Genomic Testing and Therapies for Breast Cancer in Clinical Practice

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Abstract

Purpose: Given the likely proliferation of targeted testing and treatment strategies for cancer, a better understanding of the utilization patterns of human epidermal growth factor receptor 2 (*HER2*) testing and trastuzumab and newer gene expression profiling (GEP) for risk stratification and chemotherapy decision making are important.

Study Design: Cross-sectional.

Methods: We performed a medical record review of women age 35 to 65 years diagnosed between 2006 and 2007 with invasive localized breast cancer, identified using claims from a large national health plan (N = 775).

Results: Almost all women received *HER2* testing (96.9%), and 24.9% of women with an accepted indication received GEP. Unexplained socioeconomic differences in GEP use were apparent after adjusting for age and clinical characteristics; specifically, GEP use increased with income. For example, those in the lowest income category (< $40,000) were less likely than those with an income of $125,000 or more to receive GEP (odds ratio, 0.34; 95% CI, 0.16 to 0.73). A majority of women (57.7%) with *HER2*-positive disease received trastuzumab; among these women, differences in age and clinical characteristics were not apparent, although surprisingly, those in the lowest income category were more likely than those in the high-income category to receive trastuzumab ($P = .02$). Among women who did not have a positive *HER2* test, 3.9% still received trastuzumab. Receipt of adjuvant chemotherapy increased as GEP score indicated greater risk of recurrence.

Conclusion: Identifying and eliminating unnecessary variation in the use of these expensive tests and treatments should be part of quality improvement and efficiency programs.

Introduction

Despite the growing importance of targeted genomically based tests and treatments for cancer, evidence of use in practice is limited.[1,2] Understanding these utilization patterns is critical to developing thoughtful health care delivery models and policies. Breast cancer care provides two key clinical cases for understanding the use of targeted tests and treatments for cancer.

First is the use of human epidermal growth factor receptor 2 (*HER2*) testing to guide trastuzumab (Herceptin; Genentech, South San Francisco, CA) therapy, one of the most successful evidence-based examples of using a targeted test to determine who should receive a specific therapy. *HER2* is an oncogene that is amplified in approximately 25% to 30% of breast cancers and is associated with decreased survival.[3] Trastuzumab is a monoclonal antibody targeting *HER2*. Because the benefits of trastuzumab are highly associated with *HER2* status,[4-7] professional organizations recommend *HER2* testing for all primary breast cancers at diagnosis.[8-10] Yet implementation of these guidelines in practice has been complicated.[11] Two types of tests have been approved: immunohistochemistry (IHC) and fluorescent in situ hybridization (FISH). IHC is less expensive and more widely available but has poorer reliability.[9,12] This has led to debate about the best testing strategy,[1,13] fueled by the high cost of the drug.[14,15]

The second example—gene expression profiling (GEP)—has generated intense interest, because it may improve prognostic information and predict response to adjuvant chemotherapy.[16-19] Guidelines suggest that a majority of women with node-negative, estrogen receptor–positive breast cancer should be offered chemotherapy, but because only a minority will experience recurrence, some patients may receive little benefit.[10,20] GEP may identify women who are at low risk of recurrence, who may therefore forego chemotherapy.[18] Use of GEP to tailor chemotherapy is less firmly established than the use of *HER2* testing to guide trastuzumab.

Given the likely proliferation of genomically based testing and treatment strategies for cancer, better understanding of utilization regarding these two examples is important. Our objectives were to evaluate use of targeted tests (*HER2* and GEP) and the associated treatment decisions (trastuzumab and adjuvant chemotherapy) in clinical practice.

Methods

Population

We identified women age 35 to 65 years with incident breast cancer diagnosed between July 1, 2006, and June 30, 2007, who received health insurance coverage through Aetna (Hartford, CT), a national health benefits company. Potentially eligible women were identified from claims data.[22] We included women who were continuously enrolled from 24 months before to 12 months after diagnosis. Records were requested from the primary medical oncologist and surgeon. We initially identified 2,121 women in the claims. We requested records until we reached the prespecified sample size determined by our budget of 800 abstracted records. At the time of abstraction, 517 women were found to be ineligible, because they did not have invasive breast cancer (ie, they had carcinoma in situ only). We

abstracted medical records for 787 women with invasive breast cancer. Women with abstracted records were not statistically different from the population of eligible women in terms of age, household income, comorbidity, type of breast cancer surgery, or census region, but they were less likely to have health maintenance organization (HMO) plans (29.4% *v* 34.6%; $P = .01$). Because few women (n = 7) had stage IV cancer or were missing stage information (n = 5), we excluded these women to focus on women with early-stage cancer. We abstracted records for 775 women with early-stage cancer.

