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HER2 Evaluation and Its Impact on Breast Cancer Treatment Decisions

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Genetic · Herceptin · Translation · Trastuzumab

Abstract
Background: Eighteen to twenty percent of breast cancer tumors show abnormal amplification of the Human Epidermal growth factor Receptor 2 *(HER2)* gene and increased expression of the associated protein. *HER2* amplification is associated with rapid tumor proliferation and shorter disease-free and overall survival. Because women with *HER2* amplification are more likely to benefit from treatment with the drug trastuzumab, testing for *HER2* is recommended to guide therapy. However, little is known about use of *HER2* testing in real-world settings. This study examined uptake, use, appropriateness of *HER2* testing, and the relationship between *HER2* test results and treatment decisions. ***Methods:*** We assessed electronic data from 3,634 patients with invasive breast cancer diagnosed from 1998 to 2007 in a large integrated health system. We collected data on patient and tumor characteristics, *HER2* testing status, test results, and trastuzumab treatment. ***Results:*** From 1998 to 2000, the percent of patients who underwent *HER2* evaluation increased from 12 to 94%; <3% of women with ductal carcinoma in situ, for whom *HER2* testing is not recommended, were tested. Trastuzumab use increased 5-fold after 2004, when guidelines expanded to include recommending adjuvant treatment for early-stage breast cancer in addition to metastatic treatment. Ninety-five percent of women receiving trastuzumab had a positive *HER2* result. After 2004, 55% of women with invasive breast cancer and overexpression of *HER2* received trastuzumab treatment; this ranged from 44% of women with localized breast cancer to 80% of women with distant metastatic disease. ***Conclusions:*** These findings illustrate appropriate and effective implementation of a *HER2* testing strategy in a managed care setting.

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Introduction

Breast cancer is the second-most deadly malignancy in women [1] and accounts for one-fourth of all expected new female cancer cases. In 2009, about 92,000 American women were diagnosed with breast cancer and over 40,000 are expected to die of the disease [2]. Many women with early-stage breast cancer are offered adjuvant chemotherapy to prevent recurrence. While new genetic-based technologies that can help predict cancer recurrence or treatment response present exciting opportunities for improving outcomes, little is known about how such technologies are being incorporated into practice and whether they are being used appropriately to make treatment recommendations [3, 4].

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Human Epidermal growth factor Receptor 2 *(HER2)* is a gene that influences cell growth, division and repair; a normal cell has 2 copies of *HER2*. About 18–20% of breast cancers have amplification of this gene [5–7], which is associated with rapid tumor proliferation, shorter disease-free survival and poorer overall survival [8–10]. Trastuzumab (Herceptin®, Genentech Inc., San Francisco, Calif., USA) acts by targeting production of the HER2 protein to prevent the growth of HER2-positive cancer cells, thereby reducing recurrence of disease and reducing mortality [11–15]. However, trastuzumab only benefits women with *HER2* gene amplification, is expensive (USD 44,000–65,000 per year [16, 17]) and can be cardiotoxic [18]. Therefore, selecting appropriate patients to receive trastuzumab is vital.

Currently, 2 types of tests are approved by the U.S. Food and Drug Administration for determining *HER2* status. The immunohistochemistry (IHC)-based test (e.g. DAKO HercepTest; Ventana Pathway) measures production of HER2 protein by the tumor. Test results are ranked as 0, 1+ (negative), 2+ (equivocal), or 3+ (positive). The fluorescence in situ hybridization (FISH) test (e.g. Vysis PathVysion; Ventana INFORM HER2 probe) quantifies the number of copies of the *HER2* gene in tumor cells. A positive HER2 test is defined as IHC 3+ and, to a lesser extent, IHC 2+ [19–21] or a *HER2*:CEP17 ratio >2 [22, 23]. While some reports suggest that FISH technology more accurately predicts response to trastuzumab than IHC technology [24], a recent summary report indicates that the 2 tests are comparable if careful validation testing is performed [25]. *HER2* testing may also predict response to several systemic therapies, including anthracyclines and resistance to endocrine therapy, although the evidence is not always consistent [10, 26–45].

