A Method of Deriving Estimates of Health State Utilities for Patients With Metastatic Breast Cancer

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ABSTRACT: Patient-level health-related quality of life (HRQOL) for different stages of metastatic breast cancer (MBC) and chemotherapy regimen toxicities are useful for health economic assessments. However, it is rare that health state utility data used to quantify HRQOL can be derived directly from clinical trials. The authors used an indirect approach to deriving health state utilities for patients with MBC by mapping HRQOL data using a published regression algorithm. A linear mixed-effects model was used to regress explanatory variables. The results were then compared with utility estimates from a previously reported vignette study of patients with MBC in order to examine potential differences between the results. Observed baseline/stable MBC health state utility mean scores were similar between patients in the eribulin and capecitabine treatment arms. Most toxicities associated with eribulin and capecitabine led to a decline in utility scores. The estimated health state utilities were consistent with published values from the vignette study, although the vignette method appears to estimate a much larger impact of disease progression and adverse events on health state utilities. The disutility associated with disease progression is approximately twice as great as according to the vignette method. These findings could be an important influence on any estimates of cost-effectiveness of treatments for MBC.

KEY WORDS: health state utilities, metastatic breast cancer, adverse events, cost-effectiveness, health-related quality of life

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Breast cancer is the most common malignant disease in women, affecting approximately 1 in 8 women worldwide.[1,2] In addition, approximately 4–10% of women who have breast cancer develop metastatic breast cancer (MBC).[3] MBC remains a leading cause of cancer death in Western countries.[4] Despite advances in the diagnosis and treatment of MBC, the median survival of women with the disease is just 18–24 months, and fewer than 5% are alive and disease free at 5 years.[5-8] Patients with advanced MBC experience unrelieved physical symptoms, especially pain, fatigue, dyspnea, and reduced appetite.[9] As a result, MBC is associated with the greatest reduction in health-related quality of life (HRQOL) when compared with earlier stages of breast cancer.[10,11] Currently, there are no curative treatment options available; goals of current treatments are to prolong patient survival, relieve symptoms, and maintain quality of life.[1,2]

As a consequence of the significant worsening of HRQOL associated with metastatic disease, palliative care often becomes paramount in patients with MBC.[12] Cancer patients in palliative care report reduced HRQOL and worsening of depression and anxiety.[13,14] Understanding the patient burden due

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Table 1. Adverse Events Considered for Disutility Health State

Blood and lymphatic system disorders	Neutropenia Anemia Leukopenia Febrile neutropenia
Gastrointestinal disorders	Nausea Constipation Diarrhea Vomiting Stomatitis Dyspepsia
General disorders and administration site conditions	Asthenia/fatigue Pyrexia
Inflammatory disorders	Mucosal inflammation Weight loss
Metabolism and nutrition disorders	Anorexia
Musculoskeletal and connective disorders	Arthralgia/myalgia Back pain Back pain and pain in extremity
Nervous system disorders	Headache Peripheral neuropathy
Respiratory, thoracic, and mediastinal disorders	Dyspnea Cough Skin and subcutaneous disorders Alopecia Palmar-plantar erythrodysesthesia

to illness requires an understanding of all factors impacting the patient's perspective (ie, symptoms and HRQOL) from the start of treatment.[15,16] In metastatic disease, baseline HRQOL and patient-reported symptoms have been reported as prognostic factors for survival.[17] For example, patient-reported endpoints such as appetite loss, fatigue, and physical functioning have been found to be predictive of survival in multiple studies. Moreover, appetite loss was shown to be highly correlated with increased fatigue and decreased role functioning and physical functioning.[15,17]

Patient-level health state utilities are used in health economic assessments to quantify HRQOL for different stages of MBC and toxicities commonly associated with chemotherapy regimens. However, it is rare that data on health state utilities are derived directly from clinical trials, because generic measures of HRQOL that can be used to estimate utilities, such as the EQ-5D, are commonly left out of trial protocols. When EQ-5D or similar data are not available, there are two main methods that have been used to estimate health state utilities: directly, from vignette studies that describe the health states or derivation of preference-based measures from an existing condition-specific scale;[18] or indirectly, by "mapping" utilities from disease-specific scales. Examples of other methods, such as developing a utility instrument measure directly from a disease-specific instrument, do exist but are far less prevalent in the literature.

