Published in final edited form as:
Breast Cancer Res Treat. 2011 November ; 130(2): 619–626. doi:10.1007/s10549-011-1628-6.

Gene Expression Profile Testing for Breast Cancer and the Use of Chemotherapy, Serious Adverse Effects, and Costs of Care

Jennifer S. Haas, MD, MSPH,
Division of General Medicine and Primary Care, Brigham and Women's Hospital, Boston, MA

Su-Ying Liang, PhD,
University of California, San Francisco, San Francisco, CA

Michael J. Hassett, MD, MPH,
Dana-Farber Cancer Institute, Boston, MA

Stephen Shiboski, PhD,
University of California, San Francisco, San Francisco, CA

Elena B. Elkin, PhD, and
Memorial Sloan-Kettering Cancer Center, New York, NY

Kathryn A. Phillips, PhD
University of California, San Francisco, San Francisco, CA

Abstract

Background—As gene expression profile (GEP) testing for breast cancer may provide additional prognostic information to guide the use of adjuvant chemotherapy, we examined the association between GEP testing and use of chemotherapy, serious chemotherapy-related adverse effects, and total charges during the 12 months following diagnosis.

Methods—Medical record review was conducted for women age 30 to 64 years, with incident, non-metastatic, invasive breast cancer diagnosed 2006–2008 in a large, national health plan.

Results—Of 534 patients, 25.8% received GEP testing, 68.2% received chemotherapy, and 10.5% experienced a serious chemotherapy-related adverse effect. GEP testing was most commonly used in women at moderate clinical risk of recurrence (52.0% vs. 25.0% of low-risk women and 5.5% of high-risk). Controlling for the propensity to receive GEP testing, women who had GEP were less likely to receive chemotherapy (propensity adjusted odds ratio, 95% confidence interval 0.62, 0.39 – 0.99). Use of GEP was associated with more chemotherapy use among women at low risk based on clinical characteristics (OR = 42.19; CI 2.50 – 711.82), but less use among women with a high risk based on clinical characteristics (OR = 0.12 CI 0.03 – 0.47). Use of GEP was not associated with chemotherapy for the moderate risk group. There was no significant relationship between GEP use and either serious chemotherapy-associated adverse effects or total charges.

Conclusions—While GEP testing was associated with an overall decrease in adjuvant chemotherapy, we did not find differences in serious chemotherapy-associated adverse events or charges during the 12 months following diagnosis.

Correspondence and Reprint Requests to: Jennifer S. Haas, MD, MSPH; Division of General Medicine and Primary Care, 1620 Tremont Street, Boston, MA 02120. Phone: 617-525-6652, Fax: 617-732-7072, jhaas@partners.org.

Financial Disclosures:
Drs. Haas, Phillips, and Liang received funding from a research grant from the Aetna Foundation for earlier related research.

Keywords

breast cancer; utilization; genomics

Introduction

Each year in the US more than 200,000 women are diagnosed with breast cancer, about half with early-stage disease [1]. Guidelines suggest that a majority of women with node-negative, estrogen receptor-positive breast cancer should be offered chemotherapy [2, 3], but as only a minority will have a recurrence, some patients receive little benefit yet experience substantial short and long-term toxicity [4]. Better identification of the women most likely to benefit from adjuvant chemotherapy would be an important advance in the management of women with non-metastatic breast cancer. From a societal perspective, the costs of adjuvant chemotherapy for non-metastatic breast cancer are substantial, as the total payment by Medicare for the initial treatment of women with breast cancer exceeded $1 billion in 2002 [5].

Because of the complexities of deciding on the best course of treatment for an individual woman and because of the substantial societal costs associated with the use of adjuvant chemotherapy, there has been intense interest in using genetic information to improve our assessment of recurrence risk among women with non-metastatic breast cancer. Several studies suggest that the genetic profile of a tumor may promote better classification of recurrence risk beyond traditional tumor characteristics, such as tumor size, axillary lymph node involvement and histology [6–9]. Using DNA micro-array or real-time polymerase chain reaction (RT-PCR) technology, it is now possible describe the expression profile of a series of genes and to link that expression profile with an important clinical event, such as recurrence free survival or predicted benefit from chemotherapy [10]. OncotypeDX (Genomic Health, Redwood City, CA) the most commonly available commercial gene expression profile (GEP) test in the US, provides prognostic and predictive information for women with hormone-receptor positive invasive breast cancer. Data from the manufacturer suggests rapid dissemination since its introduction in 2004 [11]. The test costs about $4,000 [12], and economic analyses suggest that GEP-guided therapy is either cost-saving or associated with a modest incremental cost-effectiveness ratio (ICER) as compared to traditional risk stratification approaches [7, 13–18].

