The Economic and Clinical Outcomes and Policy Implications of Gene Expression Profiling in Breast Cancer Care

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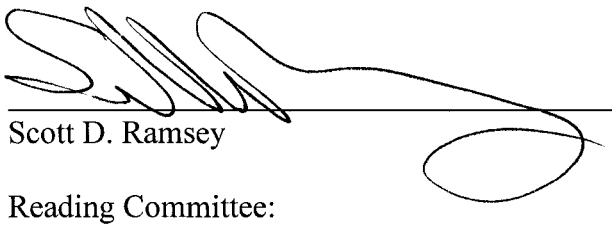

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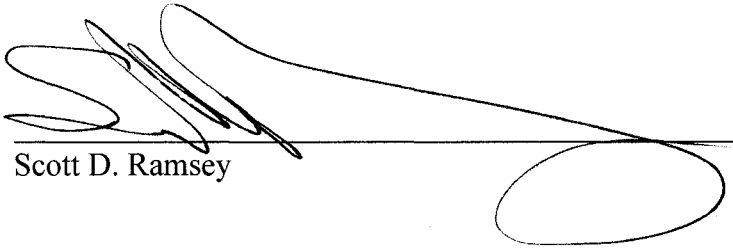

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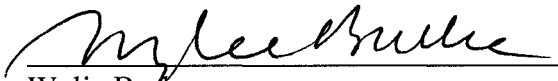

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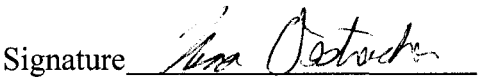
Signature 

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ABSTRACT

The Economic and Clinical Outcomes and Policy Implications of Gene Expression Profiling in Breast Cancer Care

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In the U.S., the majority of premenopausal breast cancer patients are recommended by clinical guidelines to receive adjuvant chemotherapy to prevent disease progression and increase survival. However, low-risk patients may be experiencing the side effects of chemotherapy, with no corresponding benefit, which may also lead to spending on unnecessary treatment by healthcare payers. In response to this situation, new genomic assays have been marketed or are in development that profile the biology of the tumor cells and may be better able to identify high-risk patients than the current guidelines. However, the clinical, economic and patient outcomes associated with these approaches are unknown. We compared the cost-utility of one of these genomic assays developed by investigators at the Netherlands Cancer Institute to NIH guidelines in a cohort of 44 year-old women with early stage breast cancer. We utilized a decision analytic model that was informed by empiric and literature-based estimates, and model parameters were varied in sensitivity analyses. As an input to the decision model, the costs of adjuvant

chemotherapy have a large influence on results. Thus, an accurate estimate of these costs was needed. We conducted a cost study to estimate the direct medical costs of adjuvant chemotherapy in this young patient population to inform the decision model and to better understand the economic burden of this treatment modality. We estimated these costs to be $21,684, so they constitute a substantial component of breast cancer treatment costs. For the cost-utility analysis, we found that the genomic assay was much more specific, but less sensitive than NIH guidelines in detecting high-risk women. As a result, the improvement in quality of life due to avoiding chemotherapy appeared to be offset by an increased risk of breast cancer progression. It appears that these genomic assays, which have yet to be validated or demonstrated to be in equipoise with current NIH guidelines, require additional refinement and validation before implementation in clinical practice. Our study highlights the value of cost-utility analysis in clarifying the tradeoffs between life expectancy, quality of life and costs in the era of genetic assays.

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ACKNOWLEDGMENTS

I wish to express my gratitude to my talented and dedicated committee members Dave Veenstra, Scott Ramsey, Wylie Burke and Jeannine McCune. Also, Hannah Linden has contributed wonderful and invaluable clinical insights to our cost analysis and decision model. Additionally, to Janne Abullarade, this dissertation would not have been possible without your hard work, dedication and tutelage. A special thanks to my mentors Dave Veenstra and Emily White, who have had a profound impact on my research interests and future career path. Lastly, thanks to my awesome friends for keeping my head above water, providing love and laughter throughout this process.

DEDICATION

For Mom, Dad, Charlie and Mr. Sweetie, whose love and support I feel every day.

INTRODUCTION

Breast cancer is the leading incident cancer among women of all major ethnicities in the United States and is the second highest source of cancer mortality (*1*). Current NIH guidelines (*2*) recommend adjuvant chemotherapy for those with a high likelihood of recurrence based on characteristics that do not pertain to the actual behavior of the tumor, such as patient age. Additionally, the utilization of tumor size, HER2 status and tumor grade for risk assessment in clinical practice has only been marginally useful. Because these criteria are such imprecise predictors, it is thought that there are many women are treated with chemotherapy for whom this treatment provides no benefit, and yields a large cost to the healthcare payer.

The hope for the future of breast cancer treatment is for it to be personalized ("the right drug for the right patient"), targeted to the specific tumor and the molecular pathways that drive its growth. Accordingly, gene expression profiling has been proposed as an alternative way to identify patients for adjuvant chemotherapy, potentially sparing low-risk patients from the harmful side effects of adjuvant chemotherapy and sparing healthcare resources. These genomic assays are in development (*3,4*) or currently marketed for clinical use (*5*) and stand to influence which patients receive chemotherapy. However, questions have arisen as to the clinical validity of genomic assays such as those used for gene expression profiling. For gene expression profiling, clinical validity refers to the accuracy and

predictive values of these techniques to detect those women whose tumors will go on to metastasize.

In considering the adoption of a genetic test into clinical practice, the clinical utility, or usefulness of a genetic test in a clinical setting, is paramount. There are many aspects to clinical utility, but a key component is the accuracy/predictive value of the test. In other words, clinical benefits are related directly to the performance of the test. Other aspects of clinical utility relate to efficacy of clinical management based on test results and acceptability of the technology to the payer and patient. Faced with a setting of limited healthcare resources, the payer is concerned with the efficient use of these resources, and considers the incremental clinical and economic benefits of the candidate technology over the standard of care, also taking patient-centered outcomes into account. These incremental benefits are often expressed as a cost-effectiveness ratio, or cost/life year saved or a cost-utility ratio (cost/quality-adjusted life year saved (QALY), which takes patient preferences into account.

Our cost-utility analysis of gene expression profiling vs. NIH guidelines for the identification of early stage breast cancer patients for adjuvant chemotherapy is the first attempt to quantify the incremental benefits of using this technology in clinical practice. It is important to note that there are many gene expression profiles in existence, performed on different types of microarrays and patient populations, utilizing a multitude of techniques to derive the genes that form the profile, which may differ to a great degree from profile to profile. Our study has many strengths,

but it is important to note we have evaluated only one profile in this constellation of profiles. The profile we used for our analysis was developed in the Netherlands, and has shown great promise for accurate prediction of high-risk women (compared to NIH guidelines) in early studies (*6*), so any inferences we make are necessarily limited to this genetic profile.

There is a dearth of relevant information about costs of care in breast cancer treatment, which is especially true for premenopausal women, for whom breast cancer is more rare, yet treatment is more costly (*7*). This type of information is important to inform economic models and understand tradeoffs between different modalities in breast cancer, and to better understand the economic burden of the disease. Since gene expression profiling seeks to identify fewer patients for chemotherapy by having greater specificity and better stratifying patients into risk groups than the NIH guidelines, the costs of chemotherapy are an especially important component of our model. Because the existing literature was inadequate for us to accurately identify these costs, we undertook our own analysis of chemotherapy costs utilizing statistical methods developed in the last decade (*8*). We hope that this analysis will shed light on the economic burden of chemotherapy in the context of other treatment modalities for breast cancer, and to better understand the tradeoffs between different treatment strategies in breast cancer, such as in our evaluation of gene expression profiling.

Chapter 1: Costs of Adjuvant Chemotherapy in Early Stage Breast Cancer Patients

OVERVIEW

Background: In the U.S., the majority of premenopausal early stage breast cancer patients are treated with adjuvant chemotherapy, which may cause substantial morbidity in patients and carries a large economic burden to the health care system. Additionally, new genomic assays are in development that will influence who receives chemotherapy, and adjuvant chemotherapy costs are a critical input to economic models for these assays. However, there have been few formal analyses of the costs of adjuvant chemotherapy, especially in young women, and none have been performed in a managed care setting. Our objective was to evaluate the costs of adjuvant chemotherapy in early stage breast cancer patients using an attributable cost approach.

Patients and Methods: The attributable cost approach was used to estimate cancer-related costs as the difference between total costs of female breast cancer patients and costs of age- and gender-matched control subjects without breast cancer. Attributable costs were derived using the Kaplan-Meier Sample Average Estimator. We identified breast cancer cases from a linked database of claims records from Regence Blue Shield, a managed care organization in the Pacific Northwest, and the Cancer Surveillance System registry for western Washington State. Resource prices were based on reimbursements for drugs and procedures from Regence Blue Shield.

Results: We identified 1,239 breast cancer cases for the analysis. Adjuvant chemotherapy attributable costs were estimated to be $21,684 (95% CI $17,630-$25,737). Costs appeared to decrease with increasing age at diagnosis, with total costs of $18,648 (95% CI $9,975-$27,321), $20,038 (95% CI $13,427-$26,649) and $21,985 (95% CI $16,686-$27,284) for women 60+, 50-59 and < 50 years, respectively. Also, costs were higher for regional disease ($35,851, 95% CI $28,044-$43,657), as compared to local disease ($14,116, 95% CI $10,242-$17,991).