In this study, we used an indirect approach to deriving health state utilities for patients with MBC by mapping HRQOL data using a published algorithm. The results of the indirect approach were compared with utility estimates from a previously reported vignette study of patients with MBC in order to examine potential differences between the results, which may prove important for cost-effectiveness studies.[19,20]

INDIRECT DERIVATION OF HEALTH STATE UTILITIES

Patient Population

HRQOL data was obtained from a Phase 3, open-label, two-arm, parallel, randomized, multicenter clinical trial (Phase 3 Open Label, Randomized Two-Parallel-Arm Multicenter Study of E7389 (Halaven® [eribulin] versus Xeloda® [capecitabine]; E7389-G000-301) that included 1102 patients with locally advanced MBC that had received prior anthracycline- and taxane-based therapy. Patients must have had documented evidence of progression during or after their most recent anti-cancer therapy (results published elsewhere).[21]

Patients were stratified at randomization by geographic region and the HER2 (human epidermal growth factor receptor 2) status of their cancer (positive, negative, or unknown) and were randomly assigned (1:1) to receive 21-day cycles of eribulin mesylate 1.4 mg/m^2 (equivalent to 1.23 mg/m^2 eribulin, expressed as free base) intravenously over 2–5 minutes on Days 1 and 8 (n = 554), or capecitabine 1.25 g/m^2 orally twice daily on Days 1 to 14 (n = 548) as their first-line, second-line, or third-line chemotherapy for advanced/metastatic disease.[21] Patients received study treatment until disease progression, unacceptable toxicity, or patient or investigator request to discontinue.[21] Tumor response and disease progression were assessed with magnetic resonance imaging (MRI) or computed tomography (CT) scans, x-rays, and bone scans.

Patient-Reported Outcome (PRO) Instruments

HRQOL was assessed in the parent study using the validated cancer-specific questionnaire EORTC QLQ-C30 (Version 3.0).[22-24] The EORTC QLQ-C30 consists of 30 questions addressing 5 functional scales (physical, role, cognitive, emotional, and social),[9] symptom scales (fatigue, pain, nausea and vomiting, dyspnea, appetite loss, sleep disturbance, constipation, and diarrhea), and 1 global health/HRQOL scale. All scale scores for EORTC QLQ-C30 were transformed to range from 0 to 100. Higher scores in the functional scales represented a superior level of functioning and better HRQOL, whereas higher scores in the symptom scales or items represented worse symptoms/problems.

Questionnaires were administered at baseline, at 6 weeks,

AEs more common to ERI
AEs more common to CAP

	Eribulin (n = 503)		Capecitabine (n = 247)	
	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
Neutropenia	54%	46%	16%	5%
Febrile neutropenia	2%	2%	1%	1%
Leukopenia	31%	15%	10%	2%
Alopecia (hair loss)	35%	0%	18%	0%
Peripheral neuropathy	13%	3%	7%	1%
Hand-foot syndrome	0%	0%	45%	14%
Diarrhea	14$	1$	29%	5%
Nausea	22%	0%	24%	2%
Vomiting	12%	0%	17%	2%
Decreased appetite	13%	1%	15%	2%
Fatigue	17%	2%	15%	2%

Figure 1. Incidences of Common AEs in >10% (All Grades) or 2% (Grade 3 or Higher) of All Patients[10]
Abbreviations: AE, adverse events; CAP, capecitabine; ERI, eribulin.

and at 3, 6, 12, 18, and 24 months, or until disease progression or initiation of other antitumor treatment (including those initiated after study termination). The initial questionnaire was completed in the clinic before randomization. Post-baseline questionnaires were completed in the clinic before any study-related procedures were administered or tumor assessment results were communicated to the patient. Patients were asked to complete questionnaires at each clinic visit, even if they had refused on the previous occasion. Questionnaires were completed without conferring with friends or relatives, and patients were instructed to complete all questions even if they considered them to be irrelevant.

