

Utilization of HER2 Genetic Testing in a Multi-Institutional Observational Study

Katrina A. B. Goddard, PhD; Erin J. Aiello Bowles, MPH; Heather Spencer Feigelson, PhD, MPH; Laurel A. Habel, PhD; Sharon Hensley Alford, PhD; Catherine A. McCarty, PhD, MPH; Larissa Nekhlyudov, MD, MPH; Adedayo A. Onitilo, MD, MSCR, FACP; Alanna K. Rahm, PhD, MS; and Jennifer A. Webster, MS

Introduction: Human epidermal growth factor receptor 2 (HER2) expression is amplified in about 20% of breast cancer tumors, and evaluation of HER2 status should influence therapy selection. A critical gap in our knowledge is the real-world implementation of HER2 testing and its impact on treatment decisions for women diagnosed with breast cancer.

Objectives: To assess use of HER2 testing, to describe characteristics of patients who do or do not receive HER2 testing, to describe which HER2 tests were used (fluorescence in situ hybridization or immunohistochemistry), and to evaluate trastuzumab use as a function of HER2 results.

Study Design: The population included 6460 women diagnosed with invasive breast cancer between 1999 and 2007 at 8 geographically distributed Cancer Research Network healthcare delivery systems in the United States.

Methods: Electronic records were used to identify patient and tumor characteristics and treatment with trastuzumab. Chart abstraction was performed for 400 women (50 per site) to identify receipt of HER2 testing and results.

Results: More than 90% of study participants received HER2 testing. Everyone who received trastuzumab had a HER2 test, and nearly all (>95%) who received trastuzumab had a positive HER2 test result recorded in their medical chart. Most (77%) eligible patients with a positive HER2 test result diagnosed after 2005 received trastuzumab. This study expands upon previous work in individual health plans.

Conclusions: HER2 status has been successfully incorporated into medical practice to guide treatment decisions for breast cancer patients in diverse integrated healthcare delivery settings.

(Am J Manag Care. 2012;18(11):704-712)

For author information and disclosures, see end of text.

In 2011, about 230,000 women in the United States were newly diagnosed with invasive breast cancer.¹ About 40,000 of these women are expected to die of this disease. Recent advances in medicine utilizing genetic-based technologies better predict cancer recurrence or response to various treatments and present an important opportunity for patients and their physicians to individualize therapy. However, there are limited reports in the literature about how such technologies are being incorporated into clinical practice and whether they are being used appropriately.^{2,3} As genetic-based technologies proliferate, understanding how and when these applications should be used in clinical practice becomes increasingly important.

One such genetic technology targets human epidermal growth factor receptor 2 (HER2). HER2 is a gene that influences cell growth, division, and repair. A normal cell has 2 copies of HER2. About 18% to 20% of breast cancers have HER2 gene amplification (more than 2 copies of this gene).⁴⁻⁶ HER2 amplification is associated with rapid tumor proliferation, shorter disease-free survival, and poorer overall survival.⁷⁻⁹ The drug trastuzumab (Herceptin, Genentech Inc, San Francisco, California) is indicated for individuals with breast cancer that either overexpresses the HER2 protein or amplifies the HER2 gene to prevent the growth of HER2-positive cancer cells.¹⁰⁻¹⁴ It was approved by the US Food and Drug Administration (FDA) for use in the treatment of metastatic breast cancer in 1998 based on the findings from 2 clinical trials, which showed improvement in the median time to progression of 3 to 5 months, and an increase in the overall response rate of 10% to 30%.¹⁵ Despite the fact that trastuzumab is also well established as a highly efficacious (adjuvant) antineoplastic agent for HER2-positive breast cancer, it is expensive (\$44,000-\$65,000 per year^{16,17}) and may have serious cardiotoxic effects.¹⁸ Because of these factors, selecting patients for whom trastuzumab treatment is appropriate remains vital. Trastuzumab treatment should be cautiously used for patients with preexisting cardiac dysfunction or deteriorating cardiac function even if they have a positive HER2 test result, especially older women with prior cardiac history or prior cardiotoxic therapies.

In this article
Take-Away Points / p705
www.ajmc.com
Full text and PDF
Web exclusive
eAppendix

Two types of tests are FDA approved to select patients for treatment with trastuzumab. The first test is based on immunohistochemistry (IHC) (eg, Dako HercepTest, Ventana PATHWAY), which measures membrane expression of HER2 receptor protein. The second type of test (eg, Vysis PathVysion, Ventana INFORM HER2 probe) is based on the fluorescence in situ hybridization (FISH) technology to measure the underlying gene amplification in tumor cells. In this approach, fluorescent probes are used to quantify the number of HER2 gene copies in a tumor cell. If there are 2 or more copies of the HER2 gene per chromosome 17, then a gene amplification has occurred, and the breast cancer is considered HER2 positive.

The American Society of Clinical Oncology and College of American Pathologists HER2 testing guidelines currently recommend initial testing by IHC testing and reflex testing of equivocal result (2+) by FISH testing.¹⁹ Although some reports have suggested that the FISH technology more accurately predicts response to trastuzumab than IHC technology,²⁰ a recent summary report indicates that both technologies perform equally well if carefully validated testing is performed.¹⁹ Cost may also be a factor in the selection of test modality, because the FISH test is generally more expensive to perform than the IHC test. For both testing methods, underlying quantitative measures can be translated into a dichotomous positive/negative finding. Both tests are considered equivocal when the quantitative measures are near the threshold for a positive result. Retesting might resolve these equivocal findings.¹⁹ Increased error rates and inconsistent results are also introduced by decentralized testing, particularly for centers with a low volume of testing. Thus, Wolff and colleagues¹⁹ recommend a quality assurance program for HER2 testing, and suggest various accreditation, proficiency, and competency measures for laboratories conducting HER2 testing.

