Title: Discerning the clinical relevance of biomarkers in early stage breast cancer

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Introduction

Breast cancer patients face complicated therapeutic decisions, with innumerable factors affecting these choices. Prior data have suggested that patients in the curative setting are willing to accept toxicity of adjuvant therapy for a small gain in survival[1,2]. However, the expected benefit and toxicity associated with a particular treatment is generally presented to patients based on non-individualized data derived from large populations in clinical trials. The advent of pharmacogenomic biomarkers has made it possible to refine individual risk and benefit profiles. Our prior work identified single nucleotide polymorphism (SNP) biomarkers that predicted an increased risk of anthracycline induced congestive heart failure (CHF) and taxane induced peripheral neuropathy (PN)[3,4] , both commonly used chemotherapy classes in early stage breast cancer. However, it is not clear if, and to what degree, the individual shift of risk to benefit ratio predicted by biomarkers is relevant to treatment decisions made by patients. While there are rigorous standards applied to statistical significance and validation methodology, the approach to determine clinical relevance, especially for toxicity markers, is less than clear.

Determining the clinical relevance of biomarker information on treatment decision making is complicated. The risk of each of a multitude of toxicities is variable at the individual level, and the impact this will have on decision-making depends on what other options are available with competing risks and benefits. Choice-based conjoint (CBC) analysis is a statistical technique that can be used in health outcomes research to determine how people value the features that make up a decision, in order to decide the most influential combination of factors. By estimating the relative importance of different characteristics, the impact of a specific factor on the ultimate decision can be observed[5-7]. A similar model was previously used to predict the influence of possible biomarkers in the metastatic setting and found that breast cancer patients would opt for treatment with a small likelihood of benefit despite risk of toxicity[8].

Herein, we report a CBC analysis approach to determine whether pharmacogenomic biomarker information influences a patient's choice of therapy in the curative setting with conventional regimens. Using the profiles of common anthracycline and taxane-based regimens, we sought out to quantify the relative influence of changing degrees of benefit and toxicity risk on treatment choice for patients with HER2 negative, early stage breast cancer receiving chemotherapy with curative intent. Further, we sought to determine whether these results are affected by hypothetical biomarker information and whether validated biomarkers would result in a change in preferred therapeutic regimen.

Methods

Survey

With the objective of deriving patient preferences using stated influence and CBC analysis, an online survey was developed incorporating a series of trade-offs to determine which combination of attributes had the greatest influence on choice. The survey asked whether patients had any prior experience with CHF or PN. The grade of toxicity was assessed by patient reported symptoms as none, mild, moderate or severe (see online resource Methods for exact descriptions). Patients were asked whether prior experience with CHF or PN would have an impact on the decision to take a similar treatment in the future. Most of the survey was CBC-based and presented 12 pairs of hypothetical treatment choices (example in online resource **Figure S1**). Each pair was based on benefit and risk attributes of common chemotherapy

regimens used in the adjuvant setting for early stage breast cancer: a non-taxane regimen, doxorubicin and cyclophosphamide (AC); a non-anthracycline regimen, docetaxel and cyclophosphamide (TC); and two anthracycline plus taxane regimens, doxorubicin and cyclophosphamide followed by paclitaxel (AC-T), and docetaxel, doxorubicin, and cyclophosphamide (TAC) (**Table 1**). The "base case" likelihood ranges used for benefit and toxicity were based upon published clinical trials[9-13]. The hypothetical case combinations were not meant to be exact likelihoods of the risk and benefit, but rather a reasonable depiction through which the degree of change and therefore the influence on decisions could be derived. To prevent bias, respondents were not given the names of the chemotherapy drugs represented. Possible choices included variations in level of benefit with a relative risk reduction for recurrent disease ranging from 20% to 50%. The benefit levels were customized based on the respondent's perception of their individual risk of recurrence without chemotherapy, expressed as 10%, 20%, 30%, or 40%. Those who perceived a risk "greater than 40%" were given 40% as a starting point. For each survey item, respondents were reminded of their starting perceived risk of recurrence, then given a choice between two treatment combinations described as further reducing their risk in terms of lifetime percentage of recurrence. Visual representation of these percentages was also provided (see online reference **Figure S1**). Combinations also described the likelihood of toxicities, including PN (likelihood range of 0%-60% with varied degrees of severity and duration) and CHF (likelihood range of 0%-10%). The risks of each toxicity and the likelihood of benefit were variably altered from the original base cases to mimic personalized risk provided by biomarkers. For each scenario, respondents were given the choice not to take chemotherapy.

