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Is a comparative clinical trial for breast cancer tumor markers to monitor disease recurrence warranted? A value of information analysis

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Abstract

Background—Breast cancer tumor markers are used by some clinicians to screen for disease recurrence risk. Since there is limited evidence of benefit, additional research may be warranted.

Aim—To assess the potential value of a randomized clinical trial of breast tumor marker testing in routine follow-up of high-risk, stage II–III breast cancer survivors.

Materials & methods—We developed a decision-analytic model of tumor marker testing plus standard surveillance every 3–6 months for 5 years. The expected value of sample information was calculated using probabilistic simulations and was a function of: the probability of selecting the optimal monitoring strategy with current versus future information; the impact of choosing the nonoptimal strategy; and the size of the population affected.

Results—The value of information for a randomized clinical trial involving 9000 women was US\$214 million compared with a cost of US\$30–60 million to conduct such a trial. The probability of making an alternate, nonoptimal decision and choosing testing versus no testing was 32% with current versus future information from the trial. The impact of a nonoptimal decision

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Disclosure

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was US\$2150 and size of population impacted over 10 years was 308,000. The value of improved information on overall survival was US\$105 million, quality of life US\$37 million and test performance US\$71 million.

Conclusion—Conducting a randomized clinical trial of breast cancer tumor markers appears to offer a good societal return on investment. Retrospective analyses to assess test performance and evaluation of patient quality of life using tumor markers may also offer valuable areas of research. However, alternative investments may offer even better returns in investments and, as such, the trial concept deserves further study as part of an overall research-portfolio evaluation.

Keywords

breast cancer recurrence; EVSI; expected value of sample information; quality of life; tumor marker; value of information

Among women who have completed therapy for breast cancer with curative intent, the role of tumor markers, carcinoembryonic antigen (CEA) [1,2], cancer antigen (CA)15–3 [1,2] and CA 27.29 [3], for monitoring breast cancer recurrence is uncertain. The 2007 American Society of Clinical Oncology (ASCO) guidelines recommend against their use for detecting breast cancer recurrence [101]. Despite these recommendations, in a recent internal SWOG survey, 37% of clinicians indicated that they use breast cancer tumor markers in at least some of their patients with stage II–III breast cancer to monitor for disease recurrence [4–7]. This use probably represents the perceived value to clinicians and their patients, either to provide reassurance or to detect disease recurrence as early as possible.

Arguments against serial monitoring with tumor markers are based on studies showing that intensive monitoring with exams or other diagnostic modalities does not improve survival and may lead to additional unnecessary testing. Two prospective trials evaluated intensive follow-up (including chest x-rays, bone scans, liver ultrasound and alkaline phosphatase and γ -glutamyltranspeptidase levels) versus standard follow-up in patients with early breast cancer in the 1980s and found no significant difference in overall survival [8–12]. In another study, 126 patients were retrospectively classified as having intensive or minimal follow-up [13]. This study found no significant difference in overall survival or time to recurrence.

Although these studies failed to demonstrate a benefit, they have important limitations, particularly in light of today's imaging and treatment technologies. The radiological exams in these trials were performed at 6–12-month intervals and, thus, may have minimal lead time in starting early treatment. Current diagnostic technologies, such as PET/computed tomography (CT), are likely to be more sensitive than those of previous generations. In addition, none of these trials incorporated the use of serum tumor markers, suggesting that tumor marker-initiated imaging may be a feasible surveillance option for early detection of breast cancer recurrence.

A clinical trial designed to detect the impact of breast cancer tumor markers would do much to clarify the benefits and risks of tumor marker monitoring in breast cancer survivors. Nevertheless, since survival is relatively favorable for women with local- and regional-stage

breast cancer, such a trial would require large numbers of enrolled subjects and would be very expensive to conduct.

