VALUE IN HEALTH 18 (2015) 541–546

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/jval

BRIEF REPORTS

The Lifetime Economic Burden of Inaccurate HER2 Testing: Estimating the Costs of False-Positive and False-Negative HER2 Test Results in US Patients with Early-Stage Breast Cancer

Louis P. Garrison Jr., PhD[1,2,], Joseph B. Babigumira, PhD[1,2], Anthony Masaquel, PhD[3], Bruce C.M. Wang, PhD[4], Deepa Lalla, PhD[3], Melissa Brammer, MD, MPH[3]*

[1]*VeriTech Corporation, Mercer Island, WA, USA;* [2]*University of Washington, Seattle, WA, USA;* [3]*Genentech, Inc., South San Francisco, CA, USA;* [4]*Alliance Life Sciences, Somerset, NJ, USA*

ABSTRACT

Background: Patients with breast cancer whose tumors test positive for human epidermal growth factor receptor 2 (HER2) are treated with HER2-targeted therapies such as trastuzumab, but limitations with HER2 testing may lead to false-positive (FP) or false-negative (FN) results. **Objectives:** To develop a US-level model to estimate the effect of tumor misclassification on health care costs and patient quality-adjusted life-years (QALYs). **Methods:** Decision analysis was used to estimate the number of patients with early-stage breast cancer (EBC) whose HER2 status was misclassified in 2012. FP results were assumed to generate unnecessary trastuzumab costs and unnecessary cases of trastuzumab-related cardiotoxicity. FN results were assumed to save money on trastuzumab, but with a loss of QALYs and greater risk of disease recurrence and its associated costs. QALYs were valued at $100,000 under a net monetary benefit approach. **Results:** Among 226,870 women diagnosed with EBC in 2012, 3.12% (n = 7,070) and 2.18% (n = 4,955) were estimated to have had FP and FN test results, respectively. Approximately 8400 QALYs (discounted, lifetime) were lost among women not receiving trastuzumab because of FN results. The estimated incremental per-patient lifetime burden of FP or FN results was $58,900 and $116,000, respectively. The implied incremental losses to society were $417 million and $575 million, respectively. **Conclusions:** HER2 tests result in misclassification and nonoptimal treatment of approximately 12,025 US patients with EBC annually. The total economic societal loss of nearly $1 billion suggests that improvements in HER2 testing accuracy are needed and that further clinical and economic studies are warranted.

Keywords: breast cancer, economic burden, HER2 testing, trastuzumab.

Introduction

More than 200,000 women in the United States are diagnosed with breast cancer each year [1]. Approximately 18% to 25% have disease characterized by tumors that are considered to be human epidermal growth factor receptor 2–positive, that is, overexpressing the *HER2* oncogene [2–5]. Tumor HER2 status is determined using laboratory-based methods, such as immunohistochemistry (IHC), fluorescence *in situ* hybridization (FISH), and other in situ hybridization methods. There is currently no gold standard for HER2 testing [6]. Given the limitations inherent to available HER2 tests and variation in testing practices, some tumors may be misclassified. With a false HER2-positive (FP) result, a patient's tumor is considered to be HER2-positive in the absence of HER2-positive disease. With a false HER2-negative (FN) result, a patient's tumor is considered to be HER2-negative (i.e., having normal HER2 levels) in the context of HER2-positive disease. Given that HER2-positive breast cancer is associated with a poorer prognosis than is HER2-negative disease, in the absence of HER2 targeted therapy [2,7], and that HER2 status dictates treatment course [8], the accurate determination of HER2 status is clinically important.

Multiple studies have measured the rates of concordance and discordance in HER2 status between central and local laboratories [9–13]. Central laboratories may have advantages over local laboratories because they process a larger volume of specimens, participate

Conflict of interest: L. P. Garrison, J. B. Babigumira, and B. Wang were partially sponsored in this research by Genentech, Inc., under an unrestricted contract with VeriTech Corporation. A. Masaquel and M. Brammer are salaried employees of Genentech, Inc. D. Lalla was an employee of Genentech, Inc., at the time the study was completed. She is now an employee of Palo Alto Outcomes Research, Inc.

* *Address correspondence to:* Louis P. Garrison Jr., Pharmaceutical Outcomes Research & Policy Program, University of Washington School of Pharmacy, Box 357630, Seattle, WA 98195.