Benefit Coverage

Although all women received coverage through Aetna, there were 41 different health plan products. All plans provided coverage for these tests and treatments. Onco*type* DX (Genomic Health, Redwood City, CA) is the most commonly available commercial GEP test in the United States. Aetna instituted a formal coverage policy for Onco*type* DX on December 1, 2006, with the requirement that a woman's breast cancer be estrogen receptor positive and lymph node negative, with tumor smaller than 1 cm if HER2 positive or of any size if HER2 status is negative, intermediate, or unknown.[23] Before Aetna instituted this policy, women may have had claims for Onco*type* DX paid on a case by case basis, or they could have paid out of pocket.

Sources of Data

Claims. In addition to identifying the cohort, we used claims to determine age, comorbidity,[24] and procedure (eg, breast-conserving surgery, mastectomy). Data on annual household income, derived from small area estimation,[25] were also available. Health plan products were categorized into the following plan types: indemnity, HMO, preferred provider organization, and point of service. There were no differences in referral requirements across plan type for these tests and treatments. Because the average per-member per-month cost (including coinsurance, deductible, and copayment costs) paid by all Aetna members for all outpatient claims incurred in 2009 was lower for HMO plans ($12.20) than for the other plan types ($30.92, point of service; $27.81 indemnity; $23.86, preferred provider organization), we compared women with an HMO plan with those with other plans. Information about race/ethnicity (ie, white, black, Hispanic, or other) was available from health plan records, based on self-reported data from enrollment records (35.2%), or inferred using a proprietary algorithm.[25] This algorithm is uses small area estimation with data from the current population survey and American community survey, assigning race/ethnicity on the basis of first name, surname, and geographic criteria. In a secondary analysis, we also examined claims data for January 2007 to December 2009 to obtain more recent data on use of GEP and trastuzumab.

Medical records. A standard abstraction tool was used to collect detailed clinical information, including menopausal status, cancer stage, tumor size, lymph node involvement, estrogen receptor status, use and results of any *HER2* or GEP tests, and use of trastuzumab and adjuvant chemotherapy. Medical records were reviewed by trained abstractors contracted through a third-party vendor, who released a de-identified analytic data set to the investigators.

Variables

We examined two sets of outcomes. First, we examined use of *HER2* testing and trastuzumab conditional on *HER2* results. We specifically examined type of *HER2* test (IHC, FISH, or both). Second, we identified the use of GEP and adjuvant chemotherapy. Patients were considered to have received chemotherapy if they had documentation in their medical records of any chemotherapy medications commonly administered for breast cancer (ie, adriamycin, carboplatin, cyclophosphamide, docetaxel, fluorouracil, epirubicin, paclitaxel, albumin-bound paclitaxel). GEP results were categorized according to interpretation as low-, medium-, and high-risk of recurrence.

Other covariates included age, menopausal status (pre or post), annual household income ($< \$40{,}000$, \$40,000 to \$74,999, \$75,000 to \$124,999, $\geq \$125{,}000$), comorbidity, American Joint Committee on Cancer stage definitions (I, II, III), estrogen receptor status (positive, negative), type of surgery, and region (Northeast, Midwest, South, West).

Data Analysis

We examined associations of patient characteristics with receipt of each of the targeted tests and treatments using bivariate analyses. Logistic regression was used to estimate adjusted odds ratios (ORs) and 95% CIs. Models included all factors that we believed, a priori, could potentially be associated with these outcomes. All final models included age, menopausal status, income, health plan type, comorbidity (none, one, or $\geq$ two), disease stage, estrogen receptor status, surgery, and region. Models of trastuzumab use also included both type of *HER2* test and interpreted results (negative, intermediate, positive, not done or not documented). For trastuzumab models, we separately examined use among women with and without *HER2*-positive cancer. Models of GEP use also included *HER2* results, and models of adjuvant chemotherapy included GEP

