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Oncotype-DX® gene expression profile and chemotherapy decision-making in patients with early stage breast cancer

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Executive summary

Objective

To evaluate and synthesise data relating to the laboratory performance, prognostic and predictive value of the gene expression profile Oncotype-DX (Genomic Health, Redwood City, CA) in the target population.

Clinical Need and Target Population

Randomized clinical trials have shown that 15% of women with estrogen receptor (ER)-positive lymph node-negative breast cancer treated with hormone therapy alone experience a distant recurrence at 10 years yet most patients receive chemotherapy.[1] There is a need to develop better prognostic and predictive tests to improve the selection of women who are at low risk of breast cancer recurrence and can avoid chemotherapy.

Patients with ER-positive, human epidermal receptor 2 (HER-2/neu) negative, lymph node negative breast cancer (stage I and II) represent the target population for the test. The National Cancer Registry of Ireland identified 1,500 women diagnosed with lymph node-negative breast cancer in Ireland in 2008. Assuming 75% will have ER-positive and HER-2/neu negative we can estimated 1,125 cases for which Oncotype-DX might be considered annually.

Technology being assessed

Oncotype-DX is a multi-gene assay that was developed by Genomic Health Inc, Redwood City CA, and has been commercially available since 2004.[2] To perform the test RNA is extracted from formalin-fixed paraffin embedded tumour tissue obtained from a core biopsy, lumpectomy or mastectomy specimen. Following the RNA extraction step, real time reverse-transcriptase polymerase chain reaction (RT-PCR) is performed and the expression of 16 cancer related genes and 5 controls genes is measured. The 16 genes can be divided into distinct groups according to their role in the cancer pathway, e.g. proliferation, invasion, estrogen receptor pathway, HER2 and other. Based on the level of expression of each gene a continuous variable known as the recurrence score (RS) is generated. Two cut-off points categorize patients into low (RS<18), intermediate (RS≥18<31) and high (RS≥31) risk groups corresponding to 6.8%, 14.3% and 30.5% risk of distant recurrence at 10 years after 5 years of tamoxifen therapy, respectively. These risk estimates represent the range of distant recurrence rates for HR-positive, node-negative breast cancers treated with 5 years of tamoxifen.[2]

Analytic Framework: Appendix 1

Research questions

(1) Are the laboratory performance characteristics of Oncotype-DX acceptable?
(2) How accurate is Oncotype-DX as a prognostic factor for distant recurrence?
(3) How accurate is Oncotype-DX as a predictive factor for therapeutic benefit to systemic therapy?
(4) How does Oncotype-DX compare to other prognostic/predictive factors such as tumor size, grade, patient age or integrated decision aids such as Adjuvant!?
(5) How do patients and physicians view Oncotype-DX in clinical practice?
(6) What are the cost implications of Oncotype-DX?

Research methods

Data Sources and Searches

MEDLINE (from 1996) and EMBASE (from 1980) until January 2011 were searched using some of the following medical subject heading (MeSH) "Gene expression profiling" and the following text terms; *21-gene assay, recurrence score, RT-PCR assay, Oncotype DX, breast neoplasm"* (appendix 2). Further relevant studies were identified by hand searching the references from original and review articles. Abstracts published in the proceedings of annual meetings of the American Society of Clinical Oncology (ASCO) and the San Antonio Breast Cancer Symposium (SABCS) were reviewed.

Study Selection

All validation studies examining the prognostic and predictive accuracy of Oncotype-DX were reviewed. Studies including abstracts that allowed calculation of the test properties were selected. We included articles studying populations other than the population for which the test was designed e.g. node positive patients, patients receiving neoadjuvant chemotherapy, patients receiving aromatase inhibitors, other outcomes such as loco-regional failure and breast cancer death. Articles comparing Oncotype-DX to other prognostic markers or aids were also included.

ISMO Eligibility for OncotypeDX Testing

Based on the evidence presented in a systematic review of the literature we consider OncotypeDX testing an option for patients with the following clinical characteristics;

- Patients must have operable histologically confirmed adenocarcinoma of the female breast and must have completed primary surgical treatment.
- Patients must have tumor that is ER and/or PR positive.
- Patients must have negative axillary nodes as assessed by sentinel lymph node biopsy, axillary dissection or both.
- Tumor size must be 1.1-5.0cm (or 5mm-1.0cm plus unfavourable histological features [i.e. intermediate or poor nuclear and/or histologic grade, or lymphovascular invasion]).
- Tumors must be Her2/neu negative by FISH or immunohistochemistry.
- Patients and physicians must be agreeable to initiate standard chemotherapy and hormonal therapy as adjuvant therapy

ISMO recommends that a National Registry is established to collect the clinical and pathological characteristics of those patients whose breast cancer specimens are sent for OncotypeDX testing. This will allow continuous assessment of how the test is being utilized in Ireland and can be directly compared to its utilization in other publicly-funded health care systems.

ISMO RECOMMENDATIONS AND KEY EVIDENCE

Key Question 1: Are the laboratory performance characteristics of Oncotype-DX acceptable?
Oncotype-DX has acceptable performance characteristics.
• Three studies provided evidence supporting the internal validity of Oncotype-DX (repeatability and reproducibility).[2-4] • Evidence across twelve studies showed an acceptable rate of test failure. There are no data available to support the external validity of Oncotype-DX.[3,5-15]

Qualifying statement: No inter-laboratory or external validity studies were conducted as all testing was conducted at Genomic Health reference laboratory in Redwood City California.

Key Question 2: How accurate is Oncotype-DX as a prognostic factor for distant recurrence?
Oncotype-DX provides prognostic information for ER-positive, lymph node negative, HER2-negative breast cancer patients. Recommendation: Access to Oncotype-DX should be made available to this subgroup to identify those who might avoid chemotherapy.
• In a retrospective cohort study by Paik et al [2] Oncotype-DX was performed on 668 FFPE tumor blocks from the tamoxifen arm of the trial of the NSABP B14 trial. The proportion of patients in the low-risk group who were free of distant recurrence at 10 years (93.2%) was significantly greater than the proportion in the high risk category (69.5%) ($P < 0.001$).[2] • In a retrospective cohort study by Paik et al [16] Oncotype-DX was performed on 227 FFPE tumor blocks from the tamoxifen only arm of the NSABP B20. This cohort was also used as a training set in the development of the assay and therefore test properties and prognostic ability were superior to what would be expected in an independent cohort. A high RS in the tamoxifen only group was almost 5 times as likely to be reported in patients who developed a distant recurrence at 10 years [LR 4.9, 95% CI 4.1-5.4]. A low RS was approximately four times less likely in those patients reporting a distant recurrence at 10 years [LR 0.25, 95% CI 0.0-0.5].[17] • In a nested case-control study Habel et al [3] determined the degree to which the RS could predict the risk of breast cancer-specific mortality among ER- positive lymph node negative patients. A case was a patient whose first event was death from breast cancer. For the 55 cases and 150 controls treated with tamoxifen the risk of death was positively associated with the RS analyzed as a continuous variable [RR 7.6, 95% CI 2.6-21.9]. • In a retrospective cohort study by Esteva et al [9] that included 149 lymph node negative patients who did not receive systemic therapy and had a minimum follow-up of 5 years, there was no significant difference in 10-year distant recurrence-free survival (DRFS) between RS groups reported. However, both ER-positive and negative patients were included, follow-up was short, the sample size represented only 68% of evaluable patients and high grade tumors had improved DRFS compared to low grade tumors. • Dowsett et al [14] conducted a retrospective cohort study testing the prognostic ability of Oncotype DX using archived tumor samples from 1231 postmenopausal chemotherapy-

untreated women randomized to either anastrozole or tamoxifen in the ATAC trial. The treatment arms were combined and the 9-year distant recurrence rate for women with lymph node-negative disease was 4%, 12% and 25% for the low, intermediate and high RS groups (P <0.001) and 17%, 28% and 49% (P < 0.001) for those with lymph node-positive disease.[14]

- Albain et al conducted a retrospective cohort study using archived tumor blocks from the SWOG 8814 study. For the patients with lymph node positive breast cancer treated with tamoxifen alone the 10-year disease free survival was 60%, 49% and 43% for low, intermediate and high RS categories (p=0.017). For overall survival it was 77%, 68% and 51% (p= 0.003). The numbers of events in each risk group was small and the confidence intervals overlap for the low and intermediate groups.[13]
- Goldstein et al [12] conducted a retrospective cohort study using 776 patients with 0-3 positive lymph nodes treated with four cycles of doxorubicin and cyclophosphamide or four cycles of docetaxel and cyclophosphamide followed by hormonal therapy for five years. The RS was a highly significant predictor of recurrence, including node-negative and node-positive disease (P < .001 for both) and when adjusted for other clinical variables.
- Toi et al [15] conducted a retrospective cohort study in an Asian population. Oncotype-DX was performed on 200 lymph node negative patients the Kaplan-Meier estimates of the distant recurrence rate at 10 years were 3.3% (95% confidence interval [95% CI], 1.1-10.0%), 0%, and 24.8% (95% CI, 15.7-37.8%) for those in the low-risk, intermediate-risk, and high-risk groups, respectively. The risk of distant recurrence in the low-risk group was significantly lower than that in the high-risk group when the entire Kaplan-Meier plots were compared (P < .001, log-rank test). There was a significant difference for overall survival between the low-risk and the high-risk groups (P = .008, log-rank test).

