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REVIEW

# Examining the cost-effectiveness of baseline left ventricular function assessment among breast cancer patients undergoing anthracycline-based therapy

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## Abstract

**Background** There is a lack of consensus to guide which breast cancer patients require left ventricular function assessment (LVEF) prior to anthracycline therapy; the cost-effectiveness of screening this patient population has not been previously evaluated.

**Methods** We performed a retrospective analysis of the Yale Nuclear Cardiology Database, including 702 patients with baseline equilibrium radionuclide angiography (ERNA) scan prior to anthracycline and/or trastuzumab therapy. We sought to examine associations between abnormal baseline LVEF and potential cardiac risk factors. Additionally, we designed a Markov model to determine the incremental cost-effectiveness ratio (ICER) of ERNA screening for women aged 55 with stage I–III breast cancer from a payer perspective over a lifetime horizon.

**Results** An abnormal LVEF was observed in 2% ($n = 14$) of patients. There were no significant associations on multivariate analysis performed on self-reported risk factors. Our analysis showed LVEF screening is cost-effective with ICER of $45,473 per QALY gained. For a willingness-to-pay threshold of $100,000/ QALY, LVEF screening had an 81.9% probability of being cost-effective. Under the same threshold, screening was cost-effective for non-anthracycline cardiotoxicity risk of RR $\leq$ 0.58, as compared to anthracycline regimens.

**Conclusions** Age, preexisting cardiac risk factors and coronary artery disease did not predict a baseline abnormal LVEF. While the prevalence of an abnormal baseline LVEF is low in patients with breast cancer, our results suggest that cardiac screening prior to anthracycline is cost-effective.

**Keywords** Breast cancer · Cost-effectiveness · Left ventricular function assessment · Anthracycline · Screening

## Introduction

Anthracyclines and trastuzumab have been proven to reduce the risk of cancer recurrence and increase survival of breast cancer patients, but at the expense of increased risk of developing cardiotoxicity. The rate of clinically significant cardiac events including a decline in left ventricular ejection fraction (LVEF) and congestive heart failure (CHF) has been reported in 0.5–19% of patients in clinical trials assessing adjuvant trastuzumab conducted by the North American Surgical Adjuvant Breast and Bowel Project (NSABP), North Central Cancer Treatment Group (NCCTG) and Breast International Group (BIG) [1, 2]. A 2012 meta-analysis of five trials evaluating a total of 11,991 women with HER2- positive early breast cancer confirmed a significantly increased risk of severe heart failure and reduction in LVEF in patients treated with trastuzumab versus non-trastuzumab-based adjuvant or neoadjuvant chemotherapy [2–12]. Risk factors for trastuzumab-induced cardiotoxicity include age > 60 years and prior or concomitant treatment with anthracyclines [13, 14]. While there are no definitive guidelines, most practitioners assess cardiac function in patients on trastuzumab every 3 months [15].

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Risks associated with anthracycline use are also well documented. A meta-analysis evaluating the cardiotoxicity of anthracycline agents found significantly higher risk of cardiotoxicity with anthracycline compared with non-anthracycline regimens (OR 5.53; 95% CI 2.34–12.62) [16]. Rates of doxorubicin-related CHF have been found to range from 5% with a cumulative dose of 400 mg/m$^2$ up to 48% at a cumulative dose of 700 mg/m$^2$ [17]. A Surveillance, Epidemiology, and End Results Medicare database study assessing 43,338 women with stage I to III breast cancer found in women ages 66 to 70 there was a significantly increased risk of CHF with anthracycline versus non-anthracycline regimens (HR 1.26; 95% CI 1.12–1.42) [18].

Routine monitoring of individuals treated with these agents before treatment is recommended, but there is a paucity of evidence to support specific guidelines [19, 20]. The National Comprehensive Cancer Network (NCCN) recommends assessing LVEF prior to and during treatment with trastuzumab, while the Federal Drug Administration label recommends baseline assessment of LVEF with continued imaging every 3 months during treatment. The American Society of Clinical Oncology (ASCO) and NCCN have not yet established guidelines for cardiac monitoring in patients prior to anthracycline treatment. Most practitioners monitor LVEF despite the lack of formal guidelines; however, the utility and costs of this approach are not known. Our objective was to determine the prevalence rate of an abnormal baseline LVEF in patients undergoing treatment with an anthracycline and/or trastuzumab. Our goal was to identify risk factors to determine a group of patients who are more likely to benefit from having a baseline cardiac assessment and to perform a cost-effectiveness analysis of baseline LVEF screening prior to administration of anthracycline therapy.