The Food and Drug Administration initially approved trastuzumab in 1998 for use in patients with metastatic breast cancer. In November 2006, it approved trastuzumab as an adjuvant therapy for women with lymph node-positive and HER2-positive breast cancer [12–14]. Trastuzumab is not recommended for patients with a positive *HER2* test result if they have cardiovascular risk factors. A joint guideline from the American Society of Clinical Oncologists (ASCO) and the College of American Pathologists (CAP) state that *HER2* testing should be performed for all invasive breast cancers regardless of lymph node disease status [25], and the National Comprehensive Cancer Network (NCCN) also endorsed *HER2* testing [46–50].

Despite these well-developed, evidence-based practice guidelines, however, little research has been done on this test in real-world settings. In particular, Phillips [3] indicated that little is known about what percentage of patients are tested for *HER2*, which testing methods are used, whether patients are retested to confirm indeterminate results, and how many patients with negative or equivocal results receive trastuzumab.

Our study addressed this knowledge gap by evaluating utilization and treatment patterns associated with *HER2* testing for patients with breast cancer in an integrated healthcare delivery system. We studied a cohort from this health plan with more than 12 years of electronic medical records and other data sources. We documented the uptake and use of *HER2* testing and evaluated whether testing was being done appropriately according to professional guidelines. We considered the use of IHC versus FISH testing and trastuzumab prescriptions in the context of the *HER2* test result. This study is one of the largest and most comprehensive studies illustrating the real-world use and impact of *HER2* testing.

Subjects and Methods

Study Population

Study participants were patients at Kaiser Permanente Northwest (KPNW), an integrated healthcare delivery system serving more than 470,000 members in Oregon and Southwest Washington. KPNW's members are demographically representative of the coverage area in terms of the age, gender and racial or ethnic distribution, and include about 20% of the area's population. Medicare members represent about 12% of KPNW's total membership. Members over 65 represent 12.8% of total membership, 2% are below 200% of the federal poverty level and 13% are minorities. We identified women with a primary diagnosis of breast cancer through KPNW's tumor registry. Women were eligible for the study if they were diagnosed with their first primary breast cancer between January 1, 1998 and December 31, 2007 and did not have missing data for tumor stage at diagnosis. We required that participants receive their diagnosis and initial treatment at KPNW. KPNW patients are treated at 5 area hospitals, and there are currently 10 oncologists on staff, although there were changes in staff over the 10-year study period.

The Institutional Review Board at KPNW approved this study and did not require written informed consent. The Oregon Genetic Privacy law requires health care providers to notify patients that any specimens or health information will be available for anonymous or coded genetic research unless the person 'opts out'. About 13% of KPNW's membership has opted-out, and these individuals were excluded from this study.

Data Collection

We abstracted electronic data on patient characteristics, tumor characteristics, *HER2* testing status, test results for FISH and IHC separately, and trastuzumab treatment. The centralized tumor registry contains information on all cancers diagnosed at

KPNW since 1960, and survival data is continuously updated. A trained abstractor keys items directly into the registry for each identified tumor. The pharmacy database records all prescriptions dispensed by KPNW outpatient pharmacies and includes date of dispensing, dose, prescribing physician, and unique codes using standard nomenclature to identify each drug.

HER2 *Genetic Testing*

All data used in this study are derived from testing that occurred as part of routine medical care provided by KPNW clinicians. Between 1998 and 2000, KPNW implemented an internal practice guideline of systematic screening for all women diagnosed with invasive breast cancer. According to this protocol, IHC is used as the initial HER2 test, followed by FISH testing to clarify or confirm equivocal or positive IHC findings.