Conclusions: The attributable cost of adjuvant chemotherapy in breast cancer is significant, and appears to be higher than what would be estimated by treatment guidelines. Contributors to the high costs of adjuvant chemotherapy included non-guidelines based use of chemotherapy agents, use of supportive care agents and hospitalizations. The integration of managed care claims data with clinical data from the Cancer Surveillance System registry offered a unique opportunity to derive potentially more accurate disease burden costs in oncology. The results of our study will be useful for better understanding the differences between costing methods, informing cost-effectiveness models in breast cancer and evaluating the economic burden of the disease.

BACKGROUND

Breast cancer is the leading incident cancer among women in the United States and is the second highest source of cancer mortality (*1*). Current NIH consensus guidelines (*2*) recommend adjuvant chemotherapy for breast cancer patients based on the presence of lymph node metastases or primary tumor size larger than 1 cm. Because most women who are diagnosed with breast cancer have tumors larger than 1 cm, adjuvant chemotherapy is recommended for the majority of patients, including those with early stage disease. Adjuvant chemotherapy use in community practice in patients <50 years of age with early stage disease has been reported to be in the range of 45-86%, depending on lymph node and hormone receptor status (*9,10*). Furthermore, the use of multi-agent chemotherapy and tamoxifen has been increasing over time for almost all stages and ages, suggesting that the results of clinical trials are disseminated fairly rapidly to community based physicians and their patients (*11*).

Because of the frequency and severity of breast cancer, costs of treatment are substantial, amounting to over $6 billion annually (*12*). Despite the frequency and large economic burden of chemotherapy in breast cancer, there are still relatively few papers that formally estimate costs of treatment. Thus, deriving estimates that could inform decision models of breast cancer screening, prognosis and prediction is challenging (*13,14*). For example, there are new genomic assays in development that will influence which patients receive chemotherapy (*3,4*) and one of these assays is currently marketed for clinical use (*5*). The lack of relevant

information about costs of care is especially true for premenopausal women, for whom breast cancer is more rare, yet treatment is more costly (*7*).

Previous studies of the costs of breast cancer treatment have focused on a variety of phases of treatment, treatment modalities and healthcare settings. Some studies have identified the costs incurred during the initial, continuing and terminal phases of treatment, for both a Medicare population (*15*) and at a single institution (*7*). Costs also have been evaluated for various breast cancer treatment procedures in the same setting (*16*). Other informal analyses were based on charges rather than costs (*17,18*) or included costs unrelated to the cancer (*19*). Since these analyses were published almost a decade ago, they often considered the costs of a cyclophosphamide/methotrexate/5-fluorouracil regimen, which may not be as relevant to healthcare decision makers, given that an adriamcycin/cyclophosphamide regimen is recommended by current guidelines (*2*). Few studies of the costs of adjuvant chemotherapy outside of U.S. healthcare settings have been conducted (*20,21*), and few have been in young women (*22*). To our knowledge, only one formal analysis has been performed in the U.S. (*23*) and no formal analyses in a community practice setting, or a fee for service managed care setting. Indeed, there are few population-based resources available to identify breast cancer costs in the U.S. (*15*). Thus, there is a need for cost information for specific types of treatment for specific cancer health states, that are estimated in diverse practice settings and healthcare populations.

PATIENTS AND METHODS

The objective of our analysis was to utilize attributable cost methodology (*24*) to derive the direct medical costs of adjuvant chemotherapy for women with early stage breast cancer. We estimated breast cancer attributable costs as the difference of the costs of care for breast cancer cases and the costs for age- and gender-matched controls. The attributable cost method avoids the limitations of microcosting methods (*25*) – that is, trying to identify whether each service is associated with the cancer of interest (*7*). Attributable costing estimates cancer-related costs as the difference in total costs for cases and controls and assumes that cancer costs are additive to the costs of existing comorbid conditions. Thus, it is important that the patient groups whose costs are being compared have a similar level of comorbidities at the time of cancer diagnosis to minimize bias in estimated costs. That way, attributable costing only captures costs pertaining to the cancer diagnosis and all the related changes in service that occur subsequent to the diagnosis, and not costs pertaining to the patient's underlying health condition.

Data Sources

The Institutional Review Board approved study procedures. We utilized a linked database containing information from: 1) Regence Blue Shield claims data, which includes patient-level claims records and enrollment/disenrollment dates (from which we derived costs and survival); and 2) the Cancer Surveillance System

of Western Washington, a population-based registry that is part of the national Surveillance, Epidemiology and End Results (SEER) program. In addition to the breast cancer cases, the Regence Blue Shield database contains records for other enrollees who do not have breast cancer. We randomly selected 5 controls for each case from this general Regence Blue Shield population to enhance precision of the estimates (*26*). Survival and cost data from the linked database were used to determine cancer attributable costs for each group of breast cancer cases (one group of breast cancer cases with chemotherapy, one group of breast cancer cases without chemotherapy) compared to the matched control group for each case group (*27*).

attributable costs of chemotherapy = {(costs of breast cancer cases with chemotherapy)-(costs of controls for women with chemotherapy)} – {(costs of breast cancer cases without chemotherapy)-(costs of controls for women without chemotherapy)}

We used the Regence Blue Shield database to longitudinally track care and costs for persons over the course of cancer diagnosis, treatment and follow-up. The Regence Blue Shield database contains claims data for approximately 124,000 continuously enrolled members drawn randomly from the population of 1.1 million Regence Blue Shield members in the Puget Sound region for 1995-1997. These claims were primarily generated from services delivered through preferred provider contracts that Regence Blue Shield has with its provider network. The Regence Blue Shield data include claims from physician outpatient visits, laboratory services, radiology services, hospital inpatient stays, community health services

and pharmacy. The database has information on age, sex and date of birth, dates of service, diagnostic codes and procedure codes in addition to the amounts for charges and reimbursement.

The Cancer Surveillance System registry covers an area of approximately 3 million people in 13 counties in the northwestern part of the state, including the Seattle-Puget Sound region. The registry collects information on personal identifiers (name, social security number, date of birth and reporting institution) and assigns each individual diagnosed with cancer an identification number and each diagnosis of primary cancer a sequence number. Medical record abstraction by the Cancer Surveillance System routinely includes information on the initial treatment regimen, i.e., treatment within, or documented as planned within, four months after initiation of treatment. Follow-up information (survival and diagnosis of subsequent primary cancer) is ascertained annually by the Cancer Surveillance System through a variety of data sources, including hospital cancer registries and discharge data sets, the Department of Motor Vehicles registration files, the Health Care Financing Administration and the Washington state death records.

Study Population

We identified women with a first primary early stage (local or regional) invasive breast cancer diagnosis (index diagnosis) between January 1, 1996 and December 31, 2000, who were 1) enrollees of Regence Blue Shield at the time of diagnosis, 2) not diagnosed with a second primary tumor (except for non-

melanoma skin cancer) within the 9-month period following the index diagnosis and 3) had total costs of at least $100 for the 9-month period following the index diagnosis. We chose a 9-month period following diagnosis over which to evaluate costs. Although much of the adjuvant therapy period is generally considered to occur in the first 6 months following diagnosis, we expanded the time window to account for late-processed claims. Also, we only considered women who had total costs of $100 or greater because we believed very low total costs could be suggestive of incomplete cost ascertainment. We excluded women with a history of cancer and with a second primary tumor within 9 months following diagnosis because these conditions could artificially inflate the costs of adjuvant chemotherapy.

We identified 2512 Regence enrollees diagnosed with early stage disease between 1996 and 2000 who were eligible for study. We excluded 1,087 women because they were not enrolled in Regence at the time of index diagnosis, 157 women because they had a previous or subsequent cancer diagnosis and 29 women because their total costs were less than $100. Our final study population consisted of 1,239 women with early stage breast cancer.

Adjuvant Chemotherapy Algorithm

Although the Cancer Surveillance System registry identifies whether a cancer patient received chemotherapy, it is not considered a highly sensitive source of this information (*28*). The SEER program does not routinely report information

about chemotherapy use because of concerns about underascertainment. Therefore, we developed an algorithm to determine whether a woman had received adjuvant chemotherapy utilizing data from both the Cancer Surveillance System and Regence Blue Shield. We considered a woman to have had adjuvant chemotherapy if the Cancer Surveillance System identified her as 1) having had chemotherapy ("Chemotherapy, not otherwise specified", "Chemotherapy, single agent" or "Chemotherapy, multiple agents") or 2) not having had chemotherapy or unknown chemotherapy status ("Chemotherapy, none", "Patient or guardian refused treatment", "Chemotherapy recommended by doctor, unknown if administered" or "Unknown") and she had at least one Regence Blue Shield claim for chemotherapy administration and one claim for a chemotherapy agent, both with reimbursement>0, in the 9-month period following the index diagnosis. All other eligible women in the study population who were not identified as having had chemotherapy were considered to have not had chemotherapy. Utilizing this algorithm, we identified 758 women with chemotherapy and 481 women without chemotherapy for analysis. We were not able to evaluate the validity of this algorithm because we did not have access to detailed patient medical records (e.g., medical charts). However, we believe this is a conservative approach because the algorithm required evidence from multiple types of medical claims that chemotherapy had been administered and would most likely lead to an underestimation of attributable costs.