## Methods

### Data sources

Data were obtained from the Yale Nuclear Cardiology database, which contains data on patient characteristics, self-reported comorbidities, and equilibrium radionuclide angiography (ERNA) findings. Self-reported data were collected from patients at time of ERNA acquisition and entered into the database. No additional follow-up data were collected. Available medical records from Yale-New Haven Hospital, Yale Smilow Cancer Hospital, and Yale Cancer Care Centers were reviewed to obtain data about comorbidities, cardiac imaging, and breast cancer treatment. The Yale University Human Investigation Committee approved this medical record review (HIC #1303011697).

### Study sample

We identified 702 patients who had a baseline ERNA scan prior to anthracycline and/or trastuzumab therapy for an initial diagnosis of stage I–IV breast cancer between July 2003 and May 2013. During this time, referring patients for cardiac evaluation before initiating anthracycline therapy was routine practice in our Institution and almost all patients eligible for anthracycline chemotherapy had baseline LVEF assessment. Of the 702 patients, 568 patients had available charts for review to confirm the self-reported history. Breast cancer patients who received anthracyclines and/or trastuzumab as a part of their treatment and whose baseline LVEF was determined by ERNA were included in the study. Patients were excluded if they: (1) received any chemotherapy or radiotherapy prior to their baseline ERNA, or (2) had a prior diagnosis of a cancer requiring chemotherapy or radiotherapy.

### Study design

This was a retrospective study aimed to evaluate incidence of abnormal LVEF, defined as LVEF $< 50\%$ and to identify risk factors that may be associated with an abnormal baseline LVEF in patients receiving anthracycline and/or trastuzumab chemotherapy. The following baseline patient risk factors were obtained: age, body mass index (BMI), family history of cardiac disease, history of dyslipidemia (HL), hypertension (HTN), diabetes mellitus (DM), smoking, and CAD. A patient who was a current smoker or had quit smoking in the past year prior to the baseline ERNA study was considered to have a positive smoking history.

We compared the self-reported characteristics of the 702 patients in the database to those obtained from chart reviews for 568 patients whose charts were accessible. Cohen's kappa coefficient, comparing the self-reported and chart-based risk factors, demonstrated almost perfect agreement between the 2 groups for HTN (Cohen's kappa = 0.75), HL (Cohen's kappa = 0.71), DM (Cohen's kappa = 0.89), and smoking history (Cohen's kappa = 0.66). However, for a patient history of CAD, the analysis revealed considerable discordance between the self-reported and chart reported CAD events (Cohen's kappa = 0.132). Family history of cardiac disease could not be captured consistently on chart review and therefore was only included in self-reported analysis. Given nearly identical results between self-reported and chart reviewed groups, we performed our analysis on the self-reported data.

### Statistical analysis of baseline risk factors

We summarized the descriptive statistics as frequencies for categorical variables and means and standard deviations for continuous variables. The association between the presence of individual risk factors and incidence of asymptomatic left-ventricular dysfunction (ALVD) defined as LVEF < 50 was assessed using the Fisher exact test. To identify risk factors that may be singly or jointly predictive of ALVD, we used exact logistic regression for improved inference due to the very low incidence of ALVD. We employed the R package elrm was for these computations using a Markov-chain length of 95,000 after a burn-in of 5000 iterations [21]. Statistical analyses were performed using R Statistical Software version 3.2.2 (Foundation for Statistical Computing). *P* values less than 0.05 were considered statistically significant unless otherwise indicated.

## Cost-effectiveness analysis

### Basic model and model assumptions

We designed a state-transition model to simulate clinical outcomes, estimate quality-adjusted life-years (QALYs) gained and determine the incremental cost-effectiveness ratio (ICER) of ERNA screening for women aged 55 with stage I–III breast cancer from a payer perspective over a lifetime horizon. We compared two scenarios, no baseline ERNA screening versus universal screening for left-ventricular dysfunction prior to administration of chemotherapy. We assumed for the no screening scenario, all patients received anthracycline, cyclophosphamide followed by taxane regimen (AC-T). In the ERNA screening group, we assumed that women with LVEF < 50% would have their planned chemotherapy regimen changed from AC-T to a non-anthracycline-based chemotherapy such as concurrent docetaxel and cyclophosphamide (TC). All women are initially in a no recurrence health state and subsequently each year transition to one of six health states, including no recurrence, relapse, CHF, or death due to breast cancer, CHF or other disease (Fig. 1).

