Structural Uncertainty of Markov Models for Advanced Breast Cancer: A Simulation Study of Lapatinib

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Objective. *To examine the impact of structural uncertainty of Markov models in modeling cost-effectiveness for the treatment of advanced breast cancer (ABC).* ***Methods.*** *Four common Markov models for ABC were identified and examined. Markov models 1 and 2 have 4 health states (stable-disease, responding-to-therapy, disease-progressing, and death), and Markov models 3 and 4 only have 3 health states (stable-disease, disease-progressing, and death). In models 1 and 3, the possibility of death can occur in any health state, while in models 2 and 4, the chance of dying can only occur in the disease-progressing health state. A simulation was conducted to examine the impact of using different model structures on cost-effectiveness results in the context of a combination therapy of lapatinib and capecitabine for the treatment of HER2-positive ABC. Model averaging with an assumption of equal weights in all 4 models was used to account for structural uncertainty.* ***Results.*** *Markov model 3 yielded the lowest incremental cost-effectiveness ratio (ICER) of $303,909 per quality-adjusted life year (QALY), while Markov model 1 produced the highest ICER ($495,800/QALY). At a willingness-to-pay threshold of $150,000/QALY, the probabilities that the combination therapy is considered to be cost-effective for Markov models 1, 2, 3, and 4 were 14.5%, 14.1%, 21.6%, and 17.0%, respectively. When using model averaging to synthesize different model structures, the resulting ICER was $389,270/QALY.* ***Conclusions.*** *Our study shows that modeling ABC with different Markov model structures yielded a wide range of cost-effectiveness results, suggesting the need to investigate structural uncertainty in health economic evaluation. When applied in the context of HER2-positive ABC treatment, the combination therapy with lapatinib is not cost-effective, regardless of which model was used and whether uncertainties were accounted for.* ***Key words:*** *Markov models; cost-effectiveness analysis; lapatinib; HER2-positive advanced breast cancer; simulation.* ***(Med Decis Making XXXX;XX:xx–xx)***

Received 17 May 2014 from the Department of Pharmacy Administration and Practice, Western University of Health Sciences, Pomona, CA, USA (QAL). There are no conflicts of interest and no financial support provided by any source for this study. Primary findings of this study were presented in part at the annual meeting of the Society for Medical Decision Making in Miami, Florida, 19 October 2014. Revision accepted for publication 24 November 2015.

Supplementary material for this article is available on the *Medical Decision Making* Web site at http://mdm.sagepub.com/supplemental.

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DOI: 10.1177/0272989X15622643

In economic evaluation, Markov models with discrete health states are common and one of the most powerful tools for assessing the cost-effectiveness of health interventions. They are especially useful in modeling progressive diseases with multiple health states over time.[1] In advanced breast cancer (ABC), also often referred to as metastatic breast cancer (MBC) or stage 4 breast cancer, the disease has spread beyond the breast and lymph nodes to distant organs. Patients with ABC can be treated with several therapy options to shrink the tumors (i.e., patients respond to treatment), prolong the spread of metastases, improve symptoms and quality of life, and/or extend survival; they are, however, unlikely to be cured from the disease.[2] Using a Markov approach to model ABC provides insight into the nature of optimal decisions that can aid treatment decisions in an uncertain environment. A Markov model for ABC represents a set of health states in which a patient is in before he/she eventually

dies. Nevertheless, the set of health states and assumptions of the immediate health state before a patient dies in Markov models for ABC vary among studies, thus contributing to the sources of uncertainty in modeling cost-effectiveness for ABC treatments.[3–22] There are inevitably many sources of uncertainty in decision modeling such as the choice of methodological approach used (e.g., Which decision-making perspective, time horizon, and discount rate are used? Which methodological approach is used to value health gains? What health outcomes are considered?), estimation of model parameters (e.g., What is the true value of each model parameter?), and model structures (e.g., What structural features and aspects should be incorporated to adequately represent and capture relevant characteristics of a disease and intervention being investigated?).[23–25] In economic evaluation studies, methodological and parameter uncertainties are often addressed by using a ''reference case'' and probabilistic sensitivity analyses, respectively.[23] However, structural uncertainty has received relatively little attention, although it is often a very important source of uncertainty in decision modeling.[23–29]

Given that there is a variation in the Markov model structure in modeling cost-effectiveness for ABC,[3–22] we aimed to examine the impact of structural uncertainty on overall cost-effectiveness results. The objectives of the current study were to identify the general and common Markov models used in modeling cost-effectiveness for ABC treatment and to examine the impact of using different Markov model structures on cost-effectiveness results in the context of a combination therapy of lapatinib (Tykerb; GlaxoSmithKline, Research Triangle Park, NC) and capecitabine (Xeloda; Genentech, South San Francisco, CA) for the treatment of HER2-positive ABC.

METHODS

General Markov Models for ABC

We searched on PubMed using the following search terms: (advanced breast cancer[Title/Abstract]) OR (metastatic breast cancer[Title/Abstract]) AND ((cost effectiveness[Title/Abstract]) OR (cost utility[Title/Abstract]) OR (analyses, cost [MeSH Terms])) AND (Markov[Title/Abstract]). We also searched Google Scholar and poster abstracts presented at annual conferences of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), Society for Medical Decision Making (SMDM), and American Society of Clinical Oncology (ASCO) for Markov models with discrete health states in cost-effectiveness studies of ABC or MBC up to January 9, 2014.

Four common and general Markov models for ABC/MBC were found. Markov model 1[3] has 4 health states (stable-disease, respond-to-therapy, disease-progressing, and death) with possibilities that death can occur in all health states (Figure 1). In the stable-disease health state, we denote $P_1(S\rightarrow S)$, $P_1(S\rightarrow R)$, $P_1(S\rightarrow P)$, and $P_1(S\rightarrow D)$ as the probabilities of having a stable disease (i.e., patients are stable without signs of disease progression, thus staying in the same stable-disease health state), responding to therapy (i.e., patients respond to therapy, thus moving to the respond-to-therapy health state), disease progression (i.e., the disease is progressive, and thus, patients move to the disease-progressing health state), and death, respectively. In the respond-to-therapy health state, $P_1(R\rightarrow R)$, $P_1(R\rightarrow P)$, and $P_1(R\rightarrow D)$ are the probabilities of continuing to respond to therapy (i.e., patients continue to respond to therapy, thus staying in the same respond-to-therapy health state), disease progression, and death, respectively. In the disease-progressing health state, $P_1(P\rightarrow P)$ and $P_1(P\rightarrow D)$ are denoted as the probabilities of continuing disease progression and death, respectively.

Markov model 2[4–9] also has 4 health states; however, a possibility of death can only occur in the disease-progressing health state (Figure 2). It should be noted that assumption of death not occurring from the stable-disease and respond-to-therapy health states in Markov model 2 might not be justified. However, there may be possible explanations for not modeling death from the stable-disease and respond-to-therapy health states: 1) no information reported from clinical trials, and thus, a certain assumption has to be made to estimate transition probabilities; 2) making the Markov model simple and easy to estimate transition probabilities; or 3) assuming the previously published Markov model structure was correct and applying the structure for one's own study. Similar to Markov model 1, we denote the sets of transition probabilities in the stable-disease health state as $P_2(S\rightarrow S)$, $P_2(S\rightarrow R)$, and $P_2(S\rightarrow P)$; in the respond-to-therapy health state as $P_2(R\rightarrow R)$ and $P_2(R\rightarrow P)$; and in the disease-progressing health state as $P_2(P\rightarrow P)$ and $P_2(P\rightarrow D)$.