The survey was distributed online in September 2012 and January 2013 to eligible patients with early stage, HER2 negative breast cancer who had received chemotherapy within the prior 8 years. Ongoing endocrine therapy was allowed. All patients had received prior therapy and therefore it is acknowledged that their opinions on chemotherapy choices may be biased by prior experiences. For the purposes of this study, the post-treatment population was chosen given the easier and immediate access to large numbers of patients. The survey was dispersed by a non-profit patient support organization, Living Beyond Breast Cancer (LBBC), and an online data collection company, Research Now. LBBC participants were not compensated. Research Now participants received points. Informed consent was obtained and anonymity was protected.

Statistical Analysis

The primary objective of the analysis was to demonstrate that changes in toxicity risk would significantly alter patients' therapeutic decisions. The percentage of self-reported demographic and disease related characteristics were reported. The percentage of respondents whose prior experience with toxicity influenced their future choice of treatment regimen was also reported. CBC analysis was applied to the survey data. Statistical analysis of the percentage preference share for each level of benefit and toxicity tested was performed using Sawtooth Software, utilizing a hierarchical Bayesian routine and the statistical software R version 3.3.0[14]. Confidence intervals were also calculated using the statistical software R (see online resource Methods). Subgroup analysis was performed based on the variables of perceived risk of recurrence, prior treatment setting, survey group, and prior experience with PN.

The survey itself did not refer to biomarkers. Hypothetical biomarkers were modeled to

determine shifts in benefit and toxicity that would be necessary to change treatment selection using software R. Comparing relative preference shares between two sets of risk and benefit levels allowed for the prediction of biomarker influence, with greater differences indicating more influence. Once preference shares at different risk levels were determined, a linear regression model was fitted between the preference share and risk of toxicity. The fitted model was used to determine preference share shifts for known risks of toxicities found in our prior studies of validated biomarkers for PN and CHF. In this model, it was assumed that the baseline risk of toxicity represented the total population risk without any genetic biomarker information. For PN, modeling was performed using our previously identified SNP predicting the development of common toxicity criteria (CTC) version 3.0 grade 2-4 PN (*rs3125923*)[4]. Odds ratios from the chemotherapy trials ECOG 5103 and ECOG 1199 were used[15,13] (see online resource **Figure S2**). For CHF, modeling was performed using our previously discovered SNP (*rs28714259*) predicting the development of any grade of CHF[3]. The odds ratios from two adjuvant chemotherapy trials were used, E1199 and BEATRICE[16,13] (see online resource **Figure S2**).

Results

Patient characteristics

A total of 417 patients participated. Data from 362 surveys were collected through LBBC. Data from 55 surveys were collected through Research Now. Demographic information is presented in **Table 2.** All respondents had a history of early stage, HER2 negative breast cancer and exposure to chemotherapy in the prior 8 years. All patients had completed their prescribed chemotherapy and 37% (n=153) continued to take hormone therapy. Prior side effects experienced by patients are presented in **Table 2.** Most patients perceived that their risk of breast cancer recurrence without chemotherapy was "substantially greater than 40%" (58%; n = 241).

Stated influence of prior toxicity

Based on stated influence, CHF (all grades) had the greatest impact on choice, with 35% (n = 6) of those with prior experience stating that they would be less likely to take a treatment with similar risk. Conversely, only 15% (n = 42) of patients with any grade of prior PN stated they would be less likely to take a similar treatment. However, of those with a history of self-reported *severe* PN (grade 3 by patient reporting) (n = 36), 47% reported they would be less likely to take a treatment that would cause the same degree of toxicity. For all tested side effects, a range of patients (20-35%) said they would be more likely to accept a similar treatment again, i.e. "know what it is like" (see online resource **Table S1**).