### Base-case analysis

Clinical parameters and their plausible ranges were generally extracted from previous literature (Table 1). The prevalence of ALVD was estimated as 2%, based on our finding, and consistent with prior literature [22]. We derived annual probability of distant metastasis when receiving AC-T from the NSABP B-38 clinical trial, showing that 5-year distant recurrence-free interval was 86.6% [23]. We estimated probability of distant metastasis when receiving TC using a hazard ratio of 1.23 as compared to AC-T [24]. Prior literature suggested that under enalapril treatment, the 3-year risk of progression from ALVD to CHF failure was about 30% [25], yet there is no similar data available for patients with baseline ALVD who received AC-T or TC. We assumed the annual probability of CHF for patients with baseline ALVD and receiving AC-T is

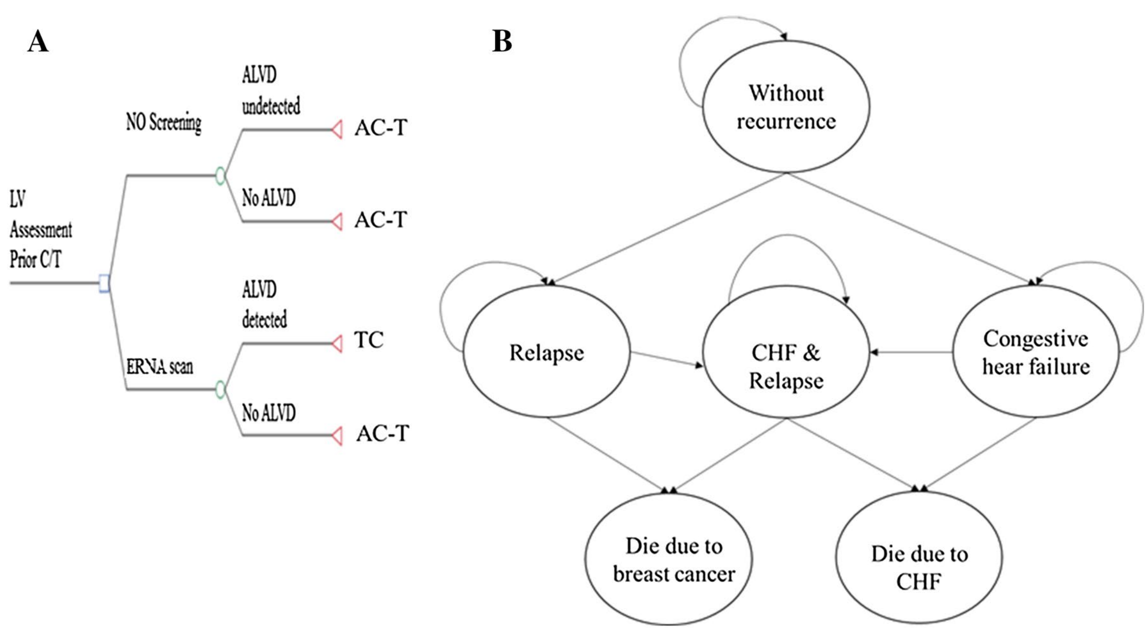


**Fig. 1** Schematic view of scenarios and Markov model. **a** Our state transition model compares no screening at baseline versus universal ERNA screening for LV dysfunction prior to chemotherapy. For the former scenario, we assume all patients received anthracycline, cyclophosphamide followed by taxane regimen (AC-T). In the ERNA screening group, we assume that women with LVEF < 50% would receive docetaxel and cyclophosphamide (TC). **b** All women are initially in a no recurrence health state and subsequently each year transition to one of six health states, including no recurrence, relapse, CHF, or death due to breast cancer, or CHF