Trastuzumab was initially approved by the FDA in 1998 for use in breast cancer patients with metastatic cancer. In November 2006, the FDA approved the use of trastuzumab in the adjuvant setting for women with lymph node–positive and HER2–positive breast cancer, following several major trials.^{11–13} Professional organizations, including a joint guideline from the American Society of Clinical Oncologists and College of American Pathologists, currently recommend that HER2 testing should be performed for all invasive breast cancers regardless of lymph node disease status.¹⁹ The National Comprehensive Cancer Network has also issued physician practice guidelines endorsing HER2 testing.^{21–24}

Take-Away Points

We evaluated real-world implementation of human epidermal growth factor receptor 2 (HER2) testing and its impact on treatment decisions for women diagnosed with breast cancer between 1999 and 2007 at 8 US integrated delivery systems. There was consistent success in implementation of HER2-guided treatment decisions for breast cancer patients in these settings.

- More than 90% of study participants received HER2 testing.
- Everyone who received trastuzumab had a HER2 test, and more than 95% of these women had a positive HER2 test result.
- Most (77%) eligible patients with a positive HER2 test result diagnosed after 2005 received trastuzumab.

Despite these evidence-based practice guidelines, there are few reports on how HER2 testing has been utilized in real-world settings. In particular, Phillips and colleagues³ highlighted the fact that little is known about how many 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. Additionally, it is not clear how trastuzumab is utilized across important subgroups such as patient age, race, and cancer stage.

To answer these questions, we conducted a large, multi-institutional study in 8 Cancer Research Network (CRN) integrated healthcare delivery systems across the United States. The organizations participating in this study provide a unique resource to address this research question by providing access to longitudinal and comprehensive electronic medical record data for populations totaling more than 6 million covered lives. We describe the real-world implementation of HER2 testing and trastuzumab prescribing in this setting.

METHODS

Study Population

The study population included 6460 women who were diagnosed with an invasive breast cancer that was 2+ cm in size or who had positive nodes at diagnosis from January 1, 1999, to December 31, 2007, and who were enrolled at one of the 8 participating CRN study sites for at least 12 months prior to diagnosis. These tumor size and lymph node status criteria were used to restrict the population to women similar to those in the adjuvant trastuzumab clinical trials. Subjects were followed for up to 12 months following diagnosis. Follow-up periods of less than 12 months were due to death or disenrollment during that period. The 8 participating study sites are geographically distributed within the United States and represent diverse populations: Group Health Cooperative (Washington), Kaiser Permanente Northwest (Oregon and Washington), Kaiser Permanente Northern California, Kaiser Permanente Colorado, Kaiser Permanente Georgia, Marshfield Clinic (Wisconsin), Henry Ford Health System

(Michigan), and Harvard Pilgrim Health Care Institute with clinical data from Harvard Vanguard Medical Associates (Massachusetts). The study population included all eligible subjects at each site except for Kaiser Permanente Northern California, which contributed data on a 10% random sample of their eligible population.

A subset of 400 cases (50 from each site) was sampled from the original cohort for detailed chart review using stratified sampling (eAppendix, available at www.ajmc.com) to ensure adequate numbers of subjects with chemotherapy exposure and the outcome of heart failure. Weights were used for some analyses, and were calculated as 1 over the probability of being sampled (ie, $1/(1/N)$, where N is the number of subjects in that stratum; $N \geq 1$, since at minimum the sampled subject belongs to the stratum). The primary purpose of the chart review was to validate electronic administrative data for chemotherapy exposure to anthracyclines or trastuzumab and the outcome of heart failure, as measured by clinical criteria and measurement of left ventricular ejection fraction, which was previously reported in a separate publication.²⁵ However, the availability of data on HER2 genetic testing from the chart abstraction allowed us to conduct this secondary analysis.

This study was approved by the institutional review boards (IRBs) at Group Health Cooperative, Marshfield Clinic Research Foundation, and Henry Ford Health System, and did not require written informed consent. The IRBs for the remaining sites ceded authority to the Group Health Cooperative IRB. A small number of health system members at each site have elected not to participate in anonymous or unconsented research protocols, and these subjects were excluded from this research study.

HER2 Genetic Testing

All genetic test results used in this study are from testing that occurred as part of routine medical care at each of the 8 participating sites. The laboratory performing the testing varied by site; however, the interpretation was similar. IHC testing for HER2 was classified as negative (0 or 1+), equivocal (2+), or positive (3+), except at Henry Ford Health System where 2+ was considered positive. FISH testing for HER2 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). At Kaiser Permanente Northern California, the cutoff for FISH positive was a HER2/CEP 17 ratio of >2.0 for all but the last year of this study, following the American Society of Clinical Oncology and College of American Pathologists recommendation to change the cut point to 2.2 in January 2007.¹⁹

We identified the internal practice guidelines for HER2 testing at each site. Since 2000, guidelines for all sites specify

that all new invasive breast cancer patients are automatically ordered a HER2 test using IHC testing. Reflex testing is performed using FISH to clarify or confirm equivocal IHC findings (at all sites) plus additional subsets including all positive IHC findings at 2 sites, cases at the discretion of the treating oncologist at 2 other sites, or cases with an IHC test result of 1+ or more positive at 1 additional site. At 1 site, the protocol was changed in October 2007 to initially test all invasive tumors for HER2 by FISH.

