Economics of Genomic Testing for Women With Breast Cancer

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Background: Creating the value proposition for innovations in personalized genomic medicine requires generation of evidence-based demonstrations of clinical utility and cost-effectiveness.

Objectives: To assess economic studies of genomic testing for women with breast cancer and to understand the value of genomic testing for multiple stakeholders.

Study Design: Literature review.

Methods: A structured review of the literature was conducted to identify and synthesize available evidence regarding economic analyses of genomic testing for breast cancer. A search was conducted using PubMed and Google Scholar for articles published between January 1, 2005, and December 31, 2010. The search was then expanded to include articles as far back as 1981. In addition, snowball methodology was used to identify and include additional articles based on frequency of author publication and frequency of citation in the literature.

Results: Of the articles reviewed, a subset of 9 articles describing specific economic analysis studies were included in a more in-depth, side-by-side comparison. This review of the literature on the economics of genomic testing for women with breast cancer found that most of the economic evidence relied on modeling rather than clinical trial data.

Conclusions: Facilitating the diffusion of new technology will require more data to satisfy the payer, provider, and societal perspectives. Conversely, willingness by payers and clinicians to consider economic modeling data as part of their evaluation of new technologies can help facilitate the diffusion of newly developed genomic tests.

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In women, breast cancer accounts for nearly 1 in 4 cancers. It is the most common cancer in women aside from skin cancer. It has the second-greatest mortality rate for women, exceeded only by lung cancer.[1] Treatment pathways for breast cancer recurrence after primary surgical and radiation therapy are complex and are based on multiple known risk factors. Women are offered adjuvant chemotherapy if the risk of recurrence is above a certain threshold.[2]

While the benefit of adjuvant chemotherapy is well established in patients with early-stage breast cancer that is estrogen receptor (ER) positive and lymph node negative, 65% of women diagnosed with invasive breast cancer have lymph node–negative disease; of these, 15% are expected to die or have distant metastasis in 10 years.[3] Currently, novel genomic evidence about the diversity of patients is challenging scientists to develop and validate more personalized approaches to treatment.

GENOMIC MEDICINE

Advances in genomic diagnostics and personalized treatment have the potential to improve health outcomes, reduce mortality, and increase quality of life for cancer patients. Genomic tests analyze the genetic profiles of patients' tumors by generating a "recurrence score" based on a particular algorithm. The recurrence score predicts the likelihood of cancer recurrence and informs decision making.

Several types of genomic tests are available today in the United States for breast cancer, including Oncotype DX, MammaPrint, and CancerTYPE ID. Oncotype DX is a 21-gene assay test that gives patients with stage 1 or 2 ER-positive, lymph node-negative breast cancer a recurrence score between 0 and 100.[4] MammaPrint is a 70-gene assay to determine the risk of cancer recurrence for ER-positive or ER-negative, lymph node–negative patients with early-stage breast cancer (stages 1 and 2).[5,6] CancerTYPE ID measures a 92-gene expression taken from a tumor biopsy to determine 30 different types of tumors. A component of the test, Breast Cancer Index, can be ordered if the tumor is the suspected primary source.[6] CancerTYPE ID is not as widely used as the other 2 tests in breast cancer.

ECONOMICS OF BREAST CANCER

The total cost of breast cancer includes the financial burdens for the

In this article
Take-Away Points / p1025
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patients, their families, and society. The National Cancer Institute estimates the national annual financial cost of breast cancer care at $13.9 billion.[7] Breast cancer care represents the largest portion of all cancer care expenditures. As the healthcare system works to find ways to pay for genomic technology and healthcare costs continue to trend upward, the potential cost savings and productivity gains associated with advances in genomic diagnostics and personalized treatment that avoid unnecessary and ineffective treatments are appealing.[8]

Take-Away Points

Many studies document the scientific basis for genomic testing for breast cancer, but few tools allow payers to assess the value of these genomic tests.

- Economic research on genomic testing for breast cancer has not involved randomized controlled trials or other direct trial data.
- Research on the economics of genomic testing will consist primarily of modeling studies for the foreseeable future.
- Payers should use economic models as the best available evidence for which genomic tests should be reimbursed.
- Payers should demand more funding for high-quality prospective trials of genomic tests with an economic evaluation.