**Table 1** Model inputs

| Model assumptions | Value (range) | Source |
|---|---|---|
| Clinical parameter | | |
| Age | 55 (35–70) | |
| Prevalence of low LV ejection fraction | 0.02 (0.01–0.03)[a] | Our findings and [25] |
| Annual metastasis probability, AC-T | 0.028 (0.025–0.033)[a] | [26] |
| Relative risk of metastasis, TC vs AC-T | 1.23 (1.01–1.45)[a] | [27] |
| Annual probability of CHF, ALVD and receiving AC-T | 0.536 (0.482–0.602)[a] | Assumption and [28] |
| Relative risk of CHF, conditional on ALVD, TC vs AC-T | 0.4 (0.2–0.8)[a,b] | [11] |
| Annual probability of CHF, no ALVD and receiving AC-T | 0.012 | [30] |
| Annual CV-specific mortality, If CHF | 0.135 (0.11–0.16)[a] | [31] |
| Annual breast-cancer specific mortality, if metastasis | 0.243 (0.189–0.297)[a] | [32] |
| Annual other-cause mortality, if no CHF and no metastasis | Age dependent | [33] |
| Costs | | |
| Cost of ERNA testing, one time | $1,210 (1000–1420)[a] | Medicare fee schedule |
| Cost of AC-T, one time | $23,550 (Fixed) | [34, 35] |
| Cost of TC, one time | $15,350 (Fixed) | [34, 35] |
| Cost for managing symptomatic CHF, first year, one time | $28,950 (fixed) | [37] |
| Cost for metastasis, first year, one time | $38,950 (fixed) | [36] |
| Cost for continuing care, no CHF and no metastasis, per year | $470 (fixed) | [39–45] |
| Cost for continuing care, CHF and no metastasis, per year | $4,650 (fixed) | [39–45] |
| Cost for continuing care, no CHF and metastasis, per year | $7,130 (fixed) | [39–45] |
| Cost for continuing care, CHF and metastasis, per year | $11,310 (fixed)[c] | [39–45] |
| Cost for end-of-life care, CHF | $54,220 (fixed) | [39–45] |
| Cost for end-of-life care, breast cancer | $57,690 (fixed) | [39–45] |
| Cost for end-of-life care, other disease | $53,040 (fixed) | [39–45] |
| Utilities, by age and health status[d] | A*B | |
| A. Utilities of healthy women according to age | | [46, 47] |
| 35–39 | 0.833 | |
| 40–44 | 0.829 | |
| 45–49 | 0.804 | |
| 50–54 | 0.78 | |
| 55–59 | 0.747 | |
| 60–64 | 0.745 | |
| 65–69 | 0.734 | |
| 70–74 | 0.716 | |
| 75–79 | 0.675 | |
| 80–84 | 0.623 | |
| > 85 | 0.59 | |
| B. Utilities according to health status[a] | | [46, 47] |
| Distant metastases | 0.6 | |
| CHF | 0.71 | |
| Distant metastasis and CHF | 0.426 | |
| Decrease in utility in the first 2 years | − 0.044 | [47] |
| Annual discount rate (QALYs and costs) | 0.03 (0–0.05) | [48] |

[a]Included in the probabilistic sensitivity analysis

[b]Range is based on authors' assumption

[c]Arthurs' calculation: $4650(CHF, no metastasis) + $7,130 (no CHF, metastasis)−$470 (no CHF and no metastasis)

[d]The utility was calculated considering age and health status. For example, utility for women aged 38 and metastasis was 0.500 (0.833*0.6)

53.6%; that is, approximately 90% would develop symptomatic CHF within 3 years. This estimation was relatively conservative, as prior literature suggested that the median time from the last dose of anthracycline to onset of CHF was shorter [26]. The relative risk of cardiotoxicity between TC and AC-T was estimated as 0.4, based on the comparison with AC [11]. Annual probability of CHF, conditional on no ALVD and receiving AC-T was estimated at 0.012 [27]. Because this estimate applied to both groups of no ERNA screening and universal screening (and will cancel out), this estimate would not change our results and was reported here for the comparison purpose. Annual CHF mortality rate was estimated at 0.135, based on the Seattle heart Failure Model [28]. Mortality rate due to metastatic breast cancer was estimated at 0.243 from prior literature [29]. Mortality due to other disease was derived from the US life table [30]. We varied cohorts of women starting at ages from 35 to 70 to determine the effect of age.

