Genetics inMedicine | EGAPP RECOMMENDATION STATEMENT

Recommendations from the EGAPP Working Group: does the use of Oncotype DX tumor gene expression profiling to guide treatment decisions improve outcomes in patients with breast cancer?

Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group*

This recommendation statement is a product of the independent EGAPP Working Group. Although the Centers for Disease Control and Prevention (CDC) provides support to the EGAPP Working Group, including staff support in the preparation of this document, recommendations made by the EGAPP Working Group should not be construed as official positions of the CDC or the US Department of Health and Human Services.

Summary of Recommendations: The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group found insufficient evidence to recommend for or against the use of Oncotype DX testing to guide chemotherapy treatment decisions in women with hormone receptor–positive, lymph node–negative, or lymph node–positive early breast cancer who are receiving endocrine therapy. This recommendation statement updates a 2009 EGAPP statement on the use of gene expression profiling tests in breast cancer. Evidence of clinical validity for Oncotype DX was confirmed as adequate. With regard to clinical utility, although there was evidence from prospective retrospective studies that the Oncotype DX test predicts benefit from chemotherapy, and there was adequate evidence that the use of Oncotype DX gene expression profiling in clinical practice changes treatment decisions regarding chemotherapy, no direct evidence was found that the use of Oncotype DX testing leads to improved clinical outcomes.

Rationale: In women with early-stage invasive breast cancer, gene expression profiling is increasingly being used as an aid to estimate the likely benefit from chemotherapy treatment. In a previous recommendation statement, the EGAPP Working Group (EWG) found adequate evidence for clinical validity of some gene expression profiling tests in predicting distant disease recurrence in women with early-stage, hormone receptor–positive, lymph-node-negative breast cancer who are treated with tamoxifen, but insufficient evidence that use of these tests for decisions about chemotherapy treatment has clinical utility. The current recommendation statement updates these findings for Oncotype DX and extends them to the population of women with lymph node–positive disease, using evidence from recent systematic reviews and other sources.

Analytic validity: The previous recommendation statement found that evidence was inadequate to enable quantitative determination of the analytic validity of Oncotype DX. Analytic validity was not reconsidered in the updated recommendation statement because there remains no gold-standard test for comparison.

Clinical validity: The EWG found that new evidence published since the original evidence review supports the clinical validity of Oncotype DX in predicting risk of distant metastases in women with hormone receptor–positive, early-stage breast cancer that is either node-negative or node-positive.

Clinical utility: No direct evidence was found that use of Oncotype DX tumor gene expression profiling to guide treatment decisions improves clinical outcomes in women with early breast cancer. There is indirect evidence, from prospective retrospective studies on archived tissue samples from randomized controlled trials, that the Oncotype DX test can predict benefit from chemotherapy. Large, prospective, randomized, controlled trials currently in progress may provide evidence of clinical utility.

Contextual issues: Until definitive evidence for clinical utility is available, clinicians must decide on a case-by-case basis whether to offer the test to patients. Although Oncotype DX testing has been reported, on the basis of economic modeling studies, to be cost-effective in several different health-care systems and to save costs in the US health-care setting, studies were based on assumptions regarding the clinical utility of the test that require confirmation by clinical trial results.

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Key Words: breast cancer; 21-gene; gene expression profile; Oncotype; recurrence; tumor gene expression

CLINICAL CONSIDERATIONS

This recommendation statement is an update to the 2009 EGAPP recommendation on breast cancer gene expression profiling.[1]

Definitions used by EGAPP

- Analytic validity refers to a test's ability to accurately and reliably measure the genotype or analyte

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of interest—in this case, the expression of mRNA by breast cancer tumor cells.
- Clinical validity defines the ability of the test to accurately and reliably identify or predict the intermediate or final outcomes of interest. The clinical validity of Oncotype DX is the prognostic accuracy of the test in predicting outcomes such as distant disease recurrence, overall survival, and disease-free survival.
- Clinical utility defines the balance of benefits and harms associated with the use of the test in practice. For Oncotype DX, clinical utility was interpreted as the balance of benefits and harms arising from use of the test to predict likely benefit from chemotherapy treatment and to guide treatment decisions. This included any value added, in terms of improving clinical outcomes, due to changes in decision making based on risk reclassification.

Patient population under consideration

These recommendations apply to women diagnosed with stage I or II, hormone receptor (HR)–positive, human epidermal growth factor receptor 2 (HER2)–negative, lymph node–negative (LN–), or lymph node–positive (LN+) breast cancer who are receiving endocrine therapy.

Considerations for practice

- National Comprehensive Cancer Network (NCCN) and other clinical guidelines recommend use of Oncotype DX testing in specific patient populations as an aid to decisions regarding adjuvant chemotherapy. The test is now in use in many clinical centers.[2,3] However, until definitive evidence for clinical utility is available, clinicians must decide on a case-by-case basis whether to offer the test to individual patients.
- If the test is offered, careful discussion and provision of educational materials are required to ensure that patients understand the limitations of the test and the potential harms and benefits resulting from its use.