IHC testing for *HER2* was conducted by the KPNW regional laboratory using the HercepTest (Dako, Carpinteria, Calif., USA) and was classified as negative (0 or 1+), equivocal (2+) or positive (3+). FISH testing for *HER2* was performed by Quest Diagnostics using the Vysis PathVysion test (Abbott Molecular, Abbott Park, Ill., USA) and was classified as negative (*HER2*/CEP 17 ratio <1.8), equivocal (*HER2*/CEP 17 ratio between 1.8 and 2.2) or positive (*HER2*/CEP 17 ratio >2.2). The standard protocol at KPNW changed in October 2007 to make FISH testing (performed at Quest Diagnostics) the initial *HER2* test. For all cases with equivocal (1.8–2.2) FISH results, and for known grade 3 tumors with negative FISH results, IHC testing was also performed by Quest Diagnostics.

Chart Abstraction

Following the initial analysis of tumor-registry data, a single abstractor manually checked a sample of data points in the categories described below against the electronic medical record using standard data collection forms. Abstracted variables included IHC and FISH test results, date of test, stage of disease at diagnosis, lymph node involvement, tumor size, and trastuzumab use. For training, we developed instructions and a set of 'practice' charts that were scored by 2 study abstractors and compared [51]. Abstraction forms were entered into an electronic database using double data entry to ensure accuracy. Two reviewers discussed unexpected values to resolve issues.

We abstracted charts in 7 categories: (1) patients with a diagnosis of noninvasive breast cancer who nevertheless received *HER2* testing (n = 11) after 1999; (2) patients with a diagnosis of invasive breast cancer who did not receive *HER2* testing (n = 154) after 1999; (3) patients who received FISH testing, but not IHC testing, after 2004 (n = 93); (4) patients with a negative IHC test result that was confirmed by FISH after 2004 (n = 87); (5) patients with an equivocal IHC test result that was not confirmed with FISH after 2004 (n = 69); (6) patients who received trastuzumab, but did not have a positive *HER2* result (n = 26); and (7) *HER2*-positive patients with distant metastatic or regional (after 2004) breast cancer who did not receive trastuzumab (n = 13 and 21, respectively). We verified findings in a random subset of patients for each category (n = 50; except categories with fewer than 50 observations).

Statistical Methods

Patients were classified as receiving trastuzumab if any of the following national drug codes were in the pharmacy records after their date of diagnosis: 50242013460, 50242013468, 50242005656, 63552047001, or if procedure code J9355 was in the procedures database. Lymph node status was dichotomized into positive (one or more positive nodes) or negative. We used SEER staging criteria [52] to define noninvasive breast cancer as patients diagnosed with ductal carcinoma in situ (DCIS) and invasive breast cancer as patients diagnosed with localized, regional or distant-metastasis breast cancer. All analyses, including descriptive statistics and summaries, were produced using R (version 2.6.2; R Foundation for Statistical Computing, www.r-project.org).

Results

Pattern of HER2 *Test Utilization*

There were 3,623 women who met the criterion of a primary breast cancer diagnosis during 1998–2007 (table 1). We excluded 31 women because of missing tumor registry data on cancer stage at diagnosis, a critical variable. Of the remaining women, about 538 (15%) had a diagnosis of DCIS or noninvasive breast cancer, and 3,054 (85%) had invasive breast cancer.

We defined women as 'evaluated' for *HER2* if they received either IHC or FISH testing. Overall, 69% of the study population was evaluated for *HER2*. However, this summary statistic obscures critical differences over time and by disease stage (fig. 1). First, according to clinical guidelines, the 15% of women with noninvasive breast cancer are not recommended for *HER2* testing. In this group, only 2.5% received *HER2* testing, and the proportion remained consistently low over the entire study period. Of those with invasive breast cancer, 81% received *HER2* testing, a proportion that substantially increased between 1998 and 2000 from 12% to over 94%. After 2000, more than 94% of invasive breast cancer patients received *HER2* testing over all years combined. Women with both invasive and noninvasive breast cancer were more likely to be evaluated for *HER2* if they were also evaluated for other tumor markers including ER status ($p < 0.0001$) and nodal involvement ($p \leq 0.007$) (table 1).