In Markov models 3[10–17] and 4,[18–22] without specifically differentiating patients whose diseases are stable and those who respond to therapy, the stable-disease and respond-to-therapy health states are combined and represented as one stable-disease health state. As a result, they have 3 health states (stable-disease, disease-progressing, and death). The

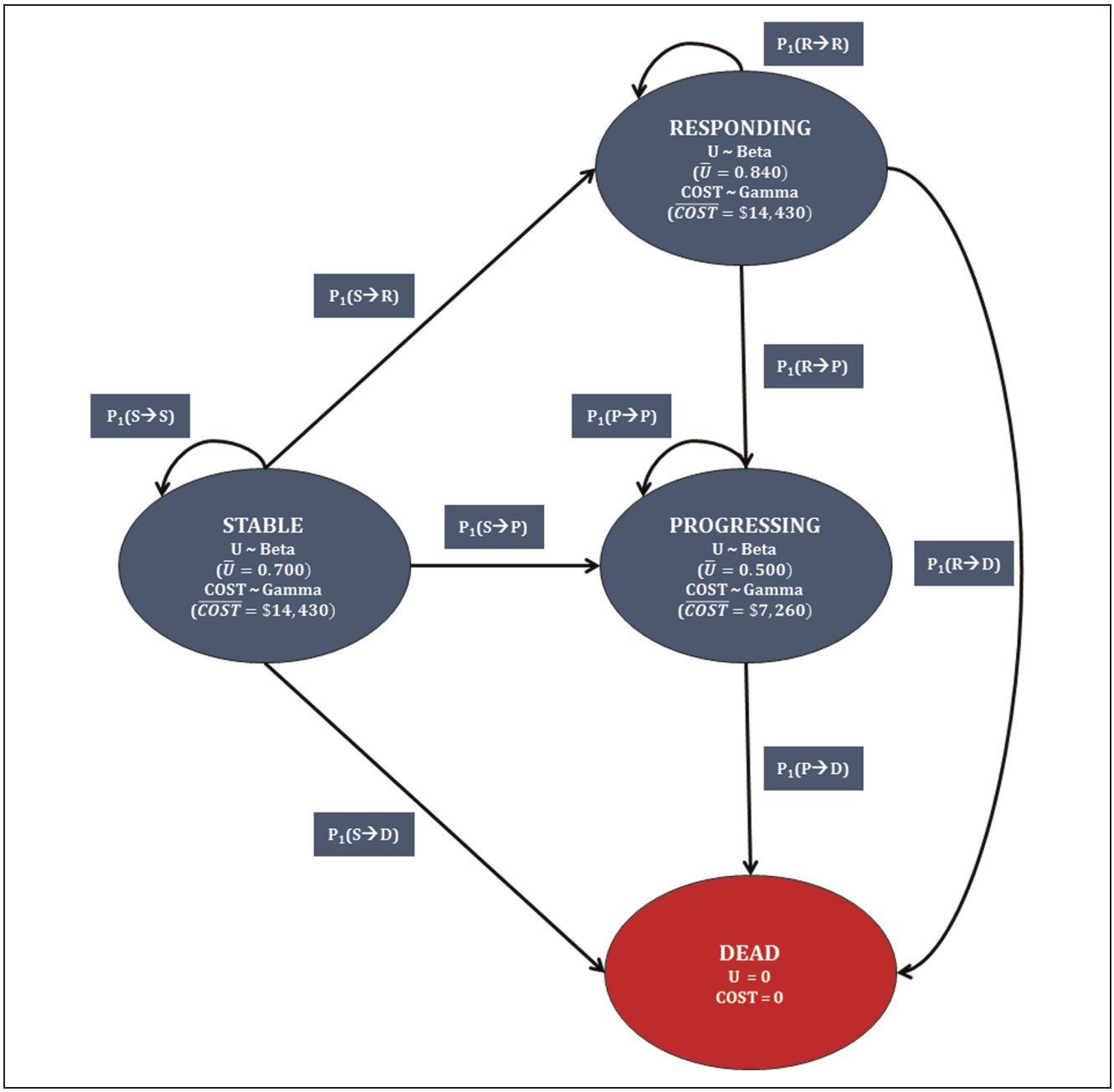

Figure 1 Markov model 1 with 4 health states.

only difference between Markov models 3 and 4 is that patients can potentially die in the stable-disease or disease-progressing health state in model 3, while a possibility of death can only occur in patients whose diseases are progressive in model 4. We denote the sets of transition probabilities in the stable-disease and disease-progressing health states for Markov model 3 as $P_3(S \rightarrow S)$, $P_3(S \rightarrow P)$, $P_3(S \rightarrow D)$ and $P_3(P \rightarrow P)$, $P_3(P \rightarrow D)$, respectively (Figure 3), and for Markov model 4 as $P_4(S \rightarrow S)$, $P_4(S \rightarrow P)$ and $P_4(P \rightarrow P)$, $P_4(P \rightarrow D)$, respectively (Figure 4).

We also found that several cost-effectiveness studies used Markov model structures that are different than the 4 general Markov models above. However,

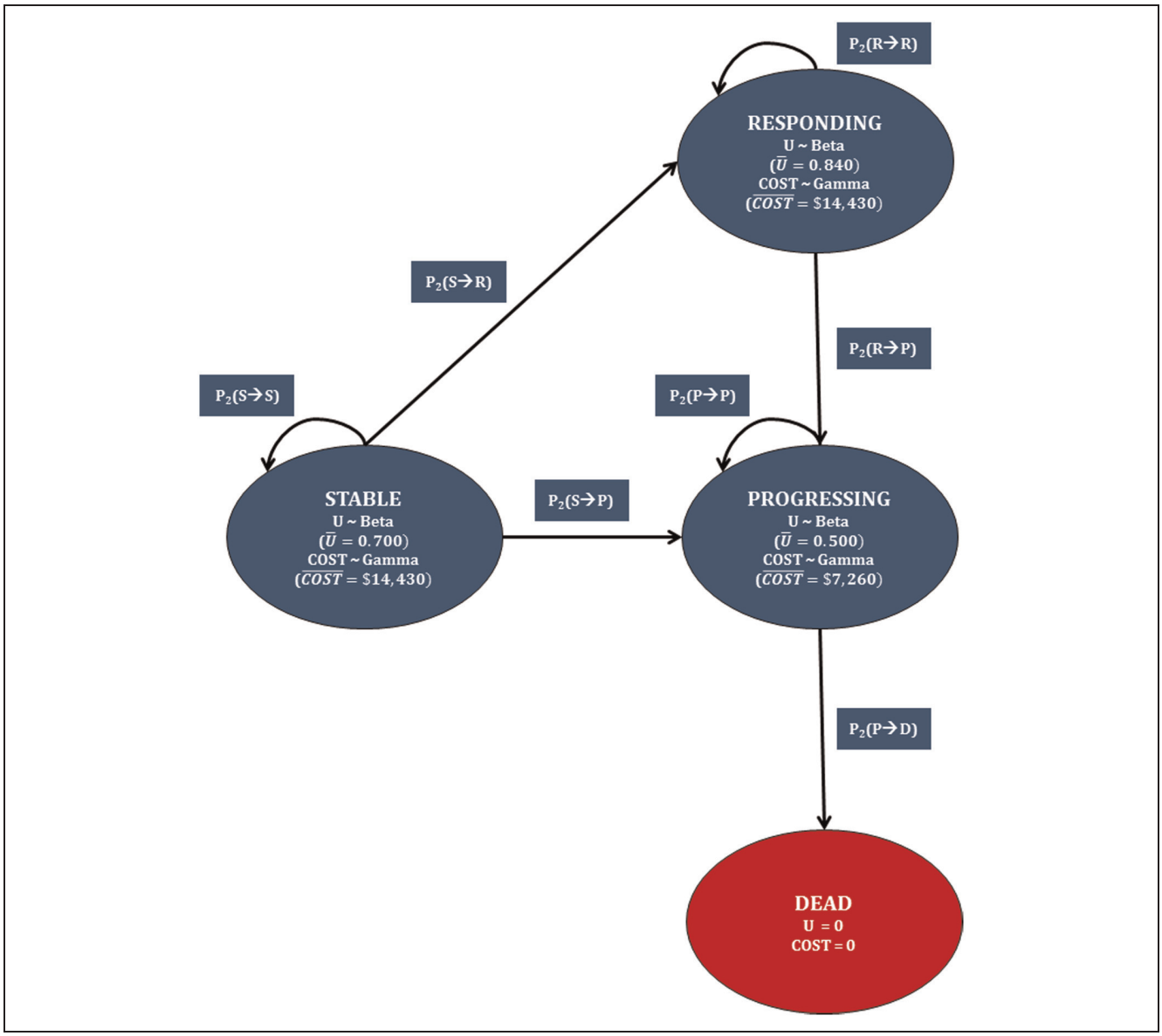

Figure 2 Markov model 2 with 4 health states.

we excluded them from our study because they provided unclear structures of Markov models[30] or their model structures included multiple lines of treatment that were developed specifically for hormonal therapies in postmenopausal patients with ABC.[31–37]

Estimating Transition Probabilities in the Markov Models

To estimate model transition probabilities, we applied the DEALE method[38–40] and the rule of ''collectively exhaustive events'' in a Markov model that requires the sum of all transition probabilities in a Markov health state to equal to one.[40] In the stable-disease health state, the monthly transition probabilities of disease progression were estimated using the same information in all 4 models, that is, median progression-free survival (PFS) obtained from relevant clinical trial(s):

$$P_1(S \to P) = P_2(S \to P) = P_3(S \to P) = P_4(S \to P) = 1 - e^{\left(-\left(-\frac{1}{PFS}\right)\times ln(1-0.5)\right)}.$$