Qualifying statement: Thirteen studies [2,3,9,10,12-16,18-21] provided evidence to support Oncotype-DX as a prognostic factor for distant recurrence and other outcomes. The studies are all retrospective however it has been proposed that well-designed retrospective analyses from well conducted prospective randomised controlled trials are of sufficient methodological quality to validate a biomarker.[22,23] Several studies included both HER2-positive and HER2-negative patients which is known to increase the risk of recurrence in lymph node negative and positive patients.[2,12,13,16] There were 55 patients in the Paik et al study with HER2-positive disease, 50 of these had high RS and they comprised 28% of the high risk group. The confounding effect of HER2 status may impact on the generalizability and strength of the effect sizes seen in multivariate models and Kaplan Meier analyses across these studies. In retrospective cohort studies using prospectively collected specimens from RCTs only a proportion of patients from the parent trial were used and therefore selection bias cannot be out-ruled.[2,12-14,16]

Key Question 3: How accurate is Oncotype-DX as a predictive factor for therapeutic benefit to systemic therapy?
There are limited data available that suggest patients with lymph node negative, hormone receptor positive, HER2-negative breast cancer and a high RS derived more benefit from CMF or CAF chemotherapy and endocrine therapy compared to similar patients with a low RS. Recommendation: Patients with a high RS should be offered chemotherapy in addition to endocrine therapy.
• Paik et al[16] examined 651 archived specimens from the NSABP B20 trial (28.9% of original trial). Patients in the tamoxifen-only arm with a high RS had a distant recurrence free survival (DRFS) of 60.5 % (95% CI, 46.2-74.8). CMF in addition to tamoxifen improved DRFS to 88.1% (95% CI, 82.0-94.2). A formal test for statistical interaction between a 50-point increment in continuous RS and chemotherapy was significant.[16] The intermediate and low RS groups did not appear to benefit from the CMF however confidence intervals were large and a benefit cannot be excluded. • In a retrospective study by Albain et al[13] the addition of CAF followed by tamoxifen (CAF-T) to patients with a high RS resulted in a statistically significant change in DFS from 43% (95% CI, 28-57%) to 55% (95% CI, 40-67%). Similar improvements were not seen in the intermediate or low RS groups. Oncotype-DX predicted for an overall survival advantage with the addition of CAF-T for patients in the high risk group, but not for the intermediate and low risk groups.[13]

Qualifying statement: Both studies included only a proportion of archived tumor blocks from their original RCTs and selection bias cannot be excluded, both included HER2-positive and negative patients. The tamoxifen only arm of the Paik et al study was used as a training set for development of the Oncotype-DX and therefore results may be biased towards optimization of prediction of recurrence. In the Albain et al study the likelihood ratio test for interaction was statistically significant in the first 5 years but not beyond. The results of both studies require validation in independent cohorts.

Key Question 4 How does Oncotype-DX compare to other prognostic/predictive factors such as tumor size, grade, patient age or integrated decision aids such as Adjuvant!?
Oncotype-DX provided information in addition to and independent of traditional clinical and clinical and pathological variables. Recommendation: Oncotype-DX can be used to provide additional information beyond that provided by standard clinical and pathological variables.
• Bryant et al. [24] reclassified 668 patients from the tamoxifen only arm of NSABP B-14 study using Adjuvant! online (AOL). Patients classified by both tests as low risk had 10 year distant recurrence rate of 5.6 % [95% CI 2.5-9]. If AOL classified a patient as intermediate/high risk and Oncotype-DX reclassified them as low risk the 10 year recurrence rate was 8.9 % [95% CI 4-14)]. The confidence intervals are wide and suggest that there may be patients who would benefit from additional therapy. If both tests classified a patient as high risk the 10 year recurrence rate was 30.7 [95% CI 24-38]. If AOL classified a patient as low risk, but Oncotype-DX indicated intermediate to high risk, the 10 year recurrence rate was 12.9 [95% CI 7-19]. • Goldstein et al.[12] examined the prognostic utility of Oncotype-DX compared to an algorithm similar to AOL but modified for outcome at 5 years and referred to as the Integrator using 465 patients from the ECOG E2197 trial.[12] There was poor concordance between predictions made by RS and the Integrator using either risk group or risk percentile classification for comparison and using both local and centrally determined tumor grade. In a proportional hazards model that included only RS and the Integrator risk percentiles, only RS remained statistically significant and the RS by Integrator interaction term was significant, indicating that the RS was independent of Integrator risk. RS lost statistical significance when the HER2-positive cohort was removed from the analysis. • Tang et al.[25] found both RS ($P < 0.001$) and AOL ($P = 0.002$) provided strong independent prognostic information in tamoxifen-treated patients from NSABP-14 and NSABP-20 RCTs. Combining RS and individual clinico-pathologic characteristics provided greater prognostic discrimination than combining RS and the composite AOL. • Most multivariate regression models including traditional clinicopathological biomarkers and the RS as independent variable observed the RS remained or trended toward being a statistically significant predictor of recurrence however there are significant limitations to these models.[2,3,12,13]

Qualifying statement: Multivariate models varied across studies. Some used centrally defined grade others used locally defined grade and this had an effect of whether RS retained statistical significance or not. There was variability in how clinical and pathological covariates were entered in the models e.g. continuous covariates such as age, tumor size, number of lymph nodes were dichotomized across all studies while the RS was entered as a continuous variable which may have maximized the information contained within the RS and minimized the power of the continuous covariates converted to categorical ones thereby favoring the continuous RS.

Key Question 5: How do patients and physicians view Oncotype-DX in clinical practice?
Evidence is limited but suggests that patients and physicians satisfaction with Oncotype-DX is acceptable. Recommendation: Oncotype-DX should be accessible to patients within the target population and independent research conducted in the Irish setting led by ISMO can further determine the impact the test has on patients and physicians.
• A prospective multicenter study assessed 89 patients and physicians prior to and after Oncotype-DX testing. The medical oncologist treatment recommendation changed for 28 patients (31.5%). Twenty-four patients (27%) changed their treatment decision. The largest change after the RS results was conversion from the medical oncologist's pre-test recommendation for chemotherapy plus hormonal therapy to post-test recommendation for hormone therapy in 20 cases (22.5%). Nine patients (10.1%) changed their treatment decision from chemotherapy plus hormones to hormone therapy. Patient satisfaction was high. There was also a significant reduction in conflict over treatment decisions, a reduction in anxiety scores, greater patient satisfaction and increased confidence with their choice of adjuvant therapy after taking the test. About 76% of medical oncologists involved in their care also found that Oncotype-DX increased their confidence in treatment recommendation.[26] • A retrospective study conducted in a community-based oncology practice included 74 patients fitting the target population examined whether the RS influences clinicians' treatment recommendations and eventual treatment. Treatment recommendations before the RS knowledge were compared with treatment recommendations after RS knowledge and to the treatment eventually administered. For 21% and 25% of patients, knowledge of the RS changed the clinicians' treatment recommendations and eventual treatment, respectively.[8] • In a study by Assad et al that involved retrospective chart review 85 women who had an Oncotype-DX performed they observed that Oncotype-DX influenced the treatment decision to provide or withhold adjuvant chemotherapy in 44% (n=37) of women.[27] • A further study by Lillie et al suggested that health literacy affected retention of information about Oncotype-DX but not the desire for information regarding it. Interviews conducted in 163 stage I or II breast cancer patients who had completed adjuvant chemotherapy and/or were receiving adjuvant hormone. [28]

Qualifying statement: There was limited evidence available for this section. ISMO recognizes that medical decision making ultimately happens in a dichotomous decision space that includes either choosing a treatment (i.e. adjuvant chemotherapy) or withholding it, therefore tests such as Oncotype-DX that yield 3 risk categories will inevitably yield a certain proportion of indeterminate results for decision making purposes.[29]

Patients and physicians can use point estimates to make an individualized decision about adjuvant chemotherapy. However, it is hard to quantify to what extent risk estimates between 10% to 20% risk of relapse (corresponding to the intermediate risk cohort with RS scores of 18-31) help patients making an informed decision versus increase their anxiety over a difficult and non-trivial health care choice. This aspect of shared medical decision making, how patients perceive and benefit from outcome estimates that involve predictions on a continuous scale when

results are far from the extreme (i.e. very bad or very good prognosis) is understudied and requires further research that will be provided through an ISMO directed field study so it is generalisable to the Irish population.

Key Question 6: What are the cost implications of Oncotype-DX?
Decisions based on RS-guided therapy were associated with increased quality adjusted survival and improved cost-effectiveness.[30-33] Recommendation: Oncotype-DX should be made available to the target population as the available evidence suggests it is cost-effective.