We manually abstracted medical charts to verify findings from the tumor registry. We estimated the KPNW protocol was not followed for <3% of patients diagnosed since 2000, after correcting for errors. For the 11 patients diagnosed since 2000 with noninvasive breast cancer who received *HER2* testing according to the tumor registry, 10 patients had a diagnosis of DCIS. The remaining patient had no tumor stage in the medical record. We were unable to find evidence of *HER2* testing in the medical chart for 3 of the 10 DCIS patients. As such, 7 of these 10 patients were correctly identified as evaluated for

Table 1. Characteristics of patients diagnosed with breast cancer in 1998–2007

Characteristics	Noninvasive breast cancer			Invasive breast cancer		
	not tested for *HER2*, n	tested for *HER2*, n	p value[a]	not tested for *HER2*, n	tested for *HER2*, n	p value[a]
Total number	525	13		579	2,475	
Age at diagnosis, years			0.03			0.4
<45	47	4		56	250	
45–59	218	2		229	971	
60–69	157	5		143	679	
≥70	103	2		151	575	
Race/ethnicity[b]			0.9			0.2
White, non-Hispanic	482	11		537	2,240	
African American	9	0		11	42	
Hispanic	5	0		10	38	
Other	12	0		8	77	
Unknown	17	2		13	78	
ER status[c]			<0.0001			<0.0001
Positive	184	13		369	2,040	
Negative	30	0		106	410	
Unknown	311	0		104	25	
Nodal involvement[d]			0.007			<0.0001
Evaluated, negative	100	7		358	1,511	
Positive	2	0		1,197	677	
Not evaluated	423	6		104	287	
SEER stage						0.02
In situ	525	13		0	0	
Localized	0	0		429	1,717	
Regional	0	0		127	679	
Distant metastasis	0	0		23	79	

[a] p values from Pearson's χ^2 test with Yates' continuity correction. [b] The comparison is for white race versus all others. [c] The comparison is whether ER status is known or unknown. [d] The comparison is whether nodes were evaluated or not.

HER2. Thus, the tumor registry correctly identified a small number of patients with noninvasive breast cancer who received *HER2* testing.

There were 154 patients diagnosed with invasive breast cancer after 1999 who did not receive *HER2* testing according to the tumor registry, although they should have received this testing according to the KPNW protocol. We conducted a chart review for a random subset of 50 of these cases and discovered that 63% of the chart-reviewed cases actually did receive an IHC or FISH test. Thus, after accounting for these errors in the tumor registry, we estimate that only about 2–3% of patients with invasive breast cancer did not receive *HER2* testing.

Fewer invasive breast cancer patients with Medicare/Medicaid insurance were evaluated for *HER2* compared with other insurance products (79% vs. 83%; p = 0.001) (fig. 1). Most patients (92%) diagnosed with noninvasive breast cancer and evaluated for *HER2* were treated inside KPNW. A slightly higher proportion of patients diagnosed with invasive breast cancer and not evaluated for *HER2* were treated outside KPNW (22% vs. 18%; p = 0.03). It is possible that this difference is a result of the fact that documentation for *HER2* testing was not available for some patients treated outside KPNW.

Use of IHC and FISH Tests

The majority of patients who underwent *HER2* testing received the IHC test (96%). FISH results were only recorded in the tumor registry database after 2004 (table 2). Forty-two percent of those diagnosed with invasive breast cancer between 2004 and 2007 (n = 1,232) received FISH testing, and 82% (433) of these also received IHC testing. About 81% of patients who received FISH testing, but not IHC testing, were diagnosed after October 2007, when KPNW adopted FISH testing as the primary *HER2* test.