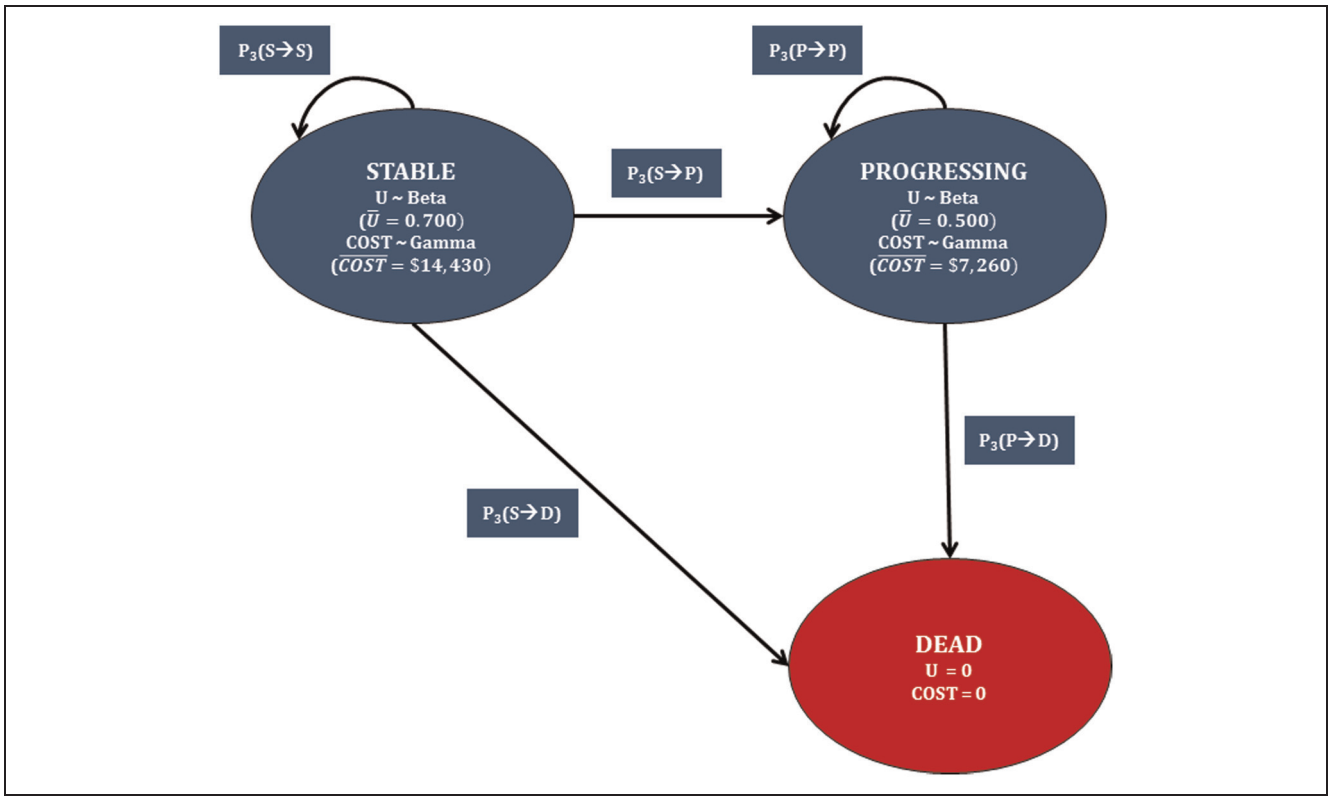

Figure 3 Markov model 3 with 3 health states.

In models 1 and 2, the monthly transition probabilities of responding to therapy could be estimated using the average overall response rate (ORR) and PFS reported from relevant clinical trial(s):

$$P_1(S \to R) = P_2(S \to R) = 1 - e^{\left(-\frac{ORR}{PFS}\right)}.$$

To estimate the monthly probability of death in the stable-disease health state in model 1, it was assumed that death rates were similar in both stable-disease and respond-to-therapy health states. Thus, it was estimated using the overall survival (OS) and PFS reported from relevant clinical trial(s):

$$P_1(S \to D) = P_1(R \to D) = 1 - e^{\left(\left(3\times\left(-\frac{1}{OS}\right)\times \ln(1-0.5) - \left(-\frac{1}{OS-PFS}\right)\times \ln(1-0.5)\right)/2\right)}.$$

Using the same information (PFS and OS) reported from the trial, the monthly transition probability of death in the stable-disease health state in model 3 was estimated as the following:

$$P_3(S \to D) = 1 - e^{\left(2\times\left(-\frac{1}{OS}\right)\times \ln(1-0.5) - \left(-\frac{1}{OS-PFS}\right)\times \ln(1-0.5)\right)}.$$

Also, applying the ''collectively exhaustive events'' rule, the monthly transition probabilities of continuing to be in a stable disease for models 1, 2, 3, and 4 were the following:

$$P_1(S \to S) = 1 - [P_1(S \to R) + P_1(S \to P) + P_1(S \to D)],$$

$$P_2(S \to S) = 1 - [(P_2(S \to R) + P_2(S \to P)],$$

$$P_3(S \to S) = 1 - [P_3(S \to P) + P_3(S \to D)], \text{and}$$

$$P_4(S \to S) = 1 - P_4(S \to P).$$

For models 1 and 2, in the respond-to-therapy health state, the monthly transition probabilities of disease progression were estimated using the median duration of response (DoR) obtained from relevant trial(s):

$$P_1(R \to P) = P_2(R \to P) = 1 - e^{\left(-\left(-\frac{1}{DoR}\right)\times ln(1-0.5)\right)}.$$

Also, the monthly transition probabilities of continuing to respond to therapy were the following:

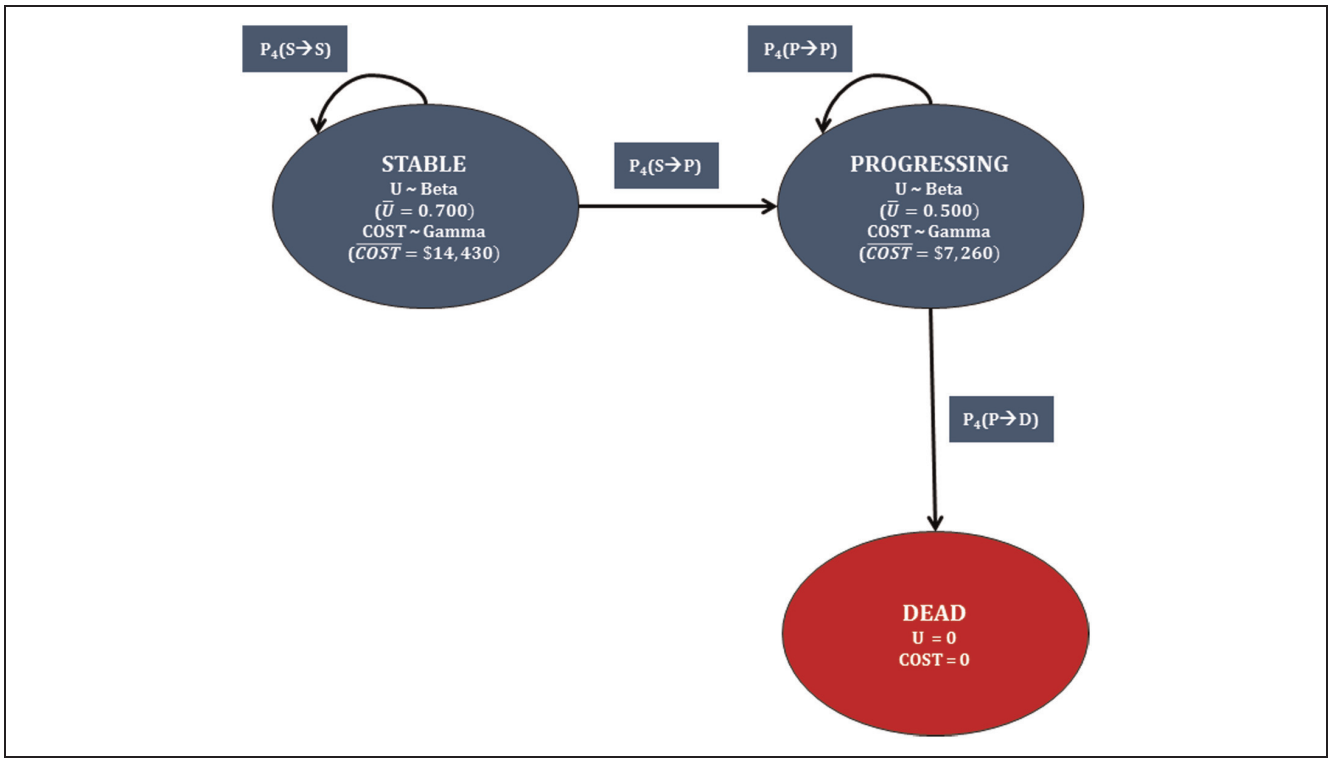

Figure 4 Markov model 4 with 3 health states.