- The Ontario Ministry of Health and Long Term Care (MOHLTC) adopted and expanded on the cost effectiveness analysis conducted by Tsoi et al and concluded that Oncotype-DX it is cost-effective to provide Oncotype-DX to all patients at any willingness to pay for a QALY. At a willingness to pay of $75,000 dollars per QALY the probabilistic sensitivity analysis found that the probability that Oncotype-DX is cost effective is 83.5% for patients identified as Adjuvant Online! low risk, 99.8% for patients identified as AOL intermediate risk, and 65.8% for patients identified as Adjuvant Online! high risk. The MOHLTC concluded that Oncotype-DX was cost effective for all patients irrespective of the Adjuvant Online risk group. [33,34]
- Hornberger *et al* conducted a cost-utility analysis using the RS in patients classified as having a low or high risk of distant recurrence based on NCCN risk criteria.[31] The analysis considered survival, quality of life and costs from a societal perspective. At baseline values, the RS applied to 100 potential patients predicted an increase in quality-adjusted survival by 8.6 years while reducing overall costs by US$202,828.
- Lyman *et al* constructed an economic model to guide the use of adjuvant systemic therapy in patients with node-negative, HR positive early stage breast cancer.[30] Three adjuvant treatment strategies were compared: (1) treat all patients with chemotherapy followed by tamoxifen (2) treat all patients with tamoxifen alone and (3) treat patients by RS-guided therapy with low risk patients receiving tamoxifen only and intermediate and high risk patients receiving chemotherapy and tamoxifen. RS-guided therapy was associated with a gain in individual life expectancy of 2.2 years compared with tamoxifen alone, and it was associated with similar life expectancy to that seen with the chemotherapy and tamoxifen strategy. An estimated net cost savings of $2,256 per patient with RS-guided therapy was seen compared with chemotherapy and tamoxifen with an incremental cost-effectiveness ratio of $1,944 per life year saved compared with tamoxifen alone.
- Kondo et al compared RS guided treatment with either treatment guided by the NCCN guideline or St Gallen recommendation in the context of Japan's health care system. RS-guided treatment was cost effective, with an incremental cost effectiveness ratios of US$ 26,065 per QALY compared with NCCN guided treatment, and US$ 10,774/QALY compared with St Gallen guided treatment. Both were well under the suggested social willingness-to-pay for one life year gain from an innovative medical intervention in Japan of US$ 52,174/QALY.[32]

Qualifying statement: This section included four studies.[30-34] The model constructed by MOHLTC did not account for local recurrence or long-term adverse effects from chemotherapy. The estimated cost saving in the Hornberger et al study was likely an underestimation as only drug cost was included in the analysis, and no indirect costs associated with chemotherapy were considered.

Other recommendations

1. American Society of Clinical Oncology (ASCO)

American Society of Clinical Oncology 2007 Update of Recommendations for the use of tumour markers in breast cancer, recommend the test for use in the prediction of risk of recurrence in patients treated with tamoxifen. The test may also be used to identify patients who are predicted to obtain the most therapeutic benefit from adjuvant tamoxifen and who may not require chemotherapy. Patients with high recurrence scores appear to achieve relatively more benefit from adjuvant chemotherapy (specifically CMF) than from tamoxifen. The guideline maintains that at this time there is insufficient data to comment on whether these conclusions generalise to hormonal therapy other than tamoxifen, or whether this applies to other chemotherapy regimens.[35]

2. The National Comprehensive Cancer Network (NCCN)

The National Comprehensive Cancer Network recommends Oncotype DX for patients with tumours that are hormone receptor-positive, HER2 negative, >5mm regardless of pathologic grade or unfavourable features. The recommendation was category 2A.[36]

3. The Ontario Health Technology Assessment Series 2010. '*Gene expression profiling for guiding adjuvant chemotherapy decisions in women with early stage breast cancer*'

In women with newly diagnosed early breast cancer that is ER and/or PR positive, HER-2/neu negative, and lymph node negative who are being treated with tamoxifen (or an aromatase inhibitor such as anastrozole for postmenopausal women): Access to Oncotype DX should be made available to patients in the above population within the context of a field evaluation.[34]

4. Evaluation of Genomic Applications in Practice and Prevention (EGAPP) working group: *'Can tumor gene expression profiling improve outcomes in patients with breast cancer?'* The existing clinical studies provide clinical validation for the ability of Oncotype DX assay to predict tumor recurrence and response to chemotherapy; however the data is considered insufficient to draw strong conclusions regarding the clinical utility of the assay for guiding treatment decisions for patients with early-stage invasive breast cancer. [37]

Burden of disease

The National Cancer Registry of Ireland in 2008 identified 1500 women with lymph node-negative breast cancer in 2008. Most have hormone receptor (HR)-positive breast cancer and are adequately treated with endocrine therapy alone however some will benefit from chemotherapy. The National Surgical and Adjuvant Breast and Bowel Project (NSABP) trials B-14 and B-20 enrolled nearly 5000 women with node negative, HR-positive breast cancer and demonstrated that patients treated with tamoxifen alone after surgery had an average 10-year distant recurrence rate of 15%.[1] Therefore, for 85% of this population, hormonal treatment was adequate systemic therapy and the treatment associated adverse effects and costs of chemotherapy could potentially have been avoided. The absolute benefit associated with the addition of chemotherapy was about 4%.[1] While these data indicate that the majority of patients did not require chemotherapy in addition to endocrine therapy identifying these patients has remained a challenge.

Decisions regarding adjuvant chemotherapy are based on prognosis i.e. risk of breast cancer recurrence, and on the likelihood of benefiting from treatment. A risk of distant recurrence of ≥ 10% is often used as the threshold at which systemic adjuvant chemotherapy is recommended. Tumor size and nodal status are important independent prognostic factors for survival for early stage breast cancer. Other important prognostic factors include histological grade (based on morphological features of the tumor), ER, PR (progesterone receptor), HER2 (human epidermal growth factor receptor 2), and the presence of lymphovascular invasion. A number of consensus and evidence-based guidelines produced by the National Comprehensive Cancer Network (NCCN)[36] the National Institutes of Health (NIH) Consensus Development criteria [38] and the St. Gallen expert opinion criteria [39] provide recommendations on the use of adjuvant chemotherapy in early breast cancer based on clinical data and tumor characteristics.

Adjuvant! Online (www.adjuvantonline.com) is a widely used freely available web-based tool. It considers multiple clinical and pathological factors and produces estimates for recurrence and mortality. In addition this program incorporates the effect of co-morbid conditions in the determination of prognosis and benefit from various therapeutic interventions. Adjuvant! Online has been independently validated by Canadian investigators and the concordance with actual recurrence and mortality rates was within 1% of predictions based on this model.[40,41]

Recently a number of prognostic tests have been developed using gene expression profiling. The most widely used commercially available test in the US is Onco*type* DX (Genomic Health Inc, Redwood City, CA). This reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assay is intended for use in HR-positive lymph node-negative, HER2-negative breast cancer patients who will receive 5 years of tamoxifen. It measures the gene expression of 16 cancer-related genes (including ER, PR, HER2 and Ki67) in paraffin-embedded tumor tissue and using a regression model calculates a recurrence score (RS) that is an estimate of the risk of developing a

distant metastases at 10 years. Two suggested cut-off points categorize patients into low (RS<18), intermediate (RS≥18<31) and high (RS≥31) risk groups corresponding to 6.8%, 14.3% and 30.5% risk of distant recurrence at 10 years after 5 years of tamoxifen therapy, respectively. These risk estimates represent the range of distant recurrence rates for HR-positive, node-negative breast cancers treated with 5 years of tamoxifen. [42]

Status of Oncotype-DX in Ireland

Through the All Ireland Cooperative Oncology Research Group (ICORG) Irish patients had access to Oncotype-DX testing as part of the Eastern Cooperative Oncology Group (ECOG) sponsored TAILORx (Trial Assigning Individualized Options for Treatment) trial. The trial opened in Ireland in Nov. 2007 and closed to accrual in August 2010. A total of 689 patients were accrued from institutions across Ireland making Ireland one of the highest accruing countries to this study. There has been no funding made available for Oncotype-DX testing since closure of the study. The current cost of the test is €3180.

ISMO Evidence-Based Guideline

A systematic review was undertaken to specifically address the following questions;

(1) What is the laboratory performance of Oncotype-DX
(2) How accurate is Oncotype-DX as a prognostic factor for distant recurrence?
(3) How accurate is Oncotype-DX as a predictive factor for therapeutic benefit?
(4) How does Oncotype-DX compare to other prognostic/predictive factors such as tumour size, grade, patient age or other integrated decision aids?
(5) How do patients and physicians view Oncotype-DX in clinical practice?
(6) What are the cost implications of Oncotype-DX?