Statistical Methods

We used a nonparametric estimation approach, the Kaplan-Meier Sample Average (KMSA), which has been shown to generate unbiased estimates of cumulative costs and uses the actual patient-level cost data for the follow-up period to be estimated (*27*). We directly estimated expected nine-month total costs for breast cancer cases and controls. The KMSA estimator of the expected total cost of care is given by:

$$E=\Sigma_i P_i * E_i ,$$

where i denotes month from diagnosis, P_i is the probability of surviving to month i, and E_i is the average cost incurred in month i among all individuals surviving to that time. E_i includes the costs for individuals surviving through month i and those dying in month i. P_i is estimated by the Kaplan-Meier survival probability based on the Cancer Surveillance System data. We report total expected costs and the 95% confidence interval around expected costs, using an expression for variance that was developed for the KMSA estimator (*8*).

Similarly, we computed the costs of care for controls, for any age A in years, as:

$$E^C(A)=\Sigma_i P_i * E_i,$$

where i denotes years after age A and P_i is estimated from U.S. life tables. We utilized life tables because information about vital status for control subjects was not available. By using survival probabilities from U.S. life tables we assumed that

the sample of controls for whom we have cost data is a representative sample in terms of their survival.

We obtained cancer attributable costs by subtracting a weighted sum of control costs from the total costs for the cases, where the weights for the controls reflected an age distribution similar to that of the cases, and was given by:

$$E^{CR}(A)=E-\Sigma_A E^C(A)*p(A),$$

where the summation was over the set of ages A in the group of cases, and the probabilities p(A) reflected the prevalence of the different ages A among the cases.

To account for controls who had less than the entire 9 months of cost data for age A+i, we made the adjustments described below. These adjustments were necessary to avoid underestimating costs for years in which control data were not available for the full 12 months and did not substantially alter the balance of decedents and survivors. The adjustments were as follows:

1) we included controls who died at age A+i only if cost data were available through their month of death.

2) controls who died after age A+i but for whom we only had data for a portion of age A+i (i.e., > 0 but < 12 months) had their total cost for age A+i estimated by their observed cost for this age multiplied by 12/m.

3) we excluded controls who only had data for a portion of age A+i (i.e., > 0 but < 9 months), but for whom it was unknown whether they died at this age.

We estimated the chemotherapy attributable costs as the difference between the cancer attributable costs of women with chemotherapy and women without chemotherapy. Thus, for the primary analysis, we assumed the costs of chemotherapy were additive and other aspects of treatment in the 9-months post-diagnosis did not differ between these 2 groups. Additionally, we estimated costs stratified by age (<50 years old, 50-59 and 60+) and stage (local and regional) because women with chemotherapy and without chemotherapy had important differences in the distributions of these factors. Since the majority of the study population (80%) was younger than 60 years of age and likely to have few comorbidities at the time of diagnosis, we did not assess the comparability of the study groups on this parameter.

Attributable cost estimates were based on Regence Blue Shield reimbursement amounts, as opposed to charges. The theoretical basis for resource costing in cost-effectiveness analysis suggests that the cost of resources used in an intervention should represent the opportunity cost, or the health benefits lost because the next-best alternative was not selected (*29*). Regence Blue Shield reimbursements are a better approximation of the true opportunity costs than provider charges. We adjusted all cost estimates to constant year 2003 dollars.

In addition to the attributable cost analysis to estimate the costs of adjuvant chemotherapy, we performed a microcosting analysis (*25*) for an adriamycin/cyclophosphamide chemotherapy regimen. We evaluated utilization of drugs, procedures and tests per clinical guidelines (*2,30-32*) and expert opinion and

applied costs to each unit of utilization using median reimbursements from Regence Blue Shield specific to the drug, procedure or test.

RESULTS

The study population (Table 1) consisted mostly of white women (92% in women with chemotherapy, 96% in women without chemotherapy). Women with chemotherapy had a younger age distribution than women without chemotherapy, with 50% of women being under 50 at the age of diagnosis, in contrast to 23% of the women without chemotherapy. Also, women with chemotherapy were much more likely to have regional disease (52%) than women without chemotherapy (8%). We were able to follow-up the majority of women for most of the 9-month period following their index diagnosis (7-9 months of follow-up in 76% of women with chemotherapy, 74% women without chemotherapy).

We estimated adjuvant chemotherapy attributable costs to be $21,684 (95% CI $17,630-$25,737, Table 2). Because the age and stage distributions differed between women with and without chemotherapy, we also estimated costs stratified by these variables. There was a modest negative age-cost gradient, with total costs of $18,648 (95% CI $9,975-$27,321), $20,038 (95% CI $13,247-$26,649) and $21,985 (95% CI $16,686-$27,284) for women 60+, 50-59 and < 50 years old, respectively. Women with regional disease incurred almost threefold higher costs ($35,851, 95% CI $28,044-$43,657) than women with local disease ($14,116, 95% CI $10,242-$17,991).

DISCUSSION

We estimated chemotherapy attributable costs to be $21,684 (95% CI $17,630-$25,737), the difference of total breast cancer attributable costs for women with and without chemotherapy. This estimate is higher than what has been found previously using different costing methods, in different study populations and healthcare settings. However, a negative age-breast cancer cost gradient and a positive stage-cost gradient make sense clinically and are consistent with previous findings (*7,33*). The overall cost estimate of almost $22,000 is much higher than the approximately $5,300 (adjusted to year 2003 dollars) found by Lokich et. al (*23*) for an adriamycin/cyclophosphamide regimen. This discrepancy is not surprising, given that these investigators excluded hospital visit and radiology charges and the cost of treating drug toxicity from their calculations. Furthermore, they conducted this analysis almost a decade ago and there have been changes in treatment patterns during this time. Lober et. al, in their study among premenopausal patients, also reported a lower cost estimate, or a cyclophosphamide/methotrexate/5-fluourouracil regimen (approximately $5,400, adjusted to year 2003 U.S. dollars). However, the authors did not include chemotherapy complications, and performed their analysis within a randomized clinical trial conducted over 15 years ago; thus, interpretation of this figure is difficult due to changes in treatment patterns and the generally poor external validity of controlled clinical trials. Hillner et. al (*17*) found a cost for adjuvant chemotherapy of approximately $16,000 (adjusted to year 2003 dollars), including

complications from chemotherapy. However, it is unclear what other utilization is included in this estimate. None of these previous analyses utilized an attributable cost approach.

Our estimated chemotherapy costs using a microcosting method were $7,932 (data not shown). Thus, results of the attributable cost analysis are nearly threefold higher than results of the microcosting analysis. We would expect the results from the attributable cost analysis to be higher than the microcosting approach, as attributable costs are derived from mean costs per patient and thus include patients for whom treatments were more extensive and complicated than would be inferred from treatment guidelines. For example, 12% of the women with chemotherapy incurred costs of $50,000 or greater, in contrast to virtually none of the women without chemotherapy. Attributable cost and microcosting methodologies produced dramatically different results, and they represent different interpretations of the economic burden of chemotherapy, each of which may be more useful in particular situations. For example, our attributable cost analysis, taking into account the full range of possible treatment outcomes within a fee for service managed care organization and deriving costs from that specific organization, may be highly useful to that payer for decision making about resource allocation but may not generalize well to other populations because the costs originated in a fee for service entity. For example, HMOs tend to have lower rates of hospitalization, shorter lengths of stay, less use of expensive technologies and more physician office visits than fee for service plans (*7*). Microcosting results,

which may not fully represent the range of possible treatment outcomes, may generalize better to other populations than attributable costing results.

We investigated the factors that may have contributed to differences in treatment costs. We examined costs for three categories of utilization in which we expected there to be differences between women with chemotherapy and women without chemotherapy: utilization of non-guidelines based chemotherapy agents, supportive care agents and hospitalizations - presumably for febrile neutropenia as a result of the chemotherapy- and for other reasons (data not shown). For non-standard chemotherapy regimens, we found that use of taxanes (docetaxel, paclitaxel) amounted to an additional cost of $1,090 per patient whereas use of trastuzumab (Herceptin^{TM}) added nominally ($36) to per patient costs. We found that utilization of erythropoeitin or darbepoeitin for anemia added $324 to per patient costs, and granulocyte colony stimulating factors (G-CSFs) for treatment or prophylaxis of neutropenia added $634 to costs. Antiemetics added $348 to costs. Finally, hospitalizations added $2,108 to per patient costs in women without chemotherapy and $4,625 in women with chemotherapy, for an additional cost of $2,517 per chemotherapy patient. Although considered together, these costs are significant, they only partially account for the large differences in treatment costs.

Another important factor that may account for the large differences in cancer attributable costs between women with chemotherapy and women without chemotherapy is possible selection bias among these 2 groups. In our study, women with chemotherapy were younger and tended to have more severe disease than

women without chemotherapy. Therefore, our assumption that the two groups are similar but for the chemotherapy may not be valid. Women who are younger are better able to tolerate, and therefore tend to be administered more aggressive therapy, and the more severe the disease, the more aggressive the therapy (*7*). We would expect these phenomena to affect not only the decision to administer chemotherapy, but also other treatment decisions and health conditions in the adjuvant therapy period following diagnosis.

