

Note: In Hungary taxanes have off-label indications for adjuvant treatment of node negative pts.
Patients and CT regimen characteristics are described on Table 1. Model parameters are described in Table 2.

Patients		N0 n=306	N1 a-c n=104
Average age (year)		60,8	60,9
		n (%)	n (%)
Menopausal state	Premenopausal	60 (19,6)	23 (22,1)
	Postmenopausal	246 (80,4)	81 (77,9)
Ki 67	Low	161 (52,6)	82 (50)
	Medium	41 (13,4)	18 (17,3)
	High	15 (4,9)	10 (9,6)
	Unknown	89 (29)	24 (23)
Histological Grade	I	94 (30,7)	27 (25,9)
	II	138 (45)	50 (48)
	III	61 (19,9)	26 (25)
	Unknown	13 (4,3)	1 (1)
Therapy (Actual)	CT + ET	23 (7,5)	39 (37,5)
	ET	283 (92,5)	65 (62,5)
Therapy (Hypothetical)	CT + ET	36 (11,8)	48 (46,2)
	ET	270 (88,2)	56 (53,8)
CT Regimens (Actual)		n=23 (%)	n=39 (%)
	AC / EC	10 (43)	8 (21)
	FAC / FEC	6 (26)	23 (59)
	TE / TEC	0 (0)	2 (5)
	CMF / MMM	2 (9)	0 (0)
	Unknown	5 (22)	6 (15)
CT Regimens (Hypothetical)	FE (100) C	36 (100)	0 (0)
	TEC	0 (0)	48 (100)

Table 1: Patients and CT regimen characteristics.

Model input	Value		
Change in CT usage	N0: Decrease in chemotherapy use -30.3% Increase chemotherapy use if Recurrence Score is high risk +7.5% N1a-c: Decrease in chemotherapy use -27.9% Increase chemotherapy use if Recurrence Score is high risk +9.0%		
QALY loss with:	CT:0.5		
	Recurrence: 7.9		
	Second primery cancer due to CT: 7.9		
Average costs		N0	N1 a-c
	CT	1 923.66 €	9 725.76 €
	Supportive Care	1 344.8 €	2 542.78 €
	Adverse events	124.77 €	195.5 €
Cost of Oncotype DX ®	3180 €		

Table 2: Model parameters

Results:

Results are described in table 3 below. According to the recent Hungarian practice the incremental cost-effectiveness ratio (ICER) is 13 894 €/QALY respectively. If the treatment would be more aggressive and the net change in CT usage would be similar to the international values the ICER would be 2 248 €/QALY respectively. The incremental cost per patient would be 833.49 €, while the QALY gain would be 0.371. (exchange rate: 1 € = 300 HUF)

Costs, per patient tested (€)	Actual Treatment	Hypothetical Treatment
Oncotype DX ®	3180	3180
Change in use of CT		
-CT drugs	-390.64	-1438.43
-Supportive care	-349.86	-528.59
-Adverese events	-32.93	-44.51
Recurrence costs	-31.02	-334.97
Total	2 375.55	833.49
QALY gain per patient tested	Actual Treatment	Hypothetical Treatment
CT related	0.099	0.147
Recurrence	0.028	0.158
Second primary cancer	0.045	0.066
Total	0.171	0.371
Cost / QALY gained (ICER)	13 893.67 €	2248.25 €

Table 3 Results

Conclusions:

The ICER associated with using Oncotype DX ® in current clinical practice (the actual scenario) is 13 894 €/QALY.
This value is favourable among the oncology related health technologies and below the "non-explicit" Hungarian willingness to pay for a QALY (12600 – 25300 €/QALY).
Oncotype DX ® is a cost-effective methodology in the Hungarian setting.
If all patients were given the most effective CT regimen (like in the hypothetical scenario), the incremental cost-effectiveness ratio associated with using Oncotype DX ® could be optimised to 2 248 €/ QALY.
These results show that the cost-effectiveness associated with using Ocnotype DX in Hungary is sensitive and could be enhanced, if all eligible patients were given the most effective CT regimens.
Sensitivity analyses showed that the cost-effectiveness results were also sensitive to the recurrence rate, the risk categorisation and the cost of chemotherapy.

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