Take-Away Points

- Despite almost universal testing for *HER2*, many women with *HER2*-positive cancer may not receive trastuzumab. There was more modest use of gene expression profiling as well as socioeconomic differences in use.
- Given the likely proliferation of targeted testing and treatment strategies for cancer, better understanding of utilization patterns in clinical practice is important to develop clinical and coverage policy.
- Identifying and eliminating unnecessary variation in the use of these expensive tests and treatment should be part of quality improvement and efficiency programs.

score. Analysis of GEP included women who met the Aetna coverage policy.[10] In primary models of adjuvant chemotherapy, we used as reference women who fit these criteria but did not receive GEP testing. In a secondary analysis, we examined the bivariate association between GEP result and adjuvant chemotherapy use among women who had received GEP testing. We did not perform multivariate analyses because of the relatively small sample size. In exploratory analysis of race/ethnicity, this variable was coded as white versus nonwhite in the models. Analyses were performed using STATA version 10 (StataCorp, College Station, TX).

Results

Sample Characteristics

Median age was 54 years, and a majority of women were postmenopausal (Table 1). Approximately one third had coverage through an HMO. Seventy-seven percent had no comorbid conditions. Breast cancer was diagnosed as stage I for 57.9%, stage II for 33.0%, and stage III for 9.0%. Poorly and moderately differentiated tumors were somewhat more common than well differentiated. A majority of tumors were estrogen receptor positive. Women lived in all four regions of the United States, with the most in the South (50.1%) and least in the West (11.0%).

HER2 Testing Strategies

Only 3.1% of women did not have documentation of any *HER2* test. The most common testing strategy was IHC (57.9%), with 19.6% of women receiving FISH and 22.4% receiving both. Use of *HER2* testing was uniform across both clinical and nonclinical factors (data not shown).

Use of Trastuzumab

Overall, 13.4% of women received trastuzumab. Type of *HER2* test and result were strongly associated with utilization ($P < .001$). Approximately one quarter of women who received trastuzumab did not have documentation of a positive *HER2* test. Among women without an *HER2*-positive test, 25 (3.9%) received trastuzumab. In these women, those who had undergone mastectomy were more likely than women who had had breast-conserving surgery to receive trastuzumab (OR, 2.83; 95% CI, 1.20 to 6.65). There was also a trend ($P < .10$) toward women in an HMO being more likely than those with other plan types to receive trastuzumab (OR, 2.69; 95% CI, 0.92 to 7.91).

Among women with an *HER2*-positive result, 57.7% received trastuzumab (Table 2). Even among those with larger tumors (≥ 2 cm), 25.9% of *HER2*-positive women did not receive trastuzumab. After adjustment, women with an annual household income less than $40,000 were more likely to receive trastuzumab than women with an income of $125,000 or greater (OR, 4.43; 95% CI, 1.22 to 16.04).

Use of GEP

Among the 393 clinically eligible women, 24.9% received GEP (Table 3). All women in this sample underwent GEP testing using Onco*type* DX. There was no significant difference in GEP use before and after implementation of the Aetna coverage policy (26.8% and 20.4%, respectively; $P = .18$). Among women who received GEP, 66.3% were characterized as having a low risk of recurrence; 24.7%, intermediate risk; and 9.0%, high risk. Use of GEP was less common among lower-income

Table 1. Characteristics of Study Sample (N = 775)

Characteristic	No.	%
Age, years		
Median	54	
Range	35-65	
35-49	271	35.0
50-65	504	65.0
Postmenopausal	499	64.4
Annual household income*		
< $40,000	185	25.1
$40,000-$74,999	256	34.8
$75,000-$124,999	172	23.4
≥ $125,000	123	16.7
Health plan type		
Health maintenance organization	228	29.4
Other†	547	70.6
Comorbidity score		
0	600	77.4
1	134	17.3
≥ 2	41	5.3
Breast cancer stage		
I	449	57.9
II	256	33.0
III	70	9.0
Tumor size, cm*		
≤ 1	209	27.7
1.01-2	302	67.6
2.01-5	219	29.0
> 5	26	3.4
Summary grade*		
Well differentiated or low	175	25.5
Moderately differentiated or intermediate	255	37.1
Poorly differentiated or high	257	37.4
Estrogen receptor status of tumor*		
Positive	578	76.0
Type of breast cancer surgery		
Breast conserving surgery	463	59.7
Mastectomy	312	40.3
Census region		
Northeast	187	24.1
Midwest	115	14.8
South	388	50.1
West	85	11.0

* Percentages calculated based on those with valid data. Data were missing for income (n = 39), tumor size (n = 19), summary grade (n = 88), and estrogen receptor status (n = 14).
† Includes point of service, indemnity, and preferred provider organization plans.