Researchers and funders are thus faced with a dilemma: is such a trial worth the investment? An emerging field in health economics, value of information (VOI) analysis, quantifies the value of future research and may be helpful in resource-allocation decisions. Based on the Bayesian decision theory [14–19], these methods provide an analytical framework to assess the societal value obtained by the reduction of uncertainty around a treatment or testing decision. The VOI is a function of: the probability of selecting the optimal monitoring strategy based on current versus future information; the clinical and economic impacts of each strategy; and the size of the population affected.

The purpose of this study was to assess the societal value of a randomized clinical trial of breast tumor marker testing in routine follow-up of high-risk, stage II–III breast cancer survivors. The findings may be useful for research funders making resource allocation decisions and for researchers optimizing clinical study designs.

Methods

Overview

This VOI analysis is focused on the clinical impact of a hypothetical trial design currently under discussion with the paper's authors. To calculate the VOI, current data were incorporated into a model of patient management and compared with optimal decisions if information from the new trial were available. Health improvements in terms of survival and quality of life (measured in quality-adjusted life years; QALYs) were then converted into a monetary value based upon a willingness-to-pay threshold. The net benefit was the difference between health outcomes gained monetized at a particular threshold value and costs incurred. This monetary amount was then multiplied over the entire affected population to obtain the value of the trial to society; the expected value of sample information (EVSI).

Trial for breast cancer tumor markers

The trial design under discussion would be a large, prospective randomized trial comparing breast cancer tumor marker-guided surveillance with standard follow-up among women who have had definitive treatment for local-and regional-stage breast cancer. A trial powered to detect a 15% improvement in survival time with the use of breast cancer tumor markers, and with survival as a primary endpoint, would require enrollment of 9000 patients. We estimate the cost of such a trial to be between US\$30 and US\$60 million, with major drivers being US\$2000 per patient for clinical trial cooperative group trial enrollment and US\$50–100 per tumor marker test [102–104]. We also assume a 25–50% insurance reimbursement rate for tumor marker testing. We do not assume there are any further costs, including startup, as the trial would leverage from existing infrastructure.

Model structure & patient population

In consultation with experts and practicing oncologists at the Fred Hutchinson Cancer Research Center (WA, USA), we developed a decision-analytic model (Figure 1) comparing the use of breast cancer tumor markers in addition to standard surveillance versus standard surveillance alone [12].

In the tumor marker testing arm, standard surveillance with clinical assessment and physical examination is accompanied by measuring serum tumor marker concentrations. Patients are examined and tested every 3 months for the first 3 years and every 6 months during years 4 and 5. Disease recurrence could occur with or without tumor marker elevation. Patients with elevated tumor marker levels (CEA or CA15-3/CA27.29) receive a second test within 1 week as a confirmation test and, if positive, are referred for confirmatory testing using a combination of modalities including bone scans, CT and PET [12]. Patients with confirmed recurrence are assigned to receive treatment if currently on observation. Patients with elevated tumor marker levels but with no evidence of disease on imaging evaluation are presumed not to have breast cancer recurrence. Patients without tumor marker elevation do not undergo imaging evaluation, but instead receive standard (not early) treatment at the time of clinical detection of disease recurrence. Patients with recurrence but without measurable disease follow standard surveillance protocols. In the standard surveillance (reference) arm, patients also undergo clinical assessment and physical examination at 3-month intervals for the first 3 years and every 6 months in year 4 and 5. Standard-of-care treatment is assumed upon detection of recurrence.

The patient population in the model consisted of women undergoing surveillance after completion of primary breast cancer therapy (surgery, chemotherapy and/or radiation therapy, as clinically indicated) for early-stage breast cancer. Patients could still be receiving hormonal or biologically targeted therapy, therapies that generally last for years after diagnosis. The population includes both pre- and post-menopausal women.

