Economic evaluation of targeted cancer interventions: Critical review and recommendations

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Abstract: Scientific advances have improved our ability to target cancer interventions to individuals who will benefit most and spare the risks and costs to those who will derive little benefit or even be harmed. Several approaches are currently used for targeting interventions for cancer risk reduction, screening, and treatment, including risk prediction algorithms for identifying high-risk subgroups and diagnostic tests for tumor markers and germline genetic mutations. Economic evaluation can inform decisions about the use of targeted interventions, which may be more costly than traditional strategies. However, assessing the impact of a targeted intervention on costs and health outcomes requires explicit consideration of the method of targeting. In this study, we describe the importance of this principle by reviewing published cost-effectiveness analyses of targeted interventions in breast cancer. Few studies we identified explicitly evaluated the relationships among the method of targeting, the accuracy of the targeting test, and outcomes of the targeted intervention. Those that did found that characteristics of targeting tests had a substantial impact on outcomes. We posit that the method of targeting and the outcomes of a targeted intervention are inextricably linked and recommend that cost-effectiveness analyses of targeted interventions explicitly consider costs and outcomes of the method of targeting. ***Genet Med*** **2011:13(10):853–860.**

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Recent decades have seen a rapid expansion in the use of genetic information to estimate disease risk, assess prognosis, and manage patient care. By identifying risk factors, prognostic factors, and predictive factors, the hope is that interventions can be tailored to maximize benefit and minimize toxicity. The role of targeted strategies has been particularly pivotal in oncology, where numerous biomarkers are used to predict cancer risk, response to the therapy, adverse events, and other clinical outcomes.

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Although targeted interventions have the potential to improve health outcomes, they often come at a high cost. These interventions often involve tests or treatments that are considerably more expensive than the prior standard of care. From a societal perspective, however, targeted therapies offer the promise of optimizing resources, so that interventions are directed to individuals who will benefit most from them and not administered to those who are likely to derive little or no benefit or even be harmed by them.

Economic analysis in general and cost-effectiveness analysis (CEA) in particular have been applied to health and medical interventions for more than a quarter century, with dramatic growth in recent years.[1] Although standardized methods for conducting and reporting CEAs have been promoted in the United States and elsewhere,[2–4] a unique feature of targeted interventions requires explicit consideration by analysts and decision makers. Specifically, in the economic assessment of a targeted intervention, the test used to identify candidates for the intervention is inseparable from the intervention itself. An economic analysis that considers the intervention in isolation from the targeting test obfuscates assumptions about the ability of the test to accurately identify candidates for the intervention and fails to fully capture all relevant health and economic outcomes.

In this article, we describe the relationship between targeting tests and targeted interventions and the importance of this relationship in assessing outcomes of a targeted strategy. We identify examples of targeted interventions relevant to breast cancer and review published CEAs, noting whether and how the authors considered the relationship between test and intervention. Finally, we offer recommendations for economic analysis of targeted interventions in breast and other cancers. Our goals are to advance the quality of economic evaluations of targeted interventions and to help consumers of these studies—clinicians, payers, and policymakers—better understand and use the information they provide.

USING TEST RESULTS TO TARGET INTERVENTIONS

Nearly all diagnostic tests give an inherently continuous result that is categorized as a basis for action, and nearly all tests must be considered imperfect predictors of a true state, rather than certain indicators of the truth. When the outcome of a targeted intervention depends on the presence or absence of the target, test results are generally dichotomized, based on some threshold applied to the underlying continuous result. In these cases, economic evaluation of a targeted strategy requires explicit consideration of test performance relative to a gold standard and how the performance characteristics of the test in the population of interest—sensitivity, specificity, positive predictive value, and negative predictive value—influence the use and outcomes of the intervention. An expensive test may be cost-effective if its high accuracy means that people who will not benefit from the intervention are spared its risks and costs or if treatment yields substantial health gains for those correctly identified by the targeting test.