E-mail: lgarrisn@u.washington.edu.

1098-3015$36.00 – see front matter

http://dx.doi.org/10.1016/j.jval.2015.01.012

in continuous quality improvement, and periodically undergo quality assessments [11]. The *FP discordance rate* is defined as the proportion of tumors classified as HER2-positive at a local laboratory but HER2-negative at a central laboratory. The *FN discordance rate* is the proportion of tumors found to be HER2-negative at a local laboratory but HER2-positive at a central laboratory. In the VIRGO study, 552 tumor samples that were HER2-negative in local laboratories were retested in a central laboratory [13]. A total of 22 were found to be HER2-positive, resulting in an FN discordance rate of 4.0% [13]. FP discordance rates as high as 20% have been reported [10–12].

The clinical and economic consequences of FP and FN test results differ. FP results lead to the use of HER2-targeted therapy with little chance of benefit, resulting in an increased risk of treatment-emergent adverse events and added treatment costs to the patient, the payer, and/or the society. Conversely, FN results deny the patient a potential net gain of 1.7 quality-adjusted life-years (QALYs), the incremental QALYs associated with HER2-targeted therapy [14]. Moreover, patients with tumors misclassified as HER2-negative are at an increased risk of disease recurrence, including progression to metastatic breast cancer and its associated health care costs.

In the current analysis, we estimated the individual and aggregate clinical and economic costs of HER2 testing inaccuracy over the lifetime of the 2012 cohort of US women diagnosed with early-stage breast cancer (EBC).

Methods

Analytic Overview

The analysis used the net monetary benefit approach to combine aggregate direct medical care costs with the monetized value of the QALYs lost. Probabilities of FP and FN test results were obtained using decision-analytic modeling. The mean cost of FP misclassification was the sum of the added cost of trastuzumab, the monetized disutility of cardiotoxicity (applied over 1 year), and the added costs of treatment for trastuzumab-related cardiotoxicity. The mean cost of FN test results was the sum of the monetized QALYs lost because of missed trastuzumab treatment plus additional recurrences minus the savings attributable to trastuzumab-related costs (i.e., trastuzumab and the treatment of trastuzumab-related cardiotoxicity). The probability and cost data were used to calculate the costs of FP and FN misclassification and the total aggregate cost of HER2 test misclassification.

Decision-Analytic Model

A decision-analytic model was developed to estimate 1) the probability that a patient's tumor HER2 status would be misclassified and 2) the associated health and economic consequences. The reference case was a patient with newly diagnosed breast cancer whose tumor was tested for HER2 status. The modeling framework classified patients into those whose tumors were truly HER2-positive and those whose tumors were truly HER2-negative (Fig. 1). Although technically unobservable, this true status classification was necessary to assess HER2 testing accuracy and to estimate the expected proportion of misclassified tumors. It was assumed that some patients' tumors were initially tested via IHC, whereas others were initially tested via FISH. For patients whose tumors were modeled as having been initially examined via IHC, individuals with tumor scores of IHC 3+ (based on 10% intense membrane staining) were considered HER2-positive and treated. Individuals with tumor scores of IHC 2+ were considered equivocal and were retested using FISH, and patients with FISH-positive tumors were treated. Patients with tumor scores of IHC 1+ or IHC 0 were regarded as HER2-negative and not treated. Of patients initially tested using FISH, those considered FISH-positive (*HER2:CEP17* ratio ≥ 2) were treated, whereas those who were FISH-negative (*HER2:CEP17* ratio <2) were not. Patients were then categorized as having truly HER2-positive (TP), truly HER2-negative (TN), FP, or FN tumors.

Probabilities and Costs

Data on probabilities and costs used in the model are presented in Table 1. The model assumes near-perfect sensitivity and specificity for FISH. The model also assumes a binomial IHC test profile (for purposes of estimating test accuracy at initial testing) by classifying tumors with IHC 3+ scores as HER2-positive and tumors with IHC 0, IHC 1+, and IHC 2+ scores as HER2-negative. We assumed that the reported sensitivity of IHC applied to a score of IHC 3+. We then used empirical estimates to distribute the complement (1 – sensitivity) among patients with test scores of IHC 0, IHC 1+, and IHC 2+. We similarly assumed that the specificity of IHC applied to combined scores of IHC 0, IHC 1+, and IHC 2+. We then used empirical estimates to derive the distribution of individual IHC results.