Methods

Data Sources and Searches

A systematic search of the literature was conducted to address the above questions. MEDLINE (from 1996) and EMBASE (from 1980) were searched using the medical subject heading (MeSH) "Gene expression profiling" and the following text terms; *21-gene assay, recurrence score, RT-PCR assay, Oncotype DX, breast neoplasm"*

Further relevant studies were identified by hand searching the references from original and review articles. Abstracts published in the proceedings of the annual meetings of the American Society of Clinical Oncology (ASCO), the San Antonio Breast Cancer Symposium and St Gallen breast cancer conference were reviewed.

Statistical Analysis

The pre-test probability for a distant recurrence was taken from the trial outcome; if a clinical trial reported a disease-free survival of 85% it was estimated that a patient meeting the trial entry criteria had a risk of distant recurrence of approximately 15%. In practice conventional clinicopathological parameters and decision aids are available for refining risk estimates so selecting the pre-test probability may underestimate an oncologist's ability to make risk estimates. The usefulness of Oncotype-DX is determined by the accuracy with which it can predict patients who will develop a distant recurrence from those who will not. The accuracy measure used in this guideline is the likelihood ratio (LR), i.e. how likely is a high recurrence score among patients who develop a distant recurrence and how likely is a high recurrence score among patients who do not develop a distant recurrence? The ratio of these two likelihoods is the

likelihood ratio and it is used throughout this guideline. A likelihood ratio of 1 indicates that a test provides little information beyond the pre-test probability.

Study Selection

All validation studies examining the prognostic and predictive accuracy of Oncotype-DX were reviewed. Studies including abstracts that allowed calculation of the test properties were selected. We also included articles that examined populations other than the population for which the test was designed e.g. node positive patients, patients receiving neoadjuvant chemotherapy and other outcomes such as loco-regional failure and breast cancer death.

Key Question 1: What is the laboratory performance of Oncotype-DX?

Three studies examined the reliability (reproducibility and repeatability) of Oncotype-DX.[2-4] Cronin et al. conducted repeat analyses across multiple days, RT-PCR plates and instruments and observed standard deviations in the RS of <1.0 for between day, between plate and within plate analyses.[4] Another study performed repeat analyses on 60 FFPE blocks from 20 patients and reported between block SD of <2.5 for 16 of the 20 patients.[3] Paik et al. examined repeatability within and between blocks by repeating the Oncotype-DX in 5 consecutive sections from 6 FFPE blocks in 2 patients. The within block RS SD was <1.0 and the total within patient SD including within and between was 2.2 RS units. There have been no between laboratory or external reproducibility studies as testing in all validation studies was performed at Genomic Health's reference laboratory in Redwood, California.

Twelve studies reported the failure of Oncotype-DX reasons given for failure included insufficient tumor sample, insufficient RNA extracted, poor signal in the 5 reference genes.[3,5-15] Failure rates reported ranged from 2.7% to 44.9% across all studies. In practice as indicated by ISMO members failure rates have been low and may reflect use recently prepared FFPE tissue and sufficient tumor tissue is being sent for testing.

Key Question 2: How accurate is the RS as a prognostic factor for distant recurrence?

a) Tamoxifen treated node-negative patients

The NSABP B14 trial randomized 2617 women with lymph node-negative, HR-positive breast cancer to tamoxifen versus placebo.[43] Oncotype-DX was performed on 668 paraffin-embedded tumor blocks from the tamoxifen arm of the trial. The proportion of patients in the low-risk group who were free of distant recurrence at 10 years (93.2%) was significantly greater than the proportion in the high risk category (69.5%) ($P < 0.001$). [2]

In this study a high RS was 2.5 times [95% CI, 1.8-3.4] more likely to be reported in patients who developed a distant recurrence at 10 years. A low RS was about 2.4 times [LR 0.4, 95% CI 0.2.-0.6] less likely to be reported in those patients reporting a distant recurrence at 10 years. The likelihood ratio for the intermediate group [LR 0.9, 95% CI, 0.5-1.5] suggested that the test provide little additional information, however, it did indicate that these patients were not falling into the low or high risk category but somewhere in between.

The pre-test probability for the cohort for the development of a distant recurrence at 10 years was 15%. The post-test probability for high, intermediate and low risk categories were 30.6%, 14% and 6.4% respectively, demonstrating the ability of the test to categorize tumors according to risk of distant recurrence (Table 1).[17]

Pre-Test Probability (%)	Risk Category (Likelihood Ratio (95% CI))	Post-Test Probability % (range)
15	High 2.3 (1.6-3.1)	28.4 (21.8-35.1)
15	Intermediate 0.9 (0.5-1.3)	13.1 (7.6-18.7)
15	Low 0.4 (0.2-0.5)	6.2 (3.6-8.8)

Table 1 Test properties calculated for Oncotype-DX performed on 668 tumor blocks from NSABP B-14.[2,17]

The sensitivity for Oncotype-DX was 76.9% [95% CI, 75.1-80.3], indicating that about 77% of patients who develop a distant recurrence have a high/intermediate RS. The specificity was 55.4% [95% CI, 54.1-56.8] indicating that 55.4% of patients who do not have a recurrence will have a low recurrence score.

The NSABP B20 trial examined the benefit of concurrent tamoxifen and chemotherapy compared to tamoxifen alone for node negative ER positive breast cancer patients.[1] Tumor specimens from the tamoxifen only arm were used as a training set in the development of the assay and therefore test properties and prognostic ability were superior to what would be expected in an independent cohort.[16] A high RS in the tamoxifen only group was almost 5 times as likely to be reported in patients who developed a distant recurrence at 10 years [LR 4.9, 95%

CI 4.1-5.4]. A low RS was approximately four times less likely in those patients reporting a distant recurrence at 10 years [LR 0.25, 95% CI 0.0-0.5] (Table 2.).[17]

Pre-Test Probability (%)	Risk Category (Likelihood Ratio (95% CI))	Post-Test Probability % (range)
12	High 4.8 (2.5-8.6)	39.8 (25.4- 54.1)
12	Intermediate 0.7 (0.04-1.6)	9.2 (0.6 -17.7)
12	Low 0.25 (0.0-0.5)	3.2 (0.1-6.4)

Table 2. Test properties for Oncotype-DX performed on 227 tumour blocks of patients who received tamoxifen only in the NSABP B-20 study.[16,17]

There was an overall pre-test probability of 12%, however post-test probabilities were 39%, 9% and 3% for high, intermediate and low risk categories respectively (Table 2). Sensitivity was 84% [95% CI 79-98] and specificity was 65% [95% CI 62.79-68.25].

A nested case-control study was conducted by Habel et al to determine the degree to which the RS could predict the risk of breast cancer-specific mortality among HR positive node negative patients.[3] A case was a patient whose first event was death from breast cancer. At each case's death, up to three controls were randomly selected from the patients alive and under follow-up, matched for age, race, tamoxifen treatment, year of diagnosis, and treating hospital. For the 55 cases and 150 controls treated with tamoxifen the risk of death was positively associated with the RS analyzed as a continuous variable [RR 7.6, 95% CI 2.6-21.9].

Risk Category	Cases n (%)	Controls n (%)	Relative Risk (95% CI)	10-year absolute risk of breast cancer death (%)
HR positive patients treated with tamoxifen (p=0.0004)				
Low	16 (29)	95(63)	1.0 reference	2.8 (1.7-3.9)
Intermediate	22(40)	35(23)	4.0 (1.8-8.8)	10.7 (6.3-14.9)
High	17(31)	20(13)	6.2 (2.4-15.8)	15.5 (7.6-22.8)
HR positive patients NOT treated with tamoxifen (p<0.0001)				
Low	40 (36)	160 (64)	1.0 reference	6.2 (4.5-7.9)
Intermediate	32 (29)	47 (19)	2.7 (1.5-5.0)	17.8 (11.8-23.3)
High	38 (35)	44 (18)	3.3 (1.8-5.9)	19.9 (14.2-25.2)

Table 3. Relative risks of breast cancer death associated with recurrence score in Habel et al study[3]

The association between RS and loco-regional recurrence was studied in 895 tamoxifen treated patients from NSABP B-14 and B-20 trials. Loco-regional recurrence was significantly associated with RS in tamoxifen treated patients (p=<0.00001) in placebo-treated patients (p=0.022) and in tamoxifen plus chemotherapy treated patients (p=0.028).[21]

b) Untreated node negative patients

In a study by Esteva et al 149 node negative patients who did not receive systemic therapy and had a minimum follow-up of 5 years, there was no significant difference in 10-year distant recurrence-free survival (DRFS) between RS groups reported.[9] However, both HR positive and negative patients were included, follow-up was short, the sample size represented only 68% of evaluable patients and high grade tumors had improved DRFS compared to low grade tumors.