Table 2. Comparison of FISH and IHC test results for invasive breast cancer patients diagnosed after 2004

IHC test result	FISH test result				
	not done	negative	equivocal	positive	total
Not done	49	76	4	12	141
Negative	538	84	2	1	625
Equivocal	69	175	8	25	277
Positive	49	55	6	75	185
Total	705	390	20	113	1,228

Confirmation of IHC Results

As table 2 shows, tumor registry data indicate inconsistent adherence to KPNW policy on FISH testing following an equivocal or positive IHC test result. However, chart review reveals better compliance. For 50 patients with an equivocal IHC test result who did not have a FISH test result in the tumor registry, chart review revealed that 88% did have a FISH test result in the medical record. Furthermore, although the KPNW protocol does not include confirmation of negative IHC test results by FISH, chart review confirmed that 88% of patients with a negative IHC test result and a FISH test result in the tumor registry did receive FISH testing. However, 12 (27%) patients did not actually have a negative IHC test result. These findings indicate that negative IHC test results are occasionally confirmed by FISH in this setting, but also highlight some apparent discrepancies in the tumor registry.

About 40% of patients who received both tests and had a positive IHC test result were found to have the opposite finding (negative result) for the FISH test (table 2). In contrast, nearly everyone who received both tests and had a negative IHC test result was found to have a consistent negative FISH result. As discussed below, these discrepancies can impact decisions about whether to treat with trastuzumab.

Does Treatment with Trastuzumab Depend on HER2 Status?

In the entire population of patients evaluated for *HER2*, 14% had a positive test result (using IHC and/or FISH) (table 3). The majority (81%) of patients who received trastuzumab had a positive *HER2* test result using IHC, FISH or both in the tumor registry. Subsequent chart review of the remaining 26 patients indicated that, in nearly all cases (95%), patients who received trastuzumab were appropriate candidates for this therapy based on their *HER2* genetic test result (table 4). Overall, <1% of patients who did not have a positive *HER2* test received trastuzumab.

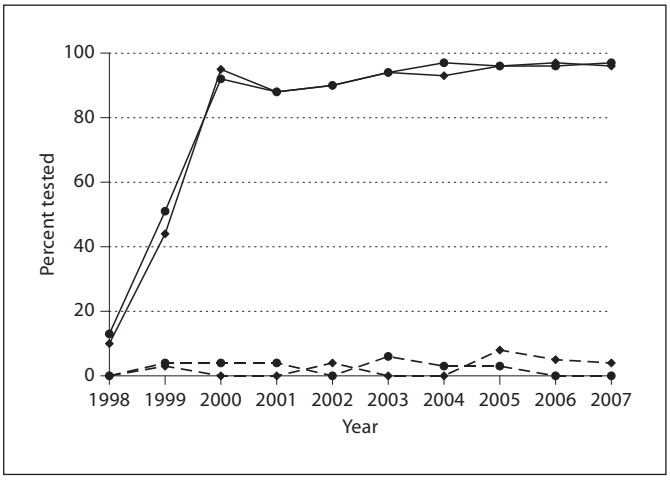

Fig. 1. Rate of *HER2* testing at KPNW from 1998 to 2007. The solid lines correspond to patients diagnosed with invasive breast cancer with Medicare/Medicaid insurance (diamonds) or with other insurance (circles), and the dashed lines correspond to patients diagnosed with ductal carcinoma in situ or noninvasive breast cancer.

Table 3 shows the proportion of patients who received trastuzumab by tumor stage and *HER2* status. Prior to 2005, only 9% of *HER2*-positive patients received trastuzumab; the majority of treated patients had regional or metastatic disease (88%), consistent with professional recommendations at that time. After 2004, trastuzumab use increased for all stages of disease, with an overall frequency of 55% among *HER2*-positive patients, and increasing use among patients with more advanced disease (up to 80% for those with distant metastatic disease). A few patients had discordant *HER2* test results for IHC

Table 3. Use of trastuzumab among breast cancer patients diagnosed between 1998–2007

SEER Stage	HER2 positive[a], (%)		HER2 discordant[b], (%)	HER2 negative/ equivocal/unknown, (%)
	1998–2004	2005–2007	2004–2007	1998–2007
In situ	0/1[c] (0)	0/0 (0)	0/0 (0)	2/537 (<1)
Localized	4/220 (2)	35/79 (44)	1/31 (3)	12/1815 (<1)
Regional	20/123 (16)	28/41 (68)	0/23 (0)	10/619 (1.6)
Distant metastasis	11/22 (50)	8/10 (80)	1/2 (50)	2/68 (3)
Total	35/366 (9)	71/130 (55)	2/56 (4)	26/3039 (0.8)