We estimated the likely affected population by assuming the tumor markers would be in use for 10 years before replacement with a different technology. The affected population is based on current Surveillance Epidemiology and End Results breast cancer incidence rates and 5-year recurrence rates [20–22]. We adopted a somewhat conservative but constant recurrence rate of 20% [16–19,102–104] compared with meta-analysis data [20], to account for the presence of newer, highly effective treatment regimes [22,23]. We assumed that 80% of recurrences are metastatic and, for simplicity, only metastatic disease was used to inform our model [24]. The annual incidence and affected population is assumed to be constant over 10 years to obtain the total affected population and these effects are assumed to take place after a trial duration of 5 years, for a total time horizon of 15 years. Future costs and health outcomes are discounted at 3% annually. All patients entering the trial, with positive and negative test results, and those recurring and not recurring would be tracked throughout the entire trial duration.

Model inputs & key assumptions

The inputs used in the model were obtained from literature references where available (Table 1). Average time to recurrence in the first 5 years was assumed to be 2 years [20]. Patients were assumed to live, on average, for 2 years after disease recurrence based upon estimates derived from the literature [25]. Costs and health outcomes within the model were discounted based on events occurring on average at the 2-year mark after initial breast cancer diagnosis. Given the lack of data on survival benefit with the use of tumor markers, our estimates were based on expert opinion of three authors (NL Henry, JR Gralow and B Barlow). We incorporated significant uncertainty into these estimates; specifically, the survival hazard ratio for early detection and treatment versus standard of care was 1.15 (95% CI: 0.9–1.4). We assumed that patients would be monitored and receive appropriate therapy immediately following confirmation of recurrence and for the duration of survival. False-positive tumor marker tests resulted in confirmatory tests including bone scans, CT and PET. Confirmatory testing using a combination of bone scan, CT and PET was assumed to have 100% sensitivity and specificity. We assumed that two-thirds of patients with recurrence required both bone scans and CT for confirmation, and one-third required bone scans, CT and PET for confirmation based on expert opinion of authors (R Thariani, NL Henry and DL Veenstra).

Quality-of-life (utility) values were based on literature values; however, there is limited consistent evidence on utility values associated with tumor marker testing in breast cancer [26,27]. These surveys reported a substantial impact in patient quality of life upon receiving a false-positive diagnosis. The duration of this impact on quality-of-life difference was assumed to be 12 months [26]. Early detection and treatment of breast cancer recurrence was assumed to provide an increased utility of 0.05 (95% CI: 0–0.1) over the course of treatment.

Test sensitivity (75% [95% CI: 65–85]) and specificity (97.9% [95.4–100]) were estimated from prospective trials using CEA and CA15-3/CA27.29 to determine breast cancer recurrence [21,28]. Given that receiver operating characteristic curves for different cutoffs can vary substantially [21], we used high mean estimates for sensitivity and specificity, assuming near-optimal criteria would be used in the trial. However, wide uncertainties were applied based on the range of values obtained in prospective trials. Costs, including those for tumor marker testing, chemotherapy and patient management, were also obtained from the literature [29] and commercial laboratories [105]. Outputs from the overall model calibrated well with data from the literature [20,26–29].

VOI calculations

EVSI calculation begins by evaluating the difference between decisions taken with current information and uncertainty (i.e., to test or not to test for tumor markers), and those taken with the addition of information obtained through a clinical trial [15,16,30,31]. This analysis includes both health outcomes and costs. Health benefits are converted into monetary units using a conversion factor that represents the societal willingness to pay for 1 year of perfect health (1 QALY). We used a willingness to pay US\$150,000 per QALY to value benefits,

based on a recent survey estimating willingness to pay for cancer therapy in the USA [32,33].

Given that uncertainty exists in current data but also data obtained from a future trial, probability distributions rather than point estimates are used in the model of the underlying clinical pathway. These results are evaluated numerically by running multiple simulations. The optimal choice is the option (to test or not to test) that provides the maximum net benefit. Making the decision to adopt a new health intervention in the presence of uncertainty incurs an opportunity cost. New information obtained through a trial is expected to reduce uncertainty and, hence, reduce opportunity loss. Multiplying this reduction by the number of relevant patients leads to the EVSI.