When a target is binary, the accuracy of the targeting test will influence both effectiveness and cost of the targeted strategy. A comprehensive economic analysis must, therefore, include the outcomes of all possible test results. There are costs and health impacts for individuals with a positive result, all of whom would receive the targeted intervention, but the consequences of a true-positive result will not be the same as those of a false-positive result. An individual with a true-positive result incurs the cost of the intervention but experiences a net gain in health outcomes if improvement in the targeted condition exceeds the expected harm of adverse effects. An individual with a false-positive result incurs the cost of the intervention but may experience a net health decline due to side effects, because in the absence of the target no health improvement would be expected. Similarly, there are costs and health impacts for individuals who have a negative test result and thus would not receive the intervention, but the consequences of a true-negative result will differ from those of a false-negative result.

A CEA restricted to a cohort with positive test results only partially captures the full range of health and economic impacts of implementing a targeted intervention, because it ignores negative test results and their consequences (Fig. 1). When the targeting test is very expensive, a CEA that ignores individuals with negative test results would exclude these costs. Such an analysis would also exclude the negative health consequences of failing to give the intervention to those with a false-negative result—individuals who truly have the target.

Some targeted interventions are directed toward individuals at high risk of a poor outcome or those who have a high likelihood of benefiting from an intervention, where the relevant "test" is a risk prediction algorithm based on multiple pieces of information, rather than a single assay, image, or other marker. As with tests for a single target, risk prediction algorithms give a result that is inherently continuous and must be categorized to inform decisions, for example, by defining subgroups of "low," "moderate," and "high" risk based on a predicted probability of the outcome of interest. However, the accuracy of such an algorithm cannot be assessed by comparison with a gold standard, because the only indicator of test performance is whether an individual experiences the predicted outcome, an event that cannot be observed at the time of testing. In these cases, the only available information regarding the relationship between predicted probability and actual outcome is from a dataset in which the algorithm has been validated.

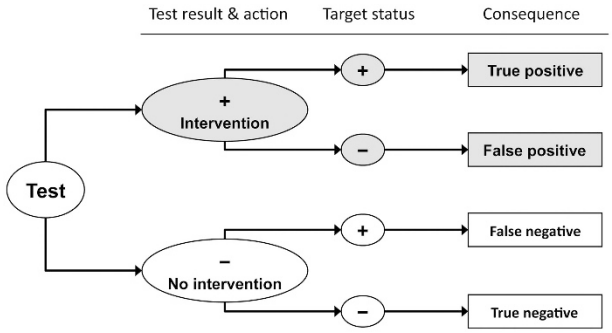

Fig. 1. Possible test results in an economic evaluation of a targeted intervention. The figure depicts test results (positive or negative), actual target status (positive or negative), and the four consequential permutations of these in an economic evaluation which explicitly considers both the targeted intervention and the method of targeting. The shaded segments represent an analysis restricted to a cohort with a positive test result.

Economic evaluation of risk-targeted interventions requires explicit consideration of the threshold risk criterion. Figure 2 shows hypothetical distributions of the predicted risk of disease recurrence in two groups of women treated for early-stage breast cancer: those who will, in fact, experience a recurrence and those who will not. In Panel A, the threshold is relatively strict; the intervention is given to a small proportion of patients, all of whom would have had a disease recurrence in the absence of the intervention. When the criterion is more lenient and individuals with a lower predicted risk are eligible for the intervention (Panel B), more patients who would have recurred receive the intervention but so too will some women who never would have had a disease recurrence. The tradeoffs associated with the threshold risk criterion—and the resulting costs, risks, and benefits of the test and intervention—will influence the cost-effectiveness of a risk-targeted strategy.

TARGETED INTERVENTIONS IN BREAST CANCER

Several targeted interventions have been widely implemented or recommended for breast cancer risk reduction and treatment (Fig. 3). Tests to identify target populations for these interventions include germline genotyping, risk prediction algorithms, tumor protein assays, tumor single-gene assays, and tumor multigene signatures. The maturity of targeted breast cancer interventions and the availability of CEAs of these interventions provide useful examples for illustrating the relationship between targeting tests and interventions and the importance of this relationship in economic analysis.