[a] Patients were defined as HER2 positive if they had a positive HER2 test result by either FISH or IHC or both, but not discordant HER2 results. [b] Patients were defined as HER2 discordant if the IHC test was positive and the FISH test was negative (n = 55) or the other way around (n = 1). [c] The ratio in each cell refers to the number of patients who received trastuzumab divided by the total number of patients in that cell.

Table 4. Reasons for treatment with trastuzumab for 26 patients without a positive *HER2* test result in the electronic tumor registry file

Tumor registry result	Chart review result
Missing *HER2* test result (10 patients)	7 patients had recurrent breast cancer with a positive *HER2* test result at recurrence, although not at initial diagnosis. 6 patients were diagnosed prior to 2000 before *HER2* testing became systematically used at initial diagnosis. 2 patients received *HER2* testing outside of KPNW. 1 patient showed no evidence of treatment with trastuzumab.
Negative *HER2* test result (7 patients)	6 patients had a positive *HER2* test result. 4 of these patients had multiple primary tumors, and the negative *HER2* result corresponded to a different tumor than the one testing positive. 1 patient had an equivocal *HER2* test result for both FISH and IHC, and the physician decided to treat with trastuzumab.
Equivocal *HER2* test result (9 patients)	5 patients had a positive *HER2* test result. In 3 patients physician notes documented a decision to treat with trastuzumab based on the equivocal *HER2* result. 1 patient received all treatment outside the KPNW system.

Table 5. Reasons for no treatment with trastuzumab among *HER2*-positive women with distant metastatic or regional (after 2004) breast cancer

Reason	Distant metastatic		Regional
	1998–2004	2005–2007	2005–2007
Patient received trastuzumab outside KPNW	1	1	3
Patient had congestive heart failure	0	0	3
Patient declined or physician decided not to treat	3	0	2
Unrecorded negative FISH result	5	1	0
Equivocal FISH result	1	0	2
No positive *HER2* result found in chart review	1	0	0
Unknown	0	0	3
Total	11	2	13

and FISH, and these patients generally did not receive trastuzumab (4% received treatment). There were several reasons why women with a positive *HER2* test did not receive trastuzumab (table 5), although chart review found that 5 out of 26 women who did not receive trastuzumab according to the tumor registry actually did receive treatment outside of KPNW.

Discussion

We conducted a retrospective analysis of patients diagnosed with breast cancer between 1998 and 2007 to evaluate the utilization and treatment patterns associated with *HER2* testing in an integrated healthcare delivery system. The prevalence of *HER2* testing in appropriate candidates with breast cancer was very high (>94%) following an initial 2-year period. Trastuzumab treatment was guided by *HER2* test results in most instances (95%), and <1% of patients with a negative or equivocal *HER2* test result were treated with trastuzumab.

These results are important for several reasons. First, there is still a great need for research describing how sophisticated genetic tests, with potentially confusing treatment ramifications, are taken up by clinicians and whether such tests are being appropriately used in treatment. This study shows that in a large integrated managed care setting, *HER2* testing is being performed on the appropriate patients, and the results are being interpreted correctly in terms of treatment implications. Only 2 other similar studies [53, 54] have been done in managed care settings. Although the sample sizes for these studies were smaller, their findings were similar to ours. Stark et al. [53] conducted a study at Henry Ford Health System (Detroit, Mich., USA) between 1999 and 2000. They reported that 51.9% of women diagnosed with primary breast cancer were evaluated for *HER2*. Barron et al. [54] reviewed the charts of 380 patients in commercial health plans diagnosed in 2005 through mid-2006. *HER2* testing occurred in 98.1% of patients with invasive breast cancer, and only one patient (out of 52) who received trastuzumab did not have a documented positive *HER2* test result. For *HER2*-positive women diagnosed with stage 2 or higher breast cancer (n = 45), 87% received trastuzumab.