The relative impact of particular subsets of parameters (expected value of sample partial information), such as survival and quality of life, can also be estimated in EVSI. The analysis was conducted with 10,000 simulations run for each set of parameters.

Scenario analyses

We examined a range of trial sizes ($n = 100\text{--}9000$) to evaluate the impact of trial size on the value of research. Given the uncertainty in the potential survival benefit afforded through asymptomatic detection of breast cancer recurrence using tumor markers, we conducted a sensitivity analysis exploring scenarios in which the confidence in expert opinion varied over a wide range. In addition, we also conducted analyses evaluating the relative value of specific types of information (expected value of sample partial information) gained in the trial, specifically patient survival, quality of life and test parameters (sensitivity/specificity). Expected values of sample partial information were obtained following standard approaches [16,30].

Results

We estimated the societal value (i.e., both society benefits and costs for the research) of a trial of breast cancer tumor markers of 9000 patients to be US\$214 million at a societal willingness to pay of US\$150,000 per QALY. These findings are based upon three factors: first, the probability of making an alternate, nonoptimal decision and choosing testing versus not testing with information available currently versus with information from a new trial was 32%. Thus the probability (incremental net benefit with testing < 0 | current information) is 0.32. Second, the average consequence of the error (opportunity loss) in terms of patients' outcomes and costs measured in monetary terms (US\$2150). And third, the population impacted over 10 years (308,000). Prior and posterior net benefit histograms are shown in Figure 2.

In our scenario analysis, the results are dependent upon multiple factors, including the size of the trial and the confidence we place in expert opinion of the effect size (Figure 3). Smaller trials can provide substantial value; however, larger trials (with more data and uncertainty reduction) provide greater value. The rate of increase slows as each further enrolled patient provides proportionally smaller uncertainty reduction, moving along the x-axis in Figure 3. We also evaluated the value of the trial under a range of willingness-to-pay

thresholds (US\$100,000–200,000 per QALY) resulting in values ranging from US\$77 million to US\$370 million.

The expert uncertainty range has a much smaller relative impact on EVSI value compared with the range of trial sizes explored. Since a trial would provide more definitive data on the impact of tumor markers on survival, a low confidence in current estimates of survival benefit leads to a higher value in future research. Thus, trial value decreases with increasing confidence in expert opinion, seen moving along the y-axis in Figure 2.

The relative contributions of different groups of parameters can be estimated by measuring how changes in specific uncertainties impact the total trial value (Figure 3). For a trial size of 9000 women, increased information on survival had a value of US\$105 million, information on test sensitivity and specificity yielded a value of US\$71 million and information on the quality of life impact of testing had a value of US\$37 million (Figure 4). Note that these values do not necessarily add to the sum value of the trial, US\$214 million. Our analysis also revealed that the trial size that maximized the net benefit of sampling (i.e., the difference between the expected value and the cost of the trial) was between 6000 and 9000 individuals, varying slightly depending upon how much confidence was expressed in expert opinion (Figure 3).

Discussion

Some evidence suggests that the use of tumor markers can be helpful. Markers have been shown to detect breast cancer recurrence approximately 5 months before regular clinical surveillance [12,28]. Several recent small studies have indicated a potential benefit in guiding treatment with serum tumor markers [12]. In one retrospective study, Nicolini *et al.* showed a benefit (13.5 ± 10 months vs 3.4 ± 2.8 months) of early treatment of patients on the basis of elevated tumor marker levels compared with those treated when metastatic disease was evident [34]. Kovner *et al.* randomized asymptomatic women with increased levels of mucinlike carcinoma-associated antigen (similar to CA15-3 and CA27.29) to tamoxifen or no tamoxifen [35]. The group receiving tamoxifen demonstrated no recurrences after 11 months, whereas seven out of 29 patients had recurred in the no tamoxifen group. However, a 5-year follow-up demonstrated a recurrence rate of 17.4% in the tamoxifen group versus 25.8% in the control group [36]. While not definitive, the results are suggestive of potential health-outcome improvements.