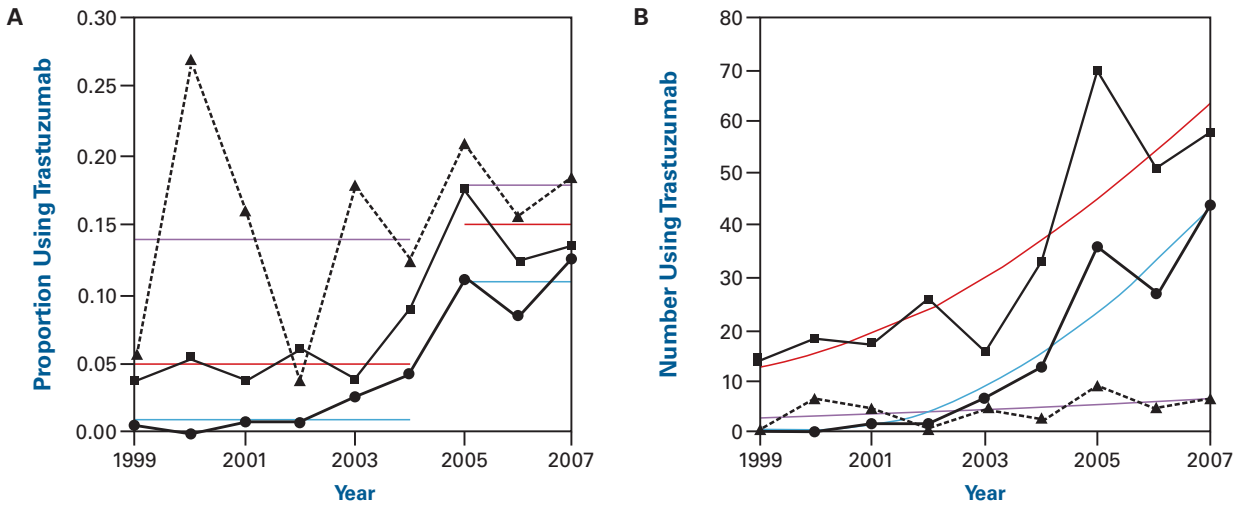
Chart Abstraction

We used stratified sampling to ensure adequate representation of the chemotherapy exposures and outcomes in the chart-reviewed sample (eAppendix). Identification of prevalent heart failure at the time of diagnosis (a possible contraindication for trastuzumab use) was also obtained exclusively from chart abstraction. The method used to define heart failure is described elsewhere.²⁶ We used standardized abstraction forms and abstractor training protocols to ensure uniform data recording across sites and abstractors. The lead project manager rereviewed 10% of charts from each CRN site for inconsistencies, inaccuracies, and missing data, and questions were referred back to the originating site for clarification. During chart review, both qualitative and quantitative descriptions of HER2 results were collected from the medical record. Any apparent discrepancies were resolved by rereview at the originating site.

Variable Definitions

Each CRN site maintains electronic health record information on its member population including membership, diagnoses, pharmacy data, and a tumor registry. From these records, we extracted electronic data on patient characteristics (age at diagnosis, sex, race, ethnicity, year of diagnosis), tumor characteristics (stage, lymph node involvement, tumor size), and chemotherapy treatment. The Charlson Comorbidity Index is a quantitative variable that was computed using diagnosis codes as previously described anchored at the date of diagnosis.²⁷ Patients were classified as receiving trastuzumab using a dichotomous indicator variable if any of the following national drug codes were in the pharmacy records after their date of diagnosis: 50242013460, 50242013468, 50242005656, or 63552047001, or if procedure code J9355 was in the procedures database. This definition was validated against data from chart abstraction and demonstrated to have high predictive value.²⁸ Lymph node status was a dichotomous indicator variable defined as positive (1 or more positive nodes) or negative. Tumor size was a quantitative trait defined as the size of the largest qualifying tumor (a small number of patients had more than 1 primary tumor during the study period). We defined invasive breast cancer using Surveillance Epidemiol-

■ **Figure 1.** Proportion (A) and Number (B) of Invasive Breast Cancer Patients Who Received Trastuzumab^a



HER2 indicates human epidermal growth factor receptor 2.

^aFor both figures, black lines indicate the observed proportions each year for subjects with localized (circle), regional (square), and distant (triangle) disease. These data on 6460 subjects do not account for HER2 status, since HER2 status was not collected in a readily available electronic format for the majority of subjects. A, Colored lines indicate the average proportion from 1999 to 2004 and from 2005 to 2007, separately, for patients with localized (blue), regional (red), and distant (purple) disease. B, Colored lines indicate a fitted trend line using polynomial regression for subjects with localized (blue), regional (red), and distant (purple) disease.

ogy and End Results (SEER) staging criteria²⁹ as patients diagnosed with localized, regional, or distant metastatic breast cancer. The primary dependent variable was receipt of HER2 testing, which was treated as a dichotomous indicator variable. Data on receipt of HER2 testing and the test result (categorical variable) were obtained exclusively from chart abstraction of the medical record.

Statistical Methods

All analyses, including descriptive statistics, summaries, and multivariate linear regression, were produced using R (version 2.11.1; R Foundation for Statistical Computing, www.r-project.org) and SAS version 9.2 (SAS Institute Inc, Cary, North Carolina). We used a Bonferroni correction to adjust the simultaneous confidence intervals. The multivariate model used a generalized linear model with receipt of HER2 testing as the dependent variable and the following independent variables: diagnosis year, race, lymph node status, SEER stage, site, age, presence of heart failure, and Charlson Comorbidity Index.