Costs and utility estimates, conditional on health states, and treatments were taken from published cost analyses or CEAs. All values were converted to 2015 USD using the consumer price index inflation calculator. Using CPT code 78483, we estimated cost of ERNA scan as $1210 from the 2007 Medicare physician fee schedule. We estimated costs of AC-T and TC, using the same rates, as $23,500 and $15,300, respectively [31, 32]. Costs for distant metastasis, [33] as well as for CHF, [34] were based on prior literature. We separated the continuing-phase costs and end-of-life costs [35], both depended on the health state [36–40]. We abstracted utility weights for each health state from the literature and then age-adjusted these utilities at 5-year increments using previously reported trends [41, 42]. Utilities varied based on age and health status [43, 44] as well as accounted for the decrease in utility in the first 2 years. Costs and utilities were discounted at an annual rate of 3% [45].

### Sensitivity analysis

We performed a series of one-way sensitivity analyses to determine the variability in the ICER as a function of the prevalence of ALVD, starting age, transition probabilities, benefits and harms between AC-T and TC, and cost of ERNA scan. We conducted a two-way sensitivity analysis to investigate how prevalence of ALVD and the starting age would influence our findings. We performed probabilistic sensitivity analysis to assess uncertainty. We used beta distributions for probability parameters, log-normal distributions for relative risk parameters, and gamma distribution for cost parameters [46]. The distributions of input parameters were drawn 100,000 times, and an acceptability curve was created. All analyses were performed on TreeAge Pro 2013 (Williamstown, MA).

## Results

### Incidence of asymptomatic left ventricular dysfunction

Of the 702 patients identified, the mean age was 52 with 91% of patients being 65 years of age or younger. Incidence of self-reported factors included HTN in 27%, HL in 22%, DM in 8%, smoking history in 19%, and known CAD in 2% (Table 2). Abnormal LVEF was found in 2% ($n = 14$) of patients.

### Factors associated with low LVEF

On univariate analysis, family history of cardiac disease showed a strong positive association with LVEF < 50% (OR 3.96; 95% CI 0.8–41.4); however, this association did not reach statistical significance ($P = 0.08$). There were no significant associations on multivariate analysis performed on self-reported risk factors.

**Table 2** Patient characteristics

| | Yale ERNA data base ($n = 702$) |
|---|---|
| LVEF (%) | |
| < 50 | 14 (2%) |
| ≥ 50 | 688 (98%) |
| Age (years) | |
| Mean | 51.9 |
| ≤ 65 | 637 (91%) |
| > 65 | 65 (9%) |
| BMI | |
| < 25 | 271 (39%) |
| 25–29 | 220 (31%) |
| ≥ 30 | 197 (28%) |
| Missing | 14 (2%) |
| Self-reported risk factors | |
| Hypertension | 187 (27%) |
| Hyperlipidemia | 156 (22%) |
| Diabetes | 59 (8%) |
| Smoking history | 131 (19%) |
| History of CAD | 13 (2%) |
| Family history of CAD | 264 (46%) |

**Table 3** Cost-effective estimates, base-case analyses

| | No screening | ERNA scan screening |
|---|---|---|
| Expected costs, $, per woman | 85,880 | 86,810 |
| Expected LY, per woman[a] | 17.38 | 17.42 |
| Expected QALY, per woman | 8.54 | 8.56 |
| Incremental costs, $ | – | 930 |
| Incremental LY gained[a] | – | 0.03[b] |
| Incremental QALY gained | – | 0.02 |
| ICER, $/QALY | – | 45,473 |

[a]Discount rate was set as 0

[b]Inconsistency was due to rounding

## Cost-effectiveness analysis of baseline cardiac function monitoring

Our analysis found that obtaining a baseline LVEF screening was cost-effective resulting in breast cancer patients who will be receiving an anthracycline-based regimen with an ICER of $45,473/QALY (Table 3). One-way sensitivity analyses showed that the results were robust across all variables we examined except the relative risk of CHF, conditional on ALVD, TC versus AC-T. These sensitivity analysis reveals baseline cardiac screening is cost-effective by the commonly accepted threshold of $100,000/ QALY for a relative risk cutoff (TC vs AC-T) of less than 0.58. (Table 3). Probabilistic sensitivity analysis showed that if willingness to pay was $100,000/QALY, baseline LVEF screening had an 81.9% probability of being cost-effective (Fig. 2). In addition, the cost-effectiveness acceptance curve showed that when the patients' willingness to pay (WTP) was larger than $50,000/QALY, baseline LVEF screening would be the optimal strategy (Fig. S1). Two-way sensitivity analysis investigating the impact of prevalence of ALVD and the starting age demonstrated the robustness of our results (Fig S2).