$$P_1(R \rightarrow R) = 1 - [P_1(R \rightarrow D) + P_1(R \rightarrow P)], \text{ and}$$

$$P_2(R \rightarrow R) = 1 - P_2(R \rightarrow P).$$

In the disease-progressing health state, the monthly transition probabilities of death could be estimated using median PFS and OS reported from relevant clinical trial(s) in all 4 models:

$$P_1(P \rightarrow D) = P_2(P \rightarrow D) = P_3(P \rightarrow D)$$
$$= P_4(P \rightarrow D) = 1 - e^{\left(-\left(-\frac{1}{OS-PFS}\right)\times ln(1-0.5)\right)}.$$

Similarly, applying the ''collectively exhaustive events'' rule, the monthly transition probabilities of continuing to disease progression in all 4 models were the following:

$$P_1(P \rightarrow P) = P_2(P \rightarrow P) = P_3(P \rightarrow P)$$
$$= P_4(P \rightarrow P) = e^{\left(-\left(-\frac{1}{OS-PFS}\right)\times ln(1-0.5)\right)}.$$

Simulation Study of the Combination Therapy of Lapatinib and Capecitabine in HER2-Positive ABC

Overall, model transition probabilities were obtained by generating relevant information, that is, average ORR, median PFS, DoR, and OS generated within their 95% confidence intervals (CIs) reported from the lapatinib clinical trial[41,42] and based on the assumed beta or gamma distribution (Table 1).

For each ORR, PFS, DoR, and OS generated within its 95% CI from the assumed distribution, a sample was created containing 4 sets of transition probabilities, one for each Markov model. Applying the fundamental matrix solution[40] to each set of transition probabilities, the overall cost, total life years, and total quality-adjusted life years (QALYs) for each Markov model in each sample were estimated accordingly.

Table 1 summarizes the transition probabilities, adjusted average costs, and health utilities[6,9,43] in each Markov health state for all 4 models with a 1.5-month cycle length for the combination therapy of lapatinib and capecitabine in HER2-positive ABC from the US societal perspective. Major components of the total costs in the stable-disease and respond-to-therapy health states included the drug costs for lapatinib and capecitabine, average treatment costs for a cardiac event and a severe diarrhea episode, and other monitoring laboratory tests such as left ventricular ejection fraction, renal function, complete blood count, and liver function.[3] Markov models 3

Table 1 Transition Probabilities, Adjusted Average Costs, and Health Utilities in Each Health State for All 4 Markov Models with 1.5-Month Cycle Length

	Lapatinib + Capecitabine		Capecitabine Alone		
	Base Case	Range[a]	Base Case	Range[a]	Reference
Stable-disease health state					
Markov model 1					
$P_1(S\rightarrow P)$	0.153	0.115–0.171	0.226	0.201–0.287	41, 42
$P_1(S\rightarrow R)$	0.055	0.047–0.078	0.050	0.045–0.061	41, 42
$P_1(S\rightarrow D)$	0.043	0.032–0.049	0.054	0.048–0.072	Assumed[b]
$P_1(S\rightarrow S) = 1 - [P_1(S\rightarrow P) + P_1(S\rightarrow R) + P_1(S\rightarrow D)]$	0.749	0.733–0.801	0.670	0.596–0.690	40
Markov model 2					
$P_2(S\rightarrow P)$	0.153	0.115–0.171	0.226	0.201–0.287	41, 42
$P_2(S\rightarrow R)$	0.055	0.047–0.078	0.050	0.045–0.061	41, 42
$P_2(S\rightarrow S) = 1 - [P_2(S\rightarrow P) + P_2(S\rightarrow R)]$	0.792	0.782–0.833	0.724	0.668–0.738	40
Markov model 3					
$P_3(S\rightarrow P)$	0.153	0.115–0.171	0.226	0.201–0.287	41, 42
$P_3(S\rightarrow D)$	0.022	0.016–0.023	0.042	0.037–0.056	41, 42
$P_3(S\rightarrow S) = 1 - [P_3(S\rightarrow P) + P_3(S\rightarrow D)]$	0.825	0.806–0.869	0.732	0.657–0.762	40
Markov model 4					
$P_4(S\rightarrow P)$	0.153	0.115–0.171	0.226	0.201–0.287	41, 42
$P_3(S\rightarrow S) = 1 - P_3(S\rightarrow P)$	0.847	0.829–0.885	0.774	0.713–0.799	40
Estimated cost,[c] $	14,430	11,544–17,316	8414	6731–10,097	3
Health utility	0.70	0.50–0.80	0.70	0.50–0.80	6, 9, 43–45
Respond-to-therapy health state					
Markov model 1					
$P_1(R\rightarrow P)$	0.131	0.121–0.193	0.138	0.130–0.169	41, 42
$P_1(R\rightarrow D)$	0.043	0.032–0.049	0.054	0.048–0.072	Assumed[b]
$P_1(R\rightarrow R) = 1 - [P_1(R\rightarrow P) + P_1(R\rightarrow D)]$	0.826	0.758–0.847	0.808	0.759–0.822	40
Markov model 2					
$P_2(R\rightarrow P)$	0.131	0.121–0.193	0.138	0.130–0.169	41, 42
$P_1(R\rightarrow R) = 1 - P_1(R\rightarrow P)$	0.869	0.807–0.879	0.862	0.831–0.870	40
Estimated cost,[c] $	14,430	11,544–17,316	8414	6731–10,097	3
Health utility	0.84	0.57–0.93	0.84	0.57–0.93	6, 9, 43–45
Disease-progressing health state					
Markov models 1, 2, 3, and 4					
$P_1(P\rightarrow D) = P_2(P\rightarrow D) = P_3(P\rightarrow D) = P_4(P\rightarrow D)$	0.105	0.079–0.121	0.088	0.078–0.118	41, 42
$P_1(P\rightarrow P) = P_2(P\rightarrow P) = P_3(P\rightarrow P) = P_4(P\rightarrow P)$	0.895	0.879–0.921	0.912	0.882–0.922	40
Estimated cost,[c] $	7260	5808–8712	7606	6085–9127	3
Health utility	0.50	0.45–0.72	0.50	0.45–0.72	6, 9, 43–45

Note: $P(S\rightarrow R)$, probability of responding to therapy; $P(S\rightarrow P)$, probability of disease progression in the stable-disease health state; $P(S\rightarrow D)$, probability of death in the stable-disease health state; $P(S\rightarrow S)$, probability of having a stable disease; $P(R\rightarrow R)$, probability of continuing to respond to therapy; $P(R\rightarrow D)$, probability of death in the respond-to-therapy health state; $P(R\rightarrow P)$, probability of disease progression in the respond-to-therapy health state; $P(P\rightarrow D)$, probability of death in the disease-progressing health state; $P(P\rightarrow P)$, probability of continuing disease progression.

[a] Model transition probabilities were estimated by generating clinical data, that is, average overall response rate (varied in the assumed beta distribution), median progression-free survival (varied in the assumed gamma distribution), duration of response (varied in the assumed gamma distribution), and overall survival (varied in the assumed gamma distribution) within their 95% confidence intervals (CIs) reported from the lapatinib clinical trial.

[b] The death rates in the stable-disease and respond-to-therapy health states were assumed to be the same.