Choice- based conjoint analysis

CBC analysis indicated that a risk/benefit profile most similar to the non-anthracycline regimen TC had the greatest share of preference at 39%, compared to AC (27%), AC-T (19%), and TAC (14%). Given its overall preference, a profile similar to TC was used as the base case to determine shifts in preference when attribute levels were changed. When evaluating all attributes in a sensitivity analysis, recurrence risk reduction and the likelihood of PN caused the largest shift in preference (**Figure 1**).

Subgroup analysis

Respondents from LBBC and Resource Now were both predicted to prefer a non-anthracycline regimen (48.3% and 37.7% for TC, p = 0.09), as well as patients treated in a community or an

academic setting (39.0% and 39.2% for TC, p = 0.47). Patients who perceived a lower risk of recurrence had a significantly higher preference for a non-anthracycline regimen than those who perceived a high risk of recurrence (52% vs 36.3% for TC, p = 0.01). Patients with a higher perceived risk of recurrence shifted more preference toward a profile similar to the anthracycline plus taxane regimen AC-T (20.6% versus 10.1%, p = 0.01) (see online resource **Table S2**).

Patients who previously experienced PN had a slightly higher preference for taxane containing regimens modeling a moderate risk of PN, and a significantly lower preference for a non-taxane containing regimen with zero risk of PN, compared to those who had not previously experienced PN. When the case scenario was changed to reflect a lower likelihood of PN, but described as severe and lifelong, patients were more likely to switch their preference to a non-taxane regimen. As shown in **Table 3**, this change was greatest in the respondents who had experienced prior PN, compared to those who had not (31.0% to 43.3% preference for AC in PN naïve patients, versus 25.5% to 47.9% preference for AC in PN experienced patients).

Biomarker modeling

Given that it was most preferred, a profile similar to TC was used as the base case for biomarker analysis. As the likelihood of benefit from taxanes increased, the preference share for any taxane-based regimen increased. At a 20% recurrence risk reduction, 41.3% of patients preferred a taxane regimen, compared to 76.1% at a 50% recurrence risk reduction (see online resource **Table S3**).

Preferences also changed based on variable risk of toxicity. As the likelihood of PN increased, the preference share for any taxane-containing regimen decreased (see online resource **Figure S3**). When using these data to model our previously identified SNP predicting grade 2-4 PN, the preference for a taxane based regimen dropped significantly when modeling the risk of being homozygous variant for the SNP (**Table 4**).

Similarly, as the likelihood of CHF related to anthracyclines increased, the fraction choosing an anthracycline-containing regimen decreased (see online resource **Figure S3**). When modeling our previously discovered SNP predicting the development of CHF, the odds ratios from two different adjuvant chemotherapy trials was used. While the OR increased from wild type to heterozygous variant in both trial cohorts, it decreased to zero when homozygous variant in the BEATRICE cohort. Overall, as risk for CHF increased, the preference for any anthracycline containing regimen decreased (**Table 5**).

Discussion

The risk to benefit ratio of chemotherapy regimens is derived from clinical trials and is applicable at the population level, but not necessarily to an individual patient. While much work remains to elucidate biomarkers that will further refine individual risk and benefit, it is important to determine what clinical relevance this will have on patient decision-making. We applied a CBC analysis on early stage, HER2 negative breast cancer patients who had received prior chemotherapy. The analysis sought to derive the importance of benefit versus risk of toxicity on treatment decision-making in the adjuvant setting for commonly used regimens with competing risk/benefit profiles. We modeled scenarios based on our prior discovery of SNPs that are significantly associated with the development of PN or CHF, to determine whether the knowledge of such biomarkers would impact hypothetical treatment choices.

