

Real-World Economic Value of a 21-Gene Assay in Early-Stage Breast Cancer

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Gene expression profiling (GEP) utilizing a 21-gene panel (Oncotype Dx; Genomic Health, Redwood City, California) in women with early-stage, axillary lymph node-negative, hormone receptor (HR)-positive, HER2/neu oncogene-negative breast cancer is able to identify a cohort in which excellent outcomes can be achieved through the use of hormonal therapy without adjuvant chemotherapy.¹⁻⁶ The assay evaluates 16 cancer-related genes and 5 reference genes to derive a recurrence score (RS) that estimates the 10-year risk of distant breast cancer recurrence. A recent analysis from the Surveillance, Epidemiology, and End Results (SEER) database on more than 21,000 patients with early-stage breast cancer and low RS, with only 7% receiving adjuvant chemotherapy, found a 5-year breast cancer-specific survival (BCSS) of 99.6%, with continuous RS correlating with BCSS with and without adjustments for age, tumor grade, tumor size, and treatments.⁵ Future analyses of the TAILORx study, the RxPONDER Trial (SWOG S1007), and the SEER database will hopefully clarify the role of GEP in patients with intermediate and high RS.

Although GEP in early-stage breast cancer has clinical utility, the cost of the Oncotype Dx assay is not trivial, at a list price of \$4175 per study. Cost-effectiveness and budget impact studies, largely based on modeling exercises rather than real-world data, have found that Oncotype Dx testing is likely to improve outcomes, reduce the proportion of patients treated with chemotherapy, and be cost effective with acceptable quality-adjusted life-year (QALY) gains from a payer's perspective.⁷⁻¹² For example, among US patients enrolled in a commercial insurance plan, Markov modeling projected a savings of \$1160 and a 2- to 3-month QALY gain with GEP testing.¹³ A recent Pennsylvania Cancer Registry review noted reduced adjuvant chemotherapy use and 1-year health expenditure savings of \$15,333 among patients younger than 55 years, but increased use of chemotherapy and higher 1-year costs for patients aged 75 to 84 years.¹⁴ As medical payment reform gradually shifts reimbursement from traditional fee-for-service to value-based models, the oncologist will be increasingly required to consider the costs of diagnostic testing.

ABSTRACT

OBJECTIVES: Value-based payment reforms shift cost-containment responsibilities to the physician. Although gene expression profiling (GEP) utilizing a 21-gene panel among patients with early-stage, axillary lymph node-negative, hormone receptor-positive, HER2/neu oncogene-negative breast cancer is able to identify a cohort that may achieve excellent outcomes without adjuvant chemotherapy, high up-front costs (list price, \$4175) could dissuade usage.

STUDY DESIGN: Retrospective review of consecutive patients with breast cancer treated at a single cancer center.

Methods: Chart review of 227 patients 70 years or younger with outpatient costs (ie, drug average sales price, reagent costs, physician charges) during first 6 months of treatment.

RESULTS: Of these patients, 68% underwent GEP, with 52%, 43%, and 5% having low, intermediate, and high recurrence risk scores, respectively. Adjuvant chemotherapy was utilized less in genomically profiled cohorts (19% vs 29%; $P = .08$) and was consistent with recommendations of the recurrence scores. The mean 6-month outpatient costs were \$24,955 with adjuvant chemotherapy and \$2654 with hormonal therapy. Patients with stage II cancer undergoing GEP received adjuvant chemotherapy at a lower frequency (28.6% vs 86.7%), but patients with stage I cancer who underwent testing were slightly more likely to receive chemotherapy (15.8% vs 14%) because the test identified patients with higher-risk tumors. Universal GEP testing of patients with stage II cancer would have resulted in net savings of \$11,494 per patient inclusive of test cost; stage I testing would have increased costs by \$4505. Similar trends for grade 2/3 tumors (-\$2394) and grade 1 tumors (+\$6047) were noted.

CONCLUSIONS: Universal GEP testing of women 70 years or younger with stage II or grade 2/3 lymph node-negative breast cancers would result in lower outpatient costs, inclusive of the diagnostic test, within the first 6-month episode of care.

Am J Manag Care. 2017;23(12):e416-e420

We therefore sought to review the use of GEP at a single center with a focus on outpatient costs incurred during the first 6 months of care.