BACKGROUND AND CLINICAL CONTEXT FOR THE RECOMMENDATION

Breast cancer is the most common cancer and the second leading cause of cancer-related death in women in the United States; approximately 232,000 new cases and 40,000 deaths were estimated for 2013.[4] In women with HR+ breast cancer, postoperative treatment with tamoxifen improves survival and reduces recurrence rates.[5,6] Currently, most breast cancer patients in the United States receive adjuvant chemotherapy treatment. For early-stage invasive breast cancer, regimens include CMF (cyclophosphamide, methotrexate, and 5-fluorouracil), anthracycline-based regimens (doxorubicin or epirubicin, with cyclophosphamide), and anthracycline-based regimens supplemented with taxanes (paclitaxel or docetaxel).[7] Results from the Early Breast Cancer Trialists' Collaborative Group meta-analysis suggest that the most effective chemotherapy regimens reduce recurrence risk on average by approximately one-third, regardless of tumor characteristics or tamoxifen use.[7]

The absolute benefit of chemotherapy depends on the absolute risk without chemotherapy. Several clinical prognostic algorithms have been developed to predict the likelihood of disease recurrence, based on factors such as patient age and menopausal status, tumor size and stage, cancer grade, lymph node involvement, and expression status for the estrogen and progesterone receptors and the HER2 protein. These algorithms include NCCN and St Gallen clinical expert guidelines, Adjuvant! Online, and the Nottingham Prognostic Index.[2,8–10] Women with LN– breast cancer that is HR+ and HER2–, with low proliferation status and generally well differentiated, have a good prognosis if treated with endocrine therapy alone, with approximately 85% remaining recurrence-free after 10 years of treatment.[11,12] In this group, even a relative-risk reduction of one-third corresponds to a very low absolute reduction in risk—one that may be insufficient to offset the adverse effects of chemotherapy, which vary by drug and regimen but can involve significant morbidity and negative impact on patients' quality of life.[13]

In recent years, attention has been focused on the development of clinically practical molecular tests that might have superior (or additional) prognostic ability to provide classifications based on clinical and histological characteristics. The aim is for such tests to be used, together with information on HR, HER2, and nodal status, to reliably differentiate between women who may be spared the debilitating effects of chemotherapy without a significant increase in their absolute risk of recurrence and those for whom adjuvant chemotherapy is likely to provide significant benefit. Several of these tests are based on measurement of the expression profiles of sets of genes related to the proliferative potential of the tumor cells. In 2007, EGAPP commissioned an evidence review that focused on three gene expression profiling tests for women with breast cancer that were clinically available in the United States at that time: Oncotype DX, MammaPrint, and the Quest H:1 test.[14]

Based on the findings of this review, in 2009 the EGAPP Working Group (EWG) published a recommendation statement summarizing and evaluating evidence for the analytic validity, clinical validity, and clinical utility of these tests in women with HR+, LN–, HER2– early breast cancer. For the Oncotype DX recurrence score (RS), the EWG concluded that there was adequate evidence regarding the association of the RS with disease recurrence and adequate evidence for its ability to predict response to chemotherapy.[1] With regard to clinical utility, the evidence was found to be insufficient, and, although the EWG noted that these technologies have potential for both benefit and harm, they "found encouraging indirect evidence for [clinical utility of] Oncotype DX."[1] Similar conclusions were reached in 2011 in an assessment of the clinical validity and utility of Oncotype DX in women with LN+ disease.[15]

Since the publication of the evidence review and EGAPP recommendation statement, several systematic reviews have been

published addressing questions relating to the clinical utility and cost-effectiveness of Oncotype DX and MammaPrint.[16–20] On the basis of an overview of the findings of five of these systematic reviews[21] and additional published evidence, the EWG decided to prepare an updated version of its 2009 recommendation statement. This update focuses on the Oncotype DX test.

Description of test and intended-use claims

Genomic Health (Redwood City, CA) states that the Oncotype DX Breast Cancer Assay "can predict the potential benefit of chemotherapy and likelihood of distant breast cancer recurrence in women with node negative or node positive, ER-positive, HER2-negative invasive breast cancer," with the aim of supporting the planning of more personalized treatment.[22] Results are reported as an RS (scale of 0–100) that correlates to a patient-specific "average rate of distant recurrence" (with a 95% CI (confidence interval)). To determine prognosis, patients are categorized as low-risk (RS <18), intermediate-risk (RS 18–30), or high-risk (RS >31). The low-risk, intermediate-risk, and high-risk categories have been reported to correspond to 10-year distant recurrence rates after 5 years of tamoxifen therapy of 6.8% (95% CI 4.0–9.6), 14.3% (95% CI 8.3–20.3), and 30.5% (95% CI 23.6–37.4), respectively.[23]

REVIEW OF SCIENTIFIC EVIDENCE

This statement summarizes the supporting scientific evidence used by the EWG to make recommendations regarding the use of the Oncotype DX tumor gene expression profiling test in women with breast cancer.