The integration of managed care data with clinical data from a cancer registry affords the opportunity to derive potentially more accurate estimates of costs in oncology, which will assist in better understanding disease burden and in developing cost-effectiveness models of cancer screening, diagnosis and treatment, particularly for the new genomic assays currently in development (*3*) or marketed (*5*) to better identify women at high risk of metastasis (*2*). However, claims-based data also have several important limitations. First, as previously mentioned, there may be selection bias among patients who did and did not receive a certain treatment. In other words, important differences may exist between these 2 groups beyond the treatment itself. Second, it may be difficult to identify whether or not a patient received a treatment. In our case, we were fortunate to have chemotherapy information from a cancer registry, but we supplemented this with the claims and developed an algorithm to identify chemotherapy patients using these 2 data sources. However, it was not possible to validate our chemotherapy algorithm, although investigators who have used similar, but more limited algorithms in breast

cancer patients have found reasonable accuracy (88% sensitivity) (*15*). Furthermore, the Cancer Surveillance System registry (and SEER in general), does not identify recurrence, so it was not possible to exclude those women who experienced recurrence from our study population. If women who experienced recurrence were differentially included in the group of women with chemotherapy, it is possible that the attributable cost estimate was biased upward, as treatment for recurrence may be costly. Indeed, we found that some women had been administered taxanes and more rarely, trastuzumab (Herceptin^{TM}), which are not recommended in the adjuvant setting for treatment of early stage breast cancer (*2*), so there may be women who experienced recurrence included in our analyses. However, our calculations for expected number of recurrences in the first 9 months following diagnosis, utilizing data from a cohort of women with similar demographics to our study population (*3*) suggest the number of recurrences during this time would likely be modest, amounting to approximately 1% of patients, so we would expect the degree of overestimation of costs due to this phenomenon to be small. Alternatively, it is possible that some of the women who were administered non-guidelines based regimens were enrolled in clinical trials, which would explain this irregular utilization.

There are several methods available to estimate healthcare costs, including but not limited to microcosting and attributable cost analyses. We chose attributable costing as our primary method, because we believed it would be difficult to determine, with claims records, which claims were for utilization related

vs. unrelated to the cancer. Therefore we expected attributable costing to be a more accurate estimate of treatment burden. The KMSA estimator is a powerful method to use in situations when there is incomplete follow-up, and loss to follow-up or mortality may affect results. In this case, there may enrollment and disenrollment from the managed care organization, and there may be deaths due to cancer or other causes. As the analytic period is extended, censoring and deaths will have a greater effect on results and it becomes more critical to use analytically appropriate methods to account for censoring and deaths. Accounting for censoring when analyzing healthcare cost data also has an important limitation. The KMSA estimator assumes each individual is accumulating costs at a constant rate over time, although this assumption may not hold in practice. In our case, patients tended to accumulate higher monthly costs in the first 3 months following diagnosis and lower costs thereafter. Therefore, patients being censored differentially contribute higher costs to the KMSA estimate, leading to an overestimation of cumulative costs. However, there may also be an underestimation of what the costs of an adjuvant chemotherapy regimen would be, considering the context of a current-day healthcare setting. Our analysis covered claims from 1996-2000, but since that time, many new and costly oncology drugs have been developed, such as Zometa^{TM} (zolendronic acid) for the treatment of hypercalcemia of malignancy. Our analysis suggests that the costs of adjuvant chemotherapy are high and make a substantial contribution to disease burden in oncology. Further investigation is merited as to the important contributors to these high costs, and

differences in treatment patterns among recipients and non-recipients of chemotherapy.

Table 1.1. Population characteristics by adjuvant chemotherapy status of 1,239 female Regence Blue Shield enrollees diagnosed with early stage breast cancer between 1996 and 2000

	Adjuvant Chemotherapy Status	
	With Chemotherapy (n=758)	Without Chemotherapy (n=481)
Characteristic	**%**	**%**
Stage		
Local	48%	92%
Regional	52%	8%
Age at diagnosis		
<50 years	50%	23%
50-59 years	37%	46%
60-69 years	13%	31%
Race		
White	92%	96%
Asian	5%	3%
Native American	1%	0%
Black	2%	1%
Chemotherapy[1]		
None	6%	85%
Chemo, NOS	9%	0%
Chemo, Single Agent	5%	0%
Chemo, Combination	78%	0%
Refused tx	0%	8%
Chemo rec, UK	1%	3%
UK	1%	4%
Total Costs		
<$5,000	5%	12%
$5,000-$10,000	5%	14%
$10,000-$25,000	42%	68%
$25,000-$50,000	37%	5%
$50,000-$100,000	10%	0%
>$100,000	2%	0%
Follow-up Time		
0 months	3%	3%
1-3 months	11%	11%
4-6 months	10%	11%

Table 1.2. KMSA overall results for adjusted adjuvant chemotherapy attributable costs[1]

		95% Confidence Interval	
	Costs	Lower Bound	Upper Bound
(a) Costs for breast cancer cases with chemotherapy	$53,537	$62,654	$55,886
(b) Costs for controls for breast cancer cases with chemotherapy	$1,156	$974	$1,339
(c) Breast cancer attributable costs - breast cancer cases with chemotherapy (a)-(b)	$52,381	$49,850	$54,912
(d) Costs for breast cancer cases without chemotherapy	$31,807	$30,452	$33,162
(e) Costs for controls for breast cancer cases without chemotherapy	$1,110	$942	$1,277
(f) Breast cancer attributable costs - breast cancer cases without chemotherapy (d)-(e)	$30,697	$29,175	$32,220
Adjuvant chemotherapy attributable costs (c)-(f)	$21,684	$17,630	$25,737

[1] Costs are adjusted to year 2003 dollars

Table 1. 3. KMSA results for adjusted adjuvant chemotherapy attributable costs by age at diagnosis and stage [1]

	Breast Cancer Attributable Costs With Chemotherapy	Breast Cancer Attributable Costs Without Chemotherapy	Chemotherapy Attributable Costs	95% Confidence Interval	
				Lower Bound	Upper Bound
Stage					
Local	$45,234	$31,118	$14,116	$10,242	$17,991
Regional	$59,880	$24,029	$35,851	$28,044	$43,657
Age					
<50	$55,519	$33,534	$21,985	$16,686	$27,284
50-59	$52,182	$32,144	$20,038	$13,427	$26,649
60+	$44,953	$26,305	$18,648	$9,975	$27,321

[1] Costs are adjusted to year 2003 dollars

Chapter 2: Gene Expression Profiling and Breast Cancer Treatment: Cost-Utility Analysis to Evaluate Prognostic Test Performance

OVERVIEW

Background: U.S. breast cancer treatment guidelines recommend adjuvant chemotherapy for patients based on tumor size and lymph node involvement. However, low risk patients may be unnecessarily treated, leading to detrimental impacts on patient quality of life and increased medical care costs. Gene expression profiling (GEP) is a potential alternative strategy to identify high-risk patients for chemotherapy, but the clinical, economic, and patient outcomes associated with this approach are unknown. We thus compared the cost-utility of gene expression profiling vs. NIH guidelines to identify early stage breast cancer patients for chemotherapy.

Patients and Methods: We developed a decision analytic model to evaluate the incremental cost and quality-adjusted life years (QALYs) in a hypothetical cohort of early stage breast cancer patients 44 years of age. The model was informed by empirical analyses and literature-based estimates. Model parameters were varied in sensitivity analyses to explore uncertainty in the results.

Results: GEP was less sensitive than NIH guidelines in detecting high-risk women (84% vs. 98%). QALYs were lower and costs were higher for GEP (QALYs difference = -0.21, cost difference = $325). In probabilistic sensitivity analyses, the 95% uncertainty interval for the QALYs difference was (–0.32, –0.09) and for the cost difference was (-$430, $1,132).

Conclusions: The improvement in quality of life due to avoiding chemotherapy with GEP vs. NIH guidelines appears to be offset by an increased risk of breast cancer progression. Our analysis suggests that GEP requires additional refinement and validation before implementation in clinical practice, and highlights the usefulness of cost-utility analysis in clarifying the tradeoffs between life expectancy, quality of life, and costs in the era of genetic assays.

Gene expression profiling is an emerging technology with significant potential. As gene expression profiling algorithms are validated in well-designed clinical studies based on standardized protocols, its value as a prognostic factor may be enhanced.

BACKGROUND

Current NIH consensus guidelines (*2*) recommend adjuvant chemotherapy for breast cancer patients based on the presence of lymph node metastases or primary tumor size larger than 1 cm to prevent disease progression and increase survival. In contradistinction, the use of endocrine therapy is based on tumor biology, whether hormone receptors are present as detected by in vitro assay (*34*). Use of the NIH guidelines results in a recommendation for chemotherapy in the majority of breast cancer patients, including those with early stage disease. Adjuvant chemotherapy use in community practice in patients <50 years of age has been reported to be in the range of 45-86%, depending on lymph node status (*9,10*). Because the NIH criteria are based on tumor size and extent of disease (stage), and

not directly on the biological characteristics of the tumor, they have limited predictive ability and may lead to treatment of women in whom disease progression would otherwise not occur. Although adjuvant chemotherapy improves 10-year overall survival by 7% in women <50 years of age (*35*), treatment carries considerable morbidity and increases medical costs.

Recently, gene expression profiling utilizing DNA microarrays has been used to examine the expression levels of large numbers of genes in tumors from a variety of cancers (*6,36-38*). The tumors can then be characterized with regard to risk of disease progression based on statistical analyses of expression patterns in relation to known clinical outcomes (*39-41*). Those tumors whose profiles have a high correlation (based on a designated cutoff for the correlation coefficient) with the good prognosis profile would be classified as "good prognosis" and would otherwise be classified as "poor prognosis". Genes may also be selected for an expression profile based on biologic function or on previously developed profiles, rather than on an empirical basis (*42*). Gene expression profiling may be applied to fresh frozen (*3*) or paraffin-embedded (*4*) tissue and utilize different types of microarrays (*43*).