Economic evaluations of targeted risk reduction and screening strategies

Germline genetic testing and multifactorial risk prediction algorithms can identify women at high risk of developing breast cancer and target preventive or screening interventions to them. Specific mutations in the *BRCA1* and *BRCA2* genes are associated with a substantially increased risk of breast cancer among carriers.[5] Breast cancer risk prediction models use relevant health information to predict a woman's risk of developing breast cancer. For example, the National Cancer Institute's Breast Cancer Risk Assessment Tool, based on the Gail model, predicts the risk of breast cancer based on a woman's age, the number of first-degree relatives with a history of breast cancer, number of prior breast biopsies, atypical hyperplasia in a biopsy specimen, age at menarche, and age at first live birth.[6] Other models use a more limited set of risk factors and may or may not include information about *BRCA1* and *BRCA2* mutations.[7]

Among women at high risk of developing breast cancer, chemoprevention, risk-reducing surgery, and intensive screening may prevent breast cancer or facilitate its detection at an early stage. In randomized clinical trials, two selective estrogen receptor modulators—tamoxifen and raloxifene—reduced the incidence of breast cancer in high-risk women.[8,9] Risk-reducing bilateral mastectomy, with or without bilateral oophorectomy, has been evaluated predominantly in women with *BRCA* mutations and has been shown to substantially reduce breast cancer incidence in these women.[10,11] Screening with advanced imaging modalities, including magnetic resonance imaging (MRI), ultrasound, and digital mammography, detects more cancers in high-risk women, compared with conventional mammography alone, although the impact of these strategies on breast cancer outcomes is uncertain.[12–14]

Several studies have assessed the cost-effectiveness of interventions to prevent breast cancer or detect it early in high-risk women,

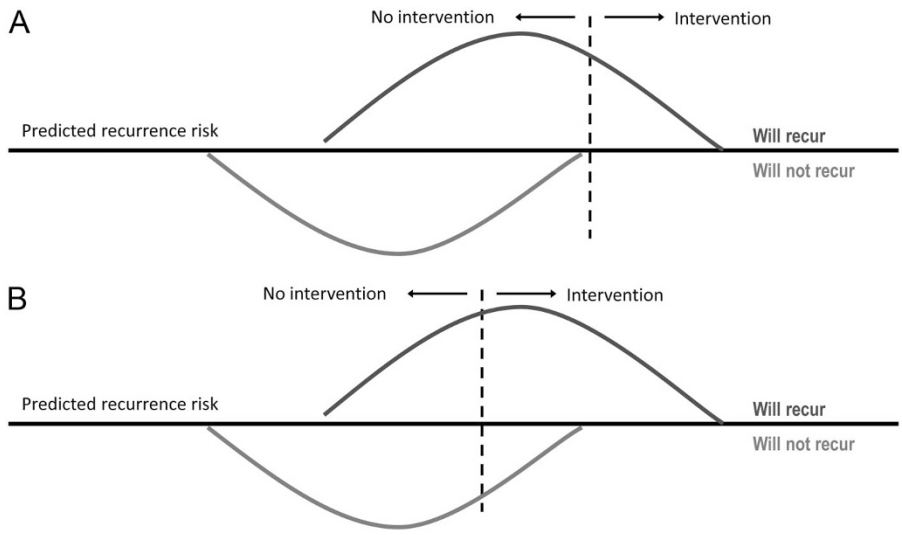

Fig. 2. Thresholds for a targeted intervention by predicted risk and actual outcome. Each panel shows hypothetical distributions of the predicted risk of disease recurrence in two groups of women treated for early-stage breast cancer: those who will experience a recurrence (top curve) and those who will not (bottom curve). The patients in each distribution to the right of the threshold risk criterion (dashed line) receive the intervention. Panel A depicts a stricter threshold for a targeted intervention, and Panel B depicts a more lenient threshold.