NEW CONTRIBUTION

Economic analysis provides a framework for assessing the value of clinical outcomes, as well as for determining how that value might differ by population.[9] This literature review improves upon previously published literature reviews of genomic testing for breast cancer by focusing on the economic evidence. We are not aware of other structured reviews on this topic that utilize the economic perspective. Our key findings are that research in this area has been limited and is likely to consist primarily of modeling studies for the foreseeable future. Additional funding, better outcomes data, and regulation are identified as barriers to adoption of this new technology.

CONCEPTUAL FRAMEWORK

An economic evaluation prioritizes the efficient use of scarce resources. As a result, economic evaluation leads to the test that best balances the trade-offs among available alternatives rather than simply selecting the cheapest or most valid test.[10] While data from randomized controlled trials are a gold standard, an economic analysis uses models to combine costs and outcomes. The combination of both types of data in a model that allows for the evaluation of the cost-effectiveness of a particular type of technology results in information that maximizes efficiency.[11]

This framework guided the snowball methodology, described in further detail in the **eAppendix** (available at **www.ajmc.com**). In order to appear in our literature review, a study had to cover the clinical area of breast cancer, with the scientific application of a genomic test. Further, the analysis had to include a cost-effectiveness analysis broadly defined. A cost-effectiveness analysis uses 2 basic building blocks—economic cost and clinical effectiveness—to assess the value of a test, drug, or other healthcare product. Value comes from calculating the incremental improvement derived from a particular test over existing technology.[12]

This conceptual framework resulted in a review of 9 studies as described in the section titled Published Studies on Economic Outcomes. Due to the small number of studies available for each topic area of the review, we present studies on an individual basis rather than presenting summary results across studies.

PUBLISHED STUDIES ON ECONOMIC OUTCOMES

Several studies have been published utilizing economic modeling methods to analyze the benefits and costs of genomic testing for breast cancer. The costs of genomic testing are 2-fold: the cost of the genomic test itself and the costs associated with false-negative or false-positive results. For a complete listing of cost variables, please see the Ishikawa Fishbone Analysis[13,14] depicted in the **Figure**. The Jefferson Population Health Continuing Professional Education Collaborative created the diagram based on the references cited in the article. Thus, the Figure is an original work based on the source material from this literature review.