METHODS

Patient Population

A retrospective chart review was performed at John Theurer Cancer Center (Hackensack, New Jersey) among previously untreated women with invasive breast cancer (stage I or II, axillary lymph node–negative [micrometastasis permitted], HR-positive [estrogen receptor or progesterone receptor], HER2/neu oncogene–negative) who underwent initial evaluations between July 1, 2010, and January 31, 2014. Women older than 70 years were excluded because preliminary analysis from this cancer center demonstrated that age was a significant factor in the decision to receive chemotherapy (23% of patients ≤70 years received chemotherapy vs 6% of patients >70 years; $P < .001$) or to perform Oncotype Dx genomic profiling (67% of patients ≤70 years underwent the profiling vs 38% of patients >70 years; $P = .001$). Women younger than 40 years were included in this analysis. Chemotherapy usage rates were higher in this age cohort (18% of patients aged 40-70 years received chemotherapy vs 43% of patients <40 years; $P < .05$) despite similar testing rates (Oncotype Dx genomic profiling performed in 64% of patients aged 40-70 years and 59% of patients <40 years; $P = .71$).

Patients were identified using the Cota Inc platform, which extracts and organizes clinical and cost data from electronic health records. All data were de-identified for secondary research analysis.

Cost Analysis

The analysis started at the time of the initial medical treatment oncology intervention (initiation of chemotherapy or hormonal treatment) and ended 6 months later. Costs of the medications were calculated at the average sales price. J-codes were used to determine administration costs. Office visit evaluation/management codes were reviewed to determine physician fees. Laboratory testing costs were calculated based on practice reagent costs. All costs related to the initial diagnostic evaluation, surgery, and radiation oncology evaluations and treatment were excluded. All costs related to hospitalizations were also excluded.

Statistical Analysis

Data presentations are descriptive using proportions for categorical variables and

TAKEAWAY POINTS

Value-based payment reforms shift cost-containment responsibilities to the physician. Although gene expression profiling utilizing a 21-gene panel among patients with early-stage, axillary lymph node–negative, hormone receptor–positive, HER2/neu oncogene–negative breast cancer is able to identify a cohort that may achieve excellent outcomes without adjuvant chemotherapy, the high up-front cost of profiling could dissuade usage. We retrospectively reviewed consecutive cases of early-stage breast cancer at a community hospital to determine the early economic impact of genomic profiling.

- ▶ Universal testing with the 21-gene breast cancer assay of all patients with stage II or grade 2 breast cancer results in outpatient cost savings within the initial 6 months following treatment initiation (inclusive of test costs) by shifting care away from chemotherapy to oral hormonal treatments.
- ▶ Testing of patients with stage I or grade 1 breast cancer adds up-front costs but may identify a few patients with unexpected higher-risk tumors, resulting in more intensive therapy and potentially improved late outcomes.

means for continuous variables. Chi-squared testing was used to analyze associations. Multivariable analyses entered variables with a $P < .1$ into the regression models. A 2-sided $P < .05$ level was considered significant.

RESULTS

Study Population and Utilization of Oncotype Dx Genomic Profiling

During the study timeframe, 227 patients with early-stage breast cancer met the inclusion criteria, having stage I or II, axillary lymph node–negative (micrometastasis permitted), HR-positive, HER2/neu oncogene–negative breast cancer. Of these, 155 (68%) underwent the Oncotype Dx 21-gene assay. By univariate analysis, grade 2/3 histology ($P = .008$), the absence of lymph node micrometastasis ($P = .07$), and treatment by a particular oncologist ($P = .009$) were each associated with an increased likelihood of undergoing genomic testing. By multivariate analysis, absence of micrometastasis and treatment by a particular oncologist remained significant predictors (both $P < .05$). Subgroup multivariate analysis of only

TABLE 1. Effect of Oncotype Dx Performance on Treatment Strategy

Stage of Breast Cancer at Diagnosis	GEP Performed	Treatment	n (%)
Stage I	Oncotype Dx performed	Chemotherapy	19 (16%)
		Hormonal therapy	111 (84%)
	Oncotype Dx not performed	Chemotherapy	8 (14%)
		Hormonal therapy	57 (86%)
Stage II	Oncotype Dx performed	Chemotherapy	10 (29%)
		Hormonal therapy	25 (71%)
	Oncotype Dx not performed	Chemotherapy	13 (87%)
		Hormonal therapy	2 (13%)

GEP indicates gene expression profiling.