The costs of FP and FN test results included the costs of 1) IHC and FISH testing, 2) chemotherapy, 3) trastuzumab, and 4) treating trastuzumab-associated cardiotoxicity and 5) the additional cost of disease recurrence for patients with tumors misclassified as FN (Table 1). The costs associated with trastuzumab included current drug costs, administration costs, left ventricular ejection fraction assessment costs, and the physician follow-up costs. The added costs of disease recurrence were estimated by multiplying the incremental number of averted disease recurrences due to trastuzumab among patients with HER2-positive EBC (based on a joint B-31/N-9831 analysis that spanned 5 years) by the discounted annual incremental cost of disease recurrence (based on cost-of-illness methods) [15]; costs were then inflated to 2012 values.

Health Outcomes

The effect of tumor misclassification on health outcomes was divided into the QALYs lost because of FN test results and the QALYs lost because of the added risk of trastuzumab-related cardiotoxicity following FP test results. The estimate for discounted, lifetime QALYs gained with or without trastuzumab treatment was obtained from a previous cost-effectiveness analysis of EBC [14]. The utility of symptomatic cardiac events on adjuvant therapy has been estimated to be 0.64 [16]. This value was multiplied by the differential rate of symptomatic cardiac complications among patients receiving treatment with paclitaxel plus trastuzumab versus paclitaxel alone.

Sensitivity Analysis

We performed a one-way sensitivity analysis to assess the effect of different input parameters on the probability of FP and FN HER2 test results. When available, we used the bounds of the 95% confidence intervals (CIs) as high and low estimates in the sensitivity analysis. When the bounds of the 95% CIs were unavailable, we used a range of $\pm 20\%$ for probabilities and $\pm 50\%$ for costs.

Results

The results of this analysis are summarized in Table 2. In the total population of patients with EBC, the individual patient probabilities of FP or FN test results were found to be 3.12% and 2.18%, respectively. Given an estimated 226,870 incident cases of EBC in 2012, the expected number of women whose tumors were misclassified as HER2-positive was estimated to be 7,070; the corresponding value for tumors misclassified as HER2-negative was 4,955. A total of 8424 QALYs (discounted, lifetime) were lost because of FN results (calculated as the number of patients with FN results