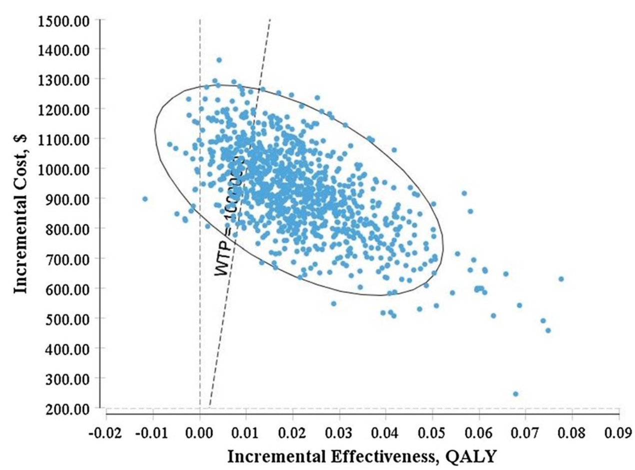


**Fig. 2** Probabilistic sensitivity analysis: incremental cost-effectiveness scatter plot probabilistic sensitivity analysis was performed by plotting the incremental cost vs incremental QALY between the two screening strategies, calculated by randomly sampling each parameter within its respective distribution. The oval delineates the 95% confidence interval of these calculations; the dotted line describes the $ 100,000 USD/ QALY willingness-to-pay threshold. Our simulation reveals a 81.9% probability of baseline LVEF screening meeting this threshold

## Follow-up repeat cardiac function monitoring

Of the 14 patients with a baseline LV dysfunction in the Yale Nuclear Cardiology Database, only two patients had a repeat ERNA. In the first patient, a second ERNA was performed 68 days after the baseline ERNA and demonstrated a decrease in the LVEF from 45 to 42%. In the second patient, six subsequent ERNAs were performed over a timeframe of 847 days, with LVEF values ranging from 42 to 51% (last value was 50%). Of the remaining 688 patients with a normal baseline LVEF, 186 underwent subsequent ERNA studies (median time: 372 days; range 25–1987 days). In this group of patients, 41 patients had an absolute decrease in LVEF of at least 10% and 25 patients had a transient decrease in their LVEF of at least 10% but subsequently normalized.

# Discussion

We found that a very small percentage (2%) of the patients included in this study had an abnormal baseline LVEF (< 50%). The only associated risk factor noted in univariable analysis was family history of cardiac disease, although it did not remain significant on multivariable analysis. We did not find a positive association with other cardiac risk factors, including obesity, age, HL, HTN, DM or history of CAD, despite the relatively large size of our study. Another study reported similar results of pretreatment echocardiograms in 220 patients with non-metastatic breast cancer undergoing anthracycline therapy (2.7% of patients had low ejection fraction, LVEF < 50%) [47]. That study found a positive association with CAD, DM, HTN and HL and low LVEF though it was not statistically significant. A recent study by Truong et al. reported the presence of an abnormal echocardiogram in 13 (2.2%, 1.2–3.7%) of 600 patients including 9 with baseline EF < 55% [48]. There were no significant differences in age, race, menopausal status, smoking history, alcohol use, body mass index, or medical comorbidities between patients with abnormal and normal results. These studies also had limited statistical power to detect significant associations with risk factors due to the very low incidence of an abnormal LVEF in the screened population.

Noninvasive monitoring of cardiac function during anthracycline therapy is endorsed by the American Heart Association/American College of Cardiology (AHA/ACC) in conjunction with the American Society of Nuclear Cardiology and the American Society of Echocardiology (ASE). The use of echocardiography at baseline and for reevaluation examinations to monitor patient's exposed to anthracyclines was given a class I recommendation by a 2003 task force of the ACC, the AHA and the ASE [49, 50]. However, these guidelines do not provide information on the optimal parameter to be followed, how frequently monitoring should be done, or the appropriate manner in which to proceed after a patient had an abnormal reading. The NCCN has no established guidelines on this topic and ASCO does not recommend baseline cardiac assessments.