[c] The estimated cost in each health state was assumed to vary within ±20% of the average costs.

and 4 assumed no difference in cost and quality-of-life outcomes between the stable-disease and respond-to-therapy health states; therefore, they were collectively combined and represented as one stable-disease health state. It should be noted that previous studies showed that patients whose tumor responded to therapy had better quality of life than those whose tumor was stable and nonprogressing.[43–45] Nevertheless, it would be very difficult to quantify costs especially during the rather short period of time that the patient's tumor responds to therapy in ABC treatment. Instead, the overall cost

Table 2 Average Total Costs, Total QALYs, ICERs, and Probabilities of Being a Cost-effective Treatment

	Lapatinib + Capecitabine	Capecitabine Alone	ICER	Probability of Cost-effective Strategy for Combination Therapy
Markov model 1				
Total cost, $	132,796	98,671	495,800/QALY	14.5% at WTP of 150,000/QALY
Total QALY	0.984	0.916		
Markov model 2				
Total cost, $	170,807	125,418	447,308/QALY	14.1% at WTP of 150,000/QALY
Total QALY	1.271	1.170		
Markov model 3				
Total cost, $	149,588	102,108	303,909/QALY	21.6% at WTP of 150,000/QALY
Total QALY	1.088	0.932		
Markov model 4				
Total cost, $	168,659	121,189	390,216/QALY	17.0% at WTP of 150,000/QALY
Total QALY	1.228	1.106		
Model averaging				
Total cost, $	155,463	111,846	389,270/QALY	15.8% at WTP of 150,000/QALY
Total QALY	1.143	1.031		

Note: At the WTP threshold of $150,000/QALY of the combination therapy with lapatinib and capecitabine relative to capecitabine monotherapy in 4 Markov models and model averaging after 10,000 simulations. ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; WTP, willingness to pay.

during the PFS period, which collectively includes both stable-disease and respond-to-therapy health states, was typically estimated. Similar to the Le and Hay study,[3] we assumed that patients whose diseases are progressive were treated with third-line therapy; thus, the average cost in the disease-progressing health state was estimated from the study by McLachlan and others.[46] In the current study, we updated the current 2013 wholesale acquisition costs for lapatinib ($31.3 per 250-mg tablet) and capecitabine ($33.2 per 500-mg tablet)[47] and adjusted other costs to 2013 US dollars using the Consumer Price Index–Medical Care component[48] (Table 3 in the Appendix).

We generated 10,000 samples for each model. To account for uncertainty in modeling cost-effectiveness for ABC treatment, model averaging was used to estimate overall cost-effectiveness results by taking the means of total costs and QALYs of the 4 models from the simulated samples, assuming equal weights in all models. We presented model uncertainty using the cost-effectiveness acceptability curves for each model as well as the overall model. All simulations and analyses were performed with the statistical software package R version 3.20 (Appendix).[49]

RESULTS

Table 2 reports the average total costs, QALYs, incremental cost-effectiveness ratios (ICERs), and probabilities at which the combination therapy with lapatinib is considered a cost-effective strategy at the willingness-to-pay threshold of $150,000/QALY for 4 Markov models and the model averaging result after simulated 10,000 samples.

Markov model 3 yielded the lowest ICER ($303,909/QALY) for the combination therapy, while model 1 produced the highest ICER of $495,800/QALY. Figure 5 shows the cost-effectiveness acceptability curves for all models, where the x-axis represented the theoretical amounts in terms of dollars that society is willing to pay to gain one QALY, and the y-axis indicated the probabilities that the combination therapy of lapatinib and capecitabine are cost-effective, corresponding to the willingness-to-pay thresholds chosen. At a willingness-to-pay threshold of $150,000/QALY, the probabilities that the combination therapy is considered to be cost-effective for Markov models 1, 2, 3, and 4 were 14.5%, 14.1%, 21.6%, and 17.0%, respectively. When using model averaging to synthesize structural uncertainty with an assumption of equal weights in all 4 models, the resulting ICER was $389,270/QALY with a 15.8% probability that the combination therapy is cost-effective.

DISCUSSION

Whether due to a lack of available information, a reduction of overall model complexity, or models

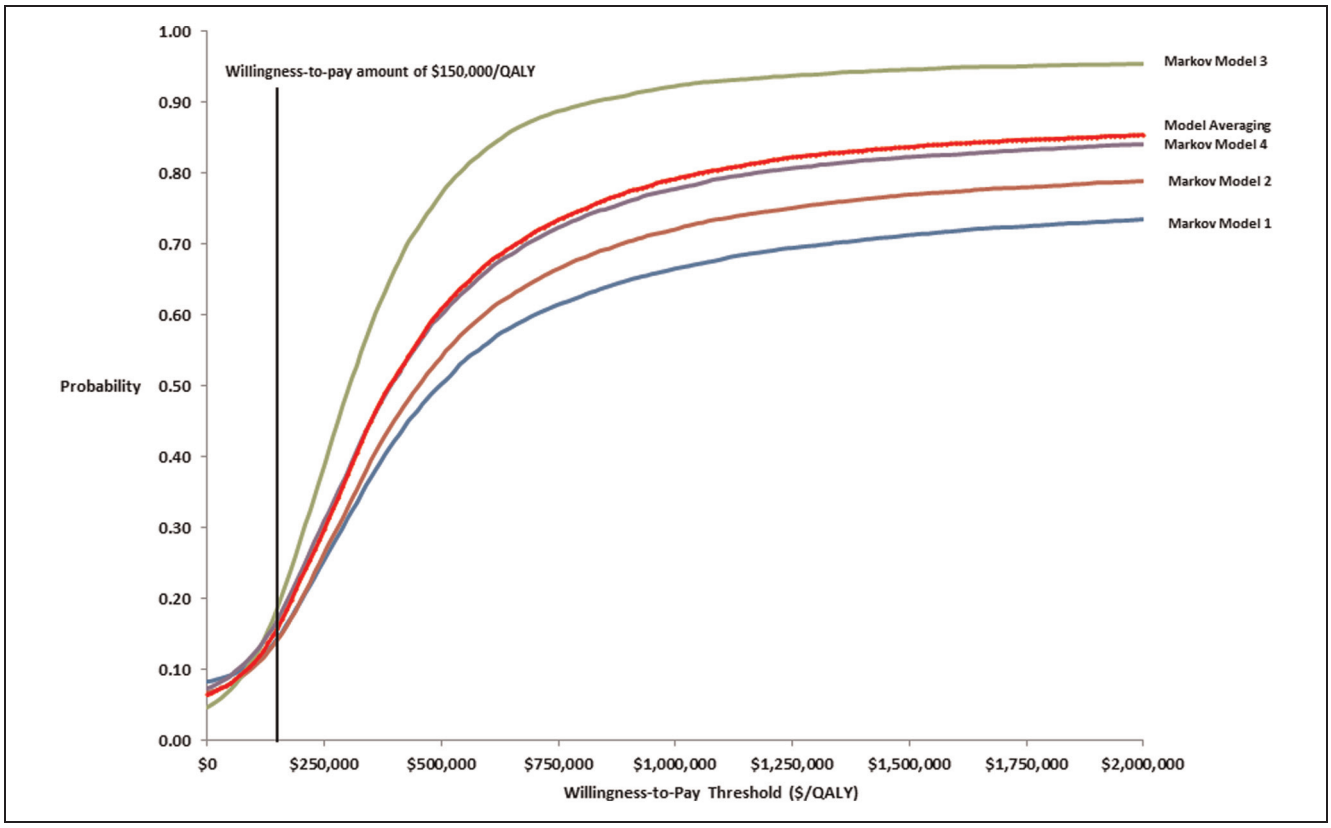

Figure 5 Cost-effectiveness acceptability curves for all models.

developed for specific diseases/treatments, there have been a number of different Markov models in modeling cost-effectiveness for ABC. Our study was motivated by the question of how structural uncertainty of Markov models in modeling ABC, that is, using Markov models with different sets of health states and assumptions, would impact overall cost-effectiveness results. In the current study, we identified 4 common Markov models from a literature search and examined their results in the context of a combination therapy of lapatinib and capecitabine for HER2-positive ABC using a simulation approach.

The major difference between the 4–health state Markov models (models 1 and 2) and 3–health state Markov models (models 3 and 4) is to distinguish patients who respond to therapy and those whose tumors are not classified as responding but are stable and nonprogressive. Thus, factors that influence outcomes of the respond-to-therapy health state in models 1 and 2 such as the ORR, DoR, and health utility value would impact their overall cost-effectiveness results. These factors were captured when we performed the overall simulation in our study.