Information about the use of GEP testing in routine clinical practice, its association with adjuvant chemotherapy decisions, and its impact on health outcomes and costs are limited [19, 20]. This information is important as new tests are often used for “off label” indications as they disseminate into practice and some groups of people may not have access to new technologies. The studies that led to the validation of this technology do not explain how it is used in routine practice or describe the full range of outcomes that could be impacted by GEP testing [21]. As the use of genomic tests to assess recurrence risk is expanding to other cancers [22], the example of GEP testing for breast cancer is an important prototype for understanding the use of this family of tests in clinical practice. Our objective was to examine the association of GEP with the use of adjuvant chemotherapy, the occurrence of serious chemotherapy-associated adverse effects, and total charges in a payer-based sample of women with non-metastatic breast cancer. As GEP may help clinicians and patients make more personalized decisions about chemotherapy use, our hypothesis was that use of GEP would be associated with fewer chemotherapy-associated adverse effects and therefore lower charges.

Methods

Population

Using claims and administrative data from a large national health plan (the name of which we cannot provide because of our data use agreement), we identified women ages 30 to 64 years with incident breast cancer diagnosed between 2006 and 2008 [23, 24]. We did not include women ≥65 years as Medicare is the primary payer for these women. We included women who were continuously enrolled in the plan from 6 months prior through 12 months following diagnosis. Medical records from each woman's primary medical oncologist and surgeon were abstracted for 534 women with stage I – III, hormone-receptor positive invasive breast cancer. This sample size was pre-determined. These women were considered eligible for GEP testing based on previous validation studies and/or clinical practice guidelines [2, 6, 9, 25].

Benefit Coverage

The health plan had a formal coverage policy for OncotypeDx beginning in January 2007, with the requirement that Genomic Health screen all orders for OncotypeDX to make sure that they fit eligibility criteria [26]. Under this policy, the health plan would not cover OncotypeDX testing if an individual received a low-risk OncotypeDX score yet decided to go ahead and receive adjuvant chemotherapy, as this suggests that the test result was not being used as intended [27]. Before this policy was implemented, women may have had claims for OncotypeDX paid on a case-by-case basis, or they could have paid out-of-pocket. Documentation of OncotypeDX in the medical record was not dependent on source of payment. OncotypeDX was the only GEP test received by women in this sample.

Sources of Data

Claims—In addition to identifying the cohort, claims were used to determine age, comorbidity [28], year of diagnosis, serious chemotherapy-associated adverse effects [23], and charges submitted during the 12 months following diagnosis to reflect the costs of care. Information about costs reimbursed by the payer were not available.

Medical Records—A standard abstraction tool was used to collect detailed clinical information, including cancer stage, tumor size, lymph node involvement, estrogen and progesterone-receptor status, HER2 receptor status, the use and results of any GEP tests, and the use of adjuvant chemotherapy. Medical records were reviewed by trained abstractors contracted through a third party vendor.

Outcomes

The primary outcomes were receipt of adjuvant chemotherapy, the occurrence of a serious chemotherapy-related adverse effect [23], and charges for medical care – all evaluated during the first 12 months following diagnosis. Patients were considered to have received chemotherapy if there was documentation in their medical record of any of the chemotherapy agents commonly administered for breast cancer (adriamycin, carboplatin, cyclophosphamide, docetaxel, fluorouracil, epirubicin, paclitaxel, albumin-bound paclitaxel). A serious chemotherapy-associated adverse event was defined as any hospitalization or emergency department visit with an associated diagnostic code for one or more condition defined as a serious chemotherapy-associated adverse event in our earlier work (e.g., nausea, diarrhea, neutropenia, infection) [23]. Total charges, reported in US dollars, were the sum of charges for hospital admissions, outpatient visits, emergency department visits, and prescription drugs submitted to the health plan. We set all charges

below 2.5% or above 97.5% of the distribution to the value of those percentiles, reducing the influence of extreme outliers [29].