Compliance with completing the HRQOL measures was ascertained from counts of completed EORTC QLQ-C30 questionnaires. Of the patients who were included in the parent study, 1062 patients (96.4%) were flagged for inclusion in the HRQOL population analysis based on baseline EORTC questionnaire completion status. Of these patients, 536 (96.8%) patients in the eribulin treatment arm and 526 (96.0%) patients who received capecitabine treatment completed the EORTC QLQ-C30 at baseline. Overall compliance for completing the EORTC questionnaires over the course of the study was ≥ 80%, except at 18 months and 24 months, when compliance fell below 80% in these limited sample sizes.

Health State Utility Derivations

Due to the fact that HRQOL data were collected in clinical study E7389-G000-301 using QLQ-C30 and the study did not include the EQ-5D, a published algorithm was used to estimate EQ-5D scores from the EORTC QLQ-C30 scores on the following scales: physical functioning (PF); emotional functioning (EF); social functioning (SF); constipation (CO); diarrhea (DI); pain (PA); and sleep (SL).[25,26] The algorithm is based on an ordinary least-squares regression algorithm model, which was derived in female patients with locally advanced breast cancer with good baseline health status, who were part of a randomized clinical trial that collected data on both the QLQ-C30 questionnaire and the EQ-5D instrument.[25] The dependent variable was the calculated overall EQ-5D utility decrement, and the explanatory variables were the calculated QLQ-C30 scores:

$$EQ\text{-}5D = 0.85927770 - 0.0069693*PF - 0.0087346*EF - 0.0039935*SF + 0.0000355*PF2 + 0.0000552*EF2 + 0.0000290*SF2 + 0.0011453*CO + 0.0039889*DI + 0.0035614*PA - 0.0003678*SL - 0.0000540*DI2 + 0.0000117*SL2$$

The EQ-5D utilities were constructed using the original UK Tariff.[27] The derived EQ-5D values were then used to predict the mean within the clinical trial population for the following health states: (1) baseline stable disease status (yes or no); (2) tumor responder (yes or no); (3) disease progression (yes or no); and (4) disutility for the major adverse events (AEs; yes or no). AEs of interest (Grade 3 and 4 only) are listed in **Table 1**.

