The 21-gene Breast Cancer Assay: Summary of Clinical Evidence

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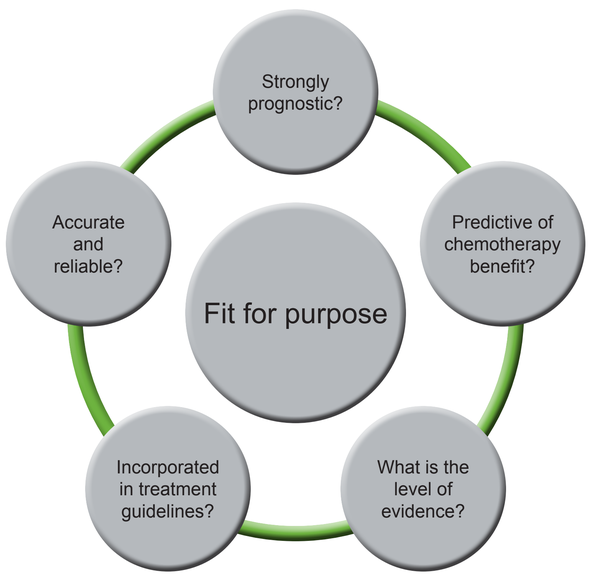
Background

- The Onco*type* DX® 21-gene breast cancer assay predicts the 10-year risk of distant recurrence and the likelihood of chemotherapy benefit in women with ER-positive, early stage invasive breast cancer.[1-13]
  - The assay has been commercially available since 2004; as of December 31, 2012, more than 10,000 physicians in over 65 countries have ordered approximately 335,000 Onco*type* DX tests.[14]
  - The Recurrence Score® result has been shown to guide treatment decisions. Multiple studies from around the world have shown that on average, physicians change initial treatment recommendations more than 30% of the time after receiving the Recurrence Score result.[15-28]
- As the use of genomic assays increases, there is a need to clearly define appropriate clinical validation and clinical utility as the results are used for treatment decisions, recommendations by payers, and treatment guidelines.
- Tests must be "Fit for Purpose" with evidence relevant to that specific purpose. Consistent results across multiple well-designed studies are required to provide evidence for analytic performance, clinical validity, and clinical utility (Figure 1).[29]

Figure 1: Fit for Purpose (Simon J Natl Cancer Inst. 2005)



- Here we summarize the studies that provide clinical validation and that support the clinical utility of the standardized Onco*type* DX Recurrence Score assay.

Methods

- Simon et al.'s criteria for level of evidence were used to classify the Onco*type* DX clinical validation studies (Table 1).[30]

Table 1: Determination of Level of Evidence (Simon J Natl Cancer Inst. 2009)

Level of evidence	Category	Study design	Validation studies available
I	A	Prospective	None required
	B	Prospective using archived samples	One or more with consistent results
II	B	Prospective using archived samples	None, or inconsistent results
	C	Prospective / observational	Two or more with consistent results
III	C	Prospective / observational	None, or one with consistent results, or inconsistent results
IV-V	D	Retrospective / observational	Not applicable*

- Controlled clinical studies that were conducted in a prospective manner using archived samples with documented clinical outcomes were classified as validation studies for prognostic or predictive utility.
- Additional studies that generated clinical evidence on the use of the score, including studies where patients received uniform treatment but were not enrolled in a clinical trial, were considered clinical evidence supporting prognostic or predictive utility.

Results

Table 2: Clinical Evidence Studies of the Onco*type* DX Breast Cancer Assay

Study	Classification	Randomized Clinical Trial	Protocol-Specified Treatment	Clinical Outcome Assessed
NSABP B-14 (2004)	Validation/ Confirmatory	X	X	10-year distant recurrence rate (6.8% , 14.3% , 30.5 % for low, intermediate, high Recurrence Score risk groups)
Gianni (2005)	Supportive		X	Pathologic complete response to neoadjuvant chemotherapy (high Recurrence Score was associated with higher likelihood of pCR; p=0.005)
NSABP B-20 (2006)	Validation/ Confirmatory	X	X	10-year distant recurrence rate (risk reduction from the addition of chemotherapy in the high risk group; no demonstrable relative risk reduction in the low risk group (0.26 vs 1.31))
Kaiser (2006)	Validation/ Confirmatory			10-year risk of breast cancer death (2.8% , 10.7%, 15.5% for low, intermediate, and high risk groups)
Chang (2007)	Supportive		X	Clinical complete response to neoadjuvant chemotherapy (> 1.7-fold increase for patients with high vs low score)
ECOG 2197 (2008)	Supportive	X	X	11.5-year disease free recurrence (score was a significant predictor of recurrence including node negative and node positive disease; p< 0.0001)
Akashi-Tanaka (2009)	Supportive		X	5-year recurrence free survival (100%, 84%, and 73% for low, intermediate, and high risk groups)
SWOG 8814 (2010)	Validation/ Confirmatory	X	X	10-year disease free survival (60% vs 43% for low vs high risk groups); 10-year breast cancer specific survival (low 92% T vs 87% CAF-T and high 54% T vs 73% CAF-T; test for interaction between score and treatment p=0.021)
TransATAC (2010)	Validation/ Confirmatory	X	X	9-year distant recurrence (4%, 12%, and 25% in low, intermediate, and high node-negative risk groups, 17%, 28%, and 49% in node-positive risk groups)
Toi (2010)	Validation/ Confirmatory			10-year distant recurrence risk (3.3% , 0%, 24.8% for low, intermediate, high risk node-negative groups; low vs high p<.001)
Masuda (2011)	Supportive		X	Clinical response to neoadjuvant hormonal therapy (59%, 59%, 20% for low, intermediate, and high risk groups)
Yardley (2011)	Supportive		X	Pathologic complete response to neoadjuvant chemotherapy (0%, 0%, 26% for low, intermediate, and high risk groups; Mantel-Haenzel chi-square p=0.002)
NSABP B-28 (2012)	Supportive	X	X	10-year distant recurrence free interval (75.8%, 57.0%, and 48.0% for low, intermediate, and high risk groups,; p<0.001)