Oncotype-DX was performed on 355 patients from the placebo arm of NSABP B-14. Distant recurrence free survival at 10 years was 85.9%, 62.2% and 68.7% for the low, intermediate and high RS groups respectively.[44] The study by Habel et al included HR positive patients not treated with tamoxifen (110 cases and 251 controls). The risk of breast cancer death was associated with RS [RR 4.1, 95% CI 2.1-8.1) but not as strongly as for the tamoxifen-treated patients.[3]

c) Node positive disease treated with tamoxifen

The SWOG 8814 study randomized 1477, ER-positive, lymph node positive, patients to tamoxifen alone or tamoxifen and an anthracycline-based chemotherapy. Oncotype DX was performed on 40% of the trial population (148 tamoxifen-treated and 219 chemotherapy-tamoxifen treated). For the patients treated with tamoxifen alone the 10-year disease free survival was 60%, 49% and 43% for low, intermediate and high RS categories (p=0.017). For overall survival it was 77%, 68% and 51% (p= 0.003). The numbers of events in each risk group was small and the confidence intervals overlap for the low and intermediate groups.[13]

d) Node negative and node positive treated with anastrozole or tamoxifen

RS was examined in 1231 patients postmenopausal chemotherapy untreated women randomized to either anastrozole or tamoxifen in the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial. There were 872 women with node negative disease (432 tamoxifen-treated and 440 anastrozole-treated), and 306 with node positive disease (152 tamoxifen-treated and 154 with anastrozole-treated). The treatment arms were combined and the 9-year distant recurrence rate for women with node negative disease was 4%, 12% and 25% for the low, intermediate and high RS groups (P <0.001) and 17%, 28% and 49% (P < 0.001) for those with node positive disease.[14]

e) Node negative or positive disease treated with chemotherapy followed by hormonal therapy

The E2197 trial included 2885 evaluable patients with 0-3 positive nodes treated with four cycles of doxorubicin and cyclophosphamide or four cycles of docetaxel and cyclophosphamide followed by hormonal therapy for five years. There was no difference in disease-free survival (DFS) between treatment arms at 76 months. RS was examined in 776 patients from this trial.[45] Test properties for the node negative (n=189) and node positive (198), HER2 negative HR positive cases are shown in table 3. Since the 5-year reported DFS for this group was 90% and the follow-up for this study was 6.3 years, a pre-test probability of recurrence was estimated at between 10-20%. The low RS group (node negative and positive) had an excellent outcome with a post-test probability of between 5.5-11% depending on the pre-test probability used.

Recurrence Score	Pre-test probability (%)	Likelihood ratio	Post-test probability (%)
High risk **node negative**, HR positive, HER2 negative patients (n=189)			
High	10-20	1.6	15.1-28.7
Intermediate	10-20	1.3	12.4-24.2
Low	10-20	0.5	5.3-11.1
Node positive, HR positive, HER2 negative patients (n=198)			
High	10-20	3.73	29.3-48.2
Intermediate	10-20	1.19	11.6-22.9
Low	10-20	0.53	5.5-11.6

Table 3 Test properties for the node negative (n=189) and node positive (n=198) subset from the E2197 trial. [17,45]

Key Question 3: How accurate is Oncotype-DX as a predictive factor for therapeutic benefit to systemic therapy?

a) Adjuvant chemotherapy benefit in node negative patients receiving tamoxifen

Oncotype-DX was performed on 651 patients (28.9% of total trial cohort) from the NSABP B20 trial to determine if it could predict the magnitude of CMF (cyclophosphamide, methotrexate, fluorouracil) benefit.[16] As noted previously under key question 2 patients in the tamoxifen-only arm were used in the training set for the development of the assay and this should be considered when interpreting the results in this section as it may lead to bias towards optimization of recurrence prediction. Patients in the tamoxifen-only arm with high RS had a DRFS of 60.5 % (95% CI, 46.2-74.8). Chemotherapy in addition to tamoxifen improved DRFS to 88.1% (95% CI, 82.0-94.2). In contrast, tamoxifen-only patients with a low RS had a DRFS of 96.8% (95% CI, 83.3-92.3). The addition of CMF altered this minimally to 95.6% (95% CI, 92.7 – 98.6). A formal test for statistical interaction between a 50-point increment in continuous RS and chemotherapy was significant.

Tamoxifen 10-year DRFS % (95% CI)		**Tamoxifen + CMF** 10-year DRFS% (95% CI)	
Low RS (135)	96.8 (93.7-99.9)	Low RS (218)	95.6 (92.7-98.6)
Intermediate RS (45)	90.9 (82.5-99.4)	Intermediate RS (89)	89.1 (82.4-95.9)
High RS (47)	60.5 (46.2-74.8)	High RS (117)	88.1 (82.0-94.2)

Table 5 Distant recurrence free survival (DRFS) at 10 years for tamoxifen alone (227) and tamoxifen + CMF (424) arms of the NSABP B-20 study. [16]

b) Adjuvant chemotherapy, node positive patients receiving tamoxifen

As previously discussed, Albain et al retrospectively assessed the RS in a subset of patients from the SWOG 8814 study.[13] For patients in the tamoxifen only arm (n=124) with a low RS the 10 year disease free survival was 60% (95% CI, 40-76%). The addition of chemotherapy to this group changed DFS non-significantly to 64% (50-75%). In contrast the addition of chemotherapy to the group with a high RS resulted in a statistically significant change in DFS from 43% (95% CI, 28-57%) to 55% (95% CI, 40-67%). Oncotype-DX predicted for an overall survival advantage with the addition of chemotherapy for patients in the high risk group, but not for the intermediate and low risk groups.

c) Prediction of response to neo-adjuvant chemotherapy

Gianni *et al* studied the gene expression profiles on the pretreatment core biopsies of 89 patients with locally advanced breast cancer who received neo-adjuvant paclitaxel and doxorubicin. The RS was positively associated with the likelihood of a pathological complete response (p=0.005).[6]

d) Prediction of response to tamoxifen in node negative patients

Paik *et al* examined the ability of Oncotype-DX to predict tamoxifen benefit comparing the DRFS by RS group in the placebo and tamoxifen only arms of the NSABP B14 study.[44] There were 645 evaluable specimens (355 placebo and 290 tamoxifen-treated). Intermediate and low risk groups benefited from tamoxifen but the high risk group derived little benefit (table 4). The test properties were superior in the tamoxifen treated arm reflecting the influence of tamoxifen and estrogen responsive genes in the generation of RS.

Placebo				**Tamoxifen**		
RS group	**Pre-Test Probability (%)**	**Risk Category (Likelihood Ratio)**	**Post-Test Probability % (range)**	**Pre-Test Probability (%)**	**Risk Category (Likelihood Ratio)**	**Post-Test Probability % (range)**
High	25	1.4 (0.9-2.1)	31.8 (22.2-41.5)	15	2.2 (1.2-3.4)	27.6 (17.8-37.8)
Inter	25	1.9 (1.1-2.9)	38.3 (27.3-49.5)	15	1.3 (0.6-2.2)	18.8 (9.6-28.3)
Low	25	0.5 (0.3-0.7)	14.4 (8.8-19.9)	15	0.4 (0.1-0.6)	6.3 (2.2-10.2)

Table 4. Predictive ability of Oncotype-DX using specimens from the placebo (n=355) and tamoxifen-treated (n=290) arms of the NSABP B-14 study.[17]

Key Question 4: How does Oncotype-DX compare to other prognostic/predictive factors such as tumor size, grade, patient age or integrated decision aids such as Adjuvant!?

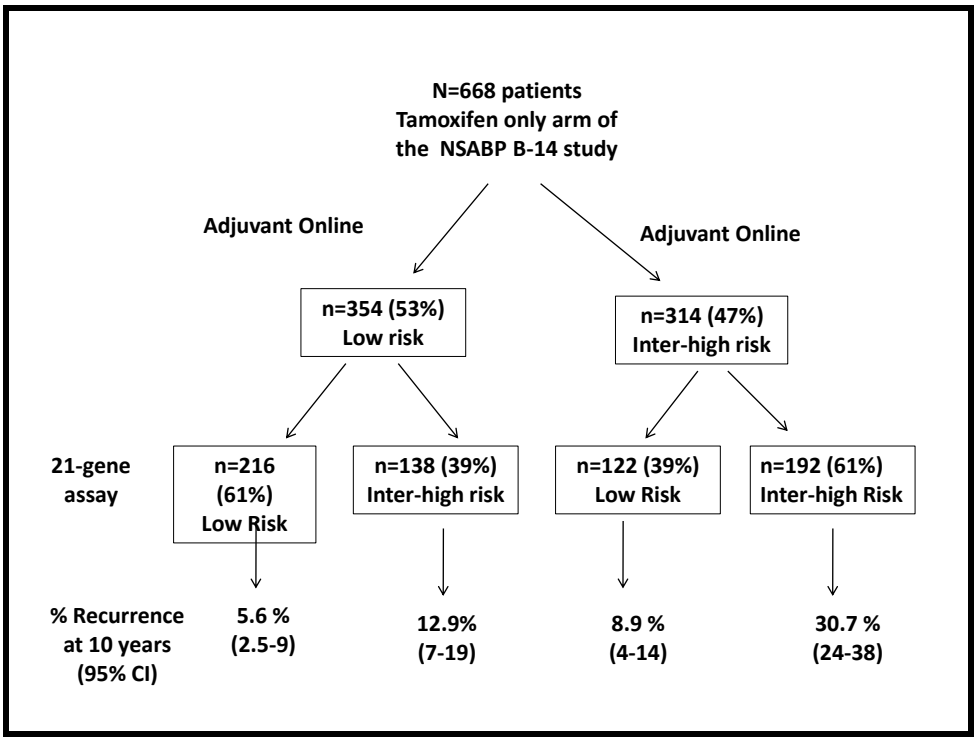
a) Adjuvant Online (AOL) and Oncotype DX