Prior studies in both the adjuvant and metastatic setting have concluded that when considering the toxicity risk versus clinical benefit of adjuvant chemotherapy, breast cancer patients are more likely to accept a risk of toxicity for a relatively small benefit[8,2,17,18]. However, few studies have evaluated the risk and benefit profiles of current therapies used with curative intent in the adjuvant setting. In a systematic review by Duric et al. evaluating patient preferences for adjuvant chemotherapy, four trials from the 1990s were evaluated using early generation regimens [2]. A more recent CBC analysis of breast cancer patients by Beusterien et al. modeled side effects and degrees of benefit; however, this included patients in the metastatic setting and did not evaluate the risk of severe, lifelong PN or CHF[18]. A study by Smith and colleagues evaluated patient preference for the profiles of paclitaxel and capecitabine using conjoint analysis, however this was performed in the metastatic setting[8]. Our study is one of the first to highlight patient preferences using profiles of current therapies used in the curative setting, focusing on the risk of life- altering toxicities like severe PN and CHF, and the first to examine preferences with risk profiles where validated biomarkers impact treatment decisions. In contrast to prior literature, our study found that patients accepted a higher likelihood of disease recurrence when faced with increased risk for severe toxicities.

In our analysis, personal experience affected treatment choices. Based on stated influence, the majority of patients who had experienced mild/moderate PN in the past would not be impacted by this when making treatment choices. In fact, a proportion of patients with prior CHF or PN would actually be more likely to take a similar treatment. However, severity of PN had a significant influence, with nearly half of patients who had experienced prior *severe* PN reporting they would be less likely to consider a similar treatment. CBC analysis showed similar results, with those who had previously experienced PN displaying a slightly higher preference for taxane-containing regimens than those with no prior PN. It is surprising that patients who suffered from toxicity would accept that toxicity again, but perhaps this reflects a familiarity and tolerability. However, patients who previously experienced PN were less likely to accept a regimen that would cause severe or lifelong PN, perhaps reflecting a population with a more nuanced understanding of the variability and impact of this toxicity.

Based on CBC analysis, the most preferred regimen was a non-anthracycline regimen similar to TC. As expected, the incremental gain in benefit in terms of reduced risk of recurrence had a substantial impact on the selected regimen. Further, unlike prior studies evaluating older regimens or those in the metastatic setting, the preference for a regimen substantially decreased as the likelihood of each toxicity increased. This change was most dramatic for CHF. When PN was estimated to be less likely but severe and irreversible, patients dramatically shifted preference to a non-taxane regimen.

Prior data have demonstrated that a patient's risk of therapy-induced toxicity can vary based on germline genotype[3,4]. When modeling the likelihood of PN after the risk associated with the most significant SNP in our prior genome-wide association study, patients were less likely to choose a taxane regimen if the likelihood of PN was similar to being homozygous variant for the SNP. Similarly, patients were less likely to choose an anthracycline regimen when their risk mimicked being homozygous variant for our previously identified SNP predicting CHF in the E1199 cohort. In the BEATRICE cohort, while risk of CHF increased for patients who were heterozygous, no CHF events were observed in homozygous variant patients, likely due to the relative infrequency of CHF events overall. Knowledge of changing risk profiles that might be provided by biomarkers appears to greatly impact treatment decisions.

An inherent weakness to the CBC analysis is that we do not know how a patient's discussion with a physician might influence choice. It is impossible to know whether a patient would make the same choice when faced with an actual therapeutic decision compared to the hypothetical scenarios. There are many factors involved in treatment decisions at the individual level that cannot be captured by survey analysis. However, aggregating responses from a larger group with prior chemotherapy experience allows us to summarize the value of a certain benefit or toxicity and identify inflection points where the group would begin to shift therapeutic decision making. In addition, a weakness of our study is that we are missing the preferences of patients who have not yet undergone treatment with chemotherapy, or patients for whom chemotherapy did not have the desired benefit. The responses are most certainly biased by individual experiences, and the respondents in our study may be more likely to choose benefit over toxicity given that none had recurred at the time of the survey. However, our interest was in patients with real life experience making such decisions, who were also removed from that experience and more likely to provide less emotionally driven responses to treatment decisions. In addition, we were ultimately interested in whether the additional information provided by biomarkers would alter the decisions of patients who are already aware of the consequences of chemotherapy toxicity.