Methods

EGAPP is a project developed by the Office of Public Health Genomics at the CDC to support a rigorous, evidence-based process for evaluating genetic tests and other genomic applications that are in transition from research to clinical and public health practice in the United States. A key goal of the EWG is to develop conclusions and recommendations regarding clinical genomic applications and to establish clear linkage to the supporting scientific evidence. The EWG members are nonfederal multidisciplinary experts convened to establish methods and processes, set priorities for review topics, participate in technical expert panels for commissioned evidence review, and develop and publish recommendations.

EWG members reviewed the original evidence report and recommendation statement, an overview of systematic reviews on clinical utility and cost-effectiveness of gene expression profiling published between 2009 and 2013,[21] key primary publications, and other sources of information. The final EWG recommendation statement was based on magnitude of effect, certainty of evidence, and consideration of contextual factors (by a process outlined in Table 6 of the Methods section of the EWG publication).[24]

Technology

Oncotype DX is a proprietary laboratory-developed test offered by a single Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory. The test uses reverse-transcription polymerase chain reaction (RT-PCR) for the detection and quantitation of mRNA in formalin-fixed, paraffin-embedded breast cancer tissue. Oncotype DX analyzes expression of 21 genes: 16 cancer-related and 5 reference genes. The test also reports results for ER, progesterone receptor, and HER2 status.

Analytic validity

EGAPP's 2009 recommendation statement concluded that because there was no gold-standard test for comparison, it was not possible to quantitatively estimate the analytic sensitivity or specificity of the Oncotype DX test. Analytic validity was not reconsidered for this update.

Clinical validity

In its 2009 recommendation statement, the EWG found that there was adequate evidence from retrospective studies on cohorts from single arms of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 and B-20 trials and from a case-control study of patients from the Kaiser Permanente tumor registry for a significant correlation between RS and clinical outcome (10-year distant recurrence

Table 1 Prognostic ability of the Oncotype RS in HR-positive, LN–, or LN+ patients treated with tamoxifen

	Population	Study type	Outcome measure	Results (95% CI)[c]		
				Low	Intermediate	High
Paik[23]	NSABP B-14 trial subset: HR+, LN–, HER2+/– (*N* = 668)	Cohort	10-year DR	6.8% (4.0–9.6)	14.3% (8.3–20.3)	30.5% (23.6–37.4)
Paik[25]	NSABP B-20 trial subset: HR+, LN–HER2+/– (*N* = 651)	Cohort	10-year DR	3.2% (0.01–16.7)	9.1% (0.6–17.5)	39.5% (25.2–53.8)
Habel[27]	Kaiser Permanente Tumor Registry: HR+, LN– (*N* = 205)	Case-control	10-year death from breast cancer	RR 1.0 (reference)	RR 4.0 (1.8–8.8)	RR 6.2 (2.4–15.8)
Dowsett[26a]	TransATAC trial subset: HR+ LN– (*N* = 872), LN+ (*N* = 306)	Cohort	9-year DR	4% (3–7); 17% (12–24)	12% (8–18); 28% (20–39)	25% (17–34); 49% (35–64)
Albain[28]	SWOG-8814 trial subset: HR+, HER2+/–, LN+ (*N* = 148)	Cohort	10-year DFS OS estimates[b]	60%; 77%	49%; 68%	43%; 51%

DFS, disease-free survival; DR, distant recurrence; OS, overall survival.

[a]Postmenopausal women treated with tamoxifen or anastrozole. [b]Stratified by the number of positive nodes: LN = 1–3 vs. LN ≥4. Stratified log-rank test $P = 0.017$ for DFS; $P = 0.003$ for OS. [c]Expressed as percentage of women with the specified outcome or risk relative to a reference group.

or death from breast cancer) in women with HR+, LN−, early-stage breast cancer.[1]

- Table 1 shows data reported from these studies and from subsequent studies of the UK-based TransATAC trial population and the SWOG-8814 trial population.[23,25–28] The TransATAC study demonstrated that the correlation between RS and distant recurrence also applies for both LN− and LN+ postmenopausal women treated with the aromatase inhibitor anastrozole.[26] The prognostic ability of the Oncotype RS in LN+ women was confirmed in a study of the SWOG-8814 trial population, although overall prognosis for this group was worse than for women with no nodal involvement.[28] Studies in the TransATAC and SWOG-8814 populations found that the prognostic value of the RS was weaker in the second 5-year period than in the initial 5 years.[26,28–30]
- In studies in the NSABP, Kaiser Permanente, and TransATAC populations, multivariate Cox proportional hazards analysis showed that a 50-point change in RS as a continuous variable remained a significant prognostic indicator in models adjusted for clinical factors, including tumor size, grade, and patient age.[23,26–28,31] In a meta-analysis of combined data sets from the NSABP and TransATAC trials, a prognostic score that combined RS with selected clinicopathological features provided improved risk assessment over RS alone ($P < 0.001$) and classified fewer patients as intermediate risk.[32]
- A recent meta-analysis of four studies using a fixed-effects model found a hazard ratio of 2.97 (95% CI 2.19–4.0) for a high RS versus an intermediate or low RS. However, this analysis combined studies on node-negative and node-positive patients and included one study in which the outcome was locoregional rather than distant recurrence.[33]
- Oncotype DX RS has been shown in a multivariate analysis to provide prognostic information in HR-+, LN−, tamoxifen-treated patients that is independent of that derived from use of the Adjuvant! algorithm.[26,31] However, integrating RS and Adjuvant!-derived scores did not improve prognostic discrimination in the NSABP B-20 data set.[31]