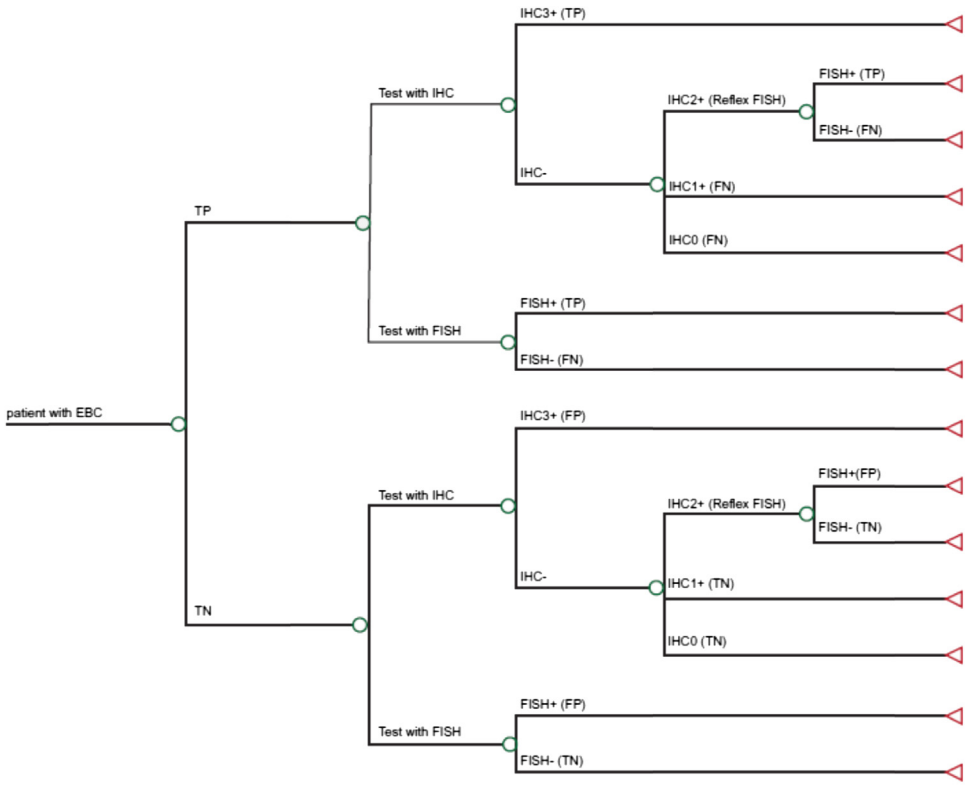

Fig. 1 – Decision-analytic model showing the potential results of HER2 testing in a patient with early-stage breast cancer (EBC), including correct classification (true positive [TP] and true negative [TN]) and misclassification (false positive [FP] and false negative [FN]). FISH, fluorescence *in situ* hybridization; HER2, human epidermal growth factor 2; IHC, immunohistochemistry.

multiplied by the mean QALY gain associated with receiving trastuzumab vs. chemotherapy in patients with HER2-positive breast cancer). The mean per-patient costs of FP and FN test results were estimated to be $58,931 and $116,004, respectively. This would result in aggregate national costs of $416 million owing to FP HER2 test results and $575 million owing to FN test results. Thus, under the base case, the total lifetime aggregate cost of HER2 testing inaccuracy in the United States would be $992 million.

After performing one-way sensitivity analyses, we found that the aggregate national societal cost of HER2 testing inaccuracy was most sensitive to changes in the following variables: 1) QALYs gained for patients on trastuzumab (range 7.4–14.1) changed the aggregate national societal cost of HER2 testing inaccuracy from $300 million to $2.45 billion; 2) the QALYs for patients not on trastuzumab (range 6.4–12.1) changed the aggregate national societal cost of HER2 testing inaccuracy from $1.45 billion to −$190 million; 3) the willingness to pay for an additional QALY (range $50,000–$150,000) changed the aggregate national societal cost of HER2 testing inaccuracy from $567 million to $1.42 billion; and 4) the specificity of FISH (range 0.76–1) changed the aggregate national societal cost of HER2 testing inaccuracy from $1.72 billion to $961 million.

Discussion

We estimated the individual patient probability of obtaining FP or FN HER2 test results to be 3.12% and 2.18%, respectively. The likelihood of tumor misclassification is affected by 1) the prevalence of HER2 overexpression in the population; 2) the accuracy of the HER2 testing method; and 3) the impact of *reflex testing*, defined as retesting an IHC 2+ tumor result with a FISH test. With regard to the first point, the exact proportion of patients in the general breast cancer population with TP tumors is unknown. What is known is that there are fewer patients with TP tumors than with TN tumors. Consequently, models such as ours that consider both HER2-positivity and HER2-negativity may be expected to yield a higher probability of tumors being misclassified as HER2-positive rather than HER2-negative because a test with a similar error rate for detecting HER2-positive and HER2-negative tumors would, by default, yield a higher proportion of FP test results because of the larger number of patients whose tumors are HER2-negative.

The accuracy of HER2 testing methods has improved over the years [17]. In the 2007 ASCO/CAP HER2 testing recommendations, FP rates as high as 20% were reported, yet after the implementation of a quality assurance program, this rate fell to the range of 5.6% to 8.6% [18]. Both IHC and FISH tests, performed in accredited laboratories, are considered acceptable. A prospective randomized controlled trial comparing outcomes (e.g., disease recurrence and overall survival) in patients with EBC whose tumors have been tested using different HER2 testing algorithms (including reflex testing) would be ideal, but is unlikely, due to feasibility issues.

In terms of the effect of reflex testing on the probability of tumor misclassification [19], patients with IHC 2+ tumors (median of 12% of all IHC test results [20]) are reflex tested with FISH. Reflex testing with FISH significantly reduces the rate of a tumor being misclassified as HER2-negative—and its associated negative clinical implications—because, in our model, the FN rate becomes the joint probability of a tumor being misclassified as HER2-negative on both initial IHC testing and reflexive FISH testing. The rate of HER2-positive misclassification using IHC testing is unaffected by reflex testing because all patients with tumors categorized as HER2-positive (both TPs and FPs) are treated. Of note, the baseline rates of FP and FN HER2 test results

Table 1 – Parameters used to inform the decision-analytic model.