The variation in model structures for ABC presented in the current study was associated with cost-effectiveness results varying between $303,909/QALY and $495,800/QALY. In other words, using a different model structure, that is, Markov model 1 instead of model 3, would result in increasing 63% of the ICER. When accounting for structural uncertainty using the model averaging method and assuming equal weights in all models, the resulting ICER was $389,270/QALY. The range of ICERs for the combination therapy with lapatinib in ABC from our analysis was very high and exceeded commonly accepted willingness-to-pay thresholds in oncology; thus, it would be unlikely to make an impact on the reimbursement decision. Nevertheless, this is a unique case where the combination therapy with lapatinib for HER2-positive ABC was a very expensive biologic, and even though it prolonged the PFS period, it did not extend OS. It would be more relevant for the reimbursement decision in cases where new anticancer drugs show significant extension in OS and are expensively priced. Moreover, in our analysis, we accounted for both parameter and structural uncertainty; thus,

the true impact of structural uncertainty on cost-effectiveness results might have been substantially clouded by the inclusion of parameter uncertainty.[50]

In the current study, it was noted that when modeling cost-effectiveness for ABC with 4 health states (Markov models 1 and 2), the resulting ICERs appeared to be close and higher than modeling it with 3 health states (Markov models 3 and 4). It is possible that the similarity of health states within the model structure, that is, either a 3–health state model or a 4–health state model, was related to less variation in their cost-effectiveness results. On another note, our simulations showed that Markov models 2 and 4 yielded both the highest average total costs and total QALYs. It might result from the delay of death, that is, patients could not die until their disease progressed, in addition to the higher costs and utility values for the response-to-therapy and stable-disease health states as compared to the disease-progressing health state; thus, more costs and QALYs were accumulated in these models than in models 1 and 3.

For our analysis, we applied the model averaging method with an assumption of equal weights in all 4 models to address structural uncertainty in the Markov model for ABC. However, it would be possible that the 4 model structures are also presented a choice between alternative and plausible values for new uncertain parameters; thus, structural uncertainty could be then parameterized.[51] Specifically, 2 uncertain parameters could be added to the overall ABC model: 1) whether patients with ABC who respond to therapy would have better outcomes as compared to those whose disease is stable and not progressing, even though they do not respond to therapy; and 2) whether patients could die due to the disease before their disease progresses. The prior distributions of these uncertain parameters might be obtained from evidence of previous studies or expert belief if available. In addition, structural uncertainty of the ABC model might be further accounted for. In our model, we only varied the cost after disease progression that was based on the assumption that all patients received additional third-line therapy. However, further possible scenarios in which the survival time after disease progression might or might not be improved in patients who received additional third-line therapy as compared to those who only received supportive care could be considered as an additional source of structural uncertainty in the ABC model.

In conclusion, the current study examined the impact of structural uncertainty of Markov models in modeling cost-effectiveness for the treatment of ABC. Overall, our simulation study of the combination therapy with lapatinib showed that Markov models with different sets of health states and assumptions produced a wide range of cost-effectiveness results. Compared to commonly accepted willingness-to-pay thresholds in oncology, the addition of lapatinib to capecitabine was clearly not cost-effective in all models. Although no reverse in the cost-effectiveness decision was observed due to the high costs in the combination therapy and its limited efficacy, our study demonstrated the importance of accounting for structural uncertainty and further suggests the need to investigate structural uncertainty in health economic evaluation.

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Appendix Table 3. Costs adjusted to 2013 U.S. Dollars.

	Adjust Cost in 2013*	Source
Cost of 250-mg Lapatinib per Tablet	$31.3	[1]
Cost of 500-mg Capecitabine per Tablet	$33.2	1]
Average Cost per Severe Diarrhea Event	$7,363	[3, 4]
Average Monthly Cost in Central Nervous System (CNS) Metastases	$10,490	[5]
Average Cost per Cardiotoxicity Event	$1,979	[6]
Average Monthly Cost after Disease Progression (Third-line Therapy)	$4,725	[2]
Average Monthly Cost after Disease Progression (Supportive and Terminal Care)	$1,143	[7]
Average Hourly Pay	$22.0	[8]

*Current costs in 2013. Previous costs were adjusted to 2013 U.S. dollars using Consumer Price Index – Medical Care.