Oncotype DX generates an estimate for the risk of distant recurrence (metastatic disease). In contrast, risk estimates generated by AOL include all causes of recurrence (local, regional, contralateral and distant recurrence). As a result recurrence risks are generally higher for AOL compared to Oncotype DX.[40]

Bryant et al reclassified the 668 patients from the tamoxifen only arm of NSABP B-14 study using AOL (Fig 1).[24] Patients classified by both tests as low risk had 10 year distant recurrence rate of 5.6 % [95% CI 2.5-9]. If AOL classified a patient as intermediate/high risk and Oncotype-DX reclassified them as low risk the 10 year recurrence rate was 8.9 % [95% CI 4-14)]. The confidence intervals here are wide and suggest that there may be patients who would benefit from additional therapy. If both tests classified a patient as high risk the 10 year recurrence rate was 30.7 [95% CI 24-38]. If AOL classified a patient as low risk, but the 21 gene assay indicated intermediate to high risk, the 10 year recurrence rate was 12.9 [95% CI 7-19].

The prognostic utility of Oncotype-DX compared to an algorithm similar to AOL but modified for outcome at 5 years and referred to as the Integrator was examined using 465 patients from the ECOG E2197 trial.[12] There was poor concordance between predictions made by RS and the Integrator using either risk group or risk percentile classification for comparison and using both local and centrally determined tumor grade. In a proportional hazards model that included only RS and the Integrator risk percentiles, only RS remained statistically significant and the RS by Integrator interaction term was significant, indicating that the RS was independent of Integrator risk.

The discriminatory ability of RS as demonstrated by ROC curves was superior. There was an increase in the relative risk of recurrence of four fold for a patient classified as low risk by the Integrator, but with a high RS. In addition, for patients with low RS and classified as high risk by the Integrator the relative risk was increased 3.15 fold. Both tests provided information that was independent of and in addition to the other. A further study involving postmenopausal women with node negative or positive disease treated with hormones (tamoxifen or anastrozole) only, found the RS and AOL were independent predictors of distant recurrence and relapse respectively. Correlation was weak between the tests ($r=0.234$).[14] Currently the genomic version of AOL incorporates the RS.



The figure 1 shows estimates of risk for breast cancer recurrence in the tamoxifen-only arm of the NSABP B-14 study and reclassification of risk using Oncotype-DX and estimates of 10 year risk of distant recurrence.[24]

Comparison of the prognostic and predictive utility of Oncotype-DX compared to Adjuvant! in node-negative, ER-positive breast cancer was studied recently including 668 tamoxifen-treated NSABP B-14 patients, 227 tamoxifen-treated NSABP B-20 patients, and 424 chemotherapy plus tamoxifen-treated B-20 patients. Adjuvant! results were also available from 1952 B-20 patients.[25] The primary endpoint was distant recurrence-free interval (DRFI). Both RS ($P < 0.001$) and Adjuvant! ($P = 0.002$) provided strong independent prognostic information in tamoxifen-treated patients. Combining RS and individual clinicopathologic characteristics provided greater prognostic discrimination than combining RS and the composite Adjuvant!. In the B-20 cohort with RS results (n = 651), RS was significantly predictive of chemotherapy benefit (interaction $P = 0.031$ for DRFI, $P = 0.011$ for overall survival [OS], $P = 0.082$ for disease-free survival [DFS]), but Adjuvant! was not (interaction $P = 0.99$, $P = 0.311$, and $P = 0.357$, respectively). However, in the larger B-20 sub-cohort (n = 1952), Adjuvant! was significantly predictive of chemotherapy benefit for OS (interaction $P = 0.009$) but not for DRFI ($P = 0.219$) or DFS ($P = 0.099$). Prognostic estimates can be optimized by combining RS and clinicopathologic information.[25]

b) Multivariate Analyses examining RS in models with individual clinicopathological factors

In multivariate models using tumor tissue from NSABP B-14, RS, age at surgery, tumor size, grade (moderate and high), HER2 amplification, and ER, the RS and high tumor grades were significant predictors of distant recurrence.[2] In the E2197 subset, RS was a significant predictor of recurrence, for node-positive and negative cases and for the HER2-negative subset.[12] In Cox proportional hazards models for recurrence, when RS, centrally determined tumor grade, HER-2 expression, tumor size, age and number of positive nodes were examined, only two to three positive nodes, young age and grade remained significant predictors, and there was a trend towards significance for RS (HR for a 50-point difference in RS=2.12; 95% CI, 0.97 to 4.65; P=.06, linear trend test). However, RS was a significant predictor when locally determined grade was used. In a model with only HER-2 negative patients, RS was not predictive, regardless of whether the tumor grade was determined locally or centrally. In contrast in the Habel et al study, in models with RS, tumor size and grade, only RS and tumor size retained statistical significance as predictors of breast cancer mortality. In the tamoxifen untreated patients, grade, size and RS were all significant predictors of breast cancer mortality when included in one model.[3] In 872 postmenopausal women with node negative disease who received no chemotherapy and were randomized to anastrozole or tamoxifen a model adjusted for age and treatment and including centrally determined tumor grade, found tumor size ($P < 0.001$) and RS ($P < 0.001$) were significant predictors of recurrence.[14]

Key Question 5: How do patients and physicians view Oncotype-DX in clinical practice?

In a prospective multicenter study 89 patients were assessed by 17 medical oncologists prior to and after Oncotype-DX testing. The medical oncologist treatment recommendation changed for 28 patients (31.5%). Twenty-four patients (27%) changed their treatment decision. The largest change after the RS results was conversion from the medical oncologist's pre-test recommendation for chemotherapy plus hormonal therapy to post-test recommendation for hormone therapy in 20 cases (22.5%). Nine patients (10.1%) changed their treatment decision from chemotherapy plus hormones to hormone therapy. Patient satisfaction was high. Ninety five percent were glad they had taken the test. There was also a significant reduction in conflict over treatment decisions, a reduction in anxiety scores, greater patient satisfaction and increased confidence with their choice of adjuvant therapy after taking the test. About 76% of medical oncologists involved in their care also found that Oncotype-DX increased their confidence in treatment recommendation.[26]

A retrospective study conducted in a community-based oncology practice included 74 patients fitting the target population examined whether the RS influences clinicians' treatment recommendations and eventual treatment. Treatment recommendations before the RS knowledge were compared with treatment recommendations after RS knowledge and to the treatment eventually administered. For 21% and 25% of patients, knowledge of the RS changed the clinicians' treatment recommendations and eventual treatment, respectively.[8]

In a study by Assad et al that involved retrospective chart review 85 women who had an Oncotype-DX performed they observed that Oncotype-DX influenced the treatment decision to provide or withhold adjuvant chemotherapy in 44% (n=37) of women.[27] A further study by Lillie et al suggested that health literacy affected retention of information about Oncotype-DX but not the desire for information regarding it. Interviews conducted in 163 stage I or II breast cancer patients who had completed adjuvant chemotherapy and/or were receiving adjuvant hormone. [28]

Overall there is little prospective data on the impact of Oncotype-DX on decision making on patients and physicians choices. This is important particularly for patients assigned to the intermediate RS group. A retrospective cohort study from a US academic tertiary referral center assessed the clinical utility of the RS in patients with breast cancers considered clinically intermediate.[29] A substantial number of cases where clinical pathologic variables yield equivocal risk, Onco*type* DX also returned intermediate risk estimates (40%) (60% if TAILORx cutoffs are used). In these instances, it is uncertain to what extent, if any, the test provided useful information. Medical decision making ultimately happens in a dichotomous decision space that

includes either choosing a treatment (i.e. adjuvant chemotherapy) or withholding it, therefore tests that yield 3 risk categories will inevitably yield a certain proportion of indeterminate results for decision making purposes.