RESULTS

Trastuzumab Treatment

Of the entire cohort of 6460 women, 7.5% (n = 483) received trastuzumab. Trastuzumab use varied by year of diagnosis and stage of disease. Although the *proportion* of subjects

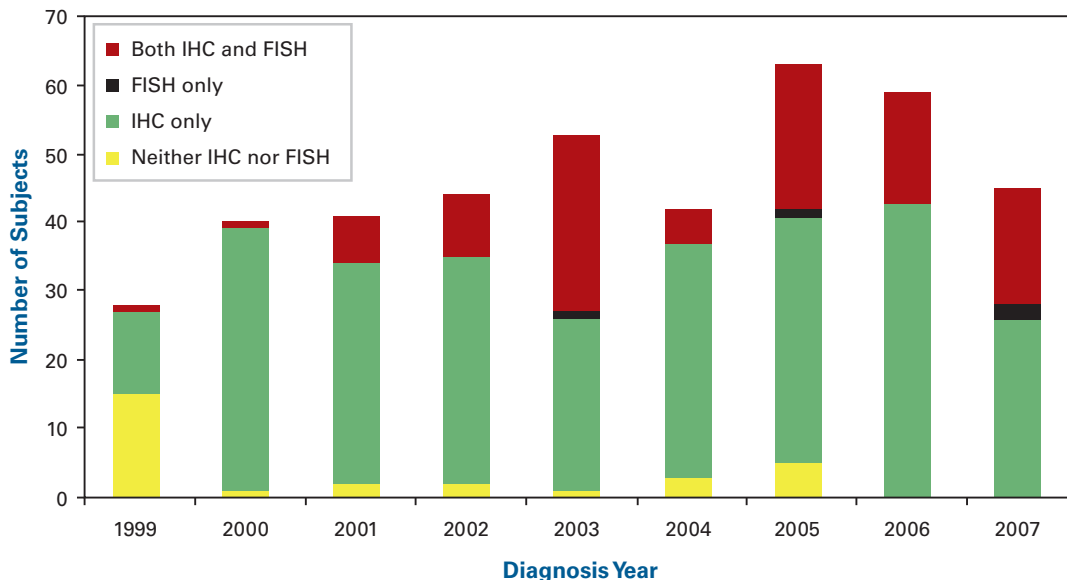
who received trastuzumab was highest among women with distant stage breast cancer (Figure 1), women with distant-stage breast cancer represented the smallest *number* of cases who received trastuzumab in every year (Figure 2), because most women are diagnosed at an earlier stage of disease. The proportion of subjects who received trastuzumab increased for all stages of disease after 2004 when professional guidelines changed (Figure 1). The proportion of women in the chart review population who received trastuzumab was 18% (72/400), which is higher than the proportion of women who received trastuzumab in the entire study population, because we intentionally overselected trastuzumab recipients for review. However, after adjustment using the weights described above, 6.4% of the chart review population received trastuzumab.

HER2 Testing Patterns

All of the sites performed IHC testing in-house, and most sites used the HercepTest kit (Dako, Carpinteria, California). All except 1 site used a reference laboratory to perform FISH testing, and all sites used the Vysis PathVysion test (Abbott Molecular, Abbott Park, Illinois). Among the 400 subjects in the chart review population, 367 had tumors tested by IHC and 94 had tumors tested by FISH. Only 30 women (7.5%) received neither test.

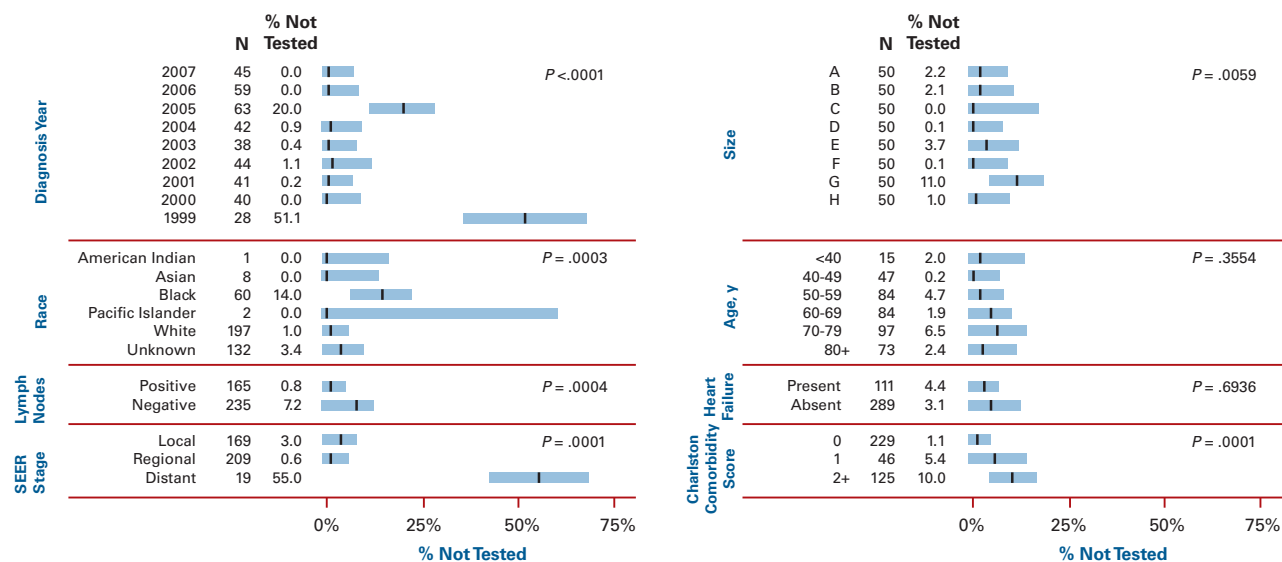
Consistent with practice guidelines at the 8 sites, nearly everyone who was tested received IHC testing, with only 4 women receiving FISH testing alone. FISH testing occurred

Figure 2. Number of Patients Who Received IHC and FISH Testing by Diagnosis Year



FISH indicates fluorescence in situ hybridization; IHC, immunohistochemistry.

Figure 3. Impact of Patient Characteristics on the Percentage of Patients Who Do Not Receive HER2 Testing^a



HER2 indicates human epidermal growth factor receptor 2; SEER, Surveillance Epidemiology and End Results.