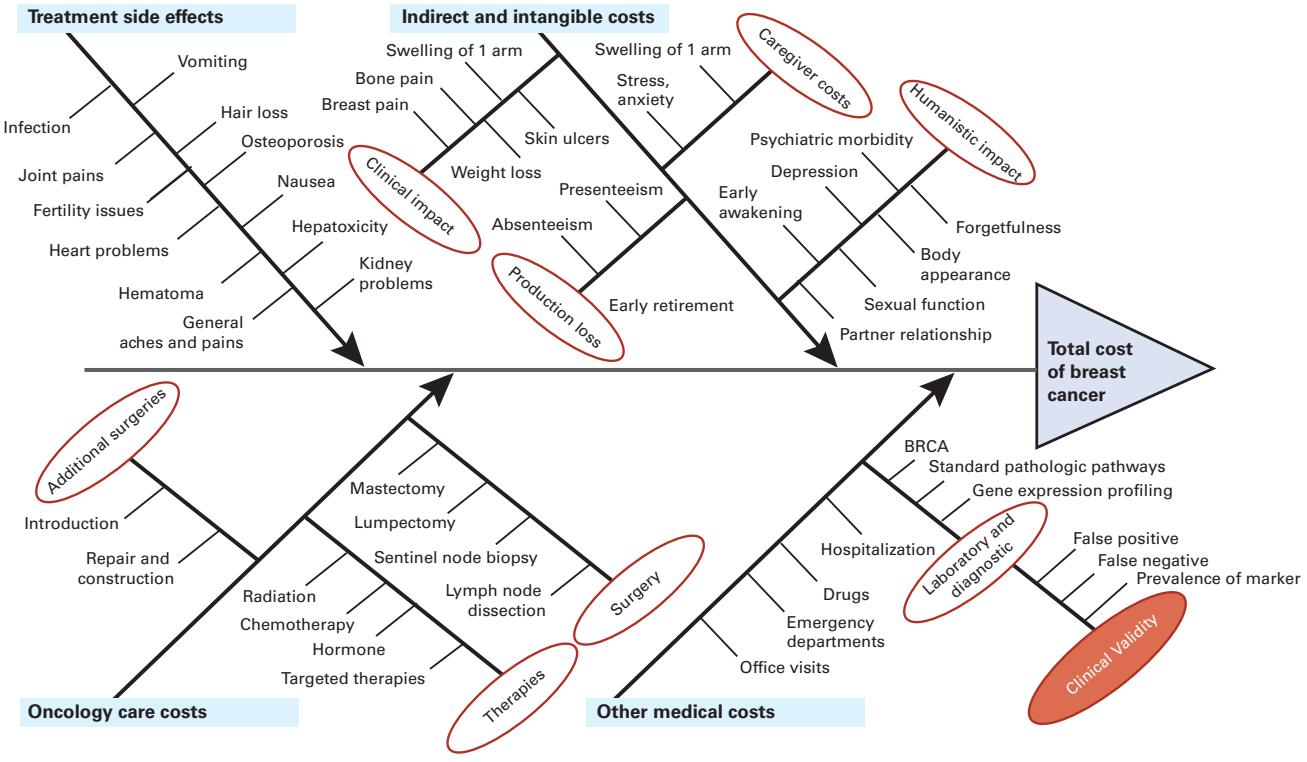
Direct Costs

The direct cost of genomic tests is clear and varies by test and payer. The evidence report commissioned by the Evaluation of Genomic Application in Practice and Prevention Working Group and the Agency for Healthcare Research and Quality identified the 3 genomic tests for women with breast cancer that are clinically available in the United States (MammaPrint, Oncotype DX, and CancerTYPE ID).[2,9] The cost is generally regarded as $3460, with a range of $1960 to $4860. The cost for a particular patient depends on factors such as insurance coverage policy and regional variability.[15]

Indirect Costs

Economic modeling studies have focused primarily on the direct costs associated with breast cancer treatment and recurrence, while failing to fully address indirect costs. For

Figure. Cost Variables Associated With Genomic Breast Cancer Treatment



patients, these indirect costs play a significant role in treatment decision making. The false-negative cost mainly includes the cost of nonfatal recurrences and mortality during recurrence or chemotherapy, and is estimated at $51,000.[16] Medical costs and related nonmedical costs of unnecessary chemotherapy are high: treatment costs varied from $10,000 to $23,000 in a prior study that was included in our side-by-side comparison.[17] In another study included in our comparison, adverse events related to chemotherapy were found to cost more than $2000 per patient.[18] In a third study included in our comparison, Bacchi and colleagues[19] stated that the 18% difference in cost between use and nonuse of an assay could be attributed to the cost of medications for prophylaxis and treatment of side effects of chemotherapy.[4]

There is limited mention of indirect costs (eg, productivity loss) in any of the published studies we reviewed. There have been attempts to estimate the burden of side effects in terms of quality of life or other patient-reported outcome measures. However, there is no systematic study that translates indirect costs into monetary terms. Data used in a payer perspective study that we reviewed focused on the avoidance of costs of long-term adjuvant chemotherapy such as infertility and second primary tumors.[20] A study by Hornberger and colleagues[21] in 2011 that was included in our comparison also did not translate indirect costs into monetary terms.

Clinical Benefits

The most significant benefit expected from tailoring treatment using genomic testing is a reduction in adverse drug effects for subpopulations that may not benefit from chemotherapy. The adverse effects of chemotherapy include nausea, vomiting, alopecia, fatigue, vasomotor symptoms, pain, and risk of infection.[22] McArdle and colleagues[23] found that 85% of patients receiving chemotherapy experienced nausea and vomiting and suffered distress, 36% of patients lost their hair, and 39% of patients developed mucosal ulceration. They also reported that depression and anxiety occurred in patients receiving chemotherapy, although psychiatric morbidity was present for some of these patients even prior to invasive surgery.

Humanistic Benefits

A major benefit of genomic testing is extended quality-adjusted life-years (QALYs). Hornberger and colleagues[24] analyzed the preliminary QALYs for using 6-month chemotherapy treatment for "low-risk" patients. Their analysis, included in our comparison, found that if the utility of chemotherapy was set at 0.5 for 6 months of treatment, then chemotherapy was of no benefit for those low-risk patients, as no gain in QALYs resulted. However, survivors who received chemotherapy tended to have greater preference for undergo-

ing chemotherapy than survivors who did not receive chemotherapy.[24] This and other previous studies have shown there is ambivalence and inconsistency in patients' reports on how they view the value of chemotherapy. The literature does not clearly provide information on reduction of QALYs for the breast cancer patients who were distant recurrence free after primary surgical and radiation therapy but who were offered chemotherapy according to current breast cancer treatment practice.