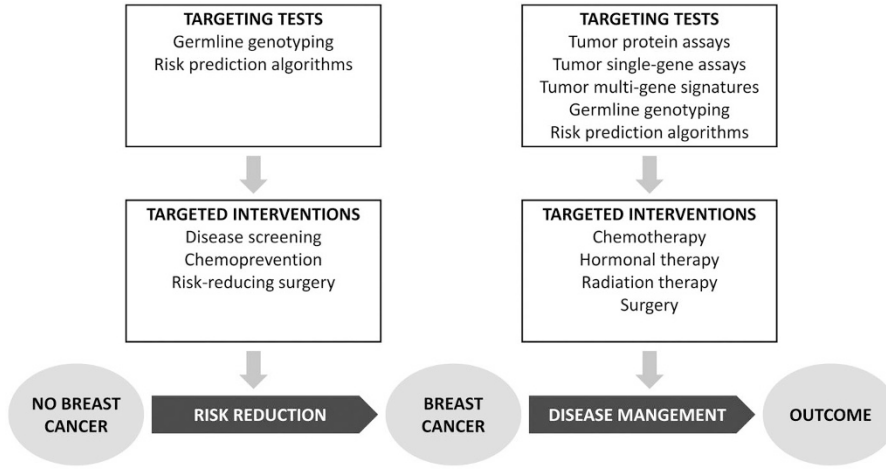

Fig. 3. Targeting test modalities and targeted interventions in the breast cancer disease continuum.

with estimated risk based on *BRCA* mutation status or a risk prediction algorithm (Table 1). Hershman et al. and Noe et al.[15,16] evaluated the cost-effectiveness of tamoxifen chemoprevention in high-risk women using data and assumptions from the Breast Cancer Prevention Trial. These studies focused on subgroups of women defined by breast cancer risk as predicted by the Gail model or by specific individual risk factors. Other studies have compared the cost-effectiveness of multiple risk reduction strategies including chemoprevention, risk-reducing surgery, and intensive surveillance, in women with a *BRCA1* or *BRCA2* mutation.[17,24] Several investigators have studied the cost-effectiveness of MRI screening in high-risk cohorts defined by *BRCA* mutation status or an algorithm-based risk prediction.[18–20]

The aforementioned studies all used decision-analytic modeling to simulate long-term health outcomes and costs, using information about breast cancer risk from clinical trials. Although most performed sensitivity analysis of breast cancer risk estimates, not all explicitly assessed the relationship between the method of targeting and the outcomes of the targeted intervention. Hershman et al.[15] performed separate analysis of four subgroups characterized by observable risk factors, finding substantial variation in the incremental cost-effectiveness of tamoxifen chemoprevention as a function of breast cancer risk. Anderson et al.[17] varied breast cancer risk estimates in *BRCA* mutation carriers and found that while the magnitude of incremental cost-effectiveness ratios (ICERs) changed, risk-reducing surgery remained preferable to chemoprevention or surveillance. Similarly, Grann et al.[24] separately analyzed women with a *BRCA1* mutation, *BRCA2* mutation, or mutation in both genes and found that the incremental cost-effectiveness of the strategies evaluated varied among these groups. Taneja et al.[20] separately analyzed *BRCA* mutation carriers and women at increased risk due to other factors, finding that the incremental cost-effectiveness of targeted MRI screening varied considerably with estimated breast cancer risk. Plevritis et al.[19]

Table 1 Cost-effectiveness studies of targeted breast cancer risk reduction interventions

Study	Intervention	Targeted group	Model inception cohort	Method of targeting evaluated?
Hershman et al.[15]	Chemoprevention	High-risk women	Women with elevated risk by specific characteristics	Separate analysis by risk group
Noe et al.[16]	Chemoprevention	High-risk women	Women with elevated risk by specific characteristics	No
Anderson et al.[17]	Risk-reducing surgery; screening; chemoprevention	*BRCA1/2* mutation carriers	*BRCA1/2* mutation carriers	No
Moore et al.[18]	MRI screening	High-risk women	Women with ≥ 15% lifetime risk by Claus algorithm	No
Plevritis et al.[19]	MRI screening	*BRCA1/2* mutation carriers	*BRCA1/2* mutation carriers	Separate analysis by *BRCA* mutation; sensitivity analysis of breast cancer risk
Taneja et al.[20]	MRI screening	High-risk women	*BRCA1/2* mutation carriers or high risk by specific characteristics	Separate analysis for gene mutation carriers and others
Grann et al.[21]	Risk-reducing surgery; screening	*BRCA1/2* mutation carriers	Cancer-free women of Ashkenazi Jewish descent	Analysis explicitly focused on testing
Holland et al.[22]	Risk-reducing surgery	*BRCA1/2* mutation carriers	Cancer-free women with concern or family history	Analysis explicitly focused on testing
Kwon et al.[23]	Risk-reducing surgery	*BRCA1/2* mutation carriers	Breast cancer patients under age 50	Analysis explicitly focused on testing

found a similar result, reporting that the incremental cost-effectiveness of targeted MRI screening was more sensitive to predicted breast cancer risk than to any other model parameter. In most of these studies, breast cancer risk was treated as a source of variability, not uncertainty. Thus, they did not directly address the impact of test performance on costs and health outcomes.