Predictors and Covariates

The predictor of interest in all analyses was receipt of a GEP test. Women were classified as having a low, moderate, or high risk breast cancer using conventional clinical characteristics based on widely disseminated clinical practice guidelines [2, 3]. Low clinical risk was defined as small, node negative cancers without high-risk features (tumor size ≤ 0.5 cm, or tumor size 0.6 to 1.0 cm with a well-differentiated grade and negative or indeterminate HER2-status); high clinical risk was defined as a node-positive cancer or a larger node-negative cancer with high risk features (size ≥ 5.0 cm and HER2-negative or indeterminate, or node-negative with a tumor size > 1.0 cm and HER2-positive); moderate clinical risk included all other cancers. GEP test results were categorized according to the groups defined by the original validation studies as low (recurrence score <18), intermediate (18–30) and high (31+) risk using the actual recurrence score [9], or when no score was available, the test interpretation. Patient and disease characteristics identified in the medical records and claims included: age (30–49, 50–64), comorbidity score (0 or 1+ chronic conditions), year of breast cancer diagnosis (2006, 2007, 2008), tumor size (<1cm, 1–2cm, 2.1–3cm, > 3cm), grade (well differentiated, moderate/poorly differentiated), nodal status (no vs. any regional lymph node involvement), estrogen- and progesterone-receptor status (one positive, both positive), and HER2-receptor status (negative/intermediate, positive).

Data Analysis

Logistic regression models were used to estimate adjusted odds ratios (OR) and 95% confidence intervals (CI) for the use of adjuvant chemotherapy and the occurrence of serious chemotherapy-associated adverse effects, conditional on GEP test use. Propensity score methods were used to control for confounding by characteristics associated with receipt of a GEP test and the study outcomes, which may be particularly important for a newer test like GEP which is not explicitly recommended [2]. We adopted this approach, rather than conventional adjustment, because outcome prevalence was low in some subgroups of interest, and the number of covariates of interest was relatively large considering the overall sample size in these groups [30]. Each woman's propensity to receive a GEP test was estimated a function of her age at diagnosis, comorbidity score, year of breast cancer diagnosis, tumor size, grade, nodal status, hormone receptor status, and HER2 receptor status, using the categories specified above. We evaluated linear, non-linear, and categorical specifications of the propensity score. The categorical specification, with propensity score classified in tertiles, was ultimately selected, although conclusions were not sensitive to the propensity score specification. The association of GEP on total charges was evaluated using propensity score-adjusted linear models, where the dependent variable was natural log-transformed total charges. Models were estimated in the full cohort and within subgroups stratified by clinically defined risk of recurrence. In a secondary analysis, among the subgroup of women who received an OncotypeDX test and had a documented result (n = 125), we examined the association of the OncotypeDX recurrence score on use of adjuvant chemotherapy, controlling for clinically defined risk of recurrence. All analyses were performed using Stata version 10 (StataCorp, College Station, TX). The study was reviewed and approved by the institutional review boards of UCSF, Partners Healthcare, and the New England Institutional Review Board.

Results

Sample Characteristics

The majority of women in the sample were between the ages of 50 and 64 years, had no comorbidity, had cancers that were stage I or II, both estrogen and progesterone-receptor positive, and HER2-negative or intermediate (Table 1). Based on clinical risk factors, 11.2% of women were categorized as having a low risk of recurrence, 38.2% had moderate risk, and 47.4% high risk. Women without comorbidity, and those with well-differentiated histology, HER2-negative or intermediate status, stage I disease, or tumor ≤ 3 cm in size were more likely than their respective counterparts to receive a GEP test. Use of GEP testing was highest among women with a moderate clinical risk of recurrence (52.0%) and lowest among those at high risk of recurrence (5.5%; $p < 0.001$ across groups). Use of GEP testing increased 110% between 2006 and 2008, although fewer women were included from 2008 because of the eligibility requirement that 12 months of claims data be available post-diagnosis.