Recent studies have suggested statistically significant differences in survival between prognostic groups based on their gene expression profiles in a cohort of 295 early stage breast cancer patients from the Netherlands Cancer Institute (*3*), and in 234 lymph node-negative, estrogen receptor positive patients from the National Surgical Adjuvant Breast and Bowel Project B-20 trial in the

U.S. (*4*). Gene expression profiling generally identifies a smaller proportion of women who would benefit from chemotherapy than the NIH guidelines. If gene expression profiling can more accurately identify women who will not develop progressive disease, it has the potential to spare those women from unnecessary chemotherapy, improve patient quality of life, and reduce the costs of cancer care. However, these potential benefits must be considered along with the costs of the assay and its accuracy compared with traditional clinical staging. The tradeoff between these factors is not clear, as no quantitative assessments have been conducted to date. It is important to weigh these risks and benefits because of the considerable human and economic burden of breast cancer. In the U.S., breast cancer is the leading incident cancer among women (*1*) and treatment costs are over $6 billion annually (*12*). To better examine the tradeoffs between gene expression profiling and the NIH guidelines, and to guide policymaking about gene expression profiling, we constructed a decision model to evaluate the cost-effectiveness of utilizing gene expression profiling vs. the NIH guidelines for risk stratification in women with early stage breast cancer.

PATIENTS AND METHODS

Our analysis considers a cohort of premenopausal women (44 years of age) with Stage I/II breast cancer requiring evaluation for risk of disease progression in order to identify them as candidates for adjuvant chemotherapy. The demographic and clinical characteristics of this target population were chosen to be similar to

those of the Netherlands Cancer Institute cohort, upon which our estimates of test performance are based, and for which we derived empirical estimates for model parameters (*3*).

Our decision model (Figure 1) compares gene expression profiling and the NIH guidelines as prognostic tests to evaluate the risk of disease progression for women with early stage breast cancer. The model begins with a decision tree depicting the prognostic categorization and treatment of women with early stage breast cancer during the 6-month period following diagnosis and is followed by a Markov model that depicts the long-term outcomes of these patients over their remaining lifetime. At the time of diagnosis, the use of either prognostic test can lead to identification of women at high risk (test-positive) or at low risk (test-negative). We assumed all test-positive women receive chemotherapy, all test-negative women do not receive chemotherapy, and all women live at least six months after diagnosis.

The possible clinical outcomes beginning 6-months post-diagnosis until death are: treatment response, disease progression, and death (Figure 1). All women begin the time period 6-months post-diagnosis in treatment response and their status can change at 12-month intervals. From treatment response, she can continue to respond to treatment, experience disease progression, or die (of a non-breast cancer related cause). The only way a woman can die of breast cancer is to die of disease progression. Disease progression was considered to be irreversible;

that is, once a woman experiences disease progression, she would no longer respond to treatment and would progress until death.

We adopted the societal perspective for this analysis. Throughout the analysis, we followed the recommendations of the Panel on Cost-Effectiveness in Health and Medicine whenever possible (*29*). We programmed the model in a Microsoft Excel spreadsheet and validated it using decision analysis software (Data 4.0, Williamstown, MA). Study procedures were approved by the University of Washington Institutional Review Board, in accordance with an assurance filed with and approved by the U.S. Department of Health and Human Services.

Model Parameters

The model parameters consisted of probabilities of clinical events, costs, and utilities. Utilities adjust survival for quality of life and range from 0 (death) to 1 (perfect health) (*29*). The value for the main analysis, range of values for the sensitivity analyses, and sources for each parameter are shown in Table 1.

Probabilities of clinical events: We calculated the probabilities of a patient being test-positive or test-negative, the baseline risk of progression for each prognostic group, and the mortality associated with disease progression from Kaplan-Meier survival analyses of patient-level data from the Netherlands Cancer Institute cohort. The Netherlands Cancer Institute cohort was a consecutive, population-based group of 295 breast cancer patients ≤52 years of age. The cohort had approximately equal

proportions of women with lymph node negative and positive disease, and the majority of the cohort (63%) did not receive adjuvant chemotherapy. The type and duration of chemotherapy was not specified in the database. The median duration of follow-up was 6.7 years. Although there appeared to be more favorable survival among women in the poor prognosis group who received chemotherapy compared to women who did not, there were approximately equal proportions of women who received chemotherapy in the gene expression profiling and the NIH guidelines poor prognosis groups, potentially avoiding substantial bias in the progression risk estimates. Death from causes other than breast cancer was obtained from life tables (*44*).

Risk reduction from adjuvant chemotherapy: Results from the Early Breast Cancer Trialists' Collaborative Group meta-analysis of adjuvant systemic therapy (*35*) suggest that for women <50 years old with risk factors for disease progression, chemotherapy reduces the 10-year risk of disease progression by 35%. We applied this risk reduction to the yearly progression risks for the poor prognosis groups. Because gene expression profiling was designed and validated to identify women at high risk of distant progressive disease, and because the prognosis of women with distant as compared to locoregional progression is less favorable (*45*), we did not consider the risk of local or regional progression. In the Netherlands Cancer Institute cohort, 4% of the women had locoregional progression, vs. 34% with distant progressive disease.

Economic Costs: We included direct medical and non-medical (time and transportation) costs in our calculations. Gene expression profiling has only recently been marketed for clinical use (at a price of $3,460) (*5*), and most insurance companies have not yet established reimbursement policies (*46*). Therefore, we also considered the costs of DNA microarray kits that are used for research (as a lower bound) (*43*), and the cost of BRCA 1/2 mutation testing (as an upper bound) (*47*).

Direct medical costs for breast cancer were based on estimates from the published literature and from a microcosting analysis we performed utilizing managed care reimbursement data. To assign costs to adjuvant chemotherapy and disease progression, we incorporated point estimates for the annual/episodic costs of breast cancer treatment from the literature. We considered studies that were conducted in a U.S. healthcare setting, estimated costs for the relevant health states, were published after 1990, and explicitly described their methods. When appropriate, we reconciled costs vs. charges and adjusted costs to be representative for the age distribution of our target population. We found a limited number of articles on chemotherapy costs in breast cancer; most costs were estimated for older chemotherapy regimens and there was substantial variation in reported results. Thus, to supplement the cost information from the literature, we performed a microcosting analysis. Utilization was based on clinical guidelines (*2,30*) and consisted of chemotherapeutic (doxorubicin and cyclophosphamide) and anti-

nausea agents, and surgical, laboratory and other procedures, such as Port-A-Cath® placement, liver function tests and chest x-ray. Resource prices were based on reimbursement rates from Regence Blue Shield, a managed care organization in the Pacific Northwest. We computed incremental costs of gene expression profiling vs. the NIH guidelines, and we assumed the results of gene expression profiling /NIH guidelines only influenced chemotherapy (adjuvant and for progressive disease). Therefore, we did not evaluate the total treatment costs for the primary tumor. All costs were represented in 2002 U.S. dollars.

We estimated direct non medical costs by multiplying the estimated number of hours spent traveling to treatment facilities and in treatment (personal communication, study pharmacist (JSM)) by the average hourly wage for women ($13.48/hour) in the U.S. (*48*). Transportation costs were estimated based on typical miles traveled per visit (20 miles), cost per mile (36 cents, per IRS automobile mileage reimbursement rates) and cost of parking ($2).

Quality of Life (Utilities): Utility weights were based on estimates reported in the literature. We considered those studies that were published after 1990 and used the standard gamble or time tradeoff methods to estimate utilities (*29*). We included studies that estimated utilities for clinical outcomes in the model, with explicitly described methods and results that were stated numerically. While it would have been preferable to utilize estimates obtained from community-based samples (*29*), few such studies were available (*49*). We assigned utilities to the following clinical

outcomes: 6-months post-diagnosis, no chemotherapy; 6-months post-diagnosis, with chemotherapy; treatment response; and disease progression.

Calculating Cost-Utility Ratios

Costs and quality-adjusted life years (QALYs) for future years were discounted at 3% per year. The incidence of distant metastasis, the incidence of breast cancer death, total QALYs and direct medical and non-medical costs were calculated for gene expression profiling and the NIH guidelines. To validate the model, the overall and progression-free survival outcomes derived from the model were compared with results from the Netherlands Cancer Institute cohort. Finally, we calculated the incremental cost-utility ratio, which is interpreted as the cost to provide 1 additional QALY. The numerator of the ratio is the difference in total costs between gene expression profiling and the NIH guidelines and the denominator is the difference in QALYs.

Sensitivity Analyses and Alternative Testing Strategies

We conducted one-way and multi-way sensitivity analyses to evaluate the effect of varying individual probabilities, costs and utilities on the model results. The one-way analyses were performed by varying one parameter at a time while holding the others fixed. All parameters in the model were included in the sensitivity analyses (Table 1). Probabilistic sensitivity analyses were performed using Monte Carlo simulation (*50*). For each of 10,000 simulations, the

probabilities, costs and utilities were randomly drawn from probability distributions that represented the uncertainty of each of the model parameters and a cost-utility ratio was calculated. We used logistic normal distributions to represent probabilities and utilities (*50*) and normal distributions for costs (*51*). The results of these simulations were summarized and yielded a mean cost-utility ratio and an "uncertainty interval" containing 95% of the values from the simulation (*51*). The uncertainty interval provides an estimate of the overall uncertainty in the model due to uncertainty in each of the model parameters. Gene expression profiling performance was varied by changing the cutoff for the minimum correlation coefficient to identify a tumor as good prognosis. In addition to evaluating the testing of all women with either gene expression profiling or the NIH guidelines, we also considered the following combined testing strategies 1) gene expression profiling for women positive on the NIH guidelines followed by chemotherapy for women who are positive on both the NIH guidelines and gene expression profiling; and 2) gene expression profiling for women negative on the NIH guidelines followed by chemotherapy for women positive on the NIH guidelines or gene expression profiling.