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TABLE 2. Observed Median Costs During Initial 6 Months of Breast Cancer Therapy Based on GEP Testing

A. Stage I Breast Cancer						
	Oncotype Dx Performed			Oncotype Dx Not Performed		
	All	Chemotherapy	Hormonal Only	All	Chemotherapy	Hormonal Only
Total observed cost	\$5698	\$21,304	\$2732	\$5230	\$22,633	\$2389
Chemotherapy	\$443	\$2774	–	\$334	\$2376	–
Administration (chemotherapy)	\$345	\$2163	–	\$262	\$1867	–
Growth factors	\$1431	\$8961	–	\$1671	\$11,903	–
Administration (growth factors)	\$90	\$566	–	\$101	\$719	–
Supportive care medications	\$686	\$4272	\$5	\$511	\$3627	\$2
Administration (SCMs)	\$6	\$0	\$7	\$3	\$0	\$4
Hormonal therapy (oral)	\$1768	\$809	\$1950	\$1607	\$393	\$1805
Hormonal therapy (IV/SQ)	\$238	\$244	\$236	\$73	\$174	\$57
Administration (IV/SQ)	\$5	\$9	\$5	\$1	\$4	\$1
Office visits (E&M)	\$527	\$1225	\$394	\$512	\$1281	\$386
Laboratory CBC	\$31	\$73	\$23	\$31	\$76	\$23
Laboratory chemistry	\$61	\$141	\$45	\$59	\$148	\$44
Laboratory CA27.29	\$66	\$66	\$66	\$66	\$66	\$66
Total office visits (mean)	3.0	7.1	2.3	2.9	7.4	2.2
B. Stage II Breast Cancer						
	Oncotype Dx Performed			Oncotype Dx Not Performed		
	All	Chemotherapy	Hormonal Only	All	Chemotherapy	Hormonal Only
Total observed cost	\$10,906	\$31,458	\$2684	\$24,711	\$28,191	\$2086
Chemotherapy	\$804	\$2814	–	\$1999	\$2307	–
Administration (chemotherapy)	\$709	\$2480	–	\$2425	\$2799	–
Growth factors	\$4635	\$16,223	–	\$13,022	\$15,025	–
Administration (growth factors)	\$276	\$965	–	\$977	\$1127	–
Supportive care medications	\$1554	\$5436	–	\$3406	\$3930	–
Administration (SCMs)	\$5	\$19	–	\$0	\$0	–
Hormonal therapy (oral)	\$1344	\$682	\$1609	\$366	\$222	\$1306
Hormonal therapy (IV/SQ)	\$397	\$139	\$500	\$154	\$178	\$0
Administration (IV/SQ)	\$8	\$3	\$10	\$9	\$11	\$0
Office visits (E&M)	\$943	\$2241	\$424	\$1945	\$2151	\$608
Laboratory CBC	\$56	\$134	\$25	\$116	\$128	\$36
Laboratory chemistry	\$109	\$258	\$49	\$224	\$248	\$70
Laboratory CA27.29	\$66	\$66	\$66	\$66	\$66	\$66
Total office visits (mean)	5	13	2	11	12	4

CA27.29 indicates cancer antigen 27.29; CBC, complete blood count; E&M, evaluation and management; GEP, gene expression profiling; IV/SQ, intravenous/subcutaneous; SCM, supportive care medication.

patients with stage I cancer revealed histologic grade 2/3 and treatment by a particular oncologist to be associated with increased rates of genomic testing, whereas in patients with stage II cancer, absence of micrometastasis, lobular histology, presence of lymphovascular invasion, and treatment by a different particular oncologist were associated with increased testing rates (all $P < .05$).

Relationship Between Results of Oncotype Dx Testing and Utilization of Chemotherapy

Among the 155 women with breast cancer who underwent the Oncotype Dx test, 81 (52%) had a low RS, 66 (43%) had intermediate, and 8 (5%) had high. Using the TAILORx scoring system, which is more conservative because it lowers the cutoff for intermediate RS

from less than 18 to less than 11, 35 (23%), 99 (64%), and 21 (14%) had a low, intermediate, and high RS, respectively.