Adjuvant Chemotherapy

More than two-thirds of women with stage I–III, hormone-receptor positive breast cancer received adjuvant chemotherapy (Table 2), and use of chemotherapy increased with conventional clinical estimates of recurrence risk. Among women in the high risk clinical group, receipt of chemotherapy was lower for women who had received a GEP test, although the number of women who received GEP in this high risk group was small (n = 14). Overall, women who received a GEP test were less likely to receive adjuvant chemotherapy (propensity adjusted odds ratio 0.62; 95% confidence interval 0.39 – 0.99). After stratifying by clinical recurrence risk, a similar association was observed among the subgroup of women at high clinical risk of recurrence (0.12; 0.03 – 0.47). Conversely, women at low clinical risk of recurrence were more likely to receive adjuvant chemotherapy if they had GEP testing (42.19; 2.50 – 711.82), although the precision of this estimate was low because of limited sample size. In a secondary analysis among 125 women with a documented GEP result, almost 60% had different clinical and GEP-specified risks of recurrence. GEP testing provided a lower recurrence estimate than traditional clinical factors in 38.4%, and a higher recurrence estimate in 18.4%. Within each clinical recurrence risk stratum, a higher GEP result was associated with a higher likelihood of receiving chemotherapy. For example, among women with an intermediate clinical risk of recurrence, chemotherapy was administered to 12.8%, 66.7% and 93.3% of those with a recurrence scores <18, 18–30 and 31+, respectively.

Serious Chemotherapy-associated Adverse Effects

Eleven percent of women had a hospital admission or emergency room visit with a diagnostic code suggestive of a serious chemotherapy-associated adverse effect (Table 3). Not surprisingly, as the clinical risk of recurrence and the probability of receiving chemotherapy increased, so too did the likelihood of experiencing a chemotherapy-related serious adverse effect. However, GEP use was not associated with the occurrence of a chemotherapy-associated adverse effect either for the entire cohort or for the sub-groups of women defined by clinical risk of recurrence.

Charges following Diagnosis

Median total charges for medical care in the first 12 months after diagnosis were $88,687 for all women in the sample (Table 4). After adjusting for the propensity to receive a GEP test, there was no significant difference in total charges between those who did and did not

receive GEP in the full sample (p = 0.91) or in the sub-groups of women defined by clinical risk of recurrence.

Discussion

In this payer-based sample, we found that GEP testing was associated with less use of adjuvant chemotherapy. In analyses stratified by risk groups using traditional clinical prognostic criteria, GEP testing was associated with less chemotherapy use among women at high clinical risk of recurrence, but was associated with more chemotherapy use among women with low clinical risk of recurrence. These results suggest that GEP testing influences both the overall rate of chemotherapy use and the type of patients who receive chemotherapy.

Among the subgroup of women who received a GEP test, more women had their risk re-classified as lower than their clinical risk. GEP may result in more personalized care by providing additional reassurance to women at low clinical risk of recurrence who could forgo adjuvant chemotherapy, and identifying women who are at high recurrence risk who may benefit from more aggressive treatment [7, 9]. We did not see any association between GEP use and the occurrence of serious chemotherapy adverse-effects or charges during the 12 months following diagnosis. Together, these findings suggest that use of GEP may result in more “personalization” of chemotherapy use, but may not be associated with reduced serious chemotherapy-associated adverse events or cost savings, at least in the short term.

Prior studies provide limited evidence regarding the relationship between GEP testing and use of chemotherapy in routine practice settings. In one study of 269 women with non-metastatic breast cancer seen at a single cancer center, adjuvant chemotherapy was given to 7% of women with low recurrence score, compared to 42% and 86% of women with intermediate and high recurrence score, respectively [19]. In a different study of women with OncotypeDX testing, an independent oncologist was asked to review each chart and make a recommendation about the need for adjuvant chemotherapy without access to this test result [31]. OncotypeDX altered chemotherapy management for 38% of women for whom this independent assessment differed from that of the treating oncologist. In a third study, receipt of a GEP test was associated with a change in treatment recommendation, typically resulting in less use of chemotherapy, for one-third of patients, consistent with our findings [32]. None of these prior studies examined the relationship between GEP use and serious chemotherapy-associated adverse events. We found that while GEP use was associated with less chemotherapy use, and changes in patterns of use within subgroups of women defined by conventional clinical characteristics, this did not appear to translate into fewer serious adverse events.