^aBlue shaded areas represent the Bonferroni adjusted 95% confidence interval around the average (black bar) from multivariate analysis. P values are the Bonferroni adjusted P values from a linear regression model, using HER2 testing status as a dichotomous independent variable and the dependent variables categorized as shown.

more frequently in the latter years of the study, possibly reflecting a phasing in of FISH testing during this time frame. Of those who received both tests, 74% had a positive or borderline IHC test result, whereas the majority of patients (69%) who received IHC testing alone had a negative HER2 result. A substantial proportion (40%) of subjects with a borderline IHC test result had no evidence of receiving FISH testing, contrary

to most site practice guidelines. Among 17 patients with a borderline IHC test result, 3 received trastuzumab. There was also large variation among sites in the proportion of subjects with a borderline IHC test who did not receive FISH testing (range 0%-63%; $P = .0043$).

Of those who did not receive either test, 50% ($n = 14$) were diagnosed in 1999, around the time that testing was initi-

Table 1. Trastuzumab Use by Disease Stage and HER2 Status^a

SEER Stage	HER2 Positive ^b	HER2 Discordant ^c	HER2 Negative or Borderline ^d	HER2 Missing ^e
Diagnosis Year Between 1999 and 2005				
Distant	2/4	—	1/9	0/4
Regional	26/50	5/11	2/88	0/6
Localized	5/9	1/6	0/89	0/20
Total	33/63 (52%)	6/17 (35%)	3/186 (2%)	0/30 (0%)
Diagnosis Year Between 2006 and 2007^f				
Distant	—	—	0/2	—
Regional	19/22	2/4	0/32	—
Localized	9/11	1/5	1/28	—
Total	28/33 (84%)	3/9 (33%)	1/62 (2%)	—
Overall Total	96	26	248	30

FISH indicates fluorescence in situ hybridization; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; SEER, Surveillance Epidemiology and End Results.

^aThe numerator is the number of patients in this category who received trastuzumab, and the denominator is the total number of patients in this category, where the category is defined by SEER stage, diagnosis date, and HER2 status. Reported counts are unweighted, descriptive observations of the chart review sample (n = 400).

^bPatients with a HER2-positive result with either IHC or FISH or both, and who did not have a HER2-negative result.

^cPatients with a HER2-positive result with IHC and a HER2-negative result for FISH or vice versa.

^dPatients who received IHC and/or FISH testing, but whose results were only negative and/or borderline.

^ePatients who did not receive HER2 testing with either IHC or FISH (n = 30) or who did receive testing, but the test failed (n = 3).

^fData for patients diagnosed between 2006 and 2007 are presented separately because the professional recommendations for trastuzumab treatment changed after 2005 to include women with regional or localized stage of disease in addition to those with distant metastatic cancer.

ated at most of the sites (Figure 3). Excluding the 28 patients diagnosed in 1999, 96% (356/372) of patients received some form of HER2 testing. The remaining 16 patients who were not tested were more likely to be older than 70 years ($P = .026$), to have distant-stage disease ($P = .0032$), to have negative lymph nodes ($P = .013$), or to have been diagnosed in 2005. We also detected differences in the proportion who did not receive testing across sites ranging from 0% to 14% ($P = .038$) and across race/ethnicity ($P = .0003$), although about one-third of the women had missing data for race/ethnicity.

Trastuzumab Use as a Function of HER2 Status

As expected based on the sampling criteria, a higher proportion (32% [119/373]) of women in the chart review sample who received HER2 testing were HER2 positive compared with population estimates.

Trastuzumab was primarily used by patients with a HER2-positive test result (Table 1). None of the patients in this sample who were not tested for HER2 status used trastuzumab. Of patients with only a HER2-negative or borderline result, 1.6% (4/255) used trastuzumab, and 35% (9/26) of patients with HER2 discordant results used trastuzumab. In these 9 discordant cases, 7 patients had positive FISH tests and 2 had a positive IHC test. Of the 17 who did not receive trastuzumab, 10 had positive FISH tests and 7 had positive IHC tests. Overall, 64% (61/96) of patients with HER2-positive results received

trastuzumab; however, this use was dependent on year of diagnosis and stage of disease. In 1999-2005 (when trastuzumab was primarily recommended for patients with distant metastatic disease) only 52% of HER2-positive patients used trastuzumab, whereas in 2006-2007 (by which time recommendations had been adopted for use of trastuzumab in all cases of invasive cancer), 84% of HER2-positive patients used trastuzumab.

Some subjects with positive HER2 status did not receive trastuzumab. Of the 6 subjects with localized or regional disease who were diagnosed after 2005 and who did not receive trastuzumab, one had heart failure at diagnosis. For the remainder, a rationale was not readily apparent based on our assessment of the comorbidity index, age at diagnosis, or other patient characteristics. In addition, 2 subjects with distant metastatic disease who were HER2 positive did not receive trastuzumab. One of these patients had heart failure at diagnosis, while the other case could not be readily explained based on patient characteristics in our data set. Other factors such as patient preference, physician opinion, unrecorded negative or borderline HER2 test results, or treatment outside of the reporting sites could explain these observations.

DISCUSSION

Selection of patients for treatment with trastuzumab based on HER2 status is one of the first examples of targeted therapy