We conducted a VOI analysis to estimate the societal benefit of conducting a trial on the use of tumor markers (CEA, CA15-3 and CA27.29) in addition to standard surveillance for breast cancer recurrence. Our analysis indicates that a recurrence comparative clinical trial may provide a good return on investment compared with the cost of the trial. The value of the trial is driven by the relatively large incidence of breast cancer, potentially meaningful impacts on overall survival, impacts of testing on patient and quality of life and uncertainty in tumor marker test performance.

The overall benefits of the trial, at US\$214 million, substantially outweigh the relatively large cost of the trial (US\$30–60 million). At a willingness to pay for health gain of US

\$150,000 per QALY (generally accepted for interventions in oncology in the USA [32,33]), the trial provides a net benefit, suggesting that the trial gives a positive return on investment to society for the resources utilized. The analysis indicates that substantial value exists in obtaining three different types of data: survival with tumor marker testing; quality of life associated with testing; and tumor marker sensitivity and specificity. Owing to problems with lead time bias, the only way to acquire reliable information regarding the benefit of tumor markers on survival is through a prospective randomized trial. While a large trial provides the highest value to society, the analysis indicates that even smaller randomized trials could provide substantial value by reducing the considerable uncertainty that exists in this area.

Our analysis suggests alternatives to randomized controlled trials could also provide substantial value. Quality-of-life metrics could be obtained by incorporating patient-outcome measures within ongoing trials or trials proposed for other testing-based interventions. Prospective data on the impact of false positives, false negatives, fear of recurrence and anxiety around imaging on management choices and patient outcomes are lacking [26,27].

Similarly, our analysis suggests considerable value can be obtained by reducing the uncertainty around tumor test marker performance. Given that tumor marker tests are already in use [37,38], appropriately controlled observational/retrospective studies could be carried out to utilize this additional data to reduce uncertainty around parameters, such as sensitivity and specificity, in actual clinical environments. Efforts to obtain outcome data from these patients already being evaluated by these tumor marker tests should be encouraged.

Our analysis has several limitations worth noting. Although the VOI approach is inherently designed to assess uncertainty regarding inputs used for our model, we further explored the potential impact of various assumptions using supplemental scenario analyses. While we relied on expert opinion for estimates of survival with early detection and treatment of breast cancer [39], we incorporated a sensitivity analysis by weighting the relative importance of these expert inputs over a wide range (Figure 3), with large uncertainty bounds. We concluded that even after incorporating the range of expert opinion, a tumor marker trial may provide substantial benefit. Quality-of-life studies used to inform model inputs exhibited substantial inter- and intra-study differences. We used a wide range of values in our model to reflect this uncertainty. Tumor marker test performance profiles were based on the best available evidence; however, given that only limited evidence, dating back several years, was available [21,28,40,41], there may have been significant improvements in the technology that we did not account for. We assumed that the trial would take 5 years and would affect the population for 10 years after conclusion. Larger trials also cost more and take more time and, as such, may not provide greater overall value [42].

The opportunity cost of conducting such a trial should also be considered, as other trials could be conducted using resources that would have been used in a tumor marker trial. It is, therefore, most effective to use VOI analysis to prioritize a research portfolio in which different investments could be made; for example, trials evaluating alternative treatments for

breast cancer. It is beyond the scope of this article to discuss the range of alternatives available for resource allocation. While the trial has a good return on investment, it does not mean that it is feasible or an optimal use of overall resources but rather that it deserves further study. It should also be noted that our analysis suggests that substantial value can be obtained through better information for test sensitivity/specificity and utility parameters, and this information could be obtained in conjunction with other trials and studies.