Several economic simulations, with a longer time horizon than our study, suggest that GEP-guided therapy is associated with modest cost-saving compared with treatment decisions based on traditional clinical risk factors [7, 13–18]. Our analysis, based on actual charges for care over a 12-month period, did not suggest a difference in costs associated with GEP test use. Based on the degree of precision of our estimates for GEP-related changes in total charges (Table 4), our sample size was sufficient to detect a relative savings as small as 16%; smaller differences may be meaningful from a societal perspective. The lack of association between GEP testing and charges may perhaps reflect that a decrease in the use of chemotherapy for some patients was in part offset by an increase in use for others.

The premise that a genomic test could facilitate more individually tailored decision-making about the use of adjuvant chemotherapy is appealing from the perspective of women, their providers, and health care systems. Ultimate assessment of the value of these tests will

depend on the availability of data regarding long-term outcomes of treatment decisions and the ability to track changes in utilization and outcomes over time. Data from ongoing randomized controlled trials to test the impact of GEP testing on outcomes will be critical to the assessment of the value of these tests [33].

Our study has several limitations. As our findings are based on observational data, we cannot conclude that GEP testing was the cause of the observed differences in the use of chemotherapy. We used propensity score adjustment to address the potential selection bias that is inherent in observational data [34]. As noted above, we did not have data on long-term outcomes, which may be particularly important for women with non-metastatic disease. Finally, all women in our study were under age 65 and received coverage from a single, large health insurer. Thus, our findings may be less generalizable to the uninsured, older breast cancer patients covered by Medicare, or to women with Medicaid. The distribution of age, stage and nodal status in our sample was similar to those observed for women with breast cancer in the Breast Cancer Surveillance Consortium [35]. Our sample does, however, include women who receive care across the US in diverse practice settings, including community-based practices.

In this study of breast cancer patients treated in routine practice settings, GEP testing was associated with an overall decline in the use of adjuvant chemotherapy. While GEP testing is being used to tailor decision-making about the use of adjuvant chemotherapy, we did not demonstrate differences in serious chemotherapy-associated adverse events or charges during the 12 months following diagnosis.

Acknowledgments

Funding:

The study was supported by a grant from the National Cancer Institute (P01CA130818).

References

1. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin. 2010 Sep-Oct;60(5): 277–300. [PubMed: 20610543]
2. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology: Breast Cancer v.1.20092009.
3. Eifel P, Axelson JA, Costa J, Crowley J, Curran WJ Jr, Deshler A, et al. National Institutes of Health Consensus Development Conference Statement: adjuvant therapy for breast cancer, November 1–3, 2000. J Natl Cancer Inst. 2001 Jul 4; 93(13):979–989. [PubMed: 11438563]
4. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005 May 14–20; 365(9472):1687–1717. [PubMed: 15894097]
5. Warren JL, Yabroff KR, Meekins A, Topor M, Lamont EB, Brown ML. Evaluation of trends in the cost of initial cancer treatment. J Natl Cancer Inst. 2008 Jun 18; 100(12):888–897. [PubMed: 18544740]
6. Paik S, Shak S, Tang G, Kim C, Baker J, Cronin M, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. N Engl J Med. 2004 Dec 30; 351(27):2817–2826. [PubMed: 15591335]
7. Goldstein LJ, Gray R, Badve S, Childs BH, Yoshizawa C, Rowley S, et al. Prognostic utility of the 21-gene assay in hormone receptor-positive operable breast cancer compared with classical clinicopathologic features. J Clin Oncol. 2008 Sep 1; 26(25):4063–4071. [PubMed: 18678838]
8. Albain, K.; Barlow, W.; Shak, S.; Hortobagyi, G.; Livingston, R.; Yeh, I., et al., editors. Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal, nodepositive, ER-positive breast cancer. San Antonio Breast Cancer Sympossium; 2007; San Antonio, TX.