RESULTS

The NIH guidelines identified 96% of the cohort as high risk, whereas gene expression profiling identified 61% as high risk and thus candidates for chemotherapy (Table 2). This prognostic categorization yielded sensitivities of

98% for the NIH guidelines and 84% for gene expression profiling. Specificities were 51% for gene expression profiling and 5% for the NIH guidelines. Taking into account test sensitivity and the 35% risk reduction in disease progression with chemotherapy, utilization of the NIH guidelines to identify and treat high-risk women with chemotherapy would have prevented 34% of women from experiencing disease progression compared to 29% for gene expression profiling. When the disutility from chemotherapy and disease progression were included, gene expression profiling and the NIH guidelines yielded 9.86 QALYs vs. 10.08 QALYs, respectively. Total costs were $11,213 for gene expression profiling and $10,888 for the NIH guidelines. Because gene expression profiling produced higher costs and lower QALYs than the NIH guidelines, it was dominated by NIH guidelines and calculation of an incremental cost-utility ratio was not appropriate (*29*).

We validated the model by calculating the overall and progression-free survival outcomes and compared them to results from the Netherlands Cancer Institute cohort. We found that the hypothetical cohort in the model experienced a higher number of events than the women in the Netherlands Cancer Institute cohort. This discrepancy occurred because we took censoring into account by utilizing Kaplan-Meier survival analyses to estimate risks of disease progression and breast cancer mortality.

Because the NIH guidelines identified such a large proportion (96%) of women as high-risk, the alternative testing strategies did not differ substantially

from the main comparison of interventions in terms of the number of women tested with gene expression profiling or the number of women treated with chemotherapy. These strategies were not considered further.

Results of Sensitivity Analyses

The tornado diagrams (Figures 2 and 3) display the results of the one-way sensitivity analyses for the five most influential parameters. QALYs were most sensitive to gene expression profiling performance, the risk reduction from chemotherapy and chemotherapy utility. Given gene expression profiling's current level of performance, there was no cutoff for the correlation coefficient between the individual tumor profile and good prognosis tumor profile that would lead to gene expression profiling producing more QALYs than the NIH guidelines. Although the difference in QALYs was sensitive to variation in the risk reduction from chemotherapy and chemotherapy utility, the NIH guidelines were favored over the parameter ranges evaluated in the sensitivity analyses. Total costs were influenced by gene expression profiling performance and costs and chemotherapy costs. If gene expression profiling costs were approximately 25% lower or chemotherapy costs were 20% higher, it could produce lower costs than the NIH guidelines if all other parameters were held constant. The multi-way probabilistic sensitivity analysis, based on 10,000 replications with values drawn from distributions for all the model parameters, demonstrated a 95% uncertainty interval of –0.32 to –0.09 for the difference in QALYs and -$430 to $1,132 for the difference in costs.

DISCUSSION

We evaluated the cost-effectiveness of utilizing gene expression profiling vs. the NIH guidelines to identify women with early stage breast cancer who would benefit from adjuvant chemotherapy. Gene expression profiling identified 35% fewer women for chemotherapy than the NIH guidelines, sparing these women from the morbidity associated with chemotherapy and saving medical costs. However, our analyses suggest that these quality of life and economic benefits are outweighed by differences in prognostic test performance. Gene expression profiling failed to identify 16% of the women who would progress, whereas the NIH guidelines failed to identify 2% of the women who would progress. Given the estimated 35% reduction in progression risk with chemotherapy, gene expression profiling would effectively prevent disease progression for 21% of women, compared to 29% for the NIH guidelines. Thus, even though the NIH guidelines have poor specificity compared to gene expression profiling, they have higher sensitivity, which has a larger impact on life expectancy and quality of life. Sensitivity analyses suggest gene expression profiling performance, i.e., the chosen threshold correlation coefficient to identify a poor prognosis tumor, was the greatest driver of quality-adjusted life expectancy and costs and that an improvement in sensitivity without sacrificing specificity may enhance quality-adjusted life expectancy and costs compared to the NIH guidelines. In other words,

if gene expression profiling could identify the women who will develop disease progression as accurately as the NIH guidelines, and continue to better identify those women whose cancers will not progress, it would yield higher quality-adjusted life expectancy and lower costs than the NIH guidelines. Although QALYs were also sensitive to the risk reduction and utility from chemotherapy, our results suggest that variation in these parameters will not lead to greater QALYs for gene expression profiling than the NIH guidelines. In contrast, the difference in overall costs was sensitive to the costs of chemotherapy and gene expression profiling, and large but not implausible changes in these costs (25% decrease for gene expression profiling, 20% increase for chemotherapy) could lead to gene expression profiling producing lower overall costs than the NIH guidelines.

Our analysis has several important limitations. There is substantial uncertainty in several of our model parameters, including the cost of gene expression profiling and the performance of gene expression profiling. Gene expression profiling has only recently been marketed for clinical use, and has been performed on a variety of patient populations utilizing different types of microarrays. Also, although approximately equal proportions of women in the gene expression profiling good and poor prognosis groups received adjuvant chemotherapy, the type and duration of chemotherapy was not specified, which may have introduced bias in the estimates of progression risk. Finally, we assumed all women in the poor prognosis groups received chemotherapy. In practice, some physicians may not follow the NIH guidelines in recommending chemotherapy or

patients may refuse chemotherapy and prevalence of chemotherapy use is considerably lower than the 96% and 61% we utilized for the NIH guidelines and gene expression profiling, respectively (*9,10*). Assuming equivalent compliance for gene expression profiling and the NIH guidelines, we would not expect imperfect compliance to have a dramatic effect on results. However, compliance with recommended treatment by patients and physicians may be enhanced with gene expression profiling, and this idea merits further study. We specified a one-time event cost associated with disease progression. However, women who initially survive disease progression may continue to accrue treatment costs associated with it, so progression costs may be underestimated, leading to an overestimate of the cost-effectiveness of gene expression profiling. In addition, we assumed a universal mortality rate from disease progression. However, the risk of mortality from disease progression may differ according to prognostic group. We were not able to accurately infer estimates of mortality for each prognostic group because of the small sample sizes.

Our analysis is the first evaluation of the impact of gene expression profiling testing on clinical outcomes, patient quality of life and economic costs. Gene expression profiling is an emerging technology with significant potential. As gene expression profiling algorithms are validated in well-designed clinical studies based on standardized protocols, its value as a prognostic factor may be enhanced. Because of the challenges of evaluating tradeoffs between life expectancy and quality of life, cost-effectiveness analysis is a useful method to assess the clinical

and economic value of gene expression profiling in clinical practice. It also highlights other issues associated with translating gene expression profiling from a research to a clinical setting, such as test validation in diverse patient populations. This cost-utility analysis of gene expression profiling technology in breast cancer patients may serve as a model for the evaluation of other gene expression profiling techniques that are in development, in breast cancer and in other cancers.

Table 2.1. Parameters used in decision model

Parameter	Reference-case Value (range)	Reference
Probabilities (annual)		
Disease progression[a]		
Gene Expression Profiling Low Risk		
Years 1-10	0.018	(*3*)
Years 11+	0.009	(*3*)
Gene Expression Profiling High Risk		
Years 1-10	0.069	(*3*)
Years 11+	0.007	(*3*)
NIH Guidelines Low Risk		
Years 1-10	0.020	(*3*)
Years 11+	0.000	(*3*)
NIH Guidelines High Risk		
Years 1-10	0.047	(*3*)
Years 11+	0.008	(*3*)
Relative risk for disease progression from adjuvant chemotherapy	65% (±25%)	(*35*)
Mortality due to disease progression	27% (±25%)	(*3,52,53*)
Mortality from other causes[b]	0.01-0.62	(*44*)
Utilities		
Post-diagnosis: no adjuvant chemotherapy	0.8 (0.6-1.0)	(*54*)
Post-diagnosis adjuvant chemotherapy	0.5 (0.3-0.9)	(*54-56*)
Treatment Response	0.9 (0.8-1.0)	(*49,54,57-59*)
Disease progression	0.3 (0.2-0.5)	(*49,58,59*)
Costs		
Gene expression profiling	$1,500 ($1,000-$2,000)	Estimated based on currently available genetic tests for breast cancer (*5*) (*43*) (*47*)
Adjuvant chemotherapy reimbursement organization,	$5,300 ($3,800-$6,800)	Microcosting analysis using rates from a managed care (*15,16,23,55,60*)
Disease progression	$25,300 ($21,300-$29,300)	(*7,15,19,33,55,56*)

[a] Progression risk depended on prognostic group and duration of treatment response
[b] Background mortality was estimated for 5-year age increments

Table 2.2. Cost-effectiveness of gene expression profiling vs. NIH guidelines

	Gene Expression Profiling	NIH Guidelines	Difference
Sensitivity	84%	98%	-14%
Specificity	51%	5%	46%
Proportion of women treated with chemotherapy	61%	96%	-35%
Expected proportion of disease progression prevented	29%	34%	-5%
Costs	$11,213	$10,888	$325
Quality- adjusted life years	9.86	10.08	-0.21

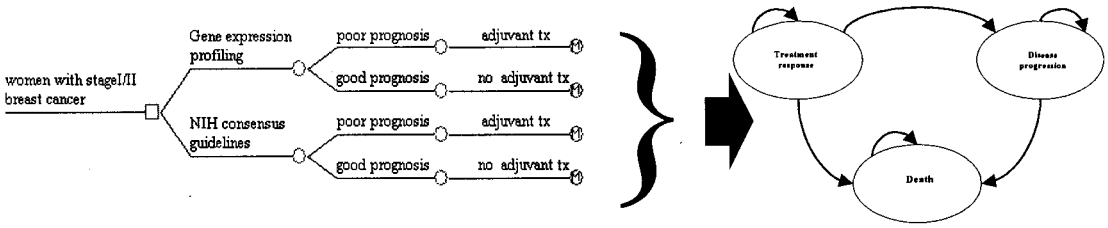

Figure 1. Diagram depicts decision model, consisting of decision tree (for the time period from diagnosis to 6-months subsequent) and a Markov model (from 6-months post-diagnosis until death), which shows all possible clinical outcomes and transitions between them.