 # DATA GENERATION PROCESS USING R PROGRAMMING LANGUAGE (VERSION 3.2.0):

```
DATAGEN <- function(i)
{
# Generating data from the clinical trial for the combination therapy of Lapatinib and Capecitabine:
ORR <- rbeta(1, 102.833, 328.333)                  # Generate Overall Response Rate (ORR) of 23.7% within its 95% CI (18.0% - 30.3%) from the assumed Beta distribution
PFS <- rgamma(1, shape = 174.31, scale = 0.03737)  # Generate Progression-Free Survival (PFS) of 6.25 months within its 95% CI (5.56 - 8.52 months) from the assumed Gamma distribution
OS <- rgamma(1, shape = 165.7784, scale = 0.09773) # Generate the Overall Survival (OS) of 15.62 months within its 95% CI between 13.59 months and 21.14 months from the assumed Gamma distribution
PPS <- OS - PFS                                    # PPS = Post Progression Survival, i.e. survival after disease progression
DoR <- rgamma(1, shape = 174.37, scale = 0.04064)  # Generate the Duration of Response (DoR) of 7.40 months within its 95% CI between 4.85 months and 8.07 months from the assumed Gamma distribution
# Generating transition probabilities based on data from the clinical trial for the combination therapy of Lapatinib and Capecitabine:
pSR <- 1 - exp(-1.5*ORR/PFS)                       # Probability from Stable to Responding state
pSP <- 1 - exp(-(1.5*(-1/PFS)*log(1 - 0.5)))       # Probability from Stable to Progressing state
rD <- 1.5*(-1/OS)*log(1 - 0.5)                     # 1.5 Monthly average Overall Death Rate
rPD <- 1.5*(-1/PPS)*log(1 - 0.5)                   # 1.5 Monthly Death Rate in the Progressing state
rSD <- (3*rD - rPD)/2                              # Overall Death Rate is the average death rates in the Stable, Responding and Progressing States assuming death rate is the same in Stable and Responding states
pSD <- 1 - exp(-rSD)                               # Probability from Stable to Dead
pRP <- 1 - exp(-(1.5*(-1/DoR)*log(1 - 0.5)))       # Probability from Responding to Progressing state
pPD <- 1 - exp(-(1.5*(-1/PPS)*log(1 - 0.5)))       # Probability from Progressing to Dead

# Generating data from the clinical trial for for the monotherapy (m) with capecitabine alone:
ORR_m <- rbeta(1, 61.339, 373.689)                 # Generate the Overall Response Rate (ORR) of 13.9% within its 95% CI between 9.5% and 19.5% from the assumed Beta distribution
PFS_m <- rgamma(1, shape = 232.708, scale = 0.01715) # Generate the Progression-Free Survival (PFS) of 4.06 months within its 95% CI between 3.07 months and 4.64 months from the assumed Gamma distribution
OS_m <- rgamma(1, shape = 227.112, scale = 0.06613) # Generate the Overall Survival (OS) of 15.37 months within its 95% CI between 11.33 months and 17.31 months from the assumed Gamma distribution
PPS_m <- OS_m - PFS_m                              # PPS = Post Progression Survival, i.e. survival after disease progression
DoR_m <- rgamma(1, shape = 497.968, scale = 0.01374) # Generate the Duration of Response (DoR) of 7.00 months within its 95% CI between 5.60 months and 7.45 months from the assumed Gamma distribution
# Generating transition probabilities based on data from the clinical trial for the monotherapy (m) with capecitabine alone:
pSR_m <- 1 - exp(-1.5*ORR_m/PFS_m)                 # Probability from Stable to Responding state
pSP_m <- 1 - exp(-(1.5*(-1/PFS_m))*log(1 - 0.5))   # Probability from Stable to Progressing state
rD_m <- 1.5*(-1/OS_m)*log(1 - 0.5)                 # 1.5 Monthly average Overall Death Rate
rPD_m <- 1.5*(-1/PPS_m)*log(1 - 0.5)               # 1.5 Monthly Death Rate in the Progressing state
rSD_m <- (3*rD_m - rPD_m)/2                        # Overall Death Rate is the average death rates in the Stable, Responding and Progressing States assuming death rate is the same in Stable and Responding states
```

```
pSD_m <- 1 - exp(-rSD_m)                          # Probability from Stable to Dead
pRP_m <- 1 - exp(-(1.5*(-1/DoR_m)*log(1 - 0.5)))  # Probability from Responding to Progressing state
pPD_m <- 1 - exp(-(1.5*(-1/PPS_m)*log(1 - 0.5)))  # Probability from Progressing to Dead

# Transition probabilities of MODEL 1 for the combination therapy of Lapatinib and Capecitabine:
## In Stable Health-State:
pSR_1 <- pSR                                      # Probability from Stable to Responding state
pSP_1 <- pSP                                      # Probability from Stable to Progressing state
pSD_1 <- pSD                                      # Probability from Stable to Dead
pSS_1 <- 1 - (pSR_1 + pSP_1 + pSD_1)              # Probability of staying in the same Stable state
## In Respond-to-Therapy Health-State:
pRP_1 <- pRP                                      # Probability from Responding to Progressing state
pRD_1 <- pSD                                      # Probability from Responding to Dead assumed to be the same as in the Stable state
pRR_1 <- 1 - (pRP_1 + pRD_1)                      # Probability of staying in the same Responding state
## In Disease-Progression Health State:
pPD_1 <- pPD                                      # Probability from Progressing to Dead
pPP_1 <- 1 - pPD_1                                # Probability of staying in the same Progressing state

# Transition probabilities of MODEL 1 for the monotherapy (m) with capecitabine alone:
## In Stable Health-State:
pSR_1_m <- pSR_m                                  # Probability from Stable to Responding state
pSP_1_m <- pSP_m                                  # Probability from Stable to Progressing state
pSD_1_m <- pSD_m                                  # Probability from Stable to Dead
pSS_1_m <- 1 - (pSR_1_m + pSP_1_m + pSD_1_m)      # Probability of staying in the same Stable state
## In Respond-to-Therapy Health-State:
pRP_1_m <- pRP_m                                  # Probability from Responding to Progressing state
pRD_1_m <- pSD_m                                  # Probability from Responding to Dead assumed to be the same as in the Stable state
pRR_1_m <- 1 - (pRP_1_m + pRD_1_m)                # Probability of staying in the same Responding state
## In Disease-Progression Health State:
pPD_1_m <- pPD_m                                  # Probability from Progressing to Dead
pPP_1_m <- 1 - pPD_1_m                            # Probability of staying in the same Progressing state

# Transition Probabilities of MODEL 2 for the combination therapy of L+C:
pSR_2 <- pSR
pSP_2 <- pSP
pSS_2 <- 1 - (pSR_2 + pSP_2)
pRP_2 <- pRP
pRR_2 <- (1 - pRP_2)
pPD_2 <- pPD
pPP_2 <- 1 - pPD_2
```

```
# Transition Probabilities of MODEL 2 for the monotherapy (m) with C:
pSR_2_m <- pSR_m
pSP_2_m <- pSP_m
pSS_2_m <- 1 - (pSR_2_m + pSP_2_m)
pRP_2_m <- pRP_m
pRR_2_m <- (1 - pRP_2_m)
pPD_2_m <- pPD_m
pPP_2_m <- 1 - pPD_2_m

# Transition Probabilities of MODEL 3 for the combination therapy of L+C:
pSP_3 <- pSP
pSD_3 <- 1 - exp(-(2*rD - rPD))          # Overall Death Rate is the average death rates in the Stable and Progressing States
pSS_3 <- 1 - (pSP_3 + pSD_3)
pPD_3 <- pPD
pPP_3 <- 1 - pPD_3

# Transition Probabilities of MODEL 3 for the monotherapy (m) with C:
pSP_3_m <- pSP_m
pSD_3_m <- 1 - exp(-(2*rD_m - rPD_m))    # Overall Death Rate is the average death rates in the Stable and Progressing States
pSS_3_m <- 1 - (pSP_3_m + pSD_3_m)
pPD_3_m <- pPD_m
pPP_3_m <- 1 - pPD_3_m

# Transition Probabilities of MODEL 4 for the combination therapy of L+C:
pSP_4 <- pSP
pSS_4 <- (1 - pSP_4)
pPD_4 <- pPD
pPP_4 <- 1 - pPD_4

# Transition Probabilities of MODEL 4 for the monotherapy (m) with C:
pSP_4_m <- pSP_m
pSS_4_m <- (1 - pSP_4_m)
pPD_4_m <- pPD_m
pPP_4_m <- 1 -     pPD_4_m

# Generating Health Utilities in the 3 health states with BETA distribution:
Utility_S <- rbeta(1, 58.5, 27.1)        # assumed base-case health utility for the stable state of 0.70 ranging from 0.50 to 0.80
Utility_R <- rbeta(1, 33.8, 7.9)         # assumed base-case health utility for the responding state of 0.84 ranging from 0.57 to 0.93
Utility_P <- rbeta(1, 64.5, 57.6)        # assumed base-case health utility for the disease-progressing state of 0.50 ranging from 0.45 to 0.72
```

```
# Generating estimated mean costs for the 3 health states (Stable, Responding, and Progressing) with GAMMA distribution for the combination therapy L+C:
TotalCost_S <- rgamma(1, shape = 25, scale = 577.2)        # estimated cost in Stable state (SD) = $14,430 ($2,886) [original cost = $6,208.17]
TotalCost_R <- rgamma(1, shape = 25, scale = 577.2)        # estimated cost in Responding state (SD) = $14,430 ($2,886) [original cost = $6,208.17]
TotalCost_P <- rgamma(1, shape = 25, scale = 290.4)        # estimated cost in Progressing state (SD) = $7,260 ($1,452) [original cost = $5,426.36]

# Generating estimated mean costs for the 3 health states (Stable, Responding, and Progressing) with GAMMA distribution for the monotherapy (m) with C:
TotalCost_S_m <- rgamma(1, shape = 25, scale = 336.56)     # estimated cost in Stable state (SD) = $8,414 ($1,683) [original cost = $1,275.46]
TotalCost_R_m <- rgamma(1, shape = 25, scale = 336.56)     # estimated cost in Responding state (SD) = $8,414 ($1,683) [original cost = $1,275.46]
TotalCost_P_m <- rgamma(1, shape = 25, scale = 304.24)     # estimated cost in Progressing state (SD) = $7,606 ($1,521) [original cost = $5,713.20]

MatrixI_2 <- diag(2)                                       # Creating 2x2 Identity Matrix I
MatrixI_3 <- diag(3)                                       # Creating 3x3 identity matrix I

# Creating Matrix Q for MODELS 1, 2, 3, and 4 for the combination therapy of L+C:
MatrixQ_1 <- matrix(c(pSS_1, pSR_1, pSP_1, 0, pRR_1, pRP_1, 0, 0, pPP_1), ncol = 3, byrow = TRUE)
MatrixQ_2 <- matrix(c(pSS_2, pSR_2, pSP_2, 0, pRR_2, pRP_2, 0, 0, pPP_2), ncol = 3, byrow = TRUE)
MatrixQ_3 <- matrix(c(pSS_3, pSP_3, 0, pPP_3), ncol = 2, byrow =TRUE)
MatrixQ_4 <- matrix(c(pSS_4, pSP_4, 0, pPP_4), ncol = 2, byrow =TRUE)

# Creating Matrix Q for MODELS 1, 2, 3, and 4 for the monotheapy (m) with C:
MatrixQ_1_m <- matrix(c(pSS_1_m, pSR_1_m, pSP_1_m, 0, pRR_1_m, pRP_1_m, 0, 0, pPP_1_m), ncol = 3, byrow = TRUE)
MatrixQ_2_m <- matrix(c(pSS_2_m, pSR_2_m, pSP_2_m, 0, pRR_2_m, pRP_2_m, 0, 0, pPP_2_m), ncol = 3, byrow = TRUE)
MatrixQ_3_m <- matrix(c(pSS_3_m, pSP_3_m, 0, pPP_3_m), ncol = 2, byrow =TRUE)
MatrixQ_4_m <- matrix(c(pSS_4_m, pSP_4_m, 0, pPP_4_m), ncol = 2, byrow =TRUE)

# Creating Matrix N = (I - Q)^1 for MODELS 1, 2, 3, and 4 for the combination therapy of L+C:
MatrixN_1 <- solve(MatrixI_3 - MatrixQ_1)
MatrixN_2 <- solve(MatrixI_3 - MatrixQ_2)
MatrixN_3 <- solve(MatrixI_2 - MatrixQ_3)
MatrixN_4 <- solve(MatrixI_2 - MatrixQ_4)

# Creating Matrix N = (I - Q)^1 for MODELS 1, 2, 3, and 4 for the monotherapy (m) with C:
MatrixN_1_m <- solve(MatrixI_3 - MatrixQ_1_m)
MatrixN_2_m <- solve(MatrixI_3 - MatrixQ_2_m)
MatrixN_3_m <- solve(MatrixI_2 - MatrixQ_3_m)
MatrixN_4_m <- solve(MatrixI_2 - MatrixQ_4_m)

# Converting number of cycles to number of years for each health state and life expectancy in MODEL 1 for the combination therapy of L+C:
cSTABLE_1 <- MatrixN_1[1, 1]                               # number of cycles in Stable state
ySTABLE_1 <- cSTABLE_1*1.5/12                              # number of years in Stable state (each cycle lasts 1.5 months)
cRESPONDING_1 <- MatrixN_1[1, 2]                           # number of cycles in Responding state
yRESPONDING_1 <- cRESPONDING_1*1.5/12                      # number of years in Responding state (each cycle lasts 1.5 months)
```

```
cPROGRESSING_1 <- MatrixN_1[1, 3]                    # number of cycles in Progressing state
yPROGRESSING_1 <- cPROGRESSING_1*1.5/12              # number of years in Progressing state (each cycle lasts 1.5 months)

LifeYears_1 <- ySTABLE_1 + yRESPONDING_1 + yPROGRESSING_1
QALY_1 <- (ySTABLE_1*Utility_S) + (yRESPONDING_1*Utility_R) + (yPROGRESSING_1*Utility_P)          # Total QALYs
TOTALCOST_1 <- (cSTABLE_1*TotalCost_S) + (cRESPONDING_1*TotalCost_R) + (cPROGRESSING_1*TotalCost_P)          # Total Cost

# Converting number of cycles to number of years for each health state and life expectancy in MODEL 1 for the monotherapy (m) with C:
cSTABLE_1_m <- MatrixN_1_m[1, 1]
ySTABLE_1_m <- cSTABLE_1_m*1.5/12

cRESPONDING_1_m <- MatrixN_1_m[1, 2]
yRESPONDING_1_m <- cRESPONDING_1_m*1.5/12

cPROGRESSING_1_m <- MatrixN_1_m[1, 3]
yPROGRESSING_1_m <- cPROGRESSING_1_m*1.5/12

LifeYears_1_m <- ySTABLE_1_m + yRESPONDING_1_m + yPROGRESSING_1_m
QALY_1_m <- (ySTABLE_1_m*Utility_S) + (yRESPONDING_1_m*Utility_R) + (yPROGRESSING_1_m*Utility_P)
TOTALCOST_1_m <- (cSTABLE_1_m*TotalCost_S_m) + (cRESPONDING_1_m*TotalCost_R_m) + (cPROGRESSING_1_m*TotalCost_P_m)

# Incremental TOTALCOST and QALY for MODEL 1:
dQALY_1 <- QALY_1 - QALY_1_m
dTOTALCOST_1 <- TOTALCOST_1 - TOTALCOST_1_m

# Converting number of cycles to number of years for each health state and life expectancy in MODEL 2 for the combination therapy of L+C:
cSTABLE_2 <- MatrixN_2[1, 1]
ySTABLE_2 <- cSTABLE_2*1.5/12

cRESPONDING_2 <- MatrixN_2[1, 2]
yRESPONDING_2 <- cRESPONDING_2*1.5/12

cPROGRESSING_2 <- MatrixN_2[1, 3]
yPROGRESSING_2 <- cPROGRESSING_2*1.5/12

LifeYears_2 <- ySTABLE_2 + yRESPONDING_2 + yPROGRESSING_2
QALY_2 <- (ySTABLE_2*Utility_S) + (yRESPONDING_2*Utility_R) + (yPROGRESSING_2*Utility_P)
TOTALCOST_2 <- (cSTABLE_2*TotalCost_S) + (cRESPONDING_2*TotalCost_R) + (cPROGRESSING_2*TotalCost_P)
```