It is notable that most patients perceived a high risk of recurrent disease greater than 40%. We did not have access to medical records and it is unclear if patients over-estimated their risk, or how they came up with this number. In addition, given that the patients in this study had not experienced a recurrence of their breast cancer, it is possible they placed additional value in whatever therapy they had previously received, whether that included chemotherapy or not. Importantly, despite the perception of a high likelihood of recurrence, these patients still exhibited substantial concerns about toxicity risks. This further highlights the discrepancy of these data with prior studies that suggest patients will accept significant toxicity for a small gain in benefit and calls for additional validation studies. It also highlights the contrast of clinically impactful and potentially irreversible toxicities modeled here with current regimens used in the curative setting.

This study demonstrates that patients consider many variables when making treatment choices, including perceived disease risk, prior experience with toxicity, added benefit, and both the likelihood and severity of toxicity. It should not be assumed that patients are accepting of a certain level of toxicity for small gains in benefit in the curative setting. In addition, the data presented here support that decision-making is affected by information that biomarkers could provide. While improvements in personalized medicine have the capacity to empower patients, some will be overwhelmed with options. Analyses such as these can provide inflection points where the majority of a patient's peers would shift therapy and can serve as a guide to the "preferred" regimen. It is exciting that genotypic markers continue to be discovered; however, this information must be clinically useful to patients to be a meaningful part of treatment discussions. While there is currently no accepted definition for clinical utility, we propose that future studies of biomarker significance include measures of clinical relevance. Future directions include similar analyses at different time points in order to determine the influence of time from treatment on choice, as well as prospective validation of both toxicity biomarkers and the clinical influence of these biomarkers, including the results presented here. As information continues to emerge, involvement of patients in dialogue surrounding their treatment choices will remain of the utmost importance.

Conflict of interest: The authors declare no conflict of interest. The authors have no financial relationship with the organizations funding this research.