In the entire population of 227 patients, 50 (22%) received adjuvant chemotherapy and 177 (78%) underwent hormonal therapy only. Patients with lower Oncotype Dx RS (traditional or TAILORx, both $P < .0001$) were less likely to receive adjuvant chemotherapy. For patients with low, intermediate, and high RS, the use of chemotherapy was 4%, 28%, and 100%, respectively (6%, 7%, and 100% with TAILORx). Among the 155 women who underwent Oncotype Dx testing, 29 (19%) received adjuvant chemotherapy. By contrast, of the 72 women who did not undergo GEP, 21 (29%) received chemotherapy ($P = .08$) (Table 1). Among women with stage I cancer who underwent Oncotype Dx testing, 19 of 120 (16%) received chemotherapy, whereas 8 of 57 (14%) women with stage I cancer who did not undergo testing received chemotherapy ($P = .83$). Among women with stage II cancer who underwent Oncotype Dx testing, 10 of 35 (29%) received chemotherapy, whereas 13 of 15 (87%) women with stage II cancer without GEP received chemotherapy ($P < .001$). Univariate analysis and multivariate analysis (all $P < .05$) revealed primary tumor size less than 2 cm, absence of lymph node micrometastasis, histologic grade 1, absence of lymphovascular invasion, lower Ki-67, and treatment by a different oncologist to be associated with a decreased usage of adjuvant chemotherapy.

Cost Analysis

Among the 50 patients who received adjuvant chemotherapy, the mean total outpatient cost of care per patient during the first 6 months of treatment was \$24,955, compared with \$2654 for the 177 patients who received hormonal therapy only (Table 2). The main drivers of costs among patients receiving chemotherapy were hematopoietic growth factors (which were more than double the cost of the chemotherapeutic agents) and supportive care medications (which were on par with the cost of the antineoplastic agents).

Outpatient costs varied by both cancer stage and performance of GEP. The average outpatient cost for 6 months of therapy for patients with stage I cancer was \$20,989 if adjuvant chemotherapy was utilized and \$2657 if hormonal therapy was administered. Patients with stage I cancer undergoing GEP received adjuvant chemotherapy at a slightly higher rate (16% of Oncotype Dx–tested patients received chemotherapy vs 14% of patients not genomically profiled). Because more patients with stage I cancer who underwent GEP received chemotherapy, the 6-month outpatient costs increased as a result of testing (\$5560 plus \$4175 Oncotype cost vs \$5230 without testing). If universal GEP testing were applied to patients with stage I cancer, a projected overall net cost increase of \$4505 per patient would occur.

By contrast, universal testing of patients with stage II cancer would result in a net cost savings of \$11,494 per profiled patient (including the \$4175 test cost). The average outpatient cost of 6 months of therapy for patients with stage II cancer was \$29,612 if adjuvant chemotherapy was utilized and \$2640 if hormonal

therapy was administered. Patients with stage II cancer undergoing GEP received adjuvant chemotherapy at a lower rate (29% of Oncotype Dx–tested patients received chemotherapy vs 87% of patients not genomically profiled). This larger shift away from chemotherapy usage associated with Oncotype Dx profiling led to the observed cost savings (expected average cost if no testing was performed was \$26,016 per patient vs \$14,522 if universal genomic profiling was performed, inclusive of \$4175 Oncotype Dx cost).

Hospitalizations

There were 54 hospitalizations during the 8 months following initiation of treatment in this cohort (who were followed longer since treatment in month 6 may impact outcomes during the next months). Among the 50 women receiving chemotherapy, 27 (54%) were hospitalized a total of 31 times. Among the 177 women receiving hormonal therapy, 16 (9%) were hospitalized a total of 23 times ($P < .0001$ by patients). The majority of the hospitalizations in the hormonal therapy group were unrelated to treatment, whereas the majority of the hospitalizations in the adjuvant chemotherapy group could be attributed to treatment.