Most studies of targeted risk-reduction strategies have compared interventions for cohorts of women whose breast cancer risk is assumed to be known. Few studies have assessed the economic impact of the decision to perform a test that yields information about breast cancer risk. Grann et al.[21] examined the cost-effectiveness of *BRCA* testing in cancer-free women of Ashkenazi Jewish descent. This analysis explicitly considered the costs and outcomes of the test itself and found that the cost-effectiveness of testing varied based on the risk-reduction strategy (mastectomy, oophorectomy, or surveillance) that was assumed to be administered to women who test positive for a *BRCA* mutation. Using a similar approach, Holland et al.[22] estimated the cost-effectiveness of *BRCA* testing in cancer-free women concerned about a mutation or with a family history of breast or ovarian cancer. They found that the incremental cost-effectiveness of *BRCA* testing varied with the probability of a mutation and with the quality-of-life benefit associated with a negative test result.

Kwon et al.[23] estimated the economic impact of *BRCA* testing in women newly diagnosed with breast cancer, finding that testing was most cost-effective for women with high-risk tumor features. Although this study focused on a different point in the breast cancer continuum, addressing a targeted disease-management intervention rather than a disease prevention intervention (Fig. 3), it followed a design quite similar to the analyses of *BRCA* testing in cancer-free women and, notably, explicitly considered costs and outcomes of the targeting test itself.

Economic evaluations of targeted treatment strategies

Efforts to target breast cancer treatment have focused primarily on systemic therapy. Beyond standard tumor characteristics such as size, regional lymph node involvement, and hormone receptor status, newer methods of guiding systemic therapy decisions include assays to detect individual tumor genes and proteins and gene expression profiles based on the activity of multiple tumor genes. Examples of these strategies include human epidermal growth factor receptor-2 (HER2) testing to identify candidates for the monoclonal antibody trastuzumab and tumor gene expression profiling (GEP) to guide the use of adjuvant chemotherapy.

Approximately 20–30% of breast cancers overexpress the HER2 protein, a product of the HER2/*neu* oncogene.[25,26] Trastuzumab, a monoclonal antibody, has demonstrated antitumor effects in HER2-overexpressing breast cancer, increasing progression-free survival in women with HER2-positive metastatic breast cancer and improving both disease-free and overall survival in women with HER2-positive early-stage breast cancer.[27–29] The American Society of Clinical Oncology, the College of American Pathologists, and the National Comprehensive Cancer Network (NCCN) recommend routine testing of all newly diagnosed breast cancers with immunohistochemistry (IHC), fluorescence in situ hybridization (FISH), or a combination of the two, and trastuzumab is only indicated for women with a positive HER2 test result.[30,31] However, IHC and FISH vary in their accuracy and performance characteristics, and the laboratories that perform these tests may vary in their procedures, accreditation, and proficiency.

Many investigators have evaluated the cost-effectiveness of trastuzumab but few explicitly examined methods of identifying

trastuzumab candidates (Table 2). Elkin et al.[32] compared seven strategies for targeting trastuzumab in women with metastatic breast cancer. Lidgren et al.[34] performed a similar analysis in the adjuvant setting, comparing five strategies for targeting trastuzumab in women with early-stage breast cancer. Both studies found that strategies involving FISH, used alone or as confirmation of positive IHC results, were optimal for targeting trastuzumab therapy. They also demonstrated the sensitivity of results to assumptions about the characteristics of the targeting test. Both found that IHC alone was dominated by a strategy involving FISH if the specificity of IHC was <100%, and Elkin et al. found a 3-fold difference in the ICER for FISH alone as the sensitivity of IHC varied between 50% and 99%. A third study compared seven different HER2 testing strategies but measured effectiveness as the number of cases with accurately determined HER2 status, thus ignoring costs and outcomes of targeted treatment with trastuzumab.[36]