■ **Table 2.** Published Reports From Individual Health Plans

Reference	Reporting Site	Diagnosis Years	No. Women With Invasive Breast Cancer	No. (%) Women Not Evaluated for HER2	No. (%) Women Who Were HER2 positive ^a	No. (%) Women Who Received Trastuzumab Without a Documented Positive HER2 Result	No. (%) HER2-Positive Women Who Received Trastuzumab
Stark, 2004 ³⁰	Henry Ford Health System	1999-2000	451	212 (48)	Not reported	Not reported	Not reported
Onitilo, 2009 ³¹	Marshfield Clinic	1998-2005	1767	612 (35) ^b	201 (18)	Not reported	Not reported
Barron, 2009 ³²	Three commercial health plans	2005–mid 2006	322	6 (2)	72 (21)	1/52 (2)	39/45 (87) stage II or higher
Webster, 2010 ³³	SW Wales Cancer Network (UK)	2006-2007	453	61 (13.5)	47 (10)	Not reported	34/47 (72.3)
Webster, 2010 ³³	SW Wales Cancer Network (UK): Cardiff & Vale only	2005-2008	121	Not reported	121 (100) ^c	Not reported	93/121 (76.8)
Coulson, 2010 ³⁴	North Trent Cancer Network (UK)	September 2007–August 2008	1319 ^d	Not reported	199 (15)	Not reported	133/199 (67)
Haas, 2011 ³⁵	Aetna	July 2006–June 2007	775	24 (3.1)	137 (18)	25/104 (24)	79/137 (57.7) stage I, II, or III
Goddard, 2012 ³⁶	Kaiser Permanente Northwest	1998-2007	3054	579 (19)	496 (14)	26/134 (19)	19/32 (60) distant metastatic 28/41 (68) regional (after 2005) 35/79 (44) localized (after 2005)

HER2 indicates human epidermal growth factor receptor 2.

^aOf those evaluated for HER2 status.

^bWomen were not tested for estrogen receptor/progesterone receptor or HER2. The data for HER2 alone were not reported separately.

^cSelected for the study on these criteria.

^dMetastatic breast cancer cases were excluded.

in oncology. In this study, more than 90% of eligible breast cancer patients received HER2 testing during the study period from 1999 to 2007. Trastuzumab use increased for all stages of breast cancer, and most women who receive trastuzumab have regional or localized disease. In the majority of cases, trastuzumab is appropriately used based on HER2 status. Everyone (100%) who received trastuzumab had a HER2 test, and nearly all (>95%) who received trastuzumab had a *positive* HER2 test result recorded in their medical chart. Most eligible patients (84%) with a positive HER2 test result diagnosed after 2005 received trastuzumab, and the majority of patients with a positive HER2 test result prior to 2005 also received trastuzumab (52%).

Our findings are consistent with several previous studies that have reported similar results from individual health plans

in the United States and the United Kingdom (Table 2). Because the studies span different time frames, we can observe a general improvement in the proportion of women who receive HER2 testing over time (from 52% in 1999-2000 to 84% in 2006-2007). This steady increase closely aligns with the time line of professional recommendations for trastuzumab use and HER2 testing, which have broadened the eligible population for this testing and treatment. In our study population, a larger proportion of patients did not receive testing in 1999 and in 2005. Although the reduced proportion in 1999 makes sense, because that was during the time frame immediately after the recommendation for HER2 testing became available, there is no immediately apparent reason for the reduced proportion in 2005. In general, a high percentage of women who are HER2 positive receive treatment with trastuzumab.

We found that practice guidelines were not followed for 40% of subjects with a HER2 borderline test result, in that FISH testing was not offered to these patients to clarify HER2 status. We also found variation across CRN sites (up to 14% of subjects did not receive HER2 testing), as well as variation based on patient characteristics. This practice variation is unlikely to be explained by financial barriers, since all of the delivery organizations involved with this study have coverage policies for this testing and treatment.

There are several important limitations in the study design. First, our study was limited to women with lymph node-positive disease or 2+ cm tumors. Second, subjects were not randomly selected for chart review, but were selected based on heart failure status and trastuzumab use. Therefore, our estimates of proportion may not represent the true estimate in the general breast cancer patient population. We attempted to compensate by presenting weighted estimates whenever possible. Third, a small proportion of HER2 tests may have been received outside of our delivery systems. These tests could be missed if the test result was not recorded in the patient's medical record. This type of error will lead to an underestimate of the rate of utilization.

Patients who used trastuzumab were overrepresented in the sample, which likely biases some estimates presented in this study. We have attempted to adjust for this bias by presenting weighted estimates, where appropriate. However, not all categories of HER2 status were well represented in the chart review sample, which limited our ability to completely account for this limitation. The chart review sample also differs from the overall cohort because the patients were older (52% vs 36% were older than 65 years), but other patient characteristics were similar, as previously described.²⁸ Nevertheless, our findings are broadly consistent with previous work on similar questions, and represent the largest number of healthcare delivery organizations in the United States that have been examined to date.

Second, because of the very large number of patients in this study (more than 6000) and the fact that HER2 status was not the primary research question for this study, our analysis is necessarily restricted to limited data that were available through electronic sources or abstracted from a limited chart review. Thus, we were not able to address some questions, such as the reasons for *not* receiving trastuzumab among HER2-positive patients. The result is not generalizable to patients with smaller and node-negative tumors.

We demonstrated rapid dissemination and implementation of HER2 testing and treatment programs across a large number of practice settings with strong concordance with professional recommendations. However, our findings also highlight unexplained practice variation, which can inform

future methods of care delivery to reduce barriers to receipt of HER2 testing.

Acknowledgments

This research was conducted at multiple sites of the HMO Cancer Research Network (CRN). The CRN consists of the research programs, enrollee populations, and databases of 14 HMO members of the HMO Research Network. The overall goal of the CRN is to conduct collaborative research to determine the effectiveness of preventive, curative, and supportive interventions for major cancers that span the natural history of those cancers among diverse populations and health systems. The 14 healthcare delivery systems, with nearly 11 million enrollees, are distinguished by their longstanding commitment to prevention and research, and collaboration among themselves and with affiliated academic institutions.

The authors would like to acknowledge the contributions of the additional CRN Pharmacovigilance Study Team members:

Group Health Research Institute, Group Health Cooperative, Seattle, WA: Edward Wagner, Roy Pardee, Nicholas Vanneeman, Lisa Temposky, Rob Wellman, Andy Bogart, David Carrell, Diana Buist, Beth Kirlin, Leah Tuzzio, and Elizabeth Trice Loggers.

Department of Population Medicine, Harvard Pilgrim Health Care Institute, Boston MA: Beth Syat and Priscilla Velentgas.