The decision model included several simplifications to keep the analysis tenable. For example, we assume that confirmatory tests are 100% specific and sensitive. Given the relative accuracy of these confirmatory techniques [43,44], we felt that using a more complex decision model would result in relatively minor changes in our results, at the cost of adding substantially more computational burden.

Finally, our analysis does not include the value provided by further activities associated with the trial, such as biobanking of samples and additional serial quality-of-life assessments to determine the long-term impact of breast cancer diagnosis/treatment on factors such as cognitive disorders and peripheral neuropathy. This additional data could add further substantial value to the trial.

Our results indicate that substantial value to society can be obtained by evaluating the clinical utility of serial tumor marker assessment for early detection of breast cancer recurrence. This value is driven by the current paucity and conflicting information in this area, the severity of outcomes, and the large population that could be affected. Positive clinical utility results could lead to widespread adoption with consequent health outcome improvements, whereas negative results could save unnecessary healthcare resource use.

Conclusion & future perspective

With increasing resource constraints on healthcare, VOI approaches are likely to be used as part of research portfolio optimization, allowing for an evaluation of the returns on future research investment. As the methodology becomes more widely known and used, the evaluation process is likely to become more efficient, allowing stakeholders a further quantitative tool to aid decision-making and to support research with the highest likely return.

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Executive summary

- We assessed the potential value of a randomized clinical trial of breast tumor marker testing in routine follow-up of high-risk, stage II–III breast cancer survivors using the expected value of sample information.
- The value of information for a randomized clinical trial involving 9000 women was US\$214 million, compared with a cost of US\$30–60 million to conduct such a trial.
- The value of improved information on overall survival was US\$105 million, quality-of-life US\$37 million and test performance US\$71 million.
- Conducting a randomized clinical trial of breast cancer tumor markers appears to offer a good societal return on investment. However, other investments may offer higher returns. Thus the trial concept and expected value of sample information should be evaluated further as part of an overall research portfolio.

Figure 1. Overall decision model schematic used in the current model
CT: Computed tomography.

Figure 2. Prior and posterior net benefit (testing benefit – no testing benefit)
(A) Prior distribution. (B) Posterior distribution.

Figure 3. Expected value of sample information values (interpolated fit) as a function of overall trial size and weighting of expert opinion

That is, how accurate we believe experts are, relative to our belief in a trial ranging from $n = 1$ to $n = 50$, on survival parameters. The z-axis represents expected value of sample information (in US\$100 millions).

Figure 4. Value of a 9000-individual trial

Breakdown is by parameter groups (note that the parameter group values do not need to add up to the total EVSI of US\$214 million).

EVSI: Expected value of sample information; Sens-spec: Sensitivity-specificity.

Table 1

Key parameter values and distributions used in the model.

Parameter	Mean value	95% CI	Distribution	Prior parameters	Ref.
Early detection and treatment (hazard ratio)	1.15	0.90–1.40	Normal	$\mu = 1.15; \sigma = 0.13$	[†]
Probability of recurrence in 5-year interval	20%	17.00–23.00	Normal	$\mu = 20%; \sigma = 3.06\%$	[20]
Tumor marker sensitivity	75%	65.00–85.00	β	$\alpha = 53; \beta = 18$	[28]
Tumor marker specificity	97.9%	96.00–99.00	β	$\alpha = 123; \beta = 2.63$	[28]
Utility: no disease	0.92	0.80–1.00	β	$\alpha = 53; \beta = 18$	[26,27,29]
Utility: standard chemotherapy	0.62	0.49–40.75	Normal	$\alpha = 25; \beta = 2.18$	[29,45]
Incremental utility: early detection and chemotherapy	0.05	0.00–0.10	β	$\alpha = 3.60; \beta = 68$	[‡]
Disutility false-positive test result (1-year duration)	0.19	0.13–10.25	Normal	$\mu = 0.19; \sigma = 0.03$	[26,27]

[†] Obtained from expert opinions.

[‡] Assumed data.