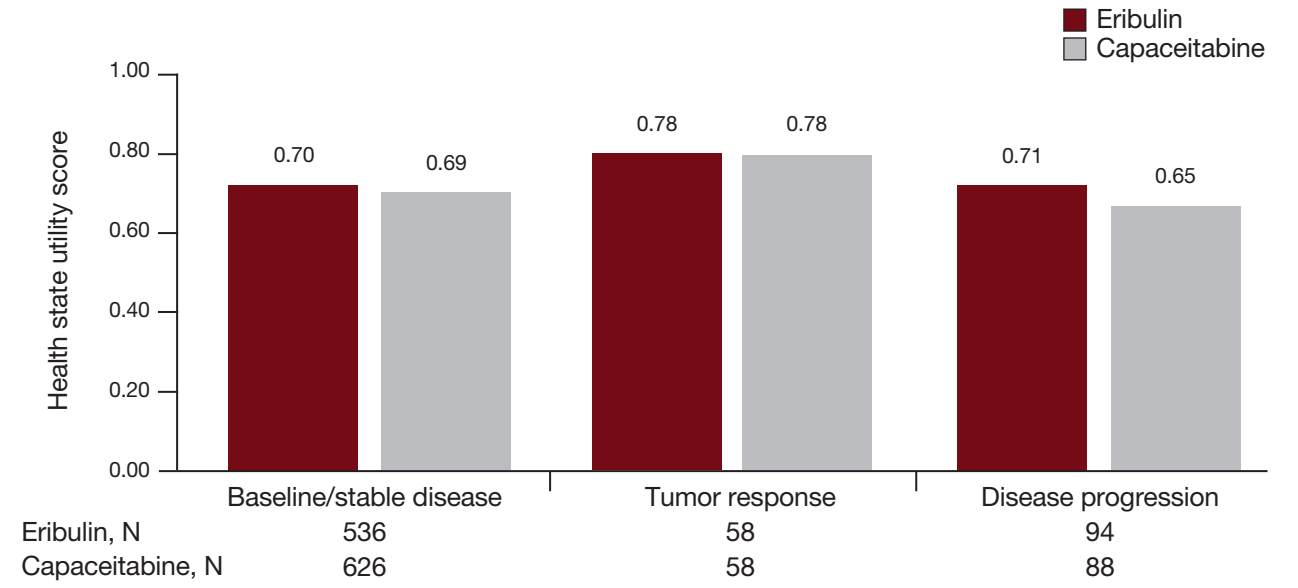

Figure 2. Estimated Health State Utilities in Metastatic Breast Cancer

Disutility Analysis

The standard of care for patients with local or advanced metastatic disease generally consists of different combination chemotherapies with potentially different toxicities for each line of treatment.[28,29] Therefore, disutility scores were calculated for specific AEs (run individually for this specific analysis) of interest.

In the E7389-G000-301 clinical study, eribulin and capecitabine treatments displayed different toxicity profiles.[21] Adverse events including neutropenia, leukopenia, anemia, alopecia, peripheral sensory neuropathy, and fatigue were more commonly observed in treatment with eribulin, while AEs including hand-foot syndrome, thrombocytopenia, diarrhea, nausea, vomiting, and decreased appetite were more commonly observed in patients treated with capecitabine (**Figure 1**).

Statistical Methods

A linear mixed-effects model was used to regress explanatory variables, including baseline transformed health state utilities and specific AEs of interest, against the change in health state utilities. A regression analysis of individual pairs of EORTC QLQ-C30 and EQ-5D scores was done using ordinary least squares. In all models, the timing of EORTC HRQOL administration and patient was included as random effects to control for unobserved, patient-specific characteristics and multiple observations per patient. All other predictors were included in the model as fixed effects.

To estimate disutility per patient, the previously derived mapping function from breast cancer data was used. The difference in observed disutilities and estimated disutilities was calculated. Estimated disutilities were regressed using ordinary least squares on the observed disutilities.

Model fit and predictive power were assessed through the adjusted R-squared, the root-mean-square error, and mean average error.

OUTCOMES

Estimated Health State Utilities

Observed baseline/stable MBC utilities were similar between treatment arms (observed mean for eribulin versus capecitabine: 0.70 versus 0.69, respectively; **Figure 2**). Tumor response was associated with utility improvement in both treatment arms (0.78 for each treatment group; **Figure 2**). For patients on capecitabine treatment who progressed, the decline in disease progression on the health state utility was slightly worse compared with E7389-treated patients (eribulin versus capecitabine: 0.71 vs 0.65, respectively) which is reflective of the clinical survival results which favor eribulin (**Figure 2**).

Disutility Analysis

Most toxicities led to a decline in utility scores. Vomiting, decreased appetite, fatigue, nausea, and diarrhea led to the highest disutility decrements (**Figure 3**). Specifically, the overall disutility value in common AEs including vomiting, decreased appetite, fatigue/asthenia, and diarrhea were in favor of eribulin treatment; and AEs including dyspnea, peripheral neuropathy, febrile neutropenia, neutropenia, and leukopenia were in favor of capecitabine treatment. In this analysis, alopecia was associated with improvement in utility, which is consistent with a previously published study showing that