Table 2. Use of Trastuzumb Among Women With *HER2*-Positive Breast Cancer

Characteristic	Total No. of Women	Women Receiving Trastuzumab		*P*	Odds Ratio	95% CI
		No.	%			
Age, years	137	79	57.7	.44	1.05	0.71 to 1.56
35-49	47	25	53.2			
50-65	90	54	60.0			
Menopausal status	137			.33		
Premenopausal	48	25	52.1		Ref	
Postmenopausal	89	54	60.7		1.45	0.46 to 4.59
Income	131			.02		
< $40,000	34	27	79.4		4.43	1.22 to 16.04
$40,000-$74,999	47	22	46.8		1.01	0.34 to 3.00
$75,000-$124,999	27	16	59.3		1.61	0.47 to 5.51
≥ $125,000	23	11	47.8		Ref	
Health plan type	137			.09		
Health maintenance organization	49	33	67.4		1.60	0.64 to 3.98
Other plan type*	88	46	52.3		Ref	
Comorbidity score	137			.68		
0	114	66	57.9		Ref	
1	16	10	62.5		1.02	0.27 to 3.80
≥ 2	7	3	42.9		0.79	0.16 to 3.83
Cancer stage	137			.03		
I	66	31	47.0		Ref	
II	52	37	71.2		1.91	0.78 to 4.70
III	19	11	57.9		1.39	0.43 to 4.54
Estrogen receptor status	136			.23		
Positive	95	52	54.7		Ref	
Negative	41	27	65.9		1.49	0.65 to 3.40
Breast cancer surgery	137			.50		
Lumpectomy	71	39	54.9		Ref	
Mastectomy	66	40	60.6		1.38	0.59 to 3.21
Census region	137			.32		
Northeast	42	25	59.5		0.99	0.43 to 2.32
Midwest	12	4	33.3		0.30	0.07 to 1.24
South	68	40	58.8		Ref	
West	15	10	66.7		1.82	0.46 to 7.16

* Includes point of service, indemnity, and preferred provider organization plans.

women. Women in the Midwest were more likely to receive GEP testing than women in the South. There was no significant variation in use of GEP by age, plan type, menopausal status, comorbidity, cancer stage, type of surgery, or *HER2* result. In secondary analyses, nonwhite women were less likely to receive GEP (OR, 0.48; 95% CI, 0.24 to 0.95). We found a trend toward less GEP use after the coverage policy change (OR, 0.59; 95% CI, 0.34 to 1.04).

Use of Chemotherapy

Among women clinically eligible for GEP, 38.9% received adjuvant chemotherapy (Table 3). Use of chemotherapy decreased with age and increased with stage. Notably, use of chemotherapy increased as GEP score indicated a higher recurrence risk, yet almost one quarter of women with a low recurrence score received chemotherapy. Although women with a low recurrence score were not statistically less likely than women who did not undergo GEP testing to receive chemotherapy (OR, 0.55; 95% CI, 0.26 to 1.16; $P = .12$), those with an intermediate or high score were more likely to do so. The coverage policy change for GEP testing was not associated with use of adjuvant chemotherapy (OR, 1.25; 95% CI, 0.73 to 2.21).

More Recent Trends

Because use of GEP and trastuzumab may be evolving, we wanted to place our medical record data from 2006 to 2008 in the context of information about care provided more recently,

Table 3. Use of GEP Testing and Adjuvant Chemotherapy Among Eligible Women (n = 393)