9. Paik S, Tang G, Shak S, Kim C, Baker J, Kim W, et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. J Clin Oncol. 2006 Aug 10; 24(23):3726–3734. [PubMed: 16720680]
10. Sotiriou C, Pusztai L. Gene-expression signatures in breast cancer. N Engl J Med. 2009 Feb 19; 360(8):790–800. [PubMed: 19228622]
11. Genomic Health 2005 Annual Report. Available from: http://investor.genomichealth.com/downloads/2005AR.pdf.
12. Breastcancer.org. OcotypeDX Test. 2011 Available from: http://www.breastcancer.org/symptoms/testing/types/oncotype_dx.jsp.
13. Lyman GH, Cosler LE, Kuderer NM, Hornberger J. 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 studies. Cancer. 2007 Mar 15; 109(6):1011–1018. [PubMed: 17311307]
14. Oestreicher N, Ramsey SD, Linden HM, McCune JS, van't Veer LJ, Burke W, et al. Gene expression profiling and breast cancer care: what are the potential benefits and policy implications? Genet Med. 2005 Jul-Aug;7(6):380–389. [PubMed: 16024969]
15. Hornberger J, Lyman GH, Chien R. Economic implications of 21-gene recurrence score assay: US multicenter experience. J Clin Oncol. 2010 Aug 1.28(22):e382. author reply e3. [PubMed: 20498396]
16. Hornberger J, Cosler LE, Lyman GH. Economic analysis of targeting chemotherapy using a 21-gene RT-PCR assay in lymph-node-negative, estrogen-receptor-positive, early-stage breast cancer. Am J Manag Care. 2005 May; 11(5):313–324. [PubMed: 15898220]
17. Tsoi DT, Inoue M, Kelly CM, Verma S, Pritchard KI. Cost-effectiveness analysis of recurrence score-guided treatment using a 21-gene assay in early breast cancer. The oncologist. 2010; 15(5): 457–465. [PubMed: 20421264]
18. Klang SH, Hammerman A, Liebermann N, Efrat N, Doberne J, Hornberger J. Economic implications of 21-gene breast cancer risk assay from the perspective of an Israeli-managed health-care organization. Value Health. 2010 Jun-Jul;13(4):381–387. [PubMed: 20412544]
19. Gold, JM.; Najita, JS.; Lester, S.; Richardson, AL.; Morganstern, DE.; Chen, WY., et al., editors. Personalizing treatment in early-stage breast cancer: The role of standard clinical factors and genomic information in adjuvant chemotherapy decision making. ASCO Annual Meeting; 2009; Orlando, FL.
20. Ademuyiwa FO, Miller A, O'Connor T, Edge SB, Thorat MA, Sledge GW, et al. The effects of oncotype DX recurrence scores on chemotherapy utilization in a multi-institutional breast cancer cohort. Breast Cancer Res Treat. 2011 Apr; 126(3):797–802. [PubMed: 21197567]
21. Marchionni L, Wilson RF, Wolff AC, Marinopoulos S, Parmigiani G, Bass EB, et al. Systematic review: gene expression profiling assays in early-stage breast cancer. Ann Intern Med. 2008 Mar 4; 148(5):358–369. [PubMed: 18252678]
22. Webber EM, Lin JS, Evelyn PW. Oncotype DX tumor gene expression profiling in stage II colon cancer. Application: prognostic, risk prediction. PLoS Curr. 2010; 2
23. Hassett MJ, O'Malley AJ, Pakes JR, Newhouse JP, Earle CC. Frequency and cost of chemotherapy-related serious adverse effects in a population sample of women with breast cancer. J Natl Cancer Inst. 2006 Aug 16; 98(16):1108–1117. [PubMed: 16912263]
24. Liang SY, Phillips KA, Wang G, Keohane C, Armstrong J, Morris WM, et al. Tradeoffs of Using Administrative Claims and Medical Records to Identify the Use of Personalized Medicine for Patients with Breast Cancer. Medical Care. in press.
25. Albain KS, Barlow WE, Shak S, Hortobagyi GN, Livingston RB, Yeh IT, et al. Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: a retrospective analysis of a randomised trial. The lancet oncology. 2010 Jan; 11(1):55–65. [PubMed: 20005174]
26. Carlson B. Payers Try New Approaches To Manage Molecular Diagnostics. Biotechnol Healthc. 2010; 7(3):26–30.
27. Deverka PA. Pharmacogenomics, evidence, and the role of payers. Public health genomics. 2009; 12(3):149–157. [PubMed: 19204417]

28. Klabunde CN, Potosky AL, Legler JM, Warren JL. Development of a comorbidity index using physician claims data. J Clin Epidemiol. 2000 Dec; 53(12):1258–1267. [PubMed: 11146273]

29. Adams JL, Mehrotra A, Thomas JW, McGlynn EA. Physician cost profiling--reliability and risk of misclassification. N Engl J Med. 2010 Mar 18; 362(11):1014–1021. [PubMed: 20237347]

30. Cepeda MS, Boston R, Farrar JT, Strom BL. Comparison of logistic regression versus propensity score when the number of events is low and there are multiple confounders. Am J Epidemiol. 2003 Aug 1; 158(3):280–287. [PubMed: 12882951]

31. Ademuyiwa FO, Miller A, O'Connor T, Edge SB, Thorat MA, Sledge GW, et al. The effects of oncotype DX recurrence scores on chemotherapy utilization in a multi-institutional breast cancer cohort. Breast Cancer Res Treat. 2011 Jan 1.