Numerous other studies have examined the cost-effectiveness of trastuzumab but did not explicitly evaluate the impact of HER2 testing strategies. Rather, they assessed the cost-effectiveness of trastuzumab in a group already identified as having HER2-positive disease, generally by the same methods used in one of the clinical trials from which they derived estimates of trastuzumab's efficacy.[35,37–46] Most ignored the costs of testing. Some assigned a total cost of testing per HER2-positive patient, reflecting the costs of testing all patients with breast cancer in the relevant clinical setting, but they explicitly addressed neither test performance nor outcomes in women with a negative test result.[33,37] As illustrated in Figure 1, analyses that focused on a group already identified by a positive HER2 test result necessarily excluded the economic and health consequences of omitting trastuzumab in women with a negative—true or false—test result. Authors of one of these studies, commenting on the omission of testing strategies from their model, noted that if testing had been included, "the ICER for trastuzumab-based therapies would be less favorable."[35]

In women with early-stage breast cancer, systemic adjuvant chemotherapy is often given to reduce the risk of disease recurrence after primary surgical treatment. The use of adjuvant chemotherapy has traditionally been guided by basic tumor characteristics, and it is generally the standard of care for women with large tumors, axillary lymph node involvement, or tumors that are not hormone responsive.[30] In women with more favorable tumor characteristics, the absolute decrease in recurrence risk associated with adjuvant chemotherapy may be quite small, and therefore, the benefits and risks of adjuvant chemotherapy must be weighed carefully. GEP involves analysis of tumor genes using DNA microarray or real-time polymerase chain reaction technology.[53] The GEP tests commercially available in the United States use tumor gene signatures from selected candidate genes to estimate a patient's risk of disease recurrence based on proprietary algorithms. GEP has been recommended as a tool for risk-stratifying patients who would not be candidates for adjuvant chemotherapy based solely on tumor features such as size, hormone receptor status, and lymph node involvement.[30,31] In these women, GEP may distinguish those who will benefit most and least from adjuvant chemotherapy.

Six studies have assessed the cost-effectiveness of GEP for targeting adjuvant chemotherapy (Table 2). Five evaluated adjuvant chemotherapy assignment based on the OncotypeDX 21-gene real-time polymerase chain reaction assay in women with node-negative, estrogen receptor-positive disease, compared with NCCN treatment guidelines,[47] with universal chemotherapy or no chemotherapy,[48,49] with treatment guided by the Adjuvant! Online risk prediction algorithm,[51] and with pretest physician recommendations.[50] Targeting adjuvant chemotherapy with GEP was either cost-saving or was associated with a modest ICER, compared with NCCN guidelines and with strategies of universal chemotherapy or no chemotherapy.[47–49] Compared with Adjuvant! Online, GEP-based chemotherapy assignment cost approximately $63,000 per quality-adjusted life-year gained.[51] In all of these studies, treatment assignment based on GEP relied on the manufacturer's classification of the test result, or recurrence score, into groups of "low," "intermediate," and "high" risk, and all assumed that in a GEP-based strategy, chemotherapy would be given to those in the intermediate- and high-risk groups. Although all performed sensitivity analysis on the recurrence risk estimates associated with each group, none evaluated strategies that involved alternative risk-stratified treatment assignment, and none explored the relationship between the thresholds for classifying recurrence scores into risk groups and the cost-effectiveness of using GEP to target chemotherapy. One study reported that results were most sensitive to assumptions about probabilities "relating to risk groups and recurrence rates."[51]

Oestreicher et al.[52] evaluated the Mammaprint 70-gene microarray-based assay in a hypothetical cohort of women younger than 55 years with Stage I or node-negative Stage II disease. Compared with NIH consensus treatment guidelines, adjuvant chemotherapy assignment based on GEP was not only less costly but also less effective. In sensitivity analysis, the authors evaluated the impact of each strategy's performance characteristics, which were estimated from the dataset in which the GEP assay was originally validated. They also explored the relationship between cost-effectiveness and the test result cutoff for defining high-risk women, and they found that at any threshold, the GEP-based strategy did not attain the sensitivity of at least 95% which would make it more cost-effective than the guideline-based strategy.