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Figures and tables

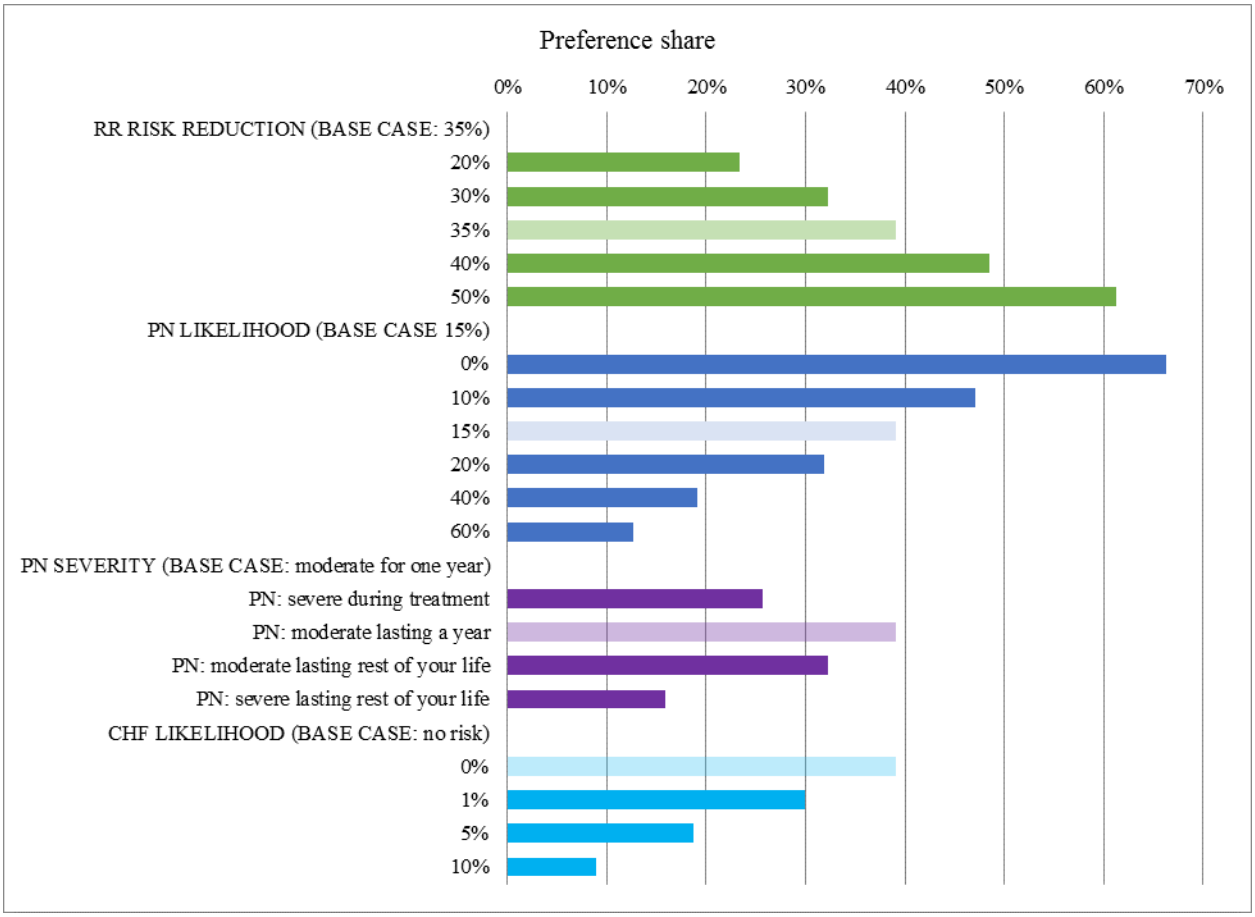

Figure 1. Sensitivity analysis showing change in preference share of responders at varied levels of attributes. A regimen with a profile similar to TC (docetaxel and cyclophosphamide) was used as the starting base case. The largest shifts in preference were seen with alterations in risk reduction benefit and in peripheral neuropathy likelihood. However, large shifts were also seen with duration and severity of PN (peripheral neuropathy), with a large drop when PN was severe and lifelong. In addition, preference dropped steeply as the risk of CHF (congestive heart failure) approached 10%.

Table 1 Base case regimens used in conjoint analysis survey

Regimen*	**AC**	**TC**	**AC-T**	**TAC**
Likelihood of benefit (%)**	27	35	43	43
PN[a] likelihood (%)	0	15	27	15
PN severity, duration	none	Moderate, 1 yr	Moderate, 1 yr	Moderate, 1 yr
CHF[b] likelihood (%)	1.5	0	1.5	1.5

*AC – doxorubicin/cyclophosphamide; TC – docetaxel/cyclophosphamide; AC-T – doxorubicin/cyclophosphamide followed by paclitaxel; TAC – docetaxel, doxorubicin, cyclophosphamide
**in terms of relative recurrence risk reduction
a – peripheral neuropathy; b – congestive heart failure

Table 2 Patient and disease related characteristics

Variable	**Percent of respondents** (N = 417) (%)
Ethnicity	
Caucasian	88
African American	5
Hispanic	4
Other	3
Age	
< 50 yrs old	35
≥ 50 yrs old	65
Married	70
Children	
Children < 22 yrs old	29
All children ≥ 22 yrs old	45
No children	25
Prefer to not answer	1
Highest education level	
High school graduate	24
Associates degree	9
Bachelor's degree	39
Post-graduate degree	28
Annual household income (dollars)	
<50,000	14
50-100,0000	36
>100,000	29
Declined to respond	21
Time since breast cancer diagnosis	
< 1 yr	10
1 – 5 yrs	61
5 – 8 yrs	29
Prior treatment setting	
Academic center	32
Community/private practice	68
Prior therapy in addition to surgery and chemotherapy	
Hormone therapy	51
Radiation	71
Prior chemotherapy side effects	
Fatigue	86
Hair loss	90
Nausea/vomiting	50
Diarrhea	23
Hand foot syndrome	14