Parameter	Base case	Low	High	Reference
Probabilities				
True HER2-positive status	0.2	0.18	0.25	[2–5]
Initial test IHC (vs. FISH)	0.8	0.40	1.00	[20,27,28]
IHC performance				[29]
Sensitivity	0.84	0.81	0.87	
Specificity	0.96	0.95	0.96	
FISH performance				Assumption
Sensitivity	0.99	0.75	0.99	
Specificity	0.99	0.85	0.99	
Empirical distribution IHC results				[20]*
IHC 0	0.36	0.18	0.54	
IHC 1+	0.36	0.18	0.54	
IHC 2+	0.12	0.06	0.18	
IHC 3+	0.16	0.08	0.24	
Initial FISH test is +	0.21	0.11	0.32	[20]*
FISH test + after initial IHC2+ result	0.30	0.15	0.45	[20]*
Costs ($)				
IHC test	134	102	166	[30]
FISH test	245	180	312	[30]
Trastuzumab	55,687	52,903	58,472	[14]
Cardiotoxicity treatment	2,200	1,100	3,918	[14]
Incremental cost of recurrence	3,931	3,735	4,128	[15]
Health outcomes				
QALYs with trastuzumab (discounted, lifetime)	11.78	7.376	14.136	[14,25]
QALYs without trastuzumab (discounted, lifetime)	10.08	6.424	12.096	[14,25]
Disutility of cardiotoxicity	0.104	0.0084	0.0125	[18,31]
Incremental risk of cardiac event on trastuzumab	0.029	0.023	0.035	[16]
Willingness to pay for a QALY ($)	100,000	50,000	250,000	[32]

FISH, fluorescence *in situ* hybridization; HER2, human epidermal growth factor 2; IHC, immunohistochemistry; QALY, quality-adjusted life-year.
* Sensitivity range corresponds to ±50% to incorporate substantial uncertainty in parameter estimate.

that are reported in the literature do not account for the joint probability of reflex testing, and are therefore higher than those reported in our model. To further minimize the likelihood that tumors will be misclassified, some analysts have argued that all negative tumors, not just those with borderline scores, should be retested [21].

In our analysis of the 2012 cohort of women newly diagnosed with EBC, the aggregate economic costs of FP and FN test results were $416 million and $575 million, respectively, for a combined opportunity cost of almost $992 million. Thus, the small probability of a tumor being misclassified as HER2-negative, 2.2%, results in a substantial expected aggregate cost of inaccuracy. The "minimum feasible" aggregate cost of HER2 testing inaccuracy (i.e., near-perfect IHC [99% sensitivity; 99% specificity] and FISH [99% sensitivity; 99% sensitivity]) and test implementation would be approximately $166 million, compared with $992 million in our base case. This is attributable to the substantial opportunity cost in terms of lost QALYs if even a single individual with HER2-positive EBC is denied HER2-targeted therapy because of HER2 testing limitations. A joint analysis of EBC trials of patients with HER2-positive disease showed that 73.7% of the patients not receiving HER2-targeted treatment were disease-free at 4-year follow-up; however, among those receiving trastuzumab, this proportion increased to 85.7%, representing a risk reduction of about 46% [18]. Newer agents such as pertuzumab have shown clinical benefit in patients with HER2-positive metastatic breast cancer [22,23] and are currently being tested in the early-stage disease setting. Although we cannot yet accurately predict which patients with HER2-positive EBC are most likely to benefit from HER2-targeted therapies, any improvements in patient outcomes with new HER2-targeted therapies will increase the costs associated with FN test results, thereby augmenting the returns on improved HER2 testing diagnostics. According to our analysis, an investment in improving HER2 testing accuracy would yield substantial economic value—more than $700 million for each annual cohort. Although newer, potentially more accurate HER2 tests, mostly based on in situ hybridization, continue to emerge, research is needed to determine the potential costs and feasibility of these new testing strategies.

The magnitude of the monetized QALY loss due to HER2 testing inaccuracy is dependent on the estimate of QALYs gained because of trastuzumab therapy as estimated in the study by Garrison et al. [14] and its underlying assumptions. Other studies suggest that the magnitude of this QALY gain is lower [24,25]; we included these estimates in sensitivity analyses. In addition, the study by Garrison et al. used data from a joint analysis of trials B-31 and N9831 that may have included some patients whose tumors were FP [26]. Consequently, this study likely underestimates the economic impact of testing inaccuracy.