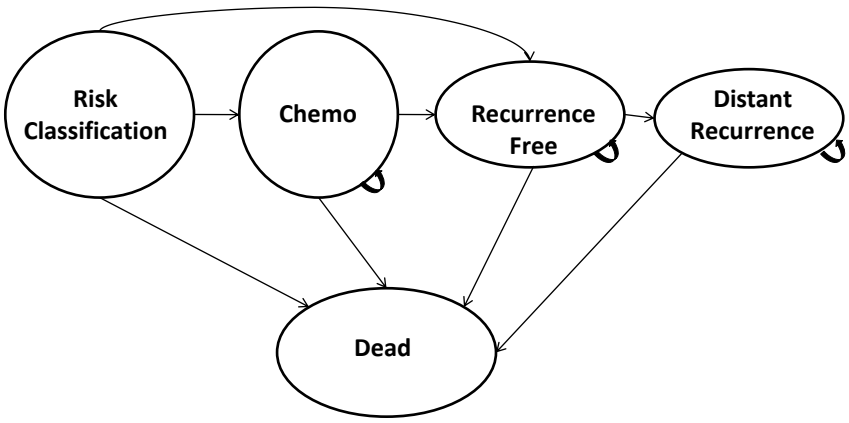
To address the important question of what constitutes the most effective therapeutic strategy for patients in the intermediate RS risk category, a large randomized clinical trial was conducted and recently closed to accrual. The objective of the Trial Assigning Individualized Options for Treatment (TAILORx) is to determine whether adjuvant hormonal therapy alone is not inferior to adjuvant chemotherapy followed by hormonal therapy for patients with an intermediate RS. It is important to note that the RS cut-offs for TAILORx have been modified so an intermediate RS is a score between 11 and 25.[46] This broadens the patient population that is considered intermediate risk compared to the original Onco*type* DX cut-offs.

The Onco*type*-DX report indicates percentage risk of distant relapse at 10 years after 5 years of tamoxifen therapy on a continuous scale, therefore patients and physicians can use this point estimate to make an individualized decision about adjuvant chemotherapy. This approach in theory, allows for adjusting treatment recommendations to the risk tolerance of individual patients. Different individuals may feel comfortable with different levels of risk of recurrence when stacked against the inconvenience, cost and side effects of adjuvant chemotherapy. However, in reality it is hard to quantify to what extent risk estimates between 10% to 20% risk of relapse (corresponding to the intermediate risk cohort with RS scores of 18-31) help patients making an informed decision versus increase their anxiety over a difficult and non-trivial, potentially life-saving health care choice. This aspect of shared medical decision making, how patients perceive and benefit from outcome estimates that involve predictions on a continuous scale when results are far from the extreme (i.e. very bad or very good prognosis), is understudied.

Key Question 6: What are the cost implications of Oncotype-DX?

Tsoi *et al* recently conducted a cost effectiveness analysis from a public-payer perspective in Ontario, Canada and found Oncotype guided treatment to be cost effective ($63,000 Canadian dollars per QALY) versus Adjuvant! Online guided treatment.[33] The analysis was adopted and built upon by Ontario Ministry of Health and Long Term Care MOHLTC.[34]

Figure 2 Schematic of Markov model, adapted from Tsoi et al. 2010



The revised analysis assumed (a) that all patients are first classified as low, intermediate or high risk using AOL (or equivalent clinical) (b) Oncotype-DX may be targeted at specific AOL risk groups (c) the RS provided by Oncotype-DX is used only to identify patients as low, intermediate or high risk (rather than considered on a continuous scale) (d) chemotherapy may be targeted at specific AOL risk groups and (where applicable) combined AOL/Oncotype risk groups; and (e) only a single chemotherapy regimen is considered for any particular AOL or combined AOL/Oncotype-DX risk group. The analysis considered a lifetime horizon. In the first cycle of the Markov model illustrated in figure 2 each patient is classified as low, intermediate or high risk using AOL and if applicable Oncotype-DX and a decision is made as to whether the patient requires chemotherapy. If chemotherapy is given the patient enters the 'chemo' state for 6 months before entering the 'recurrence-free state'. If chemotherapy is not given the patient enters the 'recurrence-free; state. If a patient develops a distant recurrence she

immediately enters the 'distant recurrence' state. At anytime a patient may die and enter the 'dead' state.

The outcome of interest was the per-patient lifetime QALYs associated with each strategy. Cost estimates were in Canadian dollars using an inflation rate of 1.6% and the cost of Oncotype-DX was $4191 CAD as of August 2010. Table 5 summarizes the results.

Patients receiving Oncotype-DX	Cost	QALYs	ICER (per QALY)
No patients	$13,298	13.34	N/A
AOL high risk only	$13,660	14.04	$518
AOL intermediate/high risk only	$13,961	14.42	$795
All patients	$17,466	14.64	$23,983

Table 5 Summarized results of the base case analysis.[34]

The analysis implies that it is cost-effective to provide Oncotype-DX to all patients at any willingness to pay for a QALY. At a willingness to pay of $75,000 dollars per QALY the probabilistic sensitivity analysis found that the probability that Oncotype-DX is cost effective is 83.5% for patients identified as AOL low risk, 99.8% for patients identified as AOL intermediate risk, and 65.8% for patients identified as AOL high risk. The MOHLTC concluded that Oncotype-DX was cost effective for all patients irrespective of the AOL risk group. The model does not account for local recurrence or long-term adverse effects from chemotherapy.

Hornberger *et al* conducted a cost-utility analysis using the RS in patients classified as having a low or high risk of distant recurrence based on NCCN risk criteria.[31] Two scenarios were considered involving patients with lymph node-negative, estrogen receptor-positive early stage breast cancer expected to receive 5 years of hormonal therapy: patients classified as high risk (tumor size >1cm, or for smaller tumors if associated high risk features) or low risk by NCCN risk criteria. Oncotype-DX was then used to reclassify these patients independently based on results from the NSABP B-14 data. The assumption was that all patients assigned as intermediate/high risk by the RS would undergo chemotherapy and all patients assigned as low risk by the RS would not receive chemotherapy. Both taxane-containing and non-taxane containing regimens were considered. Cost estimation included cost of drug, infusion, patient time, use of colony-stimulating factors (CSF) and management of chemotherapy-related side effects. The analysis considered survival, quality of life and costs from a societal perspective. At baseline values, the RS applied to 100 potential patients predicted an increase in quality-adjusted survival by 8.6 years while reducing overall costs by US$202,828.

Lyman *et al* incorporated the extended validation results for its predictive accuracy into an economic model to guide the use of adjuvant systemic therapy in patients with node-negative, HR positive early stage breast cancer.[30] Three adjuvant treatment strategies were compared: (1)

treat all patients with chemotherapy followed by tamoxifen (2) treat all patients with tamoxifen alone and (3) treat patients by RS-guided therapy with low risk patients receiving tamoxifen only and intermediate and high risk patients receiving chemotherapy and tamoxifen. RS-guided therapy was found to be associated with a gain in individual life expectancy of 2.2 years compared with tamoxifen alone, and it was associated with similar life expectancy to that seen with the chemotherapy and tamoxifen strategy. An estimated net cost savings of $2,256 per patient with RS-guided therapy was seen compared with chemotherapy and tamoxifen with an incremental cost-effectiveness ratio of $1,944 per life year saved compared with tamoxifen alone. Cost estimation included five commonly used adjuvant chemotherapy regimens (Doxorubicin cyclophosphamide x 4, dose dense (dd) doxorubicin cyclophosphamide x4 with CSF, doxorubicin cyclophosphamide -docetaxel x 8, dd doxorubicin cyclophosphamide -docetaxel x 8 with CSF, docetaxel doxorubicin cyclophosphamide x 6 with CSF). The estimated cost saving was likely an underestimation as only drug cost was included in the analysis, and no indirect costs associated with chemotherapy were considered.

A recently published cost effectiveness analysis compared RS guided treatment with either treatment guided by the NCCN guideline or St Gallen recommendation in the context of Japan's health care system. It concluded that RS guided treatment was cost effective, quoting incremental cost effectiveness ratios of US$ 26,065 per quality adjusted life year (QALY) compared with NCCN guided treatment, and US$ 10,774/QALY compared with St Gallen guided treatment. Both were well under the suggested social willingness-to-pay for one life year gain from an innovative medical intervention in Japan of US$ 52,174/QALY.[32]

Discussion

The evidence provided in this guideline was based on systematic review of the literature. Overall it was considered that the Oncotype-DX assay was well validated and offered additional prognostic information to patients and physicians that would assist clinical decision making regarding adjuvant chemotherapy in the target population (i.e. patients with lymph node negative, hormone receptor positive, HER-2/neu-negative breast cancer who will receive tamoxifen or an aromatase inhibitor). All studies were retrospective in design however with respect to the studies using prospectively collected tumor tissue from randomized controlled trials this is increasingly considered a valid approach to biomarker validation.[23,47] There was evidence to suggest patients with a high RS benefited more from the addition of chemotherapy compared to the low and intermediate RS groups. However these studies had several limitations as discussed. The studies by Paik et al[16] in lymph node negative patients and by Albain et al[13] in lymph node positive patients will need to be reproduced in independent cohorts using similarly designed studies.

We reviewed studies examining populations other than the target population e.g. lymph node positive breast cancer, patients receiving neoadjuvant chemotherapy, and outcomes other than distant recurrence free survival e.g. local recurrence. However the data was limited and additional studies are required before Oncotype-DX can be recommended in these groups.