Cognitive problems	71
Anxiety/depression	55
Peripheral neuropathy	66
Neutropenia	60
Infection	20
Congestive heart failure	4
Current quality of life*	
0 – 4	4
5 – 7	28
8 – 10	68
Perceived risk of cancer recurrence without chemotherapy**	
10%	5
20%	13
30%	12
40%	12
> 40%	58

* 0 = as bad as it can be, 10 = as good as it can be
** Patients reporting a perceived risk of recurrence >40% used 40% as their starting point for the remainder of the survey

Table 3 Choice of regimen by percent of preference share when altering risk and duration of peripheral neuropathy (PN), comparing those are were PN naïve with those who have experience with prior PN

Regimen*	**Peripheral neuropathy naïve (n = 140) (%)**				**Prior experience with peripheral neuropathy (n = 277) (%)**		
	Base case[a]	Severe PN[b]	*P***		Base case	Severe PN	*P*
AC profile	31.0	43.3	< 0.001		25.5	47.9	< 0.001
TC profile	37.4	25.1	< 0.001		40.0	23.2	< 0.001
AC -> T profile	17.3	22.1	0.06		19.4	19.4	0.5
TAC profile	12.8	7.8	< 0.001		14.5	8.5	< 0.001
None	1.5	1.7	0.28		0.6	1.1	< 0.001

*AC – doxorubicin/cyclophosphamide; TC – docetaxel/cyclophosphamide; AC-T – doxorubicin/cyclophosphamide followed by paclitaxel; TAC – docetaxel, doxorubicin, cyclophosphamide
**p – Bayesian p value
a – base case represents risk of moderate peripheral neuropathy with a likelihood of 15%, b – severe PN case represents risk of severe and lifelong PN with a likelihood of 5%

Table 4 Shift in percentage of preference for taxane containing regimens with changing degrees of peripheral neuropathy risk modeling the known biomarker *rs3125923*.

Dataset	Genotype*	Frequency of PN[a]	Preference of any T[b] (%)	95% CI	Preference of AC[c] (%)	95% CI[d]
E5103	**WT/WT**	20%	**74.2**	71.7- 76.7	**25.0**	22.6- 27.3
	WT/Var	27%	**68.2**	65.8- 70.1	**30.9**	28.5- 33.2
	Var/Var	35%	**61.4**	58.9- 63.9	**37.6**	35.2- 40.0
E1199	**WT/WT**	17%	**74.5**	72.0- 76.9	**24.7**	22.3- 27.1
	WT/Var	19%	**72.5**	70.0- 74.4	**26.6**	24.3- 29.0
	Var/Var	82%	**10.3**	5.0 – 15.5	**88.1**	83.0- 93.1

*WT/WT – homozygous wild type; WT/Var – heterozygous; Var/Var – homozygous variant
a – peripheral neuropathy; b – any taxane containing regimen; c – doxorubicin/cyclophosphamide; d – confidence interval

Table 5 Shift in percentage of preference for anthracycline containing regimens with changing degrees of congestive heart failure risk modeling the known biomarker *rs28714259*.

Dataset	Genotype*	Frequency of CHF[a]	Preference of any A[b](%)	95% CI	Preference of TC[c] (%)	95% CI[d]
E1199	**WT/WT**	1.2%	**61.4**	59.0- 63.8	**37.7**	35.3- 40.0
	WT/Var	2.3%	**56.3**	53.9- 58.6	**42.8**	40.4- 45.1
	Var/Var	3.4%	**50.6**	47.7- 53.5	**48.3**	45.4- 51.2
BEATRICE	**WT/WT**	2.4%	**61.7**	59.3- 64.1	**37.5**	35.1- 39.8

	WT/Var	5.4%	**54.4**	52.0- 56.9	**44.6**	42.1- 47.0
	Var/Var	0.0%	**67.5**	64.5- 70.6	**31.7**	28.6- 34.7

*WT/WT – homozygous wild type; WT/Var – heterozygous; Var/Var – homozygous variant

a – congestive heart failure; b – any anthracycline containing regimen; c – docetaxel/cyclophosphamide; d – confidence interval