32. Lo SS, Mumby PB, Norton J, Rychlik K, Smerage J, Kash J, et al. Prospective multicenter study of the impact of the 21-gene recurrence score assay on medical oncologist and patient adjuvant breast cancer treatment selection. J Clin Oncol. 2010 Apr 1; 28(10):1671–1676. [PubMed: 20065191]

33. Cardoso F, Van't Veer L, Rutgers E, Loi S, Mook S, Piccart-Gebhart MJ. Clinical application of the 70-gene profile: the MINDACT trial. J Clin Oncol. 2008 Feb 10; 26(5):729–735. [PubMed: 18258980]

34. Stukel TA, Fisher ES, Wennberg DE, Alter DA, Gottlieb DJ, Vermeulen MJ. Analysis of observational studies in the presence of treatment selection bias: effects of invasive cardiac management on AMI survival using propensity score and instrumental variable methods. Jama. 2007 Jan 17; 297(3):278–285. [PubMed: 17227979]

35. Kerlikowske K, Cook AJ, Buist DS, Cummings SR, Vachon C, Vacek P, et al. Breast cancer risk by breast density, menopause, and postmenopausal hormone therapy use. J Clin Oncol. 2010 Aug 20; 28(24):3830–3837. [PubMed: 20644098]

Table 1

Description of the Sample (N=534)

	N (column %)	Received a GEP Test N (row %)	p-value for comparison between categories
Received a GEP test			
Yes		138 (25.8)	
No		396 (74.2)	
Age at diagnosis:			P=0.11
30 – 49 years	209 (39.1)	46 (22.0)	
50 – 64 years	325 (61.9)	92 (28.3)	
Comorbidity score:			
0	447 (83.7)	125 (28.0)	P=0.01
≥ 1	87 (16.3)	13 (14.9)	
Breast cancer stage			
I	241 (45.1)	101 (41.9)	P<0.001
II	234 (43.8)	37 (15.8)	
III	59 (11.1)	0 (0.0)	
Tumor size			
≤ 1cm	106 (20.8)	24 (22.6)	P<0.001
1.01cm – 2cm	227 (44.5)	82 (36.1)	
2.01cm – 3cm	115 (22.5)	26 (22.6)	
> 3cm	62 (12.2)	4 (6.5)	
Axillary lymph node involvement			
None	315 (59.5)	130 (41.3)	P<0.001
Any	214 (40.5)	8 (3.7)	
Summary Grade			
Well-differentiated	127 (25.0)	46 (36.2)	P=0.001
Moderately-differentiated	236 (46.5)	65 (27.5)	
Poorly-differentiated	145 (28.5)	24 (16.6)	
Hormone receptor status			

	N (column %)	Received a GEP Test N (row %)	p-value for comparison between categories
Either ER or PR positive	75 (14.0)	19 (25.3)	P=0.91
Both ER and PR positive	459 (86.0)	119 (25.9)	
HER2 status			
Negative or intermediate	445 (84.1)	124 (27.8)	P=0.03
Positive	84 (15.9)	14 (16.7)	
Clinical risk of recurrence			
Low	60 (11.2)	15 (25.0)	P<0.001
Moderate	204 (38.2)	106 (52.0)	
High	253 (47.4)	14 (5.5)	
Unknown	17 (3.2)	3 (17.7)	
Year of diagnosis			
2006	214 (40.1)	42 (19.6)	P<0.001
2007	252 (47.2)	68 (27.0)	
2008	68 (12.7)	28 (41.2)	

Notes: Percentages calculated based on those with valid data. Data were missing for tumor size (n=24), nodal involvement (n=5), tumor grade (n=26), and HER2 status (n=5).

ER: Estrogen receptor
PR: Progesterone receptor
HER2: human epidermal growth factor receptor.