COMPARATIVE EFFECTIVENESS ANALYSES

The economic evaluation of genomic testing requires a valuation of whether the benefits of early diagnosis and treatment outweigh the costs of the test. This framework can include comparing direct and indirect costs, as well as clinical, financial, and humanistic benefits. Which costs and benefits are included depends on the study's perspective. Using decision analysis, one can choose a particular test over other diagnostic steps or interventions.

Modeling-Based Cost-Effectiveness Analysis

For the decision analysis of genomic testing, we included 3 studies that compared clinical and economic outcomes of genomic testing–guided adjuvant treatment versus guideline-based adjuvant therapy in our comparison.[7,17,25] We also included in our comparison 2 studies of different adjuvant treatment strategies: chemotherapy treatment for all patients (or no chemotherapy) or adjuvant therapy strategies guided by genomic testing.[24,26]

We included 5 cost-effectiveness studies of Oncotype DX, all of which concluded that treatment guided by genomic testing is cost-effective compared with conventional treatment selected according to guidelines. In 1 study, Lyman and colleagues[26] examined the incremental cost-effectiveness ratio associated with 3 treatment strategies: tamoxifen alone, chemotherapy followed by tamoxifen, and recurrence score–guided treatment. They found that genomic testing is cost-effective relative to the other strategies.[26] In another study, Klang and colleagues[18] applied recurrence score–guided recommendations to patients of a managed care organization in Israel. They found that treatment pathways were changed from the initial recommendation (according to traditional prognostic pathways) in 40% of patients and that the incremental cost-effectiveness ratio for using Oncotype DX was $10,770 per QALY.[18] That is well below the international norms of willingness to pay used in Israel and the threshold of $50,000 per QALY gained commonly used in the United States context (**Table**).[27]

One study included in our comparison discussed cost-effectiveness analyses of a 70-gene expression-profiling test (MammaPrint). This study, performed in 2005, found that MammaPrint had lower costs and worse outcomes, in terms of lower life expectancy and QALYs, than the National Institutes of Health clinical guidelines for treatment of breast cancer. Specifically, the study found that use of the test "resulted in an absolute 5% decrease in the proportion of cases of distant recurrence prevented, 0.21 fewer QALYs, and a cost savings of $2882."[15] A more recent study performed in 2010, also in our comparison, found that MammaPrint had a favorable incremental cost-effectiveness ratio of $7000 per QALY and $10,000 per life-year saved compared with Adjuvant! Online software guidance.[7] The contradictory findings from these 2 studies are primarily due to the control group being used—National Institutes of Health guidelines in one case and decision software in the other case. The findings may also be related to the timing of these studies, one of which was published 5 years later than the other.

Two international studies included in our comparison conducted generic cost-effectiveness analyses of genomic testing rather than selecting a specific marketed product. One European study used a different type of genomic test (189-gene expression profiling) not usually available in the US market and applied cost-minimization analysis.[28] They found that compared with conventional adjuvant chemotherapy, genomic testing is cost-effective only if the test cost is less than €2090 ($2720).[28] A Brazilian study focused on the financial impact of using genomic testing (21-gene expression profiling) by taking into account the medical costs and excluding utility or QALY measures.[19] Bacchi and colleagues[19] conducted a Web-based survey among medical oncologists in Brazil and compared the costs associated with individual decisions for treating hypothetical patients with the costs associated with 21-gene expression assay–guided decisions. They found that for a hypothetical cohort of 100 patients with access to the test, $79,400 would be saved in direct medical costs.

Perspectives Represented in Our Review

In our economic analyses we compared, payer, provider, and societal perspectives. A total of 3 studies examined the societal perspective, 4 described the payer perspective, and 2 studies used a provider perspective (Table 1).

Those studies that used the societal perspective included relevant costs and outcomes that were associated with breast cancer in their models, as well as cost utility. Including cost utility proved extremely useful.