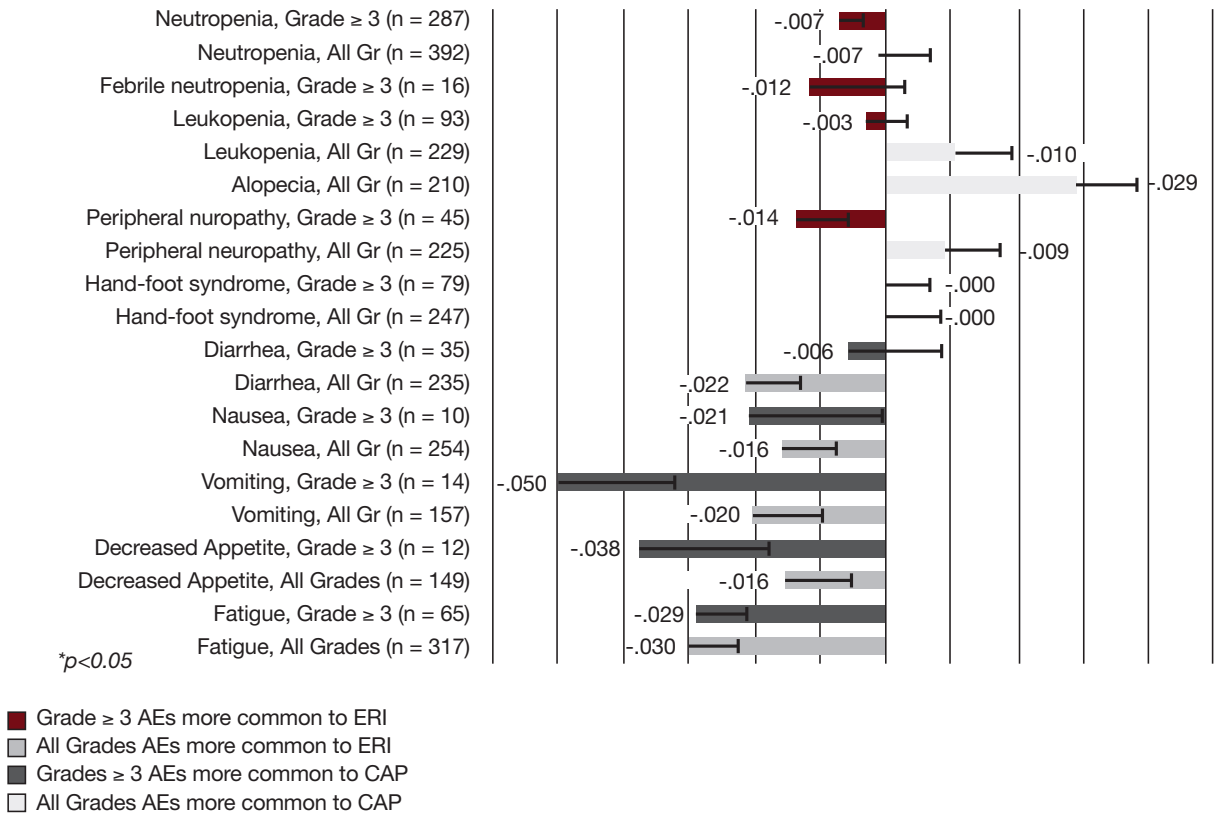

Figure 3. Disutility Values for Common AEs Calculated by Mapping Method
Abbreviations: AE, adverse events; CAP, capecitabine; ERI, eribulin.

patients with alopecia had significantly longer overall survival and progression-free survival compared with patients without alopecia.[30] However, the EORTC QLQ-C30 scale does not assess hand-foot syndrome, alopecia or peripheral neuropathy.