	Use of GEP					Use of Adjuvant Chemotherapy				
Characteristic	**No.**	**%**	**Odds Ratio**	**95% CI**	***P***	**No.**	**%**	**Odds Ratio**	**95% CI**	***P***
Age, years	98	24.9	0.84	0.66 to 1.09	.49	153	38.9	0.68	0.52 to 0.89	< .001
35-49	37	27.0				72	52.6			
50-65	61	23.8				81	31.6			
Menopausal status					.42					< .001
Premenopausal	41	27.2	Ref			80	53.0	Ref		
Postmenopausal	57	23.6	1.42	0.64 to 3.14		73	30.2	0.90	0.40 to 1.99	
Income					.01					.09
< $40,000	17	19.1	0.34	0.16 to 0.73		37	41.6	1.27	0.56 to 2.87	
$40,000-$74,999	28	20.1	0.34	0.17 to 0.67		42	30.2	0.75	0.34 to 1.67	
$75,000-$124,999	22	26.2	0.45	0.22 to 0.92		39	46.4	1.68	0.73 to 3.91	
≥ $125,000	27	41.5	Ref			25	38.5	Ref		
Health plan type					.76					.06
Health maintenance organization	25	23.8	1.04	0.59 to 1.83		49	46.7	1.51	0.87 to 2.62	
Other plan type*	73	25.4	Ref			104	36.1	Ref		
Comorbidity score					.20					.18
0	81	27.1	Ref			124	41.5	Ref		
1	12	17.1	0.54	0.27 to 1.09		21	30.0	0.80	0.42 to 1.54	
≥ 2	5	20.8	0.83	0.27 to 2.55		8	33.3	0.92	0.36 to 2.33	
Cancer stage					.24					< .001
I	83	26.4	Ref			100	31.9	Ref		
II	15	20.3	0.71	0.36 to 1.38		48	64.9	5.67	2.87 to 11.18	
Breast cancer surgery					.79					.002
Lumpectomy	65	24.5	Ref			89	33.6	Ref		
Mastectomy	33	25.8	1.08	0.63 to 1.86		64	50.0	1.68	0.98 to 2.88	
HER2 test result					.98					.33
Negative	55	24.8	Ref			87	39.2	Ref		
Intermediate	10	27.8	1.25	0.54 to 2.92		17	47.2	1.53	0.69 to 3.37	
Positive	8	25.0	0.82	0.36 to 1.85		15	46.9	1.80	0.71 to 4.58	
GEP result										< .001
Not done						115	37.8	Ref		
Low						14	23.7	0.55	0.26 to 1.16	
Medium						17	77.3	8.21	1.99 to 33.83	
High						7	87.5	13.48	2.32 to 78.35	
Region					.18					.14
Northeast	21	25.0	1.25	0.67 to 2.33		41	48.8	1.39	0.75 to 2.58	
Midwest	23	34.3	2.25	1.15 to 4.40		21	31.3	0.57	0.28 to 1.20	
South	41	21.0	Ref			75	38.5	Ref		
West	13	27.7	1.22	0.55 to 2.71		16	34.0	0.89	0.40 to 1.96	

NOTE. Eligible women were those with a tumor that was estrogen receptor positive, lymph node negative, and < 1.5 cm in size if *HER2* positive or of any size if *HER2* negative, intermediate, or unknown.
Abbreviation: GEP, gene expression profiling.
* Includes point of service, indemnity, and preferred provider organization plans.

using claims. We found that claims for GEP increased substantially through 2009 (2007, 1,175 claims; 2008, 1,802; 2009, 2,037). Conversely, we observed a small decline in claims for trastuzumab, from 18,018 in 2007 to 17,603 in 2009.

Discussion

To our knowledge, this study provides some of the first real-world evidence of how targeted tests and treatments are being used in clinical practice for insured women with early stage breast cancer. We demonstrate that *HER2* testing is widely used. Although a majority of women who received trastuzumab had documentation of an *HER2*-positive test, approximately one quarter did not, suggesting that there may be incomplete documentation of test results or overuse of this expensive treatment. Among women with an *HER2*-positive tumor, many did not receive trastuzumab, despite insurance coverage. Although some of these women had small node-negative tumors or substantial comorbidity, others may have been undertreated or

deferred this treatment. In contrast to the near-universal adoption of *HER2* testing, we found more modest use of GEP, perhaps because of lack of guidelines recommending universal use, newness of the test, and less straightforward treatment implications. We also found evidence for unexplained socioeconomic and regional differences in use. Finally, we found that GEP results are being used to tailor use of adjuvant chemotherapy, independent of traditional clinical factors.