RECOMMENDATIONS FOR ECONOMIC ASSESSMENT OF TARGETED INTERVENTIONS

Although targeted breast cancer interventions have been the subject of numerous CEAs, deficiencies in these analyses prompt concern. Most importantly, few of the studies we identified explicitly evaluated the relationships among the method of targeting, the accuracy of the targeting test, and the outcomes of the targeted intervention. Of those that did, some directly compared alternative targeting strategies in their base-case models, whereas others explored assumptions about alternative targeting strategies or test accuracy in sensitivity analysis. Regardless of the analytic method by which they evaluated alternative targeting strategies or test accuracy, all the studies that did so reached a similar conclusion: assumptions about the targeting test had a substantial impact on the estimated cost-effectiveness of the targeted intervention. On the basis of these findings, we offer the following recommendations for economic analyses of targeted cancer interventions:

1. CEAs of targeted interventions should explicitly consider the costs and outcomes of the method of targeting.
2. When the method of targeting is a test that can be compared with a gold standard, the analyst should explicitly consider the impact of the test's performance characteristics on costs and health outcomes.
3. When the method of targeting is a risk prediction algorithm, the analyst should explicitly consider the impact of thresholds for risk group definitions and subsequent actions on costs and health outcomes.

The manner in which testing and risk prediction are explicitly considered may vary, depending on the clinical context. In cases where a single test and its positivity criterion are already estab-

Table 2 Cost-effectiveness studies of targeted breast cancer disease management interventions

Study	Intervention	Targeted group	Model inception cohort	Method of targeting evaluated?
Elkin et al.[32]	Trastuzumab in metastatic setting	Patients with HER2-positive disease	Patients with metastatic disease	HER2 testing strategies modeled explicitly
Norum et al.[33]	Trastuzumab in metastatic setting	Patients with HER2-positive disease	Patients with HER2-positive disease	Included test costs, but did not compare testing strategies or evaluate test performance
Lidgren et al.[34]	Adjuvant trastuzumab	Patients with HER2-positive disease	Patients postsurgery and adjuvant chemotherapy	HER2 testing strategies modeled explicitly
Kurian et al.[35]	Adjuvant trastuzumab	Patients with HER2-positive disease	Patients with HER2-positive disease	No
Dendukuri et al.[36]	Trastuzumab in adjuvant or metastatic setting	Patients with HER2-positive disease	All newly diagnosed patients	Analysis explicitly focused on testing; treatment costs and outcomes excluded
Garrison et al.[37]	Adjuvant trastuzumab	Patients with HER2-positive disease	Patients with HER2-positive disease	Included test costs, but did not compare testing strategies or evaluate test performance
Skedgel et al.[38]	Adjuvant trastuzumab	Patients with HER2-positive disease	Patients with HER2-positive disease	No
Liberato et al.[39]	Adjuvant trastuzumab	Patients with HER2-positive disease	Patients with HER2-positive disease	No
Norum et al.[40]	Adjuvant trastuzumab	Patients with HER2-positive disease	Patients with HER2-positive disease	No
NICE[41]	Adjuvant trastuzumab	Patients with HER2-positive disease	Patients with HER2-positive disease	No
Millar and Millward[42]	Adjuvant trastuzumab	Patients with HER2-positive disease	Patients with HER2-positive disease	No
Dedes et al.[43]	Adjuvant trastuzumab	Patients with HER2-positive disease	Patients with HER2-positive disease	No
Neyt et al.[44]	Adjuvant trastuzumab	Patients with HER2-positive disease	Patients with HER2-positive disease	No
Shiroiwa et al.[45]	Adjuvant trastuzumab	Patients with HER2-positive disease	Patients with HER2-positive disease	No
Chen et al.[46]	Adjuvant trastuzumab	Patients with HER2-positive disease	Patients with HER2-positive disease	No
Hornberger et al.[47]	Adjuvant chemotherapy	Patients at high risk of recurrence by GEP	Patients with node-negative, HR-positive disease	Yes, but did not evaluate test result thresholds
Lyman et al.[48]	Adjuvant chemotherapy	Patients at high risk of recurrence by GEP	Patients with node-negative, HR-positive disease	Yes, but did not evaluate test result thresholds
Cosler et al.[49]	Adjuvant chemotherapy	Patients at high risk of recurrence by GEP	Patients with node-negative, HR-positive disease	Yes, but did not evaluate test result thresholds
Klang et al.[50]	Adjuvant chemotherapy	Patients at high risk of recurrence by GEP	Patients with node-negative, HR-positive disease	Yes, but did not evaluate test result thresholds
Tsoi et al.[51]	Adjuvant chemotherapy	Patients at high risk of recurrence by GEP	Patients with node-negative, HR-positive disease	Yes, but did not evaluate test result thresholds
Oestreicher et al.[52]	Adjuvant chemotherapy	Patients at high risk of recurrence by GEP	Patients with node-negative, HR-positive disease	Comparison of test-treat strategies and sensitivity analysis of test performance