Table 3: Prospectively Designed Studies Supporting Level of Evidence IB Clinical Validation of the Onco*type* DX Breast Cancer Assay

Study	Patient Population	Prognostic/ Predictive	Treatment	Key Study Findings
NSABP B-14	668 patients with ER-positive, node-negative breast cancer	Prognostic	Tamoxifen	"Kaplan–Meier estimates of the rates of distant recurrence at 10 years in the low-risk, intermediate-risk, and high-risk groups were 6.8%, 14.3%, and 30.5%. The rate in the low-risk group was significantly lower than that in the high-risk group (p<0.001)."
NSABP B-20	651 patients with ER-positive, node-negative breast cancer	Predictive	Tamoxifen ± CMF/MF	""The test for interaction between chemotherapy treatment and [Recurrence Score] was statistically significant (p=.038). Patients with high- [Recurrence Score] tumors had a large benefit from chemotherapy. Patients with low- [Recurrence Score] tumors derived minimal, if any, benefit from chemotherapy treatment ."
Kaiser	220 cases and 570 controls with ER-positive, node-negative breast cancer	Prognostic	± Tamoxifen	"The Recurrence Score was associated with risk of breast cancer death in ER-positive, tamoxifen-treated and -untreated patients (p=0.003 and p=0.03, respectively). At 10 years, the risks for breast cancer death in were 2.8%, 10.7%, and 15.5% for those in the low, intermediate and high risk Recurrence Score groups, respectively."
Toi	200 patients with ER-positive, node-negative breast cancer	Prognostic	Tamoxifen	"In lymph node-negative patients, the Kaplan-Meier estimates of the distant recurrence rate at 10 years were 3.3% , 0%, and 24.8% for those in the low-risk, intermediate-risk, and high-risk groups, respectively."
SWOG 8814	367 patients with ER-positive, node-positive breast cancer	Prognostic and Predictive	Tamoxifen vs Sequential CAF-Tamoxifen	"The Recurrence Score was prognostic in the tamoxifen-alone group (p=0.006). There was no benefit of CAF in patients with a low Recurrence Score (log-rank p=0.97; HR 1.02, 0.54–1.93), but an improvement in disease-free survival for those with a high Recurrence Score (log-rank p=0.033; HR 0.59, 0.35–1.01), after adjustment for number of positive nodes."
TransATAC	1,231 patients with hormone receptor-positive, node-negative/ positive breast cancer	Prognostic	Tamoxifen vs Anastrazole	"The [Recurrence Score] was significantly associated with time to distant recurrence in multivariate analyses (p<.001 for N0 and p<.002 for N+). Nine-year DR rates in low, Intermediate, and high groups were 4%, 12%, and 25%, respectively, in N0 patients and 17%, 28%, and 49%, respectively, in N+ patients. The prognostic value of [Recurrence Score] was similar in anastrozole- and tamoxifen-treated patients."

- Thirteen studies were identified that included more than 5,700 patients (>3,400 node-negative, 2,082 node-positive) (Table 2).
- All studies demonstrated an association between the score and clinical outcome (local and/or distant recurrence or neoadjuvant response).
- Six unique studies met the definition of a "validation study" (Table 3).