Clinical validity conclusions

- The EWG found adequate evidence from large studies on four populations to support the association between RS and clinical outcomes in women with HR+, HER− breast cancer that is either LN+ or LN−.
- There is adequate evidence from multivariate analyses that the prognostic information provided by the Oncotype RS remains significant when adjusted for the effects of other clinical and patient characteristics.
- At present the prognostic value of combining the RS with other clinicopathological variables is uncertain.

Clinical utility

In this context, clinical utility is the likelihood that using Oncotype DX gene expression profiling to guide management in patients with early-stage breast cancer will significantly improve health-related outcomes compared to standard clinical practice.

- No direct evidence was found regarding health benefits from use of Oncotype DX to guide decisions about adjuvant chemotherapy treatment.
- There is indirect evidence from retrospective analyses using data from the NSABP B-20 and SWOG-8814 prospective clinical trials that Oncotype DX RS predicts benefit from chemotherapy for women with LN− and LN+ disease, respectively (Table 2).[25,28,31] In the NSABP B-14 and NSABP B-20 data sets, a statistically significant interaction was reported between RS and chemotherapy benefit for a primary outcome of 10-year distant recurrence ($P = 0.038$ for B-14 and $P = 0.031$ for B-20).[25,31]
- In the NSABP B-20 data set, RS was reported to be a better predictor of chemotherapy benefit for a range of clinical outcomes than either Adjuvant! (Table 3)[31] or a score that combined RS with selected clinicopathological factors.[32]
- When evaluated by the GRADE criteria, the quality of evidence indicating that Oncotype DX RS has clinical utility was assessed as very low.[21] Low quality was not due to conflicting studies or studies demonstrating lack of benefit. Instead, it reflected important limitations in

Table 2 Selected findings on the ability of Oncotype DX RS to predict benefit from adjuvant chemotherapy[a]

Study	Population	Treatment	Outcome measures	Results[b]		
				Low	IM	High
Paik[25]	NSABP B-20 trial subset: HR+, LN−HER2+/− ($N = 651$)	Tamoxifen ($N = 227$), or Tamoxifen + CMF/MF[c] ($N = 424$)	10-year DR	RR = 1.31 (0.46–3.78)	RR = 0.61 (0.24–1.59)	RR = 0.26 (0.13–0.53)
Albain[28d]	SWOG-8814 trial subset: HR+, HER2+/, LN+ ($N = 367$)	Tamoxifen ($N = 148$), or CAF[d] followed by tamoxifen ($N = 219$)	10-year DFS; 10-year OS	HaR = 1.02 (0.54–1.93), $P = 0.97$[e]; HaR = 1.18 (0.55–2.54), $P = 0.68$	HaR = 0.72 (0.39–1.31), $P = 0.48$; HaR = 0.84 (0.40–1.78), $P = 0.65$	HaR = 0.59 (0.35–1.01), $P = 0.033$; HaR = 0.56 (0.31–1.02), $P = 0.057$

DFS, disease-free survival; DR, distant recurrence; OS, overall survival; RR, relative risk.

[a]Summaries of additional findings can be found elsewhere.[21] [b]Relative risks and hazard ratios compare the risk of recurrence (or death) for a given recurrence score group with or without chemotherapy. [c]CMF, cyclophosphamide, methotrexate, and fluorouracil; MF, methotrexate and fluorouracil. [d]CAF, cyclophosphamide, doxorubicin, and fluorouracil. [e]Hazard ratios (HaRs) from Cox regression models adjusted for the number of positive nodes; *P* values are stratified log rank values.