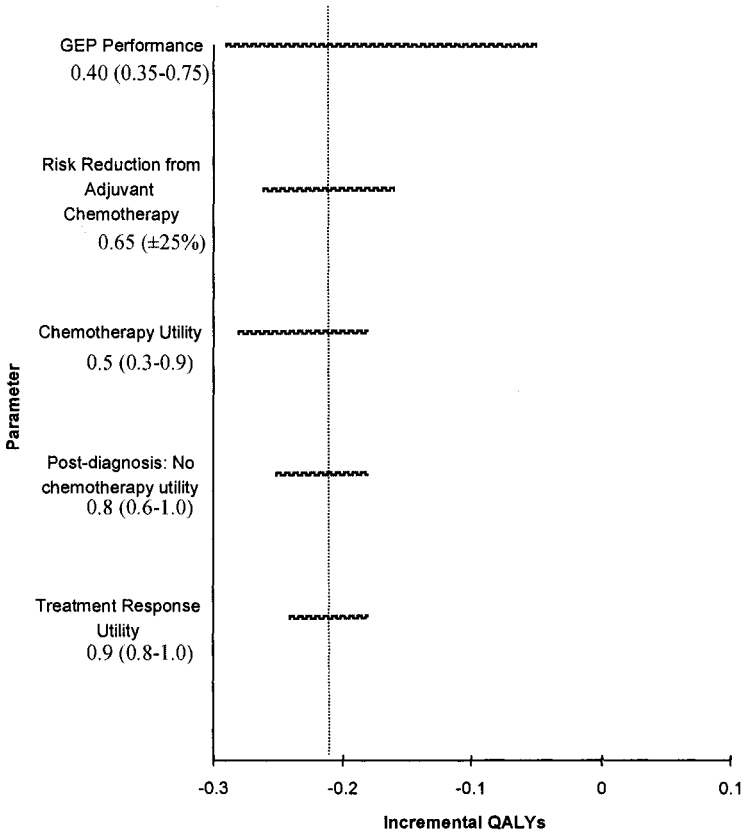

Figure 2. Diagram depicts the five most influential model parameters in determining QALYs, from most to least influential, and the effect of varying these parameters on total QALYs

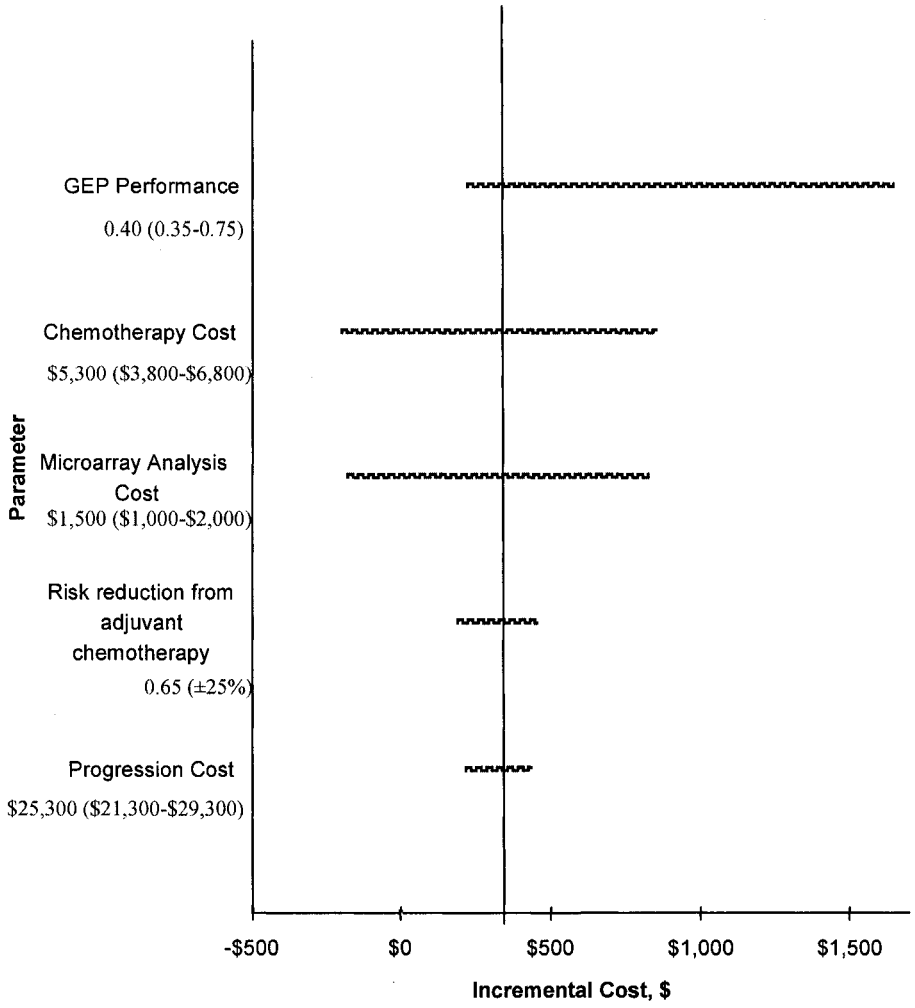

Figure 3. Diagram depicts the five most influential model parameters in determining costs, from most to least influential, and the effect of varying these parameters on total costs.

Chapter 3: Overall Summary

Cancer is a heterogeneous disease and there is great variation between patients in a tumor's natural history. It is clear that patients and cancer specialists need ways to make better treatment choices, and it is a worthy goal to spare women from unnecessary chemotherapy. This dissertation provides evidence, derived from population-based estimates of test performance, that gene expression profiling (GEP) may lead to lower life expectancy, on average, than utilization of the NIH guidelines to identify breast cancer patients for adjuvant chemotherapy. Similar to our conclusions, cancer specialists at the recent American Society of Clinical Oncology (ASCO) meeting (*61-63*) were intrigued by the potential of genomic tools, but unconvinced by their current performance. The mediocre performance of gene expression profiles developed to date, relative to standard of care, may be explained by several factors. One problem with microarrays is that multigene classifiers lose predictive value across different types of microarrays, and there are many different microarray types currently in use. Even when the same type of microarray is used, there have been persistent issues of reproducibility and validation. These problems constitute significant barriers to the dissemination of this technology in clinical practice. In order for prediction assays to be used successfully, validation of these assays must occur; there will need to be effective interdisciplinary collaboration between statisticians, clinicians and biologists, conducting thoughtfully designed prospective validation studies. Recent work conducted by Genomic Health holds promise. Using reverse transcriptase

polymerase chain reaction methods to ascertain gene expression, they have developed a profile to predict progression risk following tamoxifen use for patients with node-negative, estrogen receptor-positive disease, who are commonly considered to be at low risk of recurrence. Genomic Health and its collaborators have likely amassed the largest number of patients to date for the validation of a gene expression profile. Additionally, they have planned international trials for the use of this technology. However, it appears that the development of clinically meaningful gene expression profiles and validation of existing profiles is not keeping pace with their marketing for clinical use, and poor outcomes may result. In order for these tests to produce beneficial outcomes, it will be necessary to validate them prior to marketing them for clinical use. However, the FDA is not currently supporting this notion, as it is not actively regulating manufacturers of in-house or "home-brew" tests, such as the profile developed by Genomic Health, "Oncotype DX". To date, the sensitivity and specificity of this test have not been publicly available, so its clinical utility relative to NIH guidelines is uncertain.

Our analysis suggests that gene expression profiling requires additional refinement and validation before implementation in clinical practice, and highlights the usefulness of cost-utility analysis in clarifying the tradeoffs between life expectancy, quality of life, and costs in the era of genetic assays. The performance of gene expression profiling was the most influential component of our economic model. Even though utilization of the NIH guidelines is not considered an ideal method to identify high-risk breast cancer patients, it is the only proven decision

tool available. When the repercussions of a test failing to identify a woman at high risk may result in her premature demise, test sensitivity is critical. Once the sensitivity of gene expression profiling is equivalent to that of the NIH guidelines, the costs of chemotherapy and the technology itself will have a more important influence on the decision to adopt gene expression profiling into clinical practice.

In order to provide unbiased evidence of GEP's clinical utility, it will be necessary to conduct controlled clinical trials in which all women classified by GEP as high-risk are recommended for chemotherapy and GEP low-risk women are randomized to chemotherapy or no chemotherapy. Ultimately, the most informative studies may involve the evaluation of the incremental prognostic value of GEP over standard pathologic predictors, such as estrogen receptor status, tumor grade and proliferation markers such as Ki-67 and mitotic count, as the status of these predictors is routinely collected at the time of diagnosis.