BC, breast cancer; GEP, gene expression profile; HR, hormone receptor.

lished and widely used in routine practice, then an economic analysis of newer or experimental interventions for the targeted group might reasonably exclude test costs and accuracy from the quantitative analysis. In these cases, analysts should, at a minimum, acknowledge the role of the targeting test and comment on its cost and accuracy. However, the impacts of test cost and performance merit formal analysis when there is more than one testing option, when test timing is variable, when the positivity criterion or risk threshold is not well established, or when a new test becomes available. In addition, economic evaluations may be used to challenge established testing practices if new scientific discoveries suggest that alternative tests or nontargeted strategies may be more effective or cost-effective.

Our recommendations should not be excessively burdensome to analysts using decision-analytic simulation. Decision analysis is a formal, systematic, and quantitative method for comparing the outcomes of alternative clinical strategies under circumstances of uncertainty.[54,55] Although cost-effectiveness may also be estimated in the context of a randomized clinical trial, decision analysis offers a number of unique advantages. In a decision analysis, the analyst can compare more strategies over a longer time horizon than are typically feasible in the context of a clinical trial. Decision analysis is well suited to answering the important questions of how and when to use a targeting test, which of several available tests to use, and which action to take in response to a test result. A decision analysis can also simulate factors such as patient nonadherence, which influence outcomes in routine practice settings but are often minimized in a clinical trial.

Although the usefulness of a decision-analytic simulation depends on the quality of available data, decision analysis lends itself quite readily to the evaluation of alternative strategies and assumptions about important parameters such as test performance. Even with limited data, the analyst can model hypothetical scenarios to assess the robustness of results to assumptions about the method of targeting. Also, as technologies evolve over time, decision-analytic simulations can evaluate new scenarios. Such information is essential to clinicians, payers, and others who must often make decisions about the use of new technologies before clinical trial results are available.

CONCLUSIONS AND FUTURE APPLICATIONS

Targeted cancer prevention, screening, and treatment offer the promise of maximizing health benefits while minimizing health risks to yield an optimal gain from limited resources. The costs of cancer care have increased dramatically over time, and out-of-pocket spending can pose a serious financial burden to patients and their families.[56] The high cost of many new targeted interventions, especially targeted therapeutic agents, warrants their economic evaluation. As studies of targeted breast cancer interventions demonstrate, the strategy used to target an intervention is likely to have a substantial impact on the cost-effectiveness of the intervention. Consequently, an economic analysis that fails to consider the accuracy of the targeting test or alternative methods of targeting does not sufficiently inform decisions about adoption of the targeted intervention.

The examples reviewed in this study represent the most mature applications of targeted interventions in breast cancer. Numerous other targeted interventions are currently under investigation. These include selection of endocrine therapy based on *CYP2D6* genotype[57,58] and omission of radiation therapy in women with specific single-nucleotide polymorphisms associated with an increased risk of radiation toxicity.[59] The economic assessment of targeted interventions is relevant to other cancers as well. In colorectal cancer, for example, emerging targeted interventions include intensive screening and prophylactic surgery in individuals with Lynch syndrome or familial adenomatous polyposis who are at high risk of disease due to a germline genetic mutation[60–63] and chemotherapy assignment based on mutations in the *KRAS* gene and *UGT1a1* gene,[64,65] genes associated with response to or adverse effects of specific chemotherapeutic agents.

Targeted risk reduction, prevention, screening, and treatment are motivating substantial research activity in breast, colorectal, and other cancers. As discoveries move from bench to bedside, their high costs prompt concern about the allocation of limited healthcare resources. Comparative effectiveness research—including cost-effectiveness analysis—has been enthusiastically promoted to support informed medical decision making.[66,67] Analyses that follow the recommendations offered herein will best inform the optimal deployment and utilization of targeted cancer interventions.

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