Table 3 Oncotype DX recurrence score and Adjuvant! risk score and relative benefit from CMF/MF chemotherapy in 651 patients from the NSABP B-20 data set

Risk score category	Distant recurrence-free interval HaR (95% CI)	*P* (interaction)[a]	Overall survival HaR (95% CI)	*P* (interaction	Disease-free survival HaR (95% CI)	*P* (interaction)
RS low	1.31 (0.46–3.78)	0.031	1.37 (0.63–3.01)	0.011	0.91 (0.57–1.45)	0.082
RS IM	0.61 (0.24–1.59)		0.94 (0.4–2.25)		0.79 (0.43–1.47)	
RS high	0.26 (0.13–0.53)		0.31 (0.16–0.6)		0.41 (0.23–0.71)	
Adj low	0.58 (0.23–1.42)	0.99	1.16 (0.55–2.45)	0.357	0.97 (0.59–1.61)	0.357
Adj IM	0.54 (0.20–1.46)		0.70 0.30-1.61)		0.60 (0.33–1.09)	
Adj high	0.53 (0.25–1.1)		0.53 (0.26–1.07)		0.62 (0.36–1.05)	

CMF, cyclophosphamide, methotrexate, and fluorouracil; MF, methotrexate and fluorouracil.

[a]From likelihood ratio tests.

Data from ref. [31].

the studies, such as indirectness of the study design for providing evidence of clinical utility (no control group and actual treatment decisions were not made on the basis of Oncotype DX score) and risk of bias due to inclusion of only a subset of patients from the original clinical trial population. In addition, there was a paucity of studies demonstrating benefit. These limitations may be ameliorated in the future as the evidence base grows to include more studies evaluating health-outcome benefits beyond risk reclassification, such as toxicity of treatment and survival outcomes following testing and differential treatment. Other recent evaluations have also found no direct evidence that use of the test leads to better health outcomes in women with either LN− or LN+ disease.[15,33]

- Many recent research studies have investigated the effect of Oncotype DX RS on physician recommendations regarding chemotherapy treatment. Results from 11 studies included in recent systematic reviews suggest that use of the Oncotype DX RS led to a change in treatment recommendation for 12–74% of patients.[16–19,21] Results from six of these studies indicate that 13–34% fewer patients overall were recommended for chemotherapy after use of Oncotype DX testing.[21]
- The quality of evidence from these studies was assessed as low by GRADE criteria because the studies were highly heterogeneous with respect to patient populations and the criteria used to make initial treatment decisions.[21]
- Data are now accumulating on the effect of Oncotype DX testing on actual treatment decisions in breast cancer clinics. A survey of the care of 7,375 women treated at 11 comprehensive cancer centers and six community-based cancer centers in the United States found an overall decrease in chemotherapy use from 53.9 to 47.0% ($P < 0.001$).[3] A survey of 6,229 patients registered on an electronic health record database found an association between RS and chemotherapy use ($P < 0.001$).[34]
- In these surveys, approximately 37% of patients were in the intermediate-risk category, for whom chemotherapy benefit is uncertain, compared with 22% in the initial studies by Paik et al.[3,23,34] The prospective TAILORx trial[35,36] focuses on the intermediate-risk group, but the trial is not scheduled for completion until 2017.
- Recent studies suggest a positive impact of Oncotype DX testing on decisional conflict; i.e., its use increased patients' confidence in their decision about treatment.[37–39] One of these studies also found that testing reduced patient anxiety but did not affect overall quality of life.[37]

Clinical utility conclusions

- The EWG found no direct evidence linking Oncotype DX to improved clinical outcomes.
- Indirect evidence was found relating to components of clinical utility (ability of the test to predict benefit from chemotherapy and influence of testing on clinical practice and patients' decisions). Although the overall quality of this evidence was assessed as low or very low by GRADE criteria,[21] it should be noted that the level-of-evidence criteria developed by Simon et al.[40] assign "level 1 category B" to evidence from well-conducted tumor biomarker studies with a "prospective retrospective" design and that some professional guideline-development and technology-assessment groups accept evidence from such studies as high-quality evidence to support test use.
- For women with low or intermediate RS, for whom the benefit from chemotherapy is uncertain, the benefits of avoiding harms from chemotherapy may outweigh the potential harm from recurrence. Nevertheless, both physicians and patients should be aware of potential for harm if decisions are made to forgo chemotherapy treatment on the basis of the RS result.
- Current prospective clinical trials are expected to provide more definitive evidence regarding clinical utility in the target population and in the context of modern combination chemotherapy regimens.

Clinical trials

- The TAILORx trial (NCT00310180) of approximately 11,000 US women with estrogen receptor–positive, LN–, HER2– early breast cancer (estimated primary completion date December 2017) is designed primarily to determine the benefit of chemotherapy for women with intermediate-risk Oncotype DX results.[35,36] RS cutpoints for the trial are more conservative than those used for the commercially available test to minimize the risk of undertreatment in high-risk women. In this trial, women in the low-risk category (RS <11 rather than <18) receive adjuvant hormonal therapy and are followed to determine 10-year distant disease-free survival. High-risk women (RS >25 rather than ≥31) receive hormonal therapy and chemotherapy. Women at intermediate risk (RS 11–25 rather than 18–30) are randomized to hormonal therapy alone or hormonal therapy plus chemotherapy. Outcomes will be compared with RS, current clinicopathological criteria, and other prognostic indicators (e.g., HER2, estrogen- and progesterone-receptor status, other genes).
- The RxPONDER trial (NCT01272037; estimated enrollment 4,000, primary completion date 2022) will compare disease-free survival over the course of 15 years for women with node-positive invasive breast cancer (LN1-3) and RS ≤25 treated with either endocrine therapy alone or endocrine therapy plus chemotherapy.[41] The trial aims to determine an RS cutpoint above which chemotherapy should be recommended.