COMPARISON OF DIRECT AND INDIRECT HEALTH STATE UTILITY ESTIMATES

The results were compared with previously published values obtained for a vignette study.[19] In the study, 100 participants of the general public provided estimates of utility for MBC-related health states including the burden of the disease on treatment and six common toxicities (febrile neutropenia, stomatitis, diarrhea/vomiting, fatigue, hand-foot syndrome [grade 3/4 toxicities], and hair loss).[18] Participants were recruited from advertisements in local newspapers and from an existing University of British Columbia (UBC) database, and interviews were conducted at the UBC offices. Health states were rated using the standard gamble method.[18] Participants also completed the EQ-5D to rate their current health. The demographic profile and EQ-5D data were summarized and compared with the UK population from the 2001 national census data for England and Wales (Office of National Statistics, 2001).[18]

Health State Utilities

Derived baseline/stable MBC utilities were consistent with published values from the vignette study (mean, 0.72; **Figure 4**).[19] In addition, tumor responses were similar to previously published values from the vignette study (mean, 0.79; **Figure 4**). However, scores for disease progression were higher for patients in the clinical study compared with published vignette values (mean: 0.44; **Figure 4**).[19]

Disutilities

A comparison of the disutility for toxicities revealed that mapping and vignette utility estimates varied substantially and provided different results based on the chosen methodology (**Table 2**).

DISCUSSION

Currently, there is limited information on assessing the impact of MBC treatment using EQ-5D utilities. Understanding the burden of illness of MBC in a patient is essential to understanding all facets of impact from the patient's perspective such as symptoms and HRQOL from the start of treatment.[15,16] By using Eisai's Phase 3, randomized, clinical study E7389-G000-301 and a published algorithm[25,26]

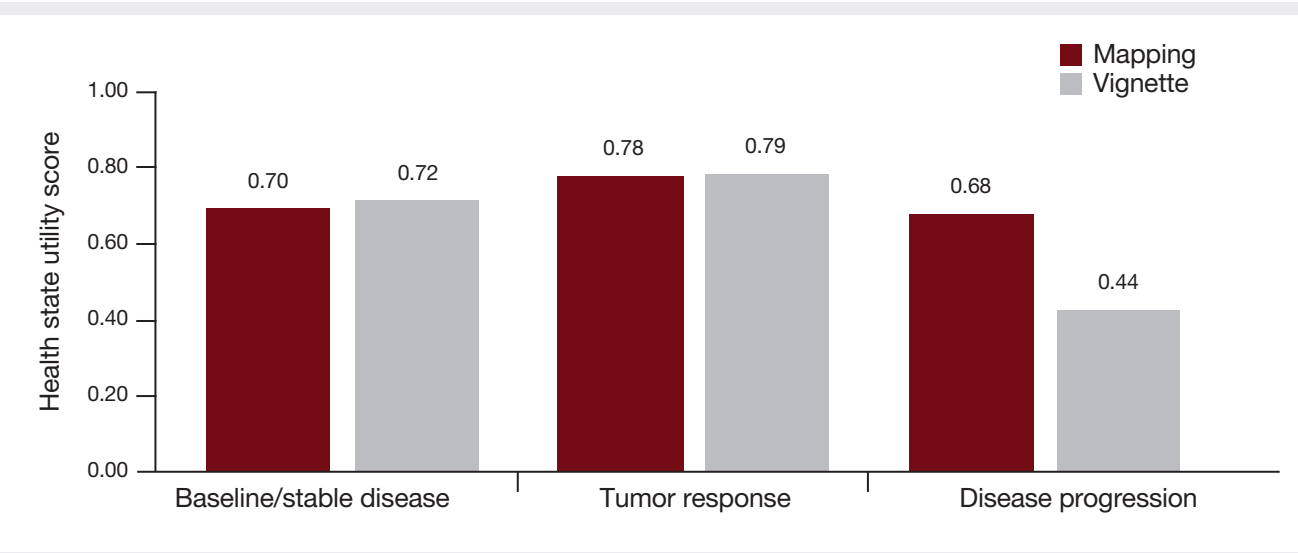

Figure 4. Direct Versus Indirect Health State Utility Estimates[26]

to convert the EORTC QLQ-C30 to EQ-5D single health state index, post-hoc analyses demonstrated tumor response was associated with an improvement in health state utilities for both the eribulin and capecitabine arms, while a decline in disease progression was clinically significantly worse in the capecitabine treated population versus the eribulin treated population. In addition, results from the disutility analysis demonstrated most toxicities led to a decline in utility scores with the highest disutility decrements for vomiting, decreased appetite, fatigue, nausea, and diarrhea.