 # Converting number of cycles to number of years for each health state and life expectancy in MODEL 2 for the monotherapy (m) with C:

```
cSTABLE_2_m <- MatrixN_2_m[1, 1]
ySTABLE_2_m <- cSTABLE_2_m*1.5/12

cRESPONDING_2_m <- MatrixN_2_m[1, 2]
yRESPONDING_2_m <- cRESPONDING_2_m*1.5/12

cPROGRESSING_2_m <- MatrixN_2_m[1, 3]
yPROGRESSING_2_m <- cPROGRESSING_2_m*1.5/12

LifeYears_2_m <- ySTABLE_2_m + yRESPONDING_2_m + yPROGRESSING_2_m
QALY_2_m <- (ySTABLE_2_m*Utility_S) + (yRESPONDING_2_m*Utility_R) + (yPROGRESSING_2_m*Utility_P)
TOTALCOST_2_m <- (cSTABLE_2_m*TotalCost_S_m) + (cRESPONDING_2_m*TotalCost_R_m) + (cPROGRESSING_2_m*TotalCost_P_m)
```

 # Incremental TOTALCOST and QALY for MODEL 2:

```
dQALY_2 <- QALY_2 - QALY_2_m
dTOTALCOST_2 <- TOTALCOST_2 - TOTALCOST_2_m
```

 # Converting number of cycles to number of years for each health state and life expectancy in MODEL 3 for the combination therapy of L+C:

```
cSTABLE_3 <- MatrixN_3[1, 1]
ySTABLE_3 <- cSTABLE_3*1.5/12

cPROGRESSING_3 <- MatrixN_3[1, 2]
yPROGRESSING_3 <- cPROGRESSING_3*1.5/12

LifeYears_3 <- ySTABLE_3 + yPROGRESSING_3
QALY_3 <- (ySTABLE_3 *Utility_S) + (yPROGRESSING_3 *Utility_P)
TOTALCOST_3 <- (cSTABLE_3*TotalCost_S) + (cPROGRESSING_3*TotalCost_P)
```

 # Converting number of cycles to number of years for each health state and life expectancy in MODEL 3 for the monotherapy (m) with C:

```
cSTABLE_3_m <- MatrixN_3_m[1, 1]
ySTABLE_3_m <- cSTABLE_3_m*1.5/12

cPROGRESSING_3_m <- MatrixN_3_m[1, 2]
yPROGRESSING_3_m <- cPROGRESSING_3_m*1.5/12

LifeYears_3_m <- ySTABLE_3_m + yPROGRESSING_3_m
QALY_3_m <- (ySTABLE_3_m*Utility_S) + (yPROGRESSING_3_m*Utility_P)
TOTALCOST_3_m <- (cSTABLE_3_m*TotalCost_S_m) + (cPROGRESSING_3_m*TotalCost_P_m)
```

```
# Incremental TOTALCOST and QALY for MODEL 3:
dQALY_3 <- QALY_3 - QALY_3_m
dTOTALCOST_3 <- TOTALCOST_3 - TOTALCOST_3_m

# Converting number of cycles to number of years for each health state and life expectancy in MODEL 4 for the combination therapy of L+C:
cSTABLE_4 <- MatrixN_4[1, 1]
ySTABLE_4 <- cSTABLE_4*1.5/12

cPROGRESSING_4 <- MatrixN_4[1, 2]
yPROGRESSING_4 <- cPROGRESSING_4*1.5/12

LifeYears_4 <- ySTABLE_4 + yPROGRESSING_4
QALY_4 <- (ySTABLE_4*Utility_S) + (yPROGRESSING_4*Utility_P)
TOTALCOST_4 <- (cSTABLE_4*TotalCost_S) + (cPROGRESSING_4*TotalCost_P)

# Converting number of cycles to number of years for each health state and life expectancy in MODEL 4 for the monotherapy (m) with C:
cSTABLE_4_m <- MatrixN_4_m [1, 1]
ySTABLE_4_m  <- cSTABLE_4_m *1.5/12

cPROGRESSING_4_m  <- MatrixN_4_m [1, 2]
yPROGRESSING_4_m  <- cPROGRESSING_4_m *1.5/12

LifeYears_4_m  <- ySTABLE_4_m + yPROGRESSING_4_m
QALY_4_m <- (ySTABLE_4_m*Utility_S) + (yPROGRESSING_4_m*Utility_P)
TOTALCOST_4_m <- (cSTABLE_4_m*TotalCost_S_m) + (cPROGRESSING_4_m*TotalCost_P_m)

# Incremental TOTALCOST and QALY for the MODEL 4:
dQALY_4 <- QALY_4 - QALY_4_m
dTOTALCOST_4 <- TOTALCOST_4 - TOTALCOST_4_m

sample <- data.frame(Utility_S, Utility_R, Utility_P, TotalCost_S, TotalCost_R, TotalCost_P, TotalCost_S_m, TotalCost_R_m, TotalCost_P_m,  LifeYears_1,
QALY_1, TOTALCOST_1, LifeYears_1_m, QALY_1_m, TOTALCOST_1_m, LifeYears_2, QALY_2, TOTALCOST_2, LifeYears_2_m, QALY_2_m,
TOTALCOST_2_m, LifeYears_3, QALY_3, TOTALCOST_3, LifeYears_3_m, QALY_3_m, TOTALCOST_3_m, LifeYears_4, QALY_4, TOTALCOST_4,
LifeYears_4_m, QALY_4_m, TOTALCOST_4_m, dQALY_1, dTOTALCOST_1, dQALY_2, dTOTALCOST_2, dQALY_3, dTOTALCOST_3, dQALY_4,
dTOTALCOST_4)

return(sample)
}

# Generating 10,000 samples (data frames):
df10000 <- sapply(1:10000, DATAGEN)
```

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