Contextual issues important to the recommendation

- As a result of guidelines recommending the use of Oncotype DX as an aid to clinical decision making in specific patient populations, Oncotype DX is now routinely used in breast cancer care at some institutions.[42] A recent survey found an increase in the use of testing from 14.7% in 2006 to 27.5% in 2008 ($P < 0.01$),[3] and current rates of use are likely to be higher. Nevertheless, there are indications that eligible African-American women may be tested at rates lower than white women;[3] further investigation of this finding will be critical if the test is demonstrated to have clinical utility.
- Moreover, it would be valuable to have a better understanding of oncologists' decisions regarding use of the test. Studies have begun to document how medical and surgical oncologists use the test, how they communicate results to patients, how well patients understand the information, and how they use it in decision making.[42–45] Although studies to date are too small to allow firm conclusions, their findings indicated that physicians generally assume the test has clinical utility and many use it as a primary tool in discussing risks and benefits of chemotherapy with women who have HR+ early breast cancer, often by directly sharing with them the report provided by Genomic Health.[42,44] Explanation and discussion of intermediate risk are very challenging, and decisions are ultimately made by incorporating consideration of other clinical factors as well as patients' views and preferences.[44] Careful presentation of test results is important[42] because approximately one-third of patients have been found to not fully understand the test and its implications,[43] and there is some evidence that patients may overestimate the accuracy of the test.[46]
- Other molecular prognostic tests that have been developed for predicting recurrence risk in early-stage breast cancer patients have also been evaluated in systematic reviews,[18,19] and recent studies have added to the evidence base for these tests.[29,30,47] Two of the tests—MammaPrint (Agendia Laboratories) and the NanoString Technologies Prosigna test (which uses the PAM50 microarray set)—have received FDA marketing approval. A third test—the Breast Cancer Index, developed by bioTheranostics from the Quest H:1 test—is offered by a single CLIA-certified laboratory. Current evidence relating to these tests is restricted to demonstration of prognostic ability, with some studies reporting performance superior to that of Oncotype DX, particularly for late recurrence beyond the first 5 years.[29,30,47] So far, no evidence is available on the ability of the tests to predict chemotherapy benefit. As some of these tests are developed and studied further, there is the potential for considerable confusion and uncertainty both for clinicians and for patients in making decisions about which, if any, test to use as an aid to treatment decisions.
- The TAILORx trial should provide quality of life data associated with testing, and this may be expected to influence future assessments of clinical utility.[35]

Cost-effectiveness

Two recent systematic reviews have reported independent cost-effectiveness analyses for Oncotype DX.[17,18] Two additional systematic reviews[19,20] summarized results from cost-effectiveness analyses reported in the included studies. Of these, only one assessed the quality of the included studies by criteria specific for economic analyses.[20] Furthermore, that review[20] included 18 cost-effectiveness studies for Oncotype DX, encompassing all 8 studies from the other review,[19] along with 10 additional studies. Quality ratings were high; however, it was noted that "the most common area where studies did not meet QHES criterion was explicit discussion of bias" and that "a number of analyses also failed to fully describe the model constructed and the assumptions used."[20] Overall, use of the Oncotype RS to guide decisions on chemotherapy treatment was found to be cost-effective from a health-payer perspective in a variety of health-care settings in different countries (evaluation settings included the United States, Canada, the United Kingdom, Ireland, Japan, Singapore, Australia, Hungary, and Israel).[20,21]

Most of these analyses used assumptions about chemotherapy benefit in different RS groups that are derived from the original

studies on Oncotype and have yet to be confirmed by clinical trials.[20,48] Approximately half (8 of the 18 included Oncotype cost-effectiveness studies) also used health-economic model structures identical or similar to that used in industry-funded cost-effectiveness studies.[20] The key driver leading to favorable estimates for cost-effectiveness was an estimated overall decrease in chemotherapy use, particularly in countries where current chemotherapy use in the absence of testing is high and where chemotherapy costs are also high (such as in the US setting, where Oncotype DX was found to save costs).[20] Use of Oncotype DX was estimated to reduce costs by approximately $2,000 per patient compared with either current clinical practice based on NCCN guidelines or treatment with tamoxifen plus chemotherapy for all patients.[20,21]

In an independent cost-effectiveness analysis carried out for the UK's National Institute for Health and Care Excellence (NICE) and using UK-specific data, Oncotype DX was predicted to lead to an overall increase in chemotherapy use (14–19%) with an incremental cost-effectiveness ratio of £26,940 per quality-adjusted life year gained compared with current clinical practice if offered to all eligible women.[18] In univariate sensitivity analysis, cost-effectiveness depended strongly on the assumed benefits of chemotherapy for each RS risk group.