Several studies compared prognostic utility of Oncotype-DX to Adjuvant Online! Both of which provide estimates for risk of relapse at 10 years. Correlation between the two tests was weak to modest.[12,14,29] This is likely explained by the fact that Adjuvant! derives its risk estimates from several important clinical and pathological variables that are not captured by Oncotype-DX, including tumor size, grade and nodal status. Oncotype-DX, considers proliferation activity and HER2 and ER expression as highly quantitative continuous variables and therefore uses these markers more efficiently than Adjuvant! The modest correlation between these two independently validated tools and the important methodological differences between the prediction models suggests that a formal combination of the two may provide the most accurate risk prediction. One study demonstrated the complementary nature of the tools by showing that Adjuvant! could correctly re-stratify patients within Oncotype-DX recurrence core groups, whereas the RS could also re-stratify patients within Adjuvant! risk groups.[12] We recommend that both decision tools are used when discussing treatment options with patients.

Many studies constructed multivariate models and included traditional clinical and pathological biomarkers as covariates in addition to the RS. Interpretation of the results of these models is limited for several reason; failure to include important clinical and pathological covariates in addition to RS, conversion of continuous covariates such as age, tumor size and nodal status into dichotomous variables, modeling of RS against individual clinical or pathological biomarkers

and not modeling them all together, by the frequent inclusion of the continuous RS with a 50 point increment when in practice decisions are not made using this wide increment rather categories with narrow RS intervals. None of the studies adequately controlled for HER-2 status. Patients with HER2-positive disease would not be eligible for Oncotype-DX testing and as reported in the Paik et al [2] study 50 of the 55 patients with HER2-positive breast cancer were classified as having a high RS. In the Goldstein et al [12] study when patients with HER2-positive breast cancer were removed and prognostic value of the RS (modeled as a 50-point increase in continuous Oncotype-DX RS) was no longer statistically significant.

Qualitative studies examining the impact of the test on patients and physicians although limited are encouraging and suggest significant user satisfaction. One study found performing Oncotype-DX influenced the treatment decision to provide or withhold adjuvant chemotherapy in 44% of patients.[27]

The available evidence indicates decisions based on RS-guided therapy were associated with increased quality adjusted survival and improved cost-effectiveness.[30-34] These studies included two Canadian cost effectiveness analyses conducted from a public payer perspective and may be most applicable to the Irish health care system. Both found the test to be cost effective and one concluded it to be so across all adjuvant online risk groups.[34]

While there is no published cost effectiveness analysis from the Irish health care perspective we can make some broad assumptions on the likely impact making the test available to the target population would have on the health budget; The National Cancer Registry of Ireland identified 1,500 women diagnosed with lymph node-negative breast cancer in Ireland in 2008. Assuming 75% will be ER-positive and HER-2/neu negative there are an estimated 1,125 cases for which Oncotype-DX might be considered. The test costs €3180 and if the uptake of Oncotype-DX in such patients was one third the total budget impact would be €893,580 per annum. This does not factor in the direct and indirect cost saving for patients who do not receive chemotherapy as a result of performing the test, or the avoidance of early and late chemotherapy-related adverse affects in patients who may otherwise have received chemotherapy.

There are currently a number of prognostic and predictive tests in various stages of development for the target population. Interesting data recently presented but yet to be validated showed that a composite prognostic profile using traditional immunohistochemical markers but measured centrally could provide quantitatively equivalent information as Oncotype-DX to clinical information.[48] ISMO is committed to updating this evidence-based guideline as additional validation studies report and new prognostic and predictive tests are developed.

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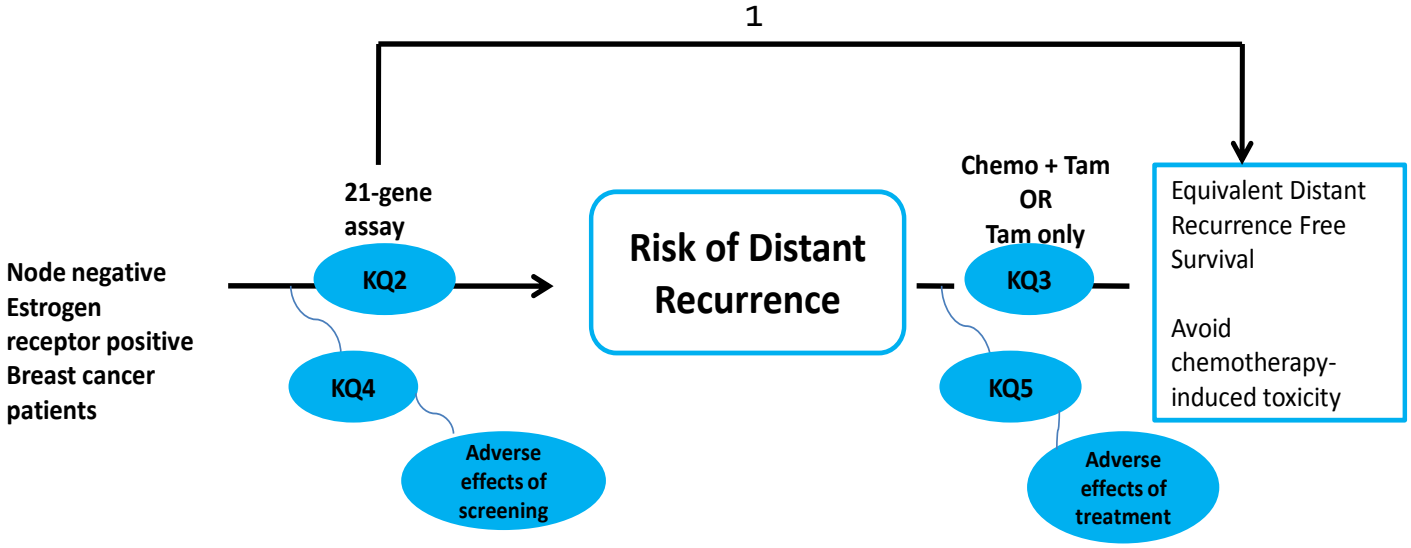
Analytic Framework for Screening with Oncotype DX Genomic Diagnostic Test for Recurrence Prognosis and Therapeutic Response Prediction in Node-Negative, Estrogen Receptor-Positive Breast Cancer.



Key question 1: *Is there direct evidence that screening node negative estrogen receptor positive breast cancer patients with the 21-gene assay will lead to equivalent distant recurrence free survival?*
Key question 2a: ***As a prognostic test what are the test properties i.e. Likelihood ratio's, sensitivity and specificity?***
Key question 2b: As a predictive test what are the test properties i.e. Likelihood ratio's, sensitivity and specificity?
Key question 2c: As a prognostic test how does it compare to other prognostic factors such as grade, tumour size, patient age etc?
Key question 3: Does treating this population on the basis of recurrence score result in equivalent distant recurrence free survival, delivery of chemotherapy to those who will derive maximum benefit and avoid toxicity in those who would derive little or no benefit?
Key question 4: ***Does screening with this diagnostic test in this population result in harm?***
Key question 5: *Does treating this population with hormones plus chemotherapy compared to hormones alone result in to equivalent distant recurrence free survival?*

Appendix 2 Search Strategy

Database: Ovid MEDLINE(R) <1996 to Jan 2011>
Search Strategy:

1 exp Breast Neoplasms/ (106227)
2 ((breast * or mammar*) adj2 (cancer* or adenocarcinoma* or neoplas* or tumo?r* or carcinoma*)).ti,ab. (8862)
3 1 or 2 (112377)
4 exp Early Diagnosis/ (8549)
5 (early or primary or stage I or stage 1 or stage II* or stage 2* or stage III* or stage 3*).ti,ab. (1000729)
6 4 or 5 (1003763)
7 3 and 6 (25823)
8 exp Carcinoma, Intraductal, Noninfiltrating/ (2755)
9 (dcis or ductal carcinoma in situ).ti,ab. (3398)
10 8 or 9 (4828)
11 7 or 10 (29550)
12 exp Gene Expression Profiling/ (52135)
13 (expression profil* or prognos* profil* or predict* profil* or mRNA expression or real-time polymerase chain reaction or reverse transcriptase polymerase chain reaction or RT-PCR or qRT-PCR or microarray* or predict* assay or prognos* assay or expression assay or predict* signature or prognos* signature or expression signature or gene signature or prognos* expression or predict* expression or gene classifier or molecular signature).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (265690)
14 (oncotype or oncotypedx or nuvoselect or rotterdam signature or metastasis score or two gene ratio or 2 gene ratio or h?i ratio or h?i test or h?i test or h?i ratio or mammaprint or 21 gene assay or 14 gene signature or 76 gene assay or 70 gene profile or two-gene expression ratio or 76 panel or breast cancer gene expression ratio or HOXB13?IL17BR or bioclassifier or invasiveness gene signature or IGS or Sorlie-Perou classifier or theros or breast cancer index).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (1594)
15 or/12-14 (267112)
16 11 and 15 (2304)
17 limit 16 to (english language and humans and yr="2006 -Current") (1213)