There are also human and institutional factors to consider when evaluating the adoption of GEP into clinical practice. For example, it is possible that even if GEP's performance were in clinical equipoise with that of the NIH criteria, the technology may not be acceptable to patients, physicians or payers. Individuals may have different attitudes towards and perceptions of risk (*64*), which will affect their valuation of GEP and whether or not to undergo or recommend chemotherapy. For instance, the withholding of chemotherapy may cause undue anxiety for some patients and they may prefer to undertake chemotherapy, along with its potentially toxic complications to have peace of mind that they have done all they could to

prevent future disease progression. Given that attitudes may differ, it is imperative that physicians communicate information about risks and benefits in a useful way for the patient so that she may make her most informed decision. Similarly, a physician may be more or less risk-averse, which will affect their likelihood of recommending chemotherapy. For instance, there may be some physicians who, when faced with a patient whose breast tumor has spread to the lymph nodes, would recommend chemotherapy regardless of the outcome of a prognostic test. To our knowledge, there is no evidence to suggest how oncologists and patients deal with the benefits and risks of chemotherapy or prognostic tests in breast cancer. Physician education is imperative to assist with this physician-patient communication. A similar amount of attention should be paid to education of healthcare providers in health communications in genetic tests for prognosis as there has been for tests of disease susceptibility (i.e., BRCA 1/2).

Physician education will be necessary not only to assist in communication with patients in the era of genetic assays, but also for their own information. Currently, there is considerable discrepancy between NIH consensus guidelines and actual use of chemotherapy in community practice (*10*), and this discrepancy may be partially attributable to lack of physician education about the guidelines. If this discrepancy is occurring because physicians perceive the guidelines are overly conservative, they may place more credence in GEP than the NIH guidelines. Also, physicians may be more likely to comply with recommendations based on GEP results, because it takes the individual patient's tumor behavior into account. Even

if GEP were validated and acceptable to patients and physicians, its diffusion could also differ by payer. Each payer may be facing different costs for chemotherapy, treatment of disease progression and other related utilization, and their enrollees may differ in demographic characteristics (e.g., age), which would affect the tradeoffs between utilization of GEP vs. NIH guidelines.

In conclusion, given that chemotherapy has been shown to be efficacious in preventing disease progression in breast cancer, and a breast cancer patient is far more likely to die from disease progression than from chemotherapy toxicity, the FDA could adopt a precautionary stance and regulate developers of gene expression profiles more strongly, requiring strict evidence of clinical utility before such tests are permitted to be marketed. Once the clinical utility of GEP relative to NIH guidelines has been demonstrated, acceptability to patients, physicians and payers can be considered.

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Education

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Concentrations: health economics, clinical epidemiology and health policy
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Master of Science
School of Public Health and Community Medicine, University of Washington, Seattle, WA
Concentration: epidemiology
1997 – 2000

Bachelor of Science, cum laude
The Wharton School, University of Pennsylvania, Philadelphia, PA
Majors: finance and economics
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Awards

PhRMA Foundation Pre-doctoral Fellowship in Health Outcomes, 2003-2004
American Foundation for Pharmaceutical Education Pre-doctoral Fellowship, 2002-2003Plein Endowed Research Fund Pre-doctoral Fellowship, 2002-2003
Cancer Prevention Research Training Grant, National Cancer Institute, 1999-2002
Winner of Committee on Affiliates Student Poster Contest, American Public Health Association Annual Meeting, 1999
John Stenner Collegiate Cycling Scholarship, 1997

Research and Professional Experience

Doctoral Research
University of Washington, Seattle, WA
Dissertation: Cost-effectiveness of DNA microarray analysis in women with early stage breast cancer
Funding: See Pre-doctoral Fellowship Awards
Dissertation Committee: David Veenstra and Scott Ramsey (Chairpersons), Jeannine McCune, Wylie Burke
Scope of Research: Studying the cost-effectiveness of utilizing DNA microarray analysis vs. standard clinical criteria to identify early stage breast cancer patients for adjuvant chemotherapy. Designing a disease simulation model using decision analytic techniques to compare long-term clinical, economic and patient outcomes among premenopausal patients undergoing evaluation for risk of disease progression to guide the use of adjuvant chemotherapy. Performing statistical analyses of retrospective cohort data, cancer registry data and administrative claims database to estimate clinical and economic parameters in model.

Research Assistant
University of Washington, Seattle WA
Advisor: Jacqueline Gardner, June 2002-September 2002
Responsibilities: Developed data collection instruments and managed and analyzed data for cohort study to assess the feasibility of community pharmacists directly initiating and managing hormonal contraceptive methods for women
Advisor: Sean Sullivan, March 2001-June 2001
Responsibilities: Evaluated medical care utilization and production loss associated with severe asthma related events within the U.S. cohort of a clinical trial

Research Fellow/Assistant
Fred Hutchinson Cancer Research Center, Group Health Cooperative Center for Health Studies, Seattle, WA
Advisor: Emily White, June 1998-June 2002
Responsibilities: Collaborated in research design and grant writing and analyzed data for studies of breast cancer surveillance technologies
Advisor: Anne McTiernan, September 1997–June 1998
Responsibilities: Developed protocol and data collection instruments for clinical trial

Research Intern
Department of Functional Restoration, Stanford University School of Medicine, Stanford, CA, January 1997 – May 1998
Responsibilities: Collaborated in study design, cleaned and analyzed data for study of muscular strength and flexibility imbalances and iliotibial band syndrome

Financial Manager
J.T. Wakimoto Management, Inc., San Jose, CA, January 1994 – August 1997
Responsibilities: Prepared budgets, cash flow projections and variance analyses for property management firm with over $350 million in assets under management

Asset Manager
Office of the Trustee of the United States Bankruptcy Court, Los Altos, CA, November 1992-December 1993
Responsibilities: Managed real estate in bankruptcy and prepared financial reports for bank creditors

Research Associate
Coopers & Lybrand, San Jose, CA, August 1990 – September 1992
Responsibilities: Performed financial analyses in connection with mergers and acquisitions transactions, expert witness testimony and fraud investigations for worldwide accounting and consulting firm

Teaching Experience

Teaching Assistant / Lab Section Leader
University of Washington, Seattle, WA
Quantitative Methods II (Biostatistics), PharmD Program, Coursemaster: David Blough
March 2002 – June 2002
Medicine, Health and Society (Human Biology), MD Program, Coursemaster: Sean Sullivan
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Professional Service

Member
Faculty Search Committee, Pharmaceutical Outcomes Research and Policy Program, University of Washington, 2003
Admissions Committee, Pharmaceutical Outcomes Research and Policy Program, University of Washington, 2003

Ad hoc Reviewer: Cancer Epidemiology Biomarkers and Prevention, JAMA

Peer-Reviewed Publications

Oestreicher N, Lehman CD, Seger DJ, Buist DS, White E. The incremental contribution of clinical breast examination to invasive cancer detection in a mammography screening program. American Journal of Roentgenology. In press.

Oestreicher N, White E, Porter PL, Malone KE. Hormonal factors and breast tumor proliferation: Do factors that affect cancer risk also affect tumor growth? Breast Cancer Research and Treatment. 2004;85: 133-42.

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McTiernan A, Ulrich C, Yancey D, Slate S, Nakamura H, **Oestreicher N**, Bowen D, Yasui Y, Potter J, Schwartz R. The Physical Activity for Total Health (PATH) Study: rationale and design. Medicine & Science in Sports & Exercise. 1999;31: 1307-12.

Manuscripts in Preparation

Oestreicher N, Veenstra DL, Linden HM, McCune JS, van't Veer LJ, Ramsey SD. Gene expression profiling and breast cancer treatment: Cost-utility analysis to evaluate prognostic test performance. Submitted to the Journal of the National Cancer Institute.

Oestreicher N, Veenstra DL, Linden HM, McCune JS, Ramsey SD. Treatment costs of early stage breast cancer. In preparation.

White E, Miglioretti DL, Yankaskas BC, Geller BM, Rosenberg RD, Kerlikowske K, Cutter G, Vacek PM, Carney PA, Buist DSM, **Oestreicher N**, Barlow W, Ballard-Barbash R, Taplin SH. The interval between screening mammograms and risk of late stage breast cancer, by age and breast density. Submitted to the Journal of the National Cancer Institute.

Conference Presentations

Oestreicher N, Veenstra DL, Linden HM, McCune JS, Ramsey SD. The costs of adjuvant chemotherapy in early stage breast cancer patients: Comparison of attributable cost and microcosting approaches. Podium presentation, International Society for Pharmaceutical Outcomes Research Annual Meeting, Arlington, VA, May 2004.

Oestreicher N, Veenstra DL, Linden HM, McCune JS, Ramsey SD, van 't Veer LJ. The cost-effectiveness of microarray analysis in premenopausal women with early stage breast cancer. Poster presentation, San Antonio Breast Cancer Symposium, San Antonio, TX, December 2003.

Oestreicher N, Veenstra DL, Linden HM, McCune JS, Ramsey SD, van 't Veer LJ. The cost-effectiveness of microarray analysis in premenopausal women with early stage breast cancer. Poster presentation, American Society of Clinical Oncology Annual Meeting, Chicago, IL, June 2003.

Gardner JS, Miller L, Blough D, Downing D, **Oestreicher N**. Improving contraception practice and delivery through community pharmacists: The Direct Access study. Poster presentation, Association for Reproductive Health Professionals Annual Meeting, Denver, CO, September 2002.

Oestreicher N, White E, Lehman CD, Mandelson MT, Porter PL, Taplin SH. Predictors of sensitivity of clinical breast examination. Poster presentation, American Society for Preventive Oncology Annual Meeting, New York, NY, March 2001.

Oestreicher N, White E, