Incorporating Tumor Characteristics to Maximize 21-Gene Assay Utility: A Cost-Effectiveness Analysis

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ABSTRACT

Background: Literature suggests that Oncotype DX (ODX) is cost-effective. These studies, however, tend to ignore clinical characteristics and have not incorporated population-based data regarding the distribution of ODX results across different clinical risk groups. Accordingly, this study assessed the cost-effectiveness of ODX across strata of clinical risk groups using population-based ODX data.

Methods: We created state-transition models to calculate costs and quality-adjusted life years (QALYs) gained over the lifetime for women with estrogen receptor (ER)-positive, HER2-negative, lymph node-negative breast cancer from a US payer perspective. Using the Connecticut Tumor Registry, we classified the 2,245 patients diagnosed in 2011 through 2013 into 3 clinical risk groups according to the PREDICT model, a risk calculator developed by the National Health Service in the United Kingdom. Within each risk group, we then determined the recurrence score (RS) distributions (<18, 18–30, and ≥31). Other input parameters were derived from the literature. Uncertainty was assessed using deterministic and probabilistic sensitivity analyses.

Results: Approximately 82.5%, 11.9%, and 5.6% of our sample were in the PREDICT low-, intermediate-, and high-risk groups, respectively. When combining these 3 groups, ODX had an incremental cost-effectiveness ratio (ICER) of $62,200 per QALY for patients aged 60 years. The ICERs, however, differed across clinical risk groups, ranging from $124,600 per QALY in the low-risk group, to $28,700 per QALY in the intermediate-risk group, to $15,700 per QALY in the high-risk group. Results were sensitive to patient age: the ICER for patients aged 45 to 75 years ranged from $77,100 to $344,600 per QALY in the high-risk group. Results were also sensitive to the distribution of ODX results across different clinical risk groups. Accordingly, this study assessed the cost-effectiveness of ODX across strata of clinical risk groups using population-based ODX data.

Conclusions: ODX is not cost-effective for women with clinical low-risk breast cancer, which constitutes most patients with ER-positive disease.


Vignette

Ms. O, a healthy 62-year-old woman, underwent screening mammography, which showed a mass in her right breast; it was biopsied and found to be cancer. She underwent breast-conserving surgery. Pathologic assessment demonstrated a 1.4-cm, well-differentiated invasive ductal carcinoma, ER-positive, HER2-negative, without lymph node involvement. Her medical oncologist used the PREDICT tool to estimate benefits of chemotherapy: the 10-year overall survival would be 88.1% with adjuvant hormone therapy and 88.8% with adjuvant chemotherapy and endocrine therapy. Her oncologist considered Oncotype DX (ODX) testing to help chemotherapy decision-making. Given the current emphasis on value-based practice, is ODX cost-effective for someone like Ms. O?

Background

Adjuvant Online (AO) and PREDICT, using clinicopathological characteristics to estimate prognosis, help oncologists make adjuvant chemotherapy decisions. Over the past decade, however, evidence has shown that gene-expression profiling can improve decision-making through its ability to more accurately identify patients who would benefit from chemotherapy. For instance, the 21-gene assay Oncotype DX (ODX; Genomic Health) is widely used in practice. ODX provides a recurrence score (RS) between 0 and 100, with scores categorized as low (RS<18), intermediate (18≤RS≤30), or high (RS≥31) risk. A body of literature has shown that ODX results have a substantial impact on chemotherapy decision-making.

Several studies have reported that ODX is cost-effective for all women with ER-positive, node-negative breast cancer. However, several important methodologic limitations may have diminished the accuracy of previous cost-effectiveness analyses (CEAs). First, these studies tended to combine all patients into a single group irrespective of their clinical and pathologic features. Such

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an approach, ignoring tumor characteristics when evaluating ODX, is not consistent with actual clinical practice because it assumes that all patients would be treated without consideration of their clinical characteristics. Furthermore, the likelihood that ODX changes chemotherapy decision-making differs across clinical risk subgroups. Even in the absence of ODX, pathologic parameters are routinely collected, have well-known prognostication values, and could predict ODX RS. Indeed, the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer do not recommend ODX for patients with tumors ≤5 mm. Yet most prior CEAs did not assess ODX across different risk groups.

Another important limitation of prior CEAs is the lack of population-level information regarding the distribution of RS in actual clinical practice. Of the few studies reporting incremental cost-effectiveness ratios (ICERs) separately by different clinicopathological risk subgroups, all used the distributions derived from clinical trials, which may not reflect real-world distributions. Furthermore, the most frequently cited data are more than 20 years old and do not include HER2 information. Thus, the generalizability of the results from these CEAs to the contemporary population is unclear. For example, researchers analyzed data from community practice and found that ODX is likely to have a high ICER, highlighting the consideration of real-world implementation in ODX economic evaluation.

Accordingly, we incorporated prevalence data from a population-based study into a model-based CEA of ODX-directed chemotherapy. We analyzed data from a population-based study of patients diagnosed with breast cancer in Connecticut between 2011 and 2013, and classified them into 3 clinical risk groups using a validated prediction tool that does not include gene expression profiling information. We then assessed ODX cost-effectiveness by comparing clinicopathological information plus ODX versus clinicopathologic information alone in all patients and further stratified by each clinical risk subgroup. We also varied age from 45 to 75 years since the cost-effectiveness of ODX is likely to vary by age. Given that the TAILORx trial showed that endocrine therapy alone and chemotherapy followed by endocrine therapy had similar efficacy in women who had RS of 11 to 25, we also conducted sensitivity analyses categorizing RS ≤25 as the low-risk group, 26 ≤ RS ≤ 30 as the intermediate-risk group, and RS ≥ 31 as the high-risk group. Our findings could provide novel insights regarding the value and utility of ODX.

Methods

Overview
We developed time-dependent state-transition models to calculate expected costs and quality-adjusted life years (QALYs) gained over a lifetime horizon associated with ODX use. The specification of strategies is summarized in a decision tree that allocated a patient cohort to 1 of 4 strategies, either with or without ODX testing (Figure 1). If ODX testing was not provided, we assumed that either all or none of the patients were receiving chemotherapy. If ODX testing was performed, we allowed either the low RS group or the low and intermediate RS groups to be spared chemotherapy. Furthermore, the chemotherapy decision-making was in conjunction with risk classification provided by PREDICT, a free online tool developed by the National Health Service in the United

Figure 1. Specification of strategies.
Abbreviation: RS, recurrence score.
*Similar models were applied to the PREDICT intermediate- and high-risk groups.
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Kingdom that integrates clinicopathological information to help with chemotherapy decision-making. This tool has been externally validated and is broadly used worldwide.

The starting age of the patient cohort was 60 years, given that the median age at breast cancer diagnosis in the United States is 62 years. We created 3 hypothetical cohorts of 60-year-old women diagnosed with estrogen receptor (ER)–positive, HER2-negative, lymph node (LN)–negative breast cancer according to the PREDICT risk classification. Per PREDICT classifications, the low-, intermediate-, and high-risk groups had a PREDICT absolute 10-year survival benefit from chemotherapy of <3% (chemotherapy was not recommended), 3% to 5% (chemotherapy discussed as a possible option), and >5% (chemotherapy recommended), respectively. Costs were measured in 2015 USD, and an annual discount rate of 3% was applied to costs and QALYs.

We assumed a willingness to pay of $100,000 per QALY, based on the commonly used threshold in the United States.

Model Structure
The schematic view of the Markov model is summarized in Figure 2. Patients entered the model in the recurrence-free state and remained in that state until they developed congestive heart failure (CHF), distant recurrence (DR), or acute myeloid leukemia (AML), or died of other diseases. We included CHF and AML because chemotherapy increases the risk of these conditions.

Following the model developed by the National Institute for Health and Care Excellence (NICE), we assumed a proportion of patients entering the DR state previously experienced a local recurrence, and no transition probabilities were used in or out of this state.

Input Parameters
From the Connecticut Tumor Registry, we identified all women with ER-positive, HER2-negative, LN-negative breast cancer diagnosed in 2011 through 2013, and their clinicopathological information. We classified them into 60 categories by age (30–39, 40–49, 50–59, 60–69, and ≥70 years), tumor grade (1, 2, and 3), and tumor size (0–10, 11–20, 21–30, and >30 mm). The 10-year breast cancer mortality reduction attributed to taxane-based chemotherapy regimen for these 60 categories was abstracted from the PREDICT website. Patients were then categorized into PREDICT low-, intermediate-, and high-risk groups based on the expected benefit of chemotherapy, as per PREDICT. We abstracted ODX results from medical records, amended pathology reports, genetic-expression profile testing logs, and Genomic Health reports.

Among patients who received ODX testing, we determined the proportion of 3 RS categories, conditional on the 3 PREDICT risk groups. We assumed the chemotherapy regimen was AC-T (4 cycles of doxorubicin/cyclophosphamide every 3 weeks followed by 12 cycles of weekly paclitaxel), and 25% of all patients treated with chemotherapy would receive granulocyte colony-stimulating factor (G-CSF) pegfilgrastim (on average 2 cycles) for the secondary prevention of febrile neutropenia. For patients who did not receive ODX testing, we assumed that the relative risk (RR) of DR attributed to AC-T was 0.58 compared with those receiving no adjuvant chemotherapy. For patients who received ODX testing, we assumed that chemotherapy did not reduce DR for the low RS group. Therefore, the intermediate and high RS groups had a low risk of DR when receiving chemotherapy. We assumed that the RR was identical.
for the intermediate and high RS groups. We calibrated the RR for these 2 RS risk groups so that the overall RR of DR attributed to AC-T was 0.58. For instance, the RR of the intermediate and high RS risk groups was 0.31 in the PREDICT low-risk group and 0.55 in the PREDICT high-risk group. Other probability parameters, such as CHF- or AML-related probabilities $^{28,29}$ and costs of ODX testing,$^{31,32}$ chemotherapy,$^{33}$ and treatment for breast cancer recurrence, CHF, AML, and terminal care, were derived from prior literature. Utility weights for each health state were abstracted from the literature $^{13,18,34–36}$ and then age-adjusted at 5-year increments using previously reported trends.$^{37–39}$ Detailed information regarding model assumptions and all model parameters, including fitted distributions, is presented in supplemental eAppendix 1 and eTable 1 (available with this article at JNCCN.org).

**Sensitivity Analyses**

We performed one-way sensitivity analyses on the variables within clinically plausible ranges of our baseline estimates (supplemental eTable 1), and tested patients aged 45 to 75 years. We also integrated the results from the TAILORX trial to explore the ICERs of ODX, assuming no chemotherapy benefit for patients with RS18$^{5}$ (supplemental eTable 2). We conducted sensitivity analyses to reflect real-world chemotherapy use patterns (supplemental eTable 3). Although ODX testing might be able to reduce chemotherapy,$^{40}$ the literature suggests that ODX decreases chemotherapy use in the clinically high-risk group but increases chemotherapy use in the clinically low-risk group.$^{41,42}$ Probabilistic sensitivity analyses were conducted using beta distributions for probability parameters and utility estimates, and gamma distributions for cost estimates.$^{43}$ The distributions of input parameters were drawn 1,000 times, and acceptability curves were created. The models were programmed using the R statistical programming language.$^{44}$ We also evaluated, in the absence of ODX, the cost-effectiveness of chemotherapy use for each clinical risk subgroup. Such analyses could examine whether the results projected by our models were consistent with the chemotherapy recommendations by the PREDICT tool.

**Results**

Between 2011 and 2013, there were 4,281 women diagnosed with ER-positive, HER2-negative, LN-negative breast cancer in the Connecticut Tumor Registry. Based on PREDICT estimates, 82.5%, 11.9%, and 5.6% were in the clinically low-, intermediate-, and high-risk groups, respectively (Table 1). Among them, 2,245 patients (54.6%) received ODX testing. The distribution of 3 clinical risk groups did not differ substantially between patients with and without ODX testing ($P=61$). Among those in the PREDICT low-risk group and who received ODX testing, 64.9% had RS<18 and 3.2% had RS≥31. In contrast, among those in the PREDICT high-risk group, 33.0% had RS<18 and 30.4% had RS≥31.

Our base-case analyses revealed that strategy 1 (no ODX testing and no patients receiving chemotherapy) incurred the lowest cost, followed by strategy 2 (ODX testing and chemotherapy for patients with RS≥31; Table 2). When we combined all 3 PREDICT risk groups, the ICER for ODX testing (in comparison with no ODX testing) was $62,200 per QALY. The ICER, however, differed substantially across PREDICT risk groups. For the PREDICT low-risk group, the ICER for ODX testing was $124,600 per QALY. In contrast, for women in the PREDICT intermediate- and high-risk groups, the ICER for ODX testing was $28,700 and $15,700 per QALY, respectively.

### Table 1. Distributions of Risk Groups and RS Among Patients With ER-Positive, HER2-Negative, LN-Negative Breast Cancer

<table>
<thead>
<tr>
<th>Clinical Risk Group</th>
<th>ODX Not Performed, n (%)</th>
<th>ODX Performed, n (%)</th>
<th>$P$ Value$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients, n (%)</strong></td>
<td>(N=4,281)</td>
<td>(N=2,036)</td>
<td>(N=2,245)</td>
</tr>
<tr>
<td><strong>Low</strong></td>
<td>3,530 (82.5%)</td>
<td>1,703 (83.6%)</td>
<td>1,827 (81.4%)</td>
</tr>
<tr>
<td><strong>Intermediate</strong></td>
<td>510 (11.9%)</td>
<td>207 (10.2%)</td>
<td>303 (13.5%)</td>
</tr>
<tr>
<td><strong>High</strong></td>
<td>241 (5.6%)</td>
<td>126 (6.2%)</td>
<td>115 (5.1%)</td>
</tr>
</tbody>
</table>

Abbreviations: ER, estrogen receptor; LN, lymph node; RS, recurrence score; ODX, Onctotype DX.

$^a$According to PREDICT estimations; 10-year breast cancer mortality reduction with chemotherapy is <3%, 3%–5%, or 5% for low-, intermediate-, or high-risk groups, respectively.

$^b$Mantel-Haenszel chi-square test between ODX not performed and ODX performed; Cramer’s $v=0.05$, indicating a negligible relationship with risk groups between the 2 groups with and without receiving ODX testing.
The ICERs for ODX testing increased with increasing age (Figure 3). For women in the PREDICT low-risk group, the ICER for ODX testing varied from $77,100 per QALY for women aged 45 years to $244,400 per QALY for women aged 75 years. In contrast, for women in the intermediate PREDICT risk group, the ICER varied from $17,600 per QALY for women aged 45 years to $80,300 per QALY for women aged 75 years. Among the women in the PREDICT high-risk group, the ICER ranged from $9,300 to $44,700 per QALY.

Deterministic sensitivity analyses where individual model parameters varied within a plausible range showed that the ICER stratified by age was robust (supplemental eTables 4 and 5). Sensitivity analyses using the TAILORx risk classification scheme showed that 92% of the PREDICT low-risk group had RS \( \leq 25 \) (supplemental eTable 6). Because ODX did not provide additional values for these patients, ODX was not cost-effective for the PREDICT low-risk group, with an ICER of $115,900 per QALY. Similar to our base-case analyses, ODX is cost-effective for the PREDICT intermediate-risk and high-risk groups. Sensitivity analyses integrating real-world chemotherapy use patterns produced similar results (supplemental eTable 7). The cost-effectiveness acceptability curves according to probabilistic sensitivity analyses showed that at willingness to pay of $100,000 per QALY, ODX testing had an 18.4% probability of being cost-effective among PREDICT low-risk patients. For the PREDICT intermediate-risk group, there was a 55.1% probability that ODX testing and chemotherapy for patients with RS \( \geq 18 \) would be the most cost-effective. Among the PREDICT high-risk patients, ODX testing and chemotherapy for patients with RS \( \geq 18 \) would be cost-effective with probability 96.6% (Figure 4).

As a secondary analysis, we compared the strategy of chemotherapy for all patients with the strategy of no chemotherapy (Table 2). The ICER of chemotherapy was $69,500 and $28,100 per QALY for the intermediate- and high-risk group, respectively. For the low-risk group, chemotherapy use incurred higher costs but lower QALY compared with no chemotherapy use. These findings were aligned with the clinical recommendations that chemotherapy not be recommended for the low-risk group, be discussed as a possible option for the intermediate-risk group, and be recommended for the high-risk group.

**Discussion**

We found that among women with ER-positive, HER2-negative, LN-negative breast cancer, ODX testing is cost-effective for those with a clinical intermediate or high risk of DR but not for those at low risk of DR. Given that most women in our population-based sample were classified as low risk, our study suggests that clinicopathologic information needs to be incorporated in ODX testing decision-making. Because screening mammography is a common practice in the United States, a high

### Table 2. Costs, Effectiveness, and Cost-Effectiveness of Providing Oncotype DX

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Oncotype DX</th>
<th>Chemotherapy</th>
<th>Mean Cost ($)</th>
<th>Mean QALY</th>
<th>ICER ($/QALY)</th>
<th>ICER ($/QALY)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strategy 1</td>
<td>No</td>
<td>No patients</td>
<td>25,000</td>
<td>8.875</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Strategy 2</td>
<td>Yes</td>
<td>If RS ≥ 31</td>
<td>28,900</td>
<td>9.393</td>
<td>62,200</td>
<td>N/A</td>
</tr>
<tr>
<td>Strategy 3</td>
<td>Yes</td>
<td>If RS ≥ 18</td>
<td>32,600</td>
<td>8.970</td>
<td>118,400</td>
<td>N/A</td>
</tr>
<tr>
<td>Strategy 4</td>
<td>No</td>
<td>All patients</td>
<td>36,600</td>
<td>8.872</td>
<td>Dominated#</td>
<td>Dominated#</td>
</tr>
<tr>
<td>PREDICT low-risk group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strategy 1</td>
<td>No</td>
<td>No patients</td>
<td>24,400</td>
<td>8.976</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Strategy 2</td>
<td>Yes</td>
<td>If RS ≥ 31</td>
<td>28,000</td>
<td>9.005</td>
<td>124,600</td>
<td>N/A</td>
</tr>
<tr>
<td>Strategy 3</td>
<td>Yes</td>
<td>If RS ≥ 18</td>
<td>31,600</td>
<td>9.032</td>
<td>134,500</td>
<td>N/A</td>
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<tr>
<td>Strategy 4</td>
<td>No</td>
<td>All patients</td>
<td>36,300</td>
<td>8.925</td>
<td>Dominated#</td>
<td>Dominated#</td>
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<tr>
<td>PREDICT intermediate-risk group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Strategy 1</td>
<td>No</td>
<td>No patients</td>
<td>26,900</td>
<td>8.503</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Strategy 2</td>
<td>Yes</td>
<td>If RS ≥ 31</td>
<td>31,900</td>
<td>8.679</td>
<td>28,700</td>
<td>N/A</td>
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<tr>
<td>Strategy 3</td>
<td>Yes</td>
<td>If RS ≥ 18</td>
<td>36,200</td>
<td>8.722</td>
<td>100,000</td>
<td>N/A</td>
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<tr>
<td>Strategy 4</td>
<td>No</td>
<td>All patients</td>
<td>37,600</td>
<td>8.658</td>
<td>Dominated#</td>
<td>69,500</td>
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<tr>
<td>PREDICT high-risk group</td>
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<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Strategy 1</td>
<td>No</td>
<td>No patients</td>
<td>29,200</td>
<td>8.068</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Strategy 2</td>
<td>Yes</td>
<td>If RS ≥ 31</td>
<td>34,400</td>
<td>8.400</td>
<td>15,700</td>
<td>N/A</td>
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<tr>
<td>Strategy 3</td>
<td>Yes</td>
<td>If RS ≥ 18</td>
<td>38,200</td>
<td>8.469</td>
<td>55,100</td>
<td>N/A</td>
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<tr>
<td>Strategy 4</td>
<td>No</td>
<td>All patients</td>
<td>38,900</td>
<td>8.414</td>
<td>Dominated#</td>
<td>28,100</td>
</tr>
</tbody>
</table>

Abbreviations: ICER, incremental cost-effectiveness ratio; N/A, not applicable; QALY, quality-adjusted life-year; RS, recurrence score.

*Comparisons only between with and without chemotherapy.

*#A “dominated” strategy costs more money and has fewer QALYs than a combination of alternative strategies.
proportion of patients have breast cancer detected early with favorable tumor characteristics.\textsuperscript{45,46}

To estimate prevalence or distributions of RS, population-based studies are preferable to randomized controlled trials (RCTs) because of the external validity consideration.\textsuperscript{14} Based on our population-based study, only 3% of patients who were classified as low-risk patients (according to their PREDICT estimation) had RS ≥31. Our results differed substantially from those of post hoc analyses of a subset of participants enrolled in an RCT\textsuperscript{11} that found that approximately 15% of the low-risk group (based on AO estimation) had RS ≥31 (supplemental eTable 8). This profound difference could lead CEAs to have an opposite conclusion. Although our classifications differed from those in the RCT (PREDICT vs AO), prior CEAs using prevalence or proportion information from RCTs may not be able to infer population estimates, because participants in RCTs could not represent the general population.

Our study has several important policy and practice implications. First, we showed that combining all patients and ignoring commonly used clinical risk factors—an approach used by most prior analyses—the overall cost-effectiveness is overestimated. When we considered all patients in aggregate, the ICER of ODX is $62,200 per QALY, which is below the generally used $100,000 per QALY threshold. Yet when we analyzed ODX in discrete risk strata, inferences regarding cost-effectiveness varied substantially. Our findings indicate that ODX testing is cost-effective for select rather than for all patients. Building on the NCCN Guidelines, which recommended ODX if tumor size is >5 mm, our results suggest that additional risk stratification tools such as PREDICT can further inform estimates of cost-effectiveness and overall clinical benefit.\textsuperscript{17}

Another important implication of our study is the association between age and cost-effectiveness. We found that the ICERs for women aged 75 years were approximately 4 times higher than those for women aged 45 years, demonstrating the substantial variability in the cost-effectiveness of ODX when considering variation in life expectancy and utility weights based on age. We followed the recommendations for practices in decision modeling\textsuperscript{48} and conducted age-specific CEAs, the results of which may inform alternative decisions regarding ODX provision to each subgroup. For instance, for the clinical low-risk group, incorporating age changes the ICER from cost-effective for women aged ≤50 years to cost-ineffective for women >70 years. Research also suggested that for patients aged ≥75 years, ODX use increased, yet chemotherapy use remained stable from 2008 to 2011,\textsuperscript{49} calling into question the potential benefits for older women.

There are important limitations to consider. First, although we have built a relatively comprehensive model, our simulation is still a simplification of reality. However, our comparisons between the groups with and without chemotherapy were consistent with the clinical chemotherapy recommendations, demonstrating the validity of our model. Sensitivity analyses also confirm the robust-
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Conclusions

Our study suggests that ODX testing is cost-effective for patients with intermediate- and high-risk ER- positive, HER2-negative, node-negative breast cancer, but not for low-risk. Because clinicopathologic information is available in current practice, it could and should be integrated into ODX testing and chemotherapy decision-making processes. The CEAs ignoring clinicopathologic information are problematic, not only because they depart from clinical practice but also because they result in inappropriate conclusions. Although RCTs are urgently needed to provide efficacy/effectiveness estimates, it is also important to have incidence and prevalence estimates from population-based data, preferably from nationwide data sets. Future research is warranted to understand how to optimize utility of ODX testing and chemotherapy for patients with breast cancer across varied risks of DR.

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Original Research

References