Several authors have suggested that patients who are scheduled to receive < 300 mg/m$^2$ total dose of doxorubicin (e.g., in the adjuvant setting for early breast cancer) without any other concurrent cardiotoxic drugs and without underlying cardiac risk factors have a low enough risk of cardiotoxicity that baseline cardiac assessment is not needed [51–53]. Additionally, routine cardiac assessment before anthracycline-based adjuvant chemotherapy did not influence the start of therapy decisions for patients < 65 years of age without underlying cardiac risk factors. It was also concluded that the data did not support routine baseline assessment of LVEF in younger women without underlying cardiac risk factors [53]. However, our results indicate that even though there is a low likelihood of finding abnormal baseline LVEF, there are no risk factors that are predictive of this condition. Patients who are found to have depressed LVEFs may be offered alternative non-anthracycline-based therapy.

For the duration of the study (2003–2013), ERNAs were widely used at our institution for the assessment of LVEF; however, recent echocardiography has become more commonly used. Currently, either echocardiography or ERNA is acceptable imaging modalities for cardiac assessment in breast cancer patients. A comparison between ERNA and echocardiographic LVEF showed better intra- and inter-observer reproducibility for ERNA-derived LVEF [54]. Whereas ERNA involves injection of radiopharmaceutical agents, echocardiograms do not. While both methods can detect diastolic dysfunction, ERNA does not detect valve abnormalities.

In an era of rising health care costs, there is a pressing need to identify risk factors and predictors of cardiotoxicity so that screening and monitoring can be tailored appropriately. We did not identify any risk factors that are associated with an increased prevalence of low baseline LVEF; however, overall the percentage of patients with decreased LVEF is low. Our simulation found that obtaining a baseline LVEF was cost-effective in all breast cancer patients who will be receiving an anthracycline-based regimen. The results may initially seem counterintuitive because only 2% of patients had asymptomatic left ventricular dysfunction. However, the cost of ERNA (or echocardiogram) is modest (unit cost of $1,210), whereas caring for CHF is very costly and anthracycline-induced cardiotoxicity is often irreversible. TC is also cheaper than AC-T ($15,350 vs. 23,550), and potentially the better regimen for patients with impaired LVEF, with substantial reduction in the occurrence of CHF and only slight decrease in breast cancer survival. The improvement in effectiveness plus downstream cost-saving would favor baseline LVEF screening to be cost-effective.

The prevalence of an abnormal baseline LVEF is very low in patients with breast cancer. Age, preexisting cardiac risk factors and CAD did not predict a baseline abnormal LVEF. Our results suggest that cardiac screening prior to anthracycline is cost-effective if we assume a 90% CHF rate at 3 years in patients with ALVD who receive AC-T chemotherapy and that the TC regimen has a cardiotoxicity relative risk ratio of < 0.58 compared to AC-T. Screening would be even more cost-effective if a higher risk population for ALVD could be identified. However, a meta-analyses of several of the published studies may be necessary to obtain adequate statistical power to assess risk factors that identify patients with risk of ALVD.

**Author contributions** MA-K: conceptualization, data curation, methodology, project administration, resources, supervision, writing; AS: formal analysis, methodology, visualization, writing; JS: data curation, formal analysis, methodology, visualization, writing; SW: data curation, formal analysis, methodology, visualization, writing; CH: conceptualization, formal analysis, writing, Esther Park – data curation, formal analysis; LP: methodology, supervision, writing; CG: methodology, supervision, writing; RR: conceptualization, supervision, project administration, writing.

## Compliance with ethical standards

**Conflict of interest** Maysa M. Abu-Khalaf MD: Received honorarium for a Consultant/Advisory role from AstraZeneca, Immunomedics, PUMA, Biothera and Agendia. Received a research grant from Novartis for an investigator-initiated clinical trial. Christos Hatzis PhD: Received remuneration from Bristol-Myers Squibb. Lajos Pusztai MD DPhil: Received honorarium for a Consultant/Advisory role from Merck, Astrazeneca, Novartis, Seattle Genetics, Pfizer, and Almac: received research funding from Merck, AstraZeneca, and Seattle Genetics. Cary P. Gross MD: Received remuneration/Travel funding from Flatiron Health and received research funding from Johnson &Johnson and NCCN/Pfizer. Raymond Russell MD, PhD: Spouse employed by ResTORbio. Spouse receives stock options from ResTORbio. All other authors declared that they have no conflict of interest.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

**Informed consent** Informed consent was waived by institutional review board for this retrospective review study.

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