Table 2

GEP testing and the receipt of adjuvant chemotherapy

		Clinical Recurrence Risk		
	All Patients	**Low**	**Moderate**	**High**
n	534	60	204	253
Received Chemotherapy	364 (68.2%)	6 (10.0%)	115 (56.4%)	234 (92.5%)
Received GEP test	138 (25.8%)	15 (25.0%)	106 (52.0%)	14 (5.5%)
Received Chemotherapy among those who had a GEP test	69 (50.0%)	5 (33.3%)	53 (50.0%)	9 (64.3%)
	Odds Ratio for Receipt of Chemotherapy (95% confidence interval)			
Received GEP test				
Unadjusted	0.34 (0.23 – 0.51)	22.00 (2.31 – 209.6)	0.58 (0.33 – 1.02)	0.11 (0.03 – 0.38)
Adjusted for propensity to receive a GEP test	0.62 (0.39 – 0.99)	42.19 (2.50 – 711.82)	0.64 (0.36 – 1.14)	0.12 (0.03 – 0.47)

NOTES: Reference in adjusted analyses is women who did not receive a GEP test. Propensity score methods were used to control for confounding by characteristics that may be associated with receipt of a GEP test. Each woman's propensity to receive a GEP test was estimated as a function of her age at diagnosis, comorbidity score, year of diagnosis, tumor size, grade, nodal status, estrogen and progesterone receptor status, and HER2 receptor status, and was categorized in tertiles in adjusted model.

Table 3

GEP testing and Serious Chemotherapy-associated Adverse Events.

		Clinical Recurrence Risk		
	All Patients	**Low**	**Moderate**	**High**
n	534	60	204	253
Occurrence of adverse event	56 (10.5%)	2 (3.3%)	21 (10.3%)	30 (11.9%)
Received GEP test	138 (25.8%)	15 (25.0%)	106 (52.0%)	14 (5.5%)
	Odds Ratio for Serious Chemotherapy-associated Adverse Events (95% confidence interval)			
Received GEP test				
Unadjusted	0.59 (0.24 – 1.22)	-	0.53 (0.21 – 1.35)	0.56 (0.07 – 4.42)
Adjusted for propensity to receive a GEP test	0.54 (0.24 – 1.22)	-	0.55 (0.21 – 1.43)	0.56 (0.06 – 4.34)

NOTES: Reference in adjusted analyses is women who did not receive a GEP test. Each woman's propensity to receive a GEP test was estimated as a function of her age at diagnosis, comorbidity score, year of diagnosis, tumor size, grade, nodal status, estrogen and progesterone receptor status, and HER2 receptor status, and was categorized in tertiles in adjusted model. Models not run for low clinical risk group because of limited sample size.

Table 4

GEP testing and total charges

		Clinical Recurrence Risk		
	All Patients	**Low**	**Moderate**	**High**
n	534	60	204	253
Median Total Charges	$ 88,687	$ 73,099	$ 74,859	$ 102,827
Received a GEP test	79,008	114,388	73,561	98,527
Did not receive a GEP test	91,138	66,939	80,181	103,242
Difference	*− $12, 130*	*$47,449*	*− $6,620*	*− $4,715*
	Coefficient (95% confidence interval)			
Ln(Total Charges)				
Received GEP				
Unadjusted	−0.15 (−0.29 – −0.01)	0.29 (−0.11 – 0.68)	−0.03 (−0.23 – 0.17)	−0.03 (−0.40 – 0.34)
Adjusted for propensity to receive a GEP test	−0.01 (−0.17 – 0.15)	0.39 (−0.11 – 0.90)	−0.01 (−0.22 – 0.19)	0.01 (−0.38 – 0.39)

NOTE: All charges submitted to insurer in 12 months following breast cancer diagnosis. Reference in adjusted analyses is women who did not receive a GEP test. Each woman's propensity to receive a GEP test was estimated as a function of her age at diagnosis, comorbidity score, year of diagnosis, tumor size, grade, nodal status, estrogen and progesterone receptor status, and HER2 receptor status, and was categorized in tertiles in adjusted model. Exponentiated regression coefficients correspond to changes in the ratio of the expected geometric means of total charges between women who received GEP and those who didn't. Taking the low risk clinical group, for example, the total charges adjusted for the propensity to receive a GEP test would be 48% (exp(0.39)=1.48) higher for women who received GEP test than women who didn't, although this difference was not statistically significant.