In a subsequent guidance document, the NICE Diagnostics Advisory Committee said that it was more appropriate to evaluate incremental cost-effectiveness ratios based on an assumption of equal chemotherapy benefit for all Oncotype DX risk categories, given the current lack of definitive evidence for the ability of Oncotype DX to predict chemotherapy benefit.[49] Under this assumption, Oncotype DX was not cost-effective at the manufacturer's stated price. However, Oncotype DX was considered cost-effective for patients at intermediate risk for distant recurrence by criteria such as the Nottingham Prognostic Index for whom the decision about chemotherapy is unclear, provided the test was provided by the manufacturer at an (undisclosed) revised price.[49]

Research gaps

The EGAPP Working Group found that research gaps identified in its original recommendation statement remain largely unaddressed. In addition to direct demonstration of clinical utility, these include the need for validation of the prognostic accuracy of Oncotype DX in different ethnic groups, for further evaluation of algorithms that integrate Oncotype DX RS with other scores or clinicopathological risk factors, and for further research to clarify how women understand and use risk information.[1] Finally, US-based cost-effectiveness analyses are needed that are independent of the test manufacturer and based on more robust evidence of the test's clinical utility.

RECOMMENDATIONS OF OTHER GROUPS

NCCN

Clinical Practice Guidelines in Oncology—Breast Cancer, 2013, version 3.2013 (ref. 2) "Pending the results of the prospective trials, the Panel considers the 21-gene RT-PCR assay as an option when evaluating patients with primary tumors characterized as 0.6 to 1.0 cm with unfavorable features or >1 cm, and node-negative, hormone receptor–positive, and HER2-negative (category 2A). In this circumstance the recurrence score may be determined to assist in estimating likelihood of recurrence and benefit from chemotherapy. The Panel emphasizes that the recurrence score should be used for decision-making only in the context of other elements of risk stratification for an individual patient."

"The additional benefit from adjuvant chemotherapy in addition to endocrine therapy is currently unclear for intermediate-risk patients (as assessed by the gene-based assays). The TAILORx and RxPONDER trials are being conducted to help answer this question." "The findings from these trials will help determine the benefit of treating patients at intermediate risk with adjuvant chemotherapy."

American Society of Clinical Oncology

2007 Update of Recommendations for the Use of Tumor Markers in Breast Cancer[50] "In newly diagnosed patients with node-negative, estrogen-receptor positive breast cancer, the Oncotype DX assay can be used to predict the risk of recurrence in patients treated with tamoxifen...[and] to identify patients who are predicted to obtain the most therapeutic benefit from adjuvant tamoxifen and may not require adjuvant chemotherapy...patients with high RSs appear to achieve relatively more benefit from adjuvant chemotherapy (specifically (C)MF) than from tamoxifen."

- The recommendation notes that testing of retrospectively collected tissues from a prospectively collected arm of a clinical trial might be considered level I (high-quality) evidence to support use of this test.[23,25]
- They add that "there are insufficient data at present to comment on whether these conclusions generalize to hormonal therapies other than tamoxifen, or whether this assay applies to other chemotherapy regimens."

European Society for Molecular Oncology

Primary Breast Cancer: ESMO Clinical Practice Guidelines 2013 (ref. 51) "Molecular signatures for ER-positive breast cancer such as Oncotype DX … are commercially available, but none of them have proven robust clinical utility so far. In some cases of difficult decision, such as grade 2 ER-positive HER2-negative and node-negative breast cancer, MammaPrint and Oncotype DX may be used in conjunction with all clinicopathological factors, to help in treatment decision-making. Results from large phase III prospective clinical trials (MINDACT [a trial of MammaPrint], TAILORx and RxPONDER) are eagerly awaited for an optimal and accurate use of these new tools in clinical practice."

IMPAKT 2012 Working Group Consensus Statement[52] "The working group found none of the genomic tests demonstrated robust evidence of clinical utility. The panel concluded that

it was not clear from the current evidence that modifying treatment decisions based on the results of a given genomic test would result in improved clinical outcome. Hence, the group did not endorse withholding chemotherapy in patients with ER-positive breast cancer solely on the basis of being low risk by the genomic test."

UK National Institute for Health and Care Excellence Diagnostics Guidance. Gene expression profiling and expanded immunohistochemistry tests to guide the use of adjuvant chemotherapy in breast cancer management: MammaPrint, Oncotype DX, IHC4, and Mammostrat. September 2013 (ref. 49)
"Oncotype DX is recommended as an option for guiding adjuvant chemotherapy decisions for people with estrogen receptor–positive (ER+), lymph node–negative (LN−), and human epidermal growth factor receptor 2–negative (HER2−) early breast cancer if:

- The person is assessed as being at intermediate risk and
- Information on the biological features of the cancer provided by Oncotype DX is likely to help in predicting the course of the disease and would therefore help when making the decision about prescribing chemotherapy and
- The manufacturer provides Oncotype DX to NHS organizations according to the confidential arrangement agreed with NICE."