Table 4: Decision Impact Trials Utilizing the Onco*type* DX Breast Cancer Assay

Country	Type of Study	# of Patients	Nodal Status	Total Percent Change in Treatment Recommendations
USA[15]	Retrospective	260	N0	34
Israel[16]	Retrospective	135	N0	25
Israel[17]	Retrospective	313	N0	40
USA[18]	Prospective	89	N0	32
Spain[19]	Prospective	107	N0	32
Canada[20]	Prospective	150	N0	30
USA[21]	Retrospective	68	N0	25
France[22]	Prospective	96	N0/N1mi	36
Germany[23]	Prospective	366	N0/N1	33
Australia[24]	Prospective	151	N0/N1	24
UK[25]	Prospective	142	N0/N1	27
Japan[26]	Prospective	90	N0/N1	38
Mexico[27]	Prospective	96	N0/N1	32
USA[28]	Retrospective	160	N1	51
Total = 2,223				

- Studies utilizing a consistent methodology that include >2,200 patients from around the world show that use of the Onco*type* DX assay yields, on average, a >30% change in treatment recommendations.
  - While changes occur in both directions (towards and away from chemotherapy), all studies show a shift away from chemotherapy and towards use of hormone therapy alone.

Table 5: Health Economic Studies Utilizing the Onco*type* DX Breast Cancer Assay

Country	Country Threshold (Willingness to pay for 1 QALY($))	Reported Findings (ICER in cost per QALY gained)	Impact
Ireland[31]	EUR 20,000	EUR 9,462	Cost Effective
UK[32]	GBP 20,000	GBP 6,232	Cost Effective
Israel[17]	USD 35,000	USD 10,700	Cost Effective
Canada[33]	CAD 75,000	CAD 63,421	Cost Effective
Canada[34]	CAD 75,000	> CAD 29,000	Cost Effective
Japan[35]	USD 50,000	USD 3,848	Cost Effective
Canada[36]	CAD 75,000	CAD 9,591	Cost Effective
Hungary[37]	EUR 12,600-25,300	EUR 9,730	Cost Effective
Australia[38]	AUS 18,000	AUS 9,986	Cost Effective
Singapore[39]	Improved outcomes (QALYs), reduced costs		Cost Saving
France[40]			Cost Saving
Germany[41]			Cost Saving
USA[42]			Cost Saving
USA[43]			Cost Saving
USA[44]			Cost Saving

- Studies show a net savings of up to $2,000 US dollars per patient tested with the Onco*type* DX assay.[44,45]
  - A reduction in chemotherapy use of approximately 30% results in $195,000 savings per 100 patients tested annually.[46]
- Results demonstrating that the assay is cost-effective/cost-saving are consistent around the world, regardless of country and local cost data.

Table 6: Clinical Guidelines Describing Use of the Onco*type* DX Assay for Invasive Breast Cancer

National Comprehensive Cancer Network® (NCCN®)	Consider use in > 0.5 cm, hormone receptor positive, HER2-negative disease pT1, pT2, or pT3; pN0 and pN1mi (≤ 2 mm axillary node metastasis)
American Society of Clinical Oncology® (ASCO®)	The Onco*type* DX assay may be used in newly diagnosed patients with node-negative, estrogen-receptor positive breast cancer: • to predict risk of recurrence in patients treated with tamoxifen • to identify patients who are predicted to obtain the most therapeutic benefit from adjuvant tamoxifen and may not require adjuvant chemotherapy Patients with high Recurrence Score results appear to achieve relatively more benefit from adjuvant chemotherapy (specifically CMF) than from tamoxifen.
St Gallen Consensus	The Onco*type* DX assay has been shown to predict chemotherapy benefit among patients with hormone receptor positive disease.
European Society for Medical Oncology (ESMO®)	The Onco*type* DX Recurrence Score result may be used to gain additional prognostic and/or predictive information to complement pathology assessment and to predict response to adjuvant chemotherapy, in particular in patients with ER-positive early breast cancer.

- The Onco*type* DX Assay is the only multigene expression assay incorporated into the NCCN, ASCO, St Gallen, and ESMO guidelines.[47-50]

Conclusions

- With the rapidly evolving dissemination of genomic assays for clinical management, there is a burden of proof to demonstrate rigorous development, analytical validation, clinical validation, and clinical utility of the assay. Clinical validation and clinical utility are distinct qualities and should be defined and studied in the populations relevant to their intended use.
- The body of evidence described here shows that the Onco*type* DX assay for invasive breast cancer meets tumor marker level IB evidence for clinical use.
  - Six prospectively-designed randomized clinical trials and confirmatory studies on archived tissue in >3,800 patients support this claim of level of evidence as defined by Simon et al.
  - An additional seven studies in 1,904 patients showed consistent results and clinical support to these validation studies.
- Clinical utility can be shown by the real-life impact of the use of the assay on treatment decisions.
  - Fourteen decision impact studies in 2,233 patients from 10 countries show that use of the assay changed treatment decisions on average in 30% of patients.
  - Eleven studies from around the world have shown that use of the Recurrence Score result in patient care is cost-effective/cost-saving.
- As a result of the extensive validation and consistent results across multiple studies, the Onco*type* DX test is the only assay incorporated into all major oncology clinical guidelines (NCCN, ASCO, St Gallen, ESMO).
- Future clinical validation studies of genomic assays and subsequent clinical utility and support studies should be held to a consistent standard for accurate interpretation and comparison so that results from different assays can be clearly understood and the results used in the appropriate manner for treatment decision making.

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