DISCUSSION

This single-institution retrospective review found that GEP using a 21-gene assay resulted in observed outpatient cost savings during the first 6 months of therapy for women with lymph node–negative, HR–positive, HER2/neu oncogene–negative breast cancer who had stage II cancer or grade 2/3 tumors, inclusive of the cost of the testing (savings of \$11,494 and \$2394, respectively). By contrast, observed outpatient health expenditures rose for women with stage I or grade 1 disease (by \$4505 and \$6047, respectively) who underwent GEP testing. Because chemotherapy–treated patients also utilized hospital–based services more frequently, inclusion of hospital costs would have further magnified these findings.

The recurrence risk scores in our series were skewed toward lower risks (52% low, 43% intermediate, and 5% high) and strongly correlated with adjuvant chemotherapy use. This finding was similar to those of a US review in which the proportions of Oncotype Dx–tested women with low, intermediate, and high RS were 51%, 39%, and 10%, which was also associated with adjuvant chemotherapy usage in 11%, 47%, and 88% of patients, respectively.¹⁵ The influence of GEP testing on subsequent adjuvant chemotherapy decisions was further supported by the findings of a Canadian study in which 38% of oncologists changed their recommendation from chemotherapy use based on GEP results and only 15% increased chemotherapy use.¹⁶ Findings of additional meta–analyses have revealed similar trends in treatment changes.^{17,18}

Importantly, none of the 236 patients in the Canadian study with grade 1 tumors had a high RS. In our study, none of the women with combined stage I and grade 1 tumors had a high RS determined

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by Oncotype Dx (0/33), thus negating any clinical benefit of GEP testing and defining a cohort where GEP testing unnecessarily raises costs.¹⁶ A survey of oncologists in Ireland found that, in the absence of GEP testing, tumor grade drives decisions, with patients with grade 1 tumors not receiving adjuvant chemotherapy but those with grade 2/3 tumors receiving it. The availability of GEP testing resulted in a reduction of adjuvant chemotherapy usage by 57% in a cohort of 592 patients, resulting in a net savings of almost €800,000 (\$2.1 million).¹⁹ In a Pennsylvania Cancer Registry review, younger patients (<50 years) accrued cost savings whereas older patients (>65 years) incurred higher healthcare expenditures with GEP testing, potentially indicating clinicians' perceptions of the value of adjuvant chemotherapy according to age.¹⁴

Another GEP assay, the 70-gene signature test (MammaPrint; Agendia Inc, Irvine, California), may also identify women with early-stage HR-positive breast cancer who could have excellent outcomes with hormonal therapy.²⁰ Cost-effectiveness models have found potential cost savings and improved QALY gains with this test, but to our knowledge, real-world data confirmation, such as the current study, is not available.²¹⁻²³

CONCLUSIONS

GEP testing using the Oncotype Dx 21-gene assay resulted in a reduction of observed outpatient costs during the initial 6 months of treatment for patients with stage II or grade 2/3 tumors among those with lymph node-negative, HR-positive, HER2/neu oncogene-negative breast cancer treated at a single institution, but increased costs for patients with stage I or grade 1 tumors. ■

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Source of Funding: This manuscript was funded by Cota Inc. Cota Inc is responsible for the contents of the analysis but has no financial interests in the assay or the study outcome.

Author Disclosures: Dr Waintraub has received lecture fees from Amgen, Bristol-Myers Squibb (BMS), Celgene, and Pfizer, and owns stock in Genomic Health, Allergan, Curis, Exelixis, BMS, Celgene, and Pfizer. Dr Pecora has received a patent from Cota and is a board member and stock owner of Cota and Caladrius. Mr Schultz is a board member and employee of Cota. Dr Goldberg is an employee and stock owner of Cota, has been a consultant and provided expert testimony for Novartis, has received honoraria from Pfizer, and has received lecture fees from Novartis and BMS. The remaining authors report no relationship or financial interest with any entity that would pose a conflict of interest with the subject matter of this article.

Authorship Information: Concept and design (SEW, DM, DMAG, ALP, KC, ES, SLG); acquisition of data (JC, RPB, KC, SLG); analysis and interpretation of data (ALP, JM, TW, HGN, KC, SLG); drafting of the manuscript (SEW, DM,

DMAG, ALP, JM, TW, HGN, KC, ES, SLG); critical revision of the manuscript for important intellectual content (SEW, DM, DMAG, ALP, TW, HGN, KC, ES, SLG); statistical analysis (JM, TW, HGN, SLG); and provision of patients or study materials (SEW, DM, DMAG, ALP).

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