This study addresses important gaps in evidence regarding utilization of *HER2* testing and trastuzumab.[26] On a positive note, virtually all women received an *HER2* test, consistent with guidelines[8-10] and similar to results of a study of 322 commercial health plan members from 2005 to 2006.[2] Use of trastuzumab in our study was lower than the rate of 70.8% described in this cohort of commercial health plan members[2] and the rate observed in a region of the United Kingdom,[27] but it was higher than the rate observed in an earlier study involving a single health care provider.[28] We do not know why some eligible women did not have documentation of use. Because all of these women had coverage for this therapy, it is likely that this finding is related to nonfinancial barriers to care. Related work has shown that women with breast cancer may not receive conventional adjuvant chemotherapy because of physician perception that the risks exceed the benefits, patient refusal, or system failures.[29] There is also concern among both patients and providers about the reliability and interpretation of *HER2* testing and uncertainty about who will benefit most from trastuzumab.[9,11,12,30,31] Finally, we do not have a definitive explanation for the counterintuitive finding that low-income women were most likely to receive trastuzumab, but we suspect this is related to factors that we did not measure (eg, employment status). Our finding that one quarter of women did not have documentation of a positive result, possibly indicating overuse, is consistent with other estimates.[32]

In contrast to the widespread use of *HER2* testing, use of GEP was more modest. This is not surprising given the more recent availability of and coverage for the test. Analysis of more recent claims data shows that GEP use is increasing, reflecting the incorporation of GEP into clinical guidelines and the decision of several high-profile insurers to provide coverage.[32] Although the test costs approximately $3,400, testing may reduce the number of low-risk women receiving adjuvant chemotherapy, which costs, on average, $10,000 per patient.[33] Little is known about use of adjuvant chemotherapy after GEP testing. Gold et al[34] examined data for 269 women with early stage breast cancer seen at a single cancer center and found that adjuvant chemotherapy was administered to 7% of women with a low recurrence score, compared with 42% and 86% of women with intermediate and high recurrence scores, respectively. Several studies have suggested that making chemotherapy treatment decisions based on GEP is more cost effective compared with traditional risk-stratification measures.[17,33,35] However, these findings should be confirmed more broadly.

Our study has several limitations. First, our data based on medical records may have incomplete information about whether tests and treatments were discussed but declined or just not documented. Second, household income and race/ethnicity information was derived largely from small area estimation.[36] We cannot address reasons for observed differences in use by income or race/ethnicity; because all of these women had insurance, differences are likely to be related to nonfinancial barriers. Third, because our data were based on retrospective medical record review, we cannot determine how physicians weigh GEP test results compared with traditional measures of recurrence risk. Finally, all women received coverage from a single large health insurer, which limits the generalizability of our findings to women with public insurance, the uninsured, or older women covered by Medicare. Despite this limitation, our sample is large and geographically diverse, and it represents a variety of practice settings. As such, it provides a snapshot of how targeted technologies and treatments for breast cancer are being used in the United States. Because these data are based on medical records, we are better able to capture test usage than studies that relying solely on claims,[37] and we have test results, which are critical to determining appropriate treatment.

As targeted tests and treatments become more central to cancer care, it is crucial that we develop evidence about use of these costly technologies in practice. To our knowledge, this study provides some of the first evidence about use of targeted testing and treatment for breast cancer and finds that although there is near-universal use of *HER2* testing, many women who are *HER2* positive may not receive trastuzumab. These findings should inform models of care and policies to ensure appropriate use of these emerging technologies.

Accepted for publication on March 25, 2011.

Acknowledgment

We thank Mike Morris and Carolyn Jevit for assistance with cohort identification, database development, and claims data preparation. The study was supported by the Aetna Foundation and National Cancer Institute (Grant No. P01CA130818-01A1).

Authors' Disclosures of Potential Conflicts of Interest

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: Joanne Armstrong, Aetna (C); Michele Toscano, Aetna (C) **Consultant or Advisory Role:** None **Stock Ownership:** Joanne Armstrong, Aetna; Michele Toscano, Aetna **Honoraria:** None **Research Funding:** Jennifer S. Haas, Aetna Foundation; Kathryn A. Phillips, Aetna Foundation; Su-Ying Lian, Aetna Foundation; Carol Keohane, Aetna Foundation **Expert Testimony:** None **Other Remuneration:** None

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DOI: 10.1200/JOP.2011.000299

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