Studies using the payer perspective compared the actual cost per QALY with the acceptable threshold in order to determine the cost-effectiveness of the assay.[21] Out-of-pocket pa-

Table. Economic Studies of Genomic Testing for Women With Breast Cancer

Product	Study Authors	Study Title	Model	Comparators	Perspective	Duration
Oncotype DX	Hornberger,[24] 2005	Economic analysis of targeting chemotherapy using a 21-gene RT-PCR assay in node-negative, estrogen-receptor-positive, early-stage breast cancer	Markov model	NCCN criteria vs recurrence score based on 21-gene RT-PCR assay	Societal	Lifetime
	Lyman,[26] 2007	Impact of a 21-gene RT-PCR assay on treatment decisions in early-stage breast cancer: an economic analysis based on prognostic and predictive validation	Cost-effectiveness analysis	Tamoxifen alone vs chemotherapy followed by tamoxifen vs recurrence score–guided therapy based on the gene RT-PCR assay	Societal	10 years
	Klang,[18] 2010	Economic implications of 21-gene breast cancer risk assay from the perspective of an Israeli managed healthcare organization	Markov model	Oncotype DX vs prognostic pathways	Israeli managed care	30 years or lifetime
	Retèl,[25] 2010	Cost-effectiveness of the 70-gene signature vs St. Gallen guidelines and Adjuvant Online for early breast cancer	Markov model	70-gene signature vs clinical pathologic test result using the St. Gallen guidelines vs pathologic test result using the Adjuvant! online software	Healthcare	20 years
	Hornberger,[21] 2011	US insurance program's experience with a multigene assay for early-stage breast cancer	Markov model	Simulated survival and costs of breast cancer with and without the use of 21-gene recurrence score	US payer perspective	Lifetime
MammaPrint	Oestreicher,[15] 2005	Gene expression profiling and breast cancer care: what are the potential benefits and policy implications?	Markov model	NIH consensus guidelines vs gene expression profiling	Societal	Lifetime
	Chen,[7] 2010	Cost-effectiveness of 70-gene MammaPrint signature in node-negative breast cancer	Markov model	70-gene MammaPrint vs Adjuvant! Online software	US payer perspective	Lifetime
	Bacchi,[19] 2010	Potential economic impact of the 21-gene expression assay on the treatment of breast cancer in Brazil	Budget analysis	Web-based survey with 30 Brazilian medical oncologists vs the 21-gene expression assay	Brazilian third-party payers	Not specified
Not specified	Marino,[28] 2010	Economic issues involved in integrating genomic testing into clinical care: the case of genomic testing to guide decision-making about chemotherapy for breast cancer patients	Budget analysis	Standard anthracyclines plus taxane chemotherapy vs strategy based on 189-gene expression signature	Healthcare provider	Clinical trial specified

NCCN indicates National Comprehensive Cancer Network; NIH, National Institutes of Health; RT-PCR, real-time polymerase chain reaction.

tient costs and indirect medical costs are not included in the payer perspective.

STRENGTHS AND WEAKNESSES OF THE PUBLISHED ECONOMIC ANALYSES

Data Versus Modeling Methods

The studies reviewed are largely based on data from clinical trials. They all rely on economic modeling methods to generate cost predictions or projections. A variety of modeling methods were used, most commonly Markov modeling. Cost-effectiveness analysis and budget impact analysis were also used.

Strengths

These economic studies took into account the opportunistic cost of having unnecessary chemotherapy for a certain subpopulation and humanistic measures such as quality of life. The majority of studies provided monetary thresholds for each

product in the market, which helped enable economic decision making about whether to use genomic testing.

Weaknesses

Economic modeling has significant limitations compared with clinical trials. Because these studies are usually extrapolated from clinical trial data, the same prognostic accuracy may not apply in a real-world setting. The Evaluation of Genomic Applications in Practice and Prevention Working Group identified 2 additional concerns. One is that details and characteristics about certain tests are not published. Additionally, "concerns about the parameter estimates, lack of sensitivity analyses to assess sources of bias, and changes in the National Comprehensive Cancer Network (NCCN) guidelines reduce the confidence and relevance of one of these studies."[2] We agree that comparative effectiveness analysis in this area is challenging because the outcome of value is more difficult to measure than clinical end points and because technology is evolving so rapidly. To improve the economic evidence base for these tests, we believe that there should be increased funding for economic evaluation and that the results of any testing should be made more transparent.

Future Research and the Case for the Economic Benefit of Genomic Testing

There is a great need for additional translational research, including both clinical and outcomes research.[29,30] There is also an opportunity to develop tests that can inform treatment decisions for subpopulations for whom current tests are not applicable, such as patients diagnosed with triple-negative breast cancer or those with ER-negative status. There may also be interest in comparative effectiveness research results from head-to-head trials comparing genomic tests and treatment outcomes.