"Research is recommended on the clinical utility of the test, including robust evidence on the impact of Oncotype DX on clinical decision-making in England (containing consideration of informal approaches compared with a formal algorithm for combining the Oncotype DX score with clinicopathological variables) and its ability to predict the benefit of chemotherapy. As part of the adoption of Oncotype DX by the [National Health Service], the Committee encourages the collection of clinical utility and any other useful data by the health system, potentially by a multicentre audit."

St Gallen Consensus Conference Guidelines 2013 (ref. 9)
"The Panel was strongly of the opinion that intrinsic subtypes, including those defined by the clinic-pathological surrogates, should influence whether or not chemotherapy was used, but not the choice of cytotoxic regimen. After clinic-pathological assessment, a slim majority of the Panel was in favor of requesting a multi-gene assay in node-negative, ER-positive and HER2-negative cases. The Panel considered that only the 21-gene RS was predictive of chemotherapy responsiveness, though a substantial minority would also endorse PAM50 or the 70-gene signature for this purpose. This led to a recommendation that selection of patients who might forego chemotherapy could be based on the 21-gene RS, but the Panel did not offer majority endorsement for PAM60, the 70-gene signature or EPClin as yet established for this purpose.

For patients with ER-positive, HER2-negative disease, the use of molecular diagnostics was felt to be unnecessary in low-risk patients such as those with a tumour size of ≤1 cm in the setting of negative lymph nodes, since chemotherapy would be unlikely to be given anyway. Similarly, patients with a higher risk such as those with a tumour size >5 cm, inflammatory breast cancer, those with four of more involved nodes, or a very low ER positivity (e.g. 5%) might not benefit from molecular diagnostics because chemotherapy would be likely to be offered in any case. Patients in whom chemotherapy was thought to be of uncertain indication and who might therefore benefit from molecular diagnostics were felt to include selected patients with node-negative disease, those with one to three positive nodes, and patients aged <35."

Cancer Care Ontario Program in Evidence-Based Care Recommendation Report MOAC-2, November 2013 (ref. 17)
Recommendations from a report comparing Oncotype DX with other tests for risk estimation and treatment decisions:

"Recommendation 1: In cases of breast carcinoma where Oncotype DX is indicated for clinical prognosis and treatment decisions, other assays should not currently be considered equivalent with respect to data generated or risk stratification." The justification for this recommendation states that "Oncotype DX is widely accepted as having clinical validity and utility based on retrospective-prospective analyses (i.e. retrospective analysis of data from previously completed prospective trials)."

"Recommendation 2: In cases where it is unclear whether or not Oncotype DX is indicated for clinical prognosis and treatment decisions, Adjuvant! Online may be used as a no-cost method to estimate the tumour recurrence risk. These assays should not be considered equivalent to Oncotype DX if the latter is indicated.

Recommendation 3: Given the preliminary status of much of the available evidence, periodic reassessment of published and ongoing trials is recommended. New evidence supporting molecular profiling tests should be reviewed at least semi-annually."

BlueCrossBlueShield Association TEC Assessment, 2014 (ref. 53) The Blue Cross and Blue Shield Medical Association Advisory Panel judged that Oncotype DX met the Association's five Technology Evaluation Center criteria.

1. "The technology must have final regulatory approval from the appropriate government regulatory bodies": Oncotype DX is available from a CLIA-licensed laboratory.
2. "The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes": The panel concluded that "the evidence was judged sufficient to permit conclusions regarding probable health outcomes."
3. "The technology must improve the net health outcome": The panel concluded that "Oncotype DX can improve the net health outcome in women with unilateral, HR-positive, node-negative breast cancer" and that "with foreknowledge of risk class, RS low-risk women may choose to avoid adverse effects of chemotherapy."

4. "The technology must be as beneficial as any established alternatives": The panel concluded that "In a significant subset of cases, Oncotype DX is likely to change the therapy decisions a patient and her physician would otherwise make using conventional risk classifiers." but noted that "Several limitations to the available evidence indicate the need for further study."
5. "The improvement must be attainable outside the investigational settings": The panel commented that "the quality of diagnostic performance obtained in practice should be similar to that obtained in the published studies; however, the effect of increased demand for the test on the capacity of a single-source laboratory is unknown."

RECENT RESULTS

Following peer review of this recommendation statement, promising 5-year disease-free survival and distant recurrence results for women in the prospective TAILORx study who had low RSs were published.[54] Although the current recommendation remains unchanged, future results from TAILORx intermediate and high RS groups might potentially demonstrate clinical utility.

DISCLOSURE

The authors declare no conflict of interest.

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