One limitation of this analysis is that it is descriptive in nature. It provides a quantitative estimate of the relative opportunity and opportunity cost of tumor misclassification, but it does not indicate what can or should be done to remedy FP and FN test results and efficiently reduce opportunity cost. Moreover, our model does not consider the 2013 ASCO/CAP HER2 testing recommendations, in which dual-probe in situ hybridization–tested tumors with a *HER2:CEP17* ratio of less than 2 can be considered positive, negative, or equivocal (or the resulting reflex testing patterns and outcomes) [19]. The 2013 ASCO/CAP HER2 testing recommendations are anticipated to reduce the burden of

Table 2 – Results of the base-case analysis.

Outcome	FP	FN
Mean per-patient costs		
Individual patient probability of misclassification	0.0312	0.0218
Mean monetized lifetime QALYs lost ($)	0	170,000
Mean cost of additional recurrences ($)	0	3,931
Mean trastuzumab costs or savings ($)	55,687	−55,687
Mean cardiotoxicity costs ($)	2,200	−2,200
Monetized QALYs lost because of cardiotoxicity ($)	1,044	0
Total per-patient cost ($)	58,931	116,044
Aggregate national estimates		
Number of patients	7,070	4,955
Aggregate monetized lifetime QALYs lost ($)	0	842.4 million
Aggregate cost of additional recurrences ($)	0	19.5 million
Aggregate trastuzumab costs or savings ($)	393.7 million	−276.0 million
Aggregate cardiotoxicity costs ($)	15.6 million	−10.9 million
Aggregate monetized QALYs lost due to cardiotoxicity ($)	7.4 million	0
Total aggregate national costs ($)	416.6 million	575.0 million

FN, false negative; FP, false positive; QALY, quality-adjusted life-year.

tumor misclassification, at least to some extent. Provided that the appropriate data on HER2 diagnostics in the clinical practice setting become available, future studies can examine this issue in relation to the base case established in the present analysis. Until such time, this study confirms that in terms of both clinical outcomes and opportunity costs (at both the individual and societal levels), FN HER2 test results have greater health consequences than do FP test results. In light of the almost $1 billion estimated annual burden associated with FP and FN test results, substantial investments in improving HER2 testing accuracy should be considered.

Source of financial support: Genentech, Inc., supported this study.

REFERENCES

[1] Siegel R, Ma J, Zou Z, et al. Cancer statistics, 2014. CA Cancer J Clin 2014;64:9–29.

[2] Yaziji H, Goldstein LC, Barry TS, et al. HER-2 testing in breast cancer using parallel tissue-based methods. JAMA 2004;291:1972–7.

[3] Slamon DJ, Clark GM, Wong SG, et al. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science 1987;235:177–82.

[4] 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;5:63–9.

[5] Ross JS, Slodkowska EA, Symmans WF, et al. The HER-2 receptor and breast cancer: ten years of targeted anti-HER-2 therapy and personalized medicine. Oncologist 2009;14:320–68.

[6] Wolff AC, Hammond ME, Schwartz JN, et al. 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;25:118–45.

[7] Berns EM, Foekens JA, van Staveren IL, et al. Oncogene amplification and prognosis in breast cancer: relationship with systemic treatment. Gene 1995;159:11–8.

[8] National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology, Breast Cancer. Available from: http://www.nccn.org. [Accessed September 10, 2014].

[9] Reddy JC, Reimann JD, Anderson SM, et al. Concordance between central and local laboratory HER2 testing from a community-based clinical study. Clin Breast Cancer 2006;7:153–7.

[10] Roche PC, Suman VJ, Jenkins RB, et al. Concordance between local and central laboratory HER2 testing in the breast intergroup trial N9831. J Natl Cancer Inst 2002;94:855–7.

[11] Perez EA, Suman VJ, Davidson NE, et al. HER2 testing by local, central, and reference laboratories in specimens from the North Central Cancer Treatment Group N9831 intergroup adjuvant trial. J Clin Oncol 2006;24:3032–8.