Genomic medicine requires additional evidence about the value of these tests to reach its full potential.[31]A value calculation requires evidence of both clinical utility and economic effectiveness.[32] Several articles discuss the barriers genomic medicine faces with regard to making the case for value. Experts recommend additional funding for trials oftranslational research, specifically in phases 2 through 4, additional evidence of clinical utility,[33] more outcomes data, and improved regulation of genomic test production.[34,35]

REGULATION AND REIMBURSEMENT POLICIES

Regulation

Genomic tests for breast cancer are relatively new. In the United States, regulation is the responsibility of the US Food and Drug Administration (FDA), which regulates genomic tests as devices. The FDA has indicated a strong preference for co-approval of genomic tests and the treatments that they test for.[36] It has issued significant guidance on genomic technologies that are subject to FDA approval. However, "the overwhelming majority of genetic tests are not currently subject to FDA scrutiny."[37] The international regulatory perspective is generally more focused on a combination of effectiveness and cost-effectiveness compared with the US perspective, which is focused solely on effectiveness. For that reason, additional cost-effectiveness studies may help with the diffusion of genomic testing outside the United States.

Reimbursement

Reimbursement for genomic testing depends upon the type of insurance, if any, that the patient has. Oncotype DX is widely utilized and reimbursed, and is often covered by Medicare. Trosman and colleagues[38] studied the approaches used by private payers to develop their coverage strategy for Oncotype DX and found that all payers prioritized clinical evidence as the most important decision factor, also taking into account medical society recommendations. The majority of payers were not concerned that Oncotype DX has not received FDA approval.

Future Study Designs

The economic analysis studies reviewed in this article make a case for the cost-effectiveness of genomic testing for breast cancer treatment decision making. While the modeling studies we reviewed do support the value proposition for genomic testing for breast cancer, more must be done to show the projected benefits that could be realized in real-world settings. Trials centered around the actual use of such tests in the breast cancer population are necessary to bolster the evidence base.[33]

Policy Implications

The cooperation of multiple stakeholders will be essential if genomic medicine is to reach its full potential. The barrier to progress for genomic medicine is the lack of empirical evidence for the clinical utility and value of genomic testing.[29,33] The literature appears to support the need for additional studies to evaluate the value of genomic testing for breast cancer.[38] The lack of translational research is mentioned repeatedly as an obstacle to establishing the clinical utility and outcomes evidence base needed to inform regulatory, coverage, and reimbursement decisions.[30] Clear stan-

dards and processes for oversight and regulation of genomic testing are also lacking.[39-41]

Currently, policy makers must evaluate these promising new technologies without full information. Additional economic evaluations can serve to reduce the regulatory uncertainty regarding a disease that affects many women, their families, and their communities.

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eAppendix. Literature Review Methodology

A structured review of the literature was conducted to identify and synthesize available evidence regarding economic analyses of genomic testing for breast cancer. A search was conducted using PubMed and Google Scholar for articles published between January 1, 2005, and December 31, 2010. The search was then expanded to include articles as far back as 1981. The search used the following terms:

- Breast cancer and personalized medicine
- Personalized medicine and genomics
- Personalized medicine
- Breast cancer and targeted therapy
- Genomics and targeted therapy
- Targeted therapy
- Personalized medicine and targeted therapy
- Genomic testing and value
- Genomic test and personalized medicine
- Genomic test and economics
- Genomic test and cost
- Genomic test and economic analysis
- Genomic test and cost-effectiveness
- Economic evaluation and genomic testing and breast cancer
- Gene expression and breast cancer and economic evaluation
- Gene expression and breast cancer and economics

In additional, snowball methodology was used to identify and include additional articles based on frequency of author publication and frequency of citation in the literature. Of the articles reviewed, a subset of 9 articles describing specific economic analysis studies was included in a more in-depth side-by-side comparison (these articles are listed in the Table). The 9 studies were selected based on the following inclusion and exclusion criteria:

Inclusion criteria:

- Cost-effectiveness analysis (cost/benefit comparison)
- English language studies.

Exclusion criteria:

- Genetic testing
- Slide-based tests: immunohistochemistry, fluorescence in situ hybridization
- Genomic tests for nonbreast cancer.

The selected studies were then compared with regard to study design, statistical analyses, and reported findings.

The review was performed by the Jefferson Population Health Continuing Professional Education Collaborative. As the authors did not separately review the articles and then work together to reach consensus on which articles to include in the review, the review should be treated as being performed by a single author.