Department of Biostatistics and Research Epidemiology, Henry Ford Health System, Detroit, MI: Heather Dakki, Karen Wells, and Steve Anteau.

Institute for Health Research, Kaiser Permanente Colorado, Denver, CO: Thomas Delate, Larry Allen, and David Magid.

Center for Health Research, Kaiser Permanente Northwest, Portland, OR: Mark Hornbrook, Joanna Bulkley, Tia Kauffman, Eresha Bluth, Chuhe Chen, Padmavati Dandamudi, and Carmel Wax.

Division of Research, Kaiser Permanente Northern California: Alan Go, Angela Capra, Jean Lee, and Luana Acton.

Center for Health Research, Kaiser Permanente Georgia, Atlanta, GA: Robert L. Davis, Mia Hemmes, Lauren Perkins, E. Darlene Brannon, Cynthia Sanders-Jones, Bonita Hollis, and L. Monique Smith.

Marshfield Clinic Research Foundation, Marshfield Clinic, Marshfield, WI: Paul Hitz, Nick Berger, Terrie Kitchner, Jessica Engel, and Deanna Cross.

National Institute of Cancer Program Office: Andrew Freedman.

Author Affiliations: From Center for Health Research (KABG, JAW), Kaiser Permanente Northwest, Portland, OR; Group Health Research Institute (EJAB), Group Health Cooperative, Seattle, WA; Institute for Health Research (HSF, AKR), Kaiser Permanente Colorado, Denver, CO; Division of Research (LAH), Kaiser Permanente Northern California, Oakland, CA; Department of Biostatistics and Research Epidemiology (SHA), Henry Ford Health System, Detroit, MI; Marshfield Clinic Research Foundation (CAM, AAO), Marshfield Clinic, Marshfield, WI; Harvard Pilgrim Health Care Institute and Harvard Medical School (LN), Department of Population Medicine, and Department of Medicine, Harvard Vanguard Medical Associates, Boston, MA; Essentia Institute of Rural Health (CAM), Duluth, MN; Department of Hematology/Oncology (AAO), Marshfield Clinic Weston Center, Weston, WI.

Funding Source: This work was supported by resources developed through a grant from the National Cancer Institute (U19 CA 79689; PI: Edward Wagner).

Author Disclosures: Dr Goddard reports receiving grants from the US Food and Drug Administration. Dr Habel reports receiving grants from Genentech. The other authors (EJAB, HSF, SHA, LN, AAO, AKR, JAW) report no relationship or financial interest with any entity that would pose a conflict of interest with the subject matter of this article.

Authorship Information: Concept and design (KABG, LN, AAO, AKR); acquisition of data (KABG, EJAB, HSF, LAH, SHA, CAM, LN, AAO, AKR); analysis and interpretation of data (KABG, EJAB, HSF, JAW); drafting of the manuscript (KABG, EJAB, AAO, AKR); critical revision of the manuscript for important intellectual content (KABG, EJAB, HSF, LAH, CAM, LN, AAO); statistical analysis (KABG, JAW); provision of study materials or patients (KABG, HSF, LAH, CAM, LN, AAO, AKR); administrative, technical, or logistic support (KABG, EJAB, LAH, JAW); and supervision (KABG, LAH, CAM).

Address correspondence to: Katrina A. B. Goddard, PhD, Senior Investigator, Center for Health Research, Kaiser Permanente Northwest, 3800 N Interstate Ave, Portland, OR 97227. E-mail: katrina.ab.goddard@kpchr.org.