[12] Paik S, Bryant J, Tan-Chiu E, et al. Real-world performance of HER2 testing–National Surgical Adjuvant Breast and Bowel Project experience. J Natl Cancer Inst 2002;94:852–4.

[13] Kaufman PA, Bloom KJ, Burris H, et al. Assessing the discordance rate between local and central HER2 testing in women with locally determined HER2-negative breast cancer. Cancer 2014;120:2657–64.

[14] Garrison LP Jr, Lubeck D, Lalla D, et al. Cost-effectiveness analysis of trastuzumab in the adjuvant setting for treatment of HER2-positive breast cancer. Cancer 2007;110:489–98.

[15] Rao S, Kubisiak J, Gilden D. Cost of illness associated with metastatic breast cancer. Breast Cancer Res Treat 2004;83:25–32.

[16] Perez EA, Suman VJ, Davidson NE, et al. Cardiac safety analysis of doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab in the North Central Cancer Treatment Group N9831 adjuvant breast cancer trial. J Clin Oncol 2008;26:1231–8.

[17] Lee JA, Shaheen M, Walke T, et al. Clinical and health economic outcomes of alternative HER2 test strategies for guiding adjuvant trastuzumab therapy. Expert Rev Pharmacoecon Outcomes Res 2012;11:325–41.

[18] Perez EA, Romond EH, Suman VJ, et al. Four-year follow-up of trastuzumab plus adjuvant chemotherapy for operable human epidermal growth factor receptor 2-positive breast cancer: joint analysis of data from NCCTG N9831 and NSABP B-31. J Clin Oncol 2011;29:3366–73.

[19] Wolff AC, Hammond ME, Hicks DG, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. Arch Pathol Lab Med 2014;138:241–56.

[20] Dendukuri N, Khetani K, McIsaac M, et al. Testing for HER2-positive breast cancer: a systematic review and cost-effectiveness analysis. CMAJ 2007;176:1429–34.

[21] Garrison LP Jr, Lalla D, Brammer M, et al. Assessing the potential cost-effectiveness of retesting IHC0, IHC1+, or FISH-negative early stage breast cancer patients for HER2 status. Cancer 2013;119:3113–22.

[22] Baselga J, Cortes J, Kim SB, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med 2012;366:109–119.

[23] Swain SM, Kim SB, Cortes J, et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA study): overall survival results from a randomised, double-blind, placebo-controlled, phase 3 study. Lancet Oncol 2013;14:461–71.

[24] Hedden L, O'Reilly S, Lohrisch C, et al. Assessing the real-world cost-effectiveness of adjuvant trastuzumab in HER-2/neu positive breast cancer. Oncologist 2012;17:164–71.

[25] 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;25:625–33.

[26] Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med 2005;353:1673–84.

[27] Schink JC, Trosman JR, Weldon CB, et al. Biomarker testing for breast, lung, and gastroesophageal cancers at NCI designated cancer centers. J Natl Cancer Inst 2014. http://dx.doi.org/10.1093/jnci/dju256: pii: dju256.

[28] Stenehjem DD, Yoo M, Unni S.K, et al. Assessment of single-institution HER2 testing patterns, rate of HER2+ disease and utilization of trastuzumab in early breast cancer. Presented at: ASCO's Quality Care Symposium, November 1-2, 2013, Manchester Grand Hyatt, San Diego, CA, 2013.

[29] Australia Medical Services Advisory Committee. Tests for HER2 gene amplification in breast cancer. Reference 38 Assessment Report. Available from: http://www.msac.gov.au/internet/msac/publishing.nsf/Content/DD14B152B3A7511DCA2575AD0082FDA2/$File/MSAC_Ref_38_Assessment_report.pdf. [Accessed September 12, 2014].
[30] Mass RD, Press MF, Anderson S, et al. Evaluation of clinical outcomes according to HER2 detection by fluorescence in situ hybridization in women with metastatic breast cancer treated with trastuzumab. Clin Breast Cancer 2005;6:240–6.
[31] Lewis EF, Johnson PA, Johnson W, et al. Preferences for quality of life or survival expressed by patients with heart failure. J Heart Lung Trans 2001;20:1016–24.
[32] Neumann PJ, Cohen JT, Weinstein MC. Updating cost-effectiveness–the curious resilience of the $50,000-per-QALY threshold. N Engl J Med 2014;371:796–7.