Two studies conducted in the UK have recently been reported [55, 56], which address similar questions in the context of a national healthcare system. In the UK, the National Institute for Health and Clinical Excellence guidance has recommended adjuvant trastuzumab for women with positive *HER2* test results with normal left ventricular ejection fraction and without cardiac contraindications to trastuzumab therapy since 2005 [57]. Coulson et al. [55] evaluated patients who received *HER2* testing between September 2007 and August 2008 in the North Trent Cancer Network. In this study, 15.1% of tested subjects were *HER2* positive, and 67% of *HER2*-positive subjects were treated with trastuzumab. The primary reasons that patients did not receive treatment were (1) age >75 years with or without general frailty or poor performance status, (2) patient refusal or (3) high cardiac risk. This study did not include subjects who did not receive *HER2* testing. Webster et al. [56] evaluated patients diagnosed with early breast cancer during 2006–2007 in the South West Wales Cancer Network. In this study, 10.4% of tested subjects were *HER2* positive, and 13.5% did not receive *HER2* testing. Patients who were not assessed for *HER2* status were primarily elderly women who did not receive surgical intervention after the initial biopsy. Among the *HER2*-positive subjects, 72.3% received trastuzumab.

In contrast, Tong et al. [58] evaluated Medicare data for patients diagnosed with breast cancer in 2005. Only 22% of patients in that study were evaluated for *HER2*, and 94% of those received IHC alone, 1% received FISH alone, and 5% received both tests. Furthermore, 61% of patients who received trastuzumab were not evaluated for *HER2*. Stark et al. [53] also indicate that the type of health insurance (capitated insurance vs. fee-for-service [FFS]) influenced the probability of receiving *HER2* testing, with an increased likelihood of testing for those with capitated insurance (OR = 1.59; p = 0.027).

This study provides a crucial stepping stone to further research in the complex field of genomic medicine. At present, very few healthcare systems have the ability to examine the uptake and use of genetic tests on a scale large enough to evaluate them systematically. Without reliable data on how genetic tests are used to inform medical decisions, we cannot achieve the next level of genomic research. In the context of *HER2* testing and treatment decisions, for example, we can now build upon the existing data to evaluate patient outcomes and adverse events that patients experience from treatment in the context of their *HER2* test result.

Nevertheless, the electronic data sources employed for this study had a few limitations. For example, we did not confirm the validity of *HER2* test results because this study focused on how clinician treatment decisions are influenced by evaluation of *HER2*, and the reported test result was the most relevant data for our research question. Additionally, we did not limit the study population

based on membership criteria, a potential limitation since some individuals may have incomplete treatment information if they left the health plan before their treatment was complete. About 8% (n = 299) of subjects in the study population had 2 years or less of membership following breast cancer diagnosis. The possibility of incomplete treatment history is particularly concerning for this group. However, when we restricted the data to only these subjects, the conclusions do not change regarding the impact of *HER2* status and disease stage on trastuzumab treatment status (data not shown). About 70% of subjects have 10 years or more of membership following breast cancer diagnosis. Finally, we identified inconsistencies between the tumor registry and the results from manual chart review, which are primarily instances of missing data in the tumor registry. Since it was not feasible to manually abstract all the records in this study, we only performed targeted chart review in situations with unexpected findings.

Our findings indicate that KPNW is systematically performing *HER2* evaluation on patients with invasive breast cancers, and the information is used to make treatment decisions. The presence of an integrated, highly-utilized and well-established electronic medical record has likely improved communication of test results between pathologists (who order/perform the test) and oncologists, who make treatment recommendations. While it is unknown whether the findings of this study are widely applicable beyond managed care settings, about 25% of Americans receive healthcare in a managed care setting [59], and these findings are directly relevant to this substantial minority of the population. These questions should be addressed in other settings for comparison, as part of an assessment for implementation research.

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