REFERENCES

- American Cancer Society. Breast Cancer Facts & Figures 2011-2012. <http://www.cancer.org/research/cancerfactsfigures/breastcancerfacts-figures/breast-cancer-facts-and-figures-2011-2012>. Published 2011-2012. Accessed October 3, 2012.
- Phillips KA. Closing the evidence gap in the use of emerging testing technologies in clinical practice. *JAMA*. 2008;300(21):2542-2544.
- Phillips KA, Liang SY, Van Bebber S; Canpers Research Group. Challenges to the translation of genomic information into clinical practice and health policy: utilization, preferences and economic value. *Curr Opin Mol Ther*. 2008;10(3):260-266.
- Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science*. 1987;235(4785):177-182.
- Yaziji H, Goldstein LC, Barry TS, et al. HER-2 testing in breast cancer using parallel tissue-based methods. *JAMA*. 2004;291(16):1972-1977.
- Owens MA, Horten BC, Da Silva MM. HER2 amplification ratios by fluorescence in situ hybridization and correlation with immunohistochemistry in a cohort of 6556 breast cancer tissues. *Clin Breast Cancer*. 2004;5(1):63-69.
- Press M, Pike M, Chazin V, et al. Her-2/neu expression in node-negative breast cancer: direct tissue quantitation by computerized image analysis and association of overexpression with increased risk of recurrent disease. *Cancer Res*. 1993;53(20):4960-4970.
- Press MF, Bernstein L, Thomas PA, et al. HER-2/neu gene amplification characterized by fluorescence in situ hybridization: poor prognosis in node-negative breast carcinomas. *J Clin Oncol*. 1997;15(8):2894-2904.
- Yamauchi H, Stearns V, Hayes DF. When is a tumor marker ready for prime time? a case study of c-erbB-2 as a predictive factor in breast cancer. *J Clin Oncol*. 2001;19(8):2334-2356.
- Slamon D, Eiermann W, Robert N et al. Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med*. 2011;365:1273-1283
- Joensuu H, Kellokumpu-Lehtinen PL, Bono P, et al; FinHer Study Investigators. Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. *N Engl J Med*. 2006;354(8):809-820.
- Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med*. 2005;353(16):1673-1684.
- Piccari-Gebhart MJ, Procter M, Leyland-Jones B, et al; Herceptin Adjuvant (HERA) Trial Study Team. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med*. 2005;353(16):1659-1672.
- The Herceptin Adjuvant (HERA) Trial Study Team. Trastuzumab following adjuvant chemotherapy in HER2-positive early stage breast cancer (HERA trial): disease-free and overall survival after 2 year follow-up. Paper presented at: 42nd Annual Meeting of the American Society of Clinical Oncology; June 2006; Atlanta, GA.
- US Food and Drug Administration. HERCEPTIN® (Trastuzumab). September 1998. <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/ucm091361.pdf>. Accessed February 16, 2011.
- Liberato NL, Marchetti M, Barosi G. Cost effectiveness of adjuvant trastuzumab in human epidermal growth factor receptor 2-positive breast cancer. *J Clin Oncol*. 2007;25(6):625-633.
- Kurian AW, Thompson RN, Gaw AF, Arai S, Ortiz R, Garber AM. A cost-effectiveness analysis of adjuvant trastuzumab regimens in early HER2/neu-positive breast cancer. *J Clin Oncol*. 2007;25(6):634-641.
- Tan-Chiu E, Yothers G, Romond E, et al. Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31. *J Clin Oncol*. 2005;23(31):7811-7819.
- Wolff AC, Hammond ME, Schwartz JN, et al; American Society of Clinical Oncology; College of American Pathologists. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. *J Clin Oncol*. 2007;25(1):118-145.
- Bartlett JM, Going JJ, Mallon EA, et al. Evaluating HER2 amplification and overexpression in breast cancer. *J Pathol*. 2001;195(4):422-428.
- National Comprehensive Cancer Network. Practice Guidelines in Oncology v2. Breast Cancer. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#breast. Published 2003. Accessed October 1, 2012.
- Carlson RW, Moench SJ, Hammond ME, et al; NCCN HER2 Testing in Breast Cancer Task Force. HER2 testing in breast cancer: NCCN Task Force report and recommendations. *J Natl Compr Canc Netw*. 2006;4(suppl 3):S1-S22.
- Carlson RW, Anderson BO, Bensinger W, et al; National Comprehensive Cancer Network. NCCN Practice Guidelines for Breast Cancer. *Oncology (Williston Park)*. 2000;14(11A):33-49.
- Carlson RW. NCCN breast cancer clinical practice guidelines in oncology: an update. *J Natl Compr Canc Netw*. 2003;1(suppl 1):S61-S63.
- Bowles EJ, Wellman R, Feigelson HS, et al; Pharmacovigilance Study Team. Risk of heart failure in breast cancer patients after anthracycline and trastuzumab treatment: a retrospective cohort study. *J Natl Cancer Inst*. 2012;104(17):1293-1305.
- Allen LA, Yood MU, Wagner EH, et al; for the Pharmacovigilance Research Group. Performance of claims-based algorithms for identifying heart failure and cardiomyopathy among patients diagnosed with breast cancer [published online May 25, 2012]. *Med Care*.
- Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol*. 1992;45(6):613-619.
- Delate T, Bowles EJA, Pardee R, et al. Validity of eight integrated healthcare delivery organizations' administrative clinical data to capture breast cancer chemotherapy exposure. *Cancer Epidemiol Biomarkers Prev*. 2012;21(4):673-680.
- Young JL Jr, Roffers SD, Ries LAG, Fritz AG, Hurlbut AA, eds. *SEER Summary Staging Manual—2000: Codes and Coding Instructions*. Bethesda, MD: National Cancer Institute; Publication 01-4969. <http://seer.cancer.gov/tools/ssml/>. Published 2001. Accessed October 2, 2012.
- Stark A, Kucera G, Lu M, Claud S, Griggs J. Influence of health insurance status on inclusion of HER-2/neu testing in the diagnostic workup of breast cancer patients. *Int J Qual Health Care*. 2004;16(6):517-521.
- Onitilo AA, Engel JM, Greenlee RT, Mukesh BN. Breast cancer subtypes based on ER/PR and Her2 expression: comparison of clinico-pathologic features and survival. *Clin Med Res*. 2009;7(1-2):4-13.
- Barron JJ, Cziraky MJ, Weisman T, Hicks DG. HER2 testing and subsequent trastuzumab treatment for breast cancer in a managed care environment. *Oncologist*. 2009;14(8):760-768.
- Webster R, Palaniappan N, Abraham J, Bertelli G, Jasani B, Barrett-Lee P. HER2 testing, adjuvant trastuzumab use and results. Our experience in South Wales. *Clin Oncol (R Coll Radiol)*. 2010;22(10):894.
- Coulson SG, Kumar VS, Manifold IM et al. Review of testing and use of adjuvant trastuzumab across a cancer network—are we treating the right patients? *Clin Oncol (R Coll Radiol)*. 2010;22(4):289-293.
- Haas JS, Phillips KA, Liang SY et al. Genomic testing and therapies for breast cancer in clinical practice. *Am J Manag Care*. 2011;17(5 Spec No):e174-e181.
- Goddard KA, Weinmann S, Richert-Boe K, Chen C, Bulkley J, Wax C. HER2 evaluation and its impact on breast cancer treatment decisions. *Public Health Genomics*. 2012;15(1):1-10. ■

■ **eAppendix.** Number of Charts Selected in Each Category

Exposure	Outcome						Percentage (n = 400)
	Prevalent CM/HF		Incident CM/HF		No CM/HF		
	LVEF Measured	No Measure	LVEF Measured	No Measure	LVEF Measured	No Measure	
Both anthracycline and trastuzumab	2	1	19	8	36	8	19%
<i>Either</i> anthracycline or trastuzumab	10	1	29	6	26	12	21%
<i>Neither</i> anthracycline nor trastuzumab	24	25	44	34	87	28	61%
Percentage (n = 400)	9%	7%	23%	12%	37%	12%	

CM indicates cardiomyopathy; HF, heart failure; LVEF, left ventricular ejection fraction.