Patient-level utility values are useful for health economic assessments. By mapping the health state utility from the EORTC QLQ-C30, in the absence of EQ-5D data, this offers a valuable perspective on the reduction in HRQOL associated with disease progression and treatment toxicity.

Patient-reported outcomes are often anchored to meaningful change thresholds. Clinically meaningful within arm differences in the EQ-5D health state utility index have been expressed in metastatic disease to be equal or greater than a 0.07-0.09 difference.[31] Patients on capecitabine experienced more detrimental impact in health state utility compared with patients on eribulin at disease progression.

This study serves to highlight many of the limitations of the vignette methodology. The vignette methodology produces a very similar estimate of utility for progression free survival (PFS) to the estimate from this prospective study. The vignette method appears to estimate a much larger impact in relation to disease progression and AEs in terms of their impact on utilities; this phenomena should be further explored in additional studies. The disutility associated with disease progression is approximately twice as great according to the vignette method and, as a result, could be a very important influence on any estimate of cost effectiveness. The impact of AEs is also estimated to be much larger than the clinical trial–based analysis suggests. This is probably due to a focusing type of effect whereby the participant in the valuation exercise is unduly influenced by the description of the AE. The vignette method is also unable to reliably measure whether there is any difference between treatments during PFS, which leaves modeling teams reliant on a single value for stable disease.

The best approach to obtain utilities for quality-adjusted life-year estimations is through the direct collection of preference-weighted measures of HRQOL (from patients in the relevant states) and parameter derivation as these approaches allow for direct data collection rather than regression estimations or derivation from the general population rather than patients. However, when direct utility data are not available, mapping is often accepted as the second best option because the data can be benchmarked in terms of EQ-5D or other generic preference-based measures of HRQOL. Empirical mapping is a good method when an algorithm is available (or can be readily developed), but concerns can be raised for the large degree of error when mapping from a condition-specific measure if there is a mismatch of the health aspects covered in the two measures that are mapped. Vignettes offer an alternative when no utility data are available either from a trial or from the literature, but the method should be treated with caution. Treatment-specific experience suggests that vignettes developed and tested in the general population may not be sensitive to addressing treatment-level variance. As indicated, these methods vary in terms of population and approach with qualitative and quantitative differences resulting in different utility estimates. It should be considered less reliable than other methods.

CONCLUSION

Utilization of different methods to estimate utilities in MBC

Table 2. Comparison of Disutility Scores From Mapping and Vignette Methods

Adverse Event	Mapping	Vignette
Fatigue	- .030	- .115
Febrile neutropenia	- .025	- .150
Diarrhea	- .022	- .103
Vomiting	- .020	- .103
Nausea	- .016	Not available
Decreased appetite	- .016	Not available
Neutropenia	- .001	Not available
Stomatitis	- .000	- .151
Hand-foot syndrome	- .000	- .116
Peripheral neuropathy	- .009	Not available
Leukopenia	- .010	Not available
Alopecia	- .029	- .114

may lead to wide value ranges with potentially significant implications to health economic evaluation. Each method has implications in terms of its impact, on any economic evaluation because the utility weights vary. Fundamentally, this analysis seems to support the view that there is no substitute for prospectively collected HRQOL where the patient is asked to provide a subjective assessment of his or her own outcomes.

In conclusion, this dataset could provide a useful alternative to the Lloyd et al[26] vignette study for cost-effectiveness analyses in MBC to allow for a more sensitive estimation of cost as the variance between these methods may lead to over- or under-estimation of cost. Therefore, it is recommended that future evaluations for treatments in MBC should use the values from the mapping function presented here rather than vignette studies because the impact of MBC, treatments, and associated AEs on patients' HRQOL should be judged by patients themselves through the use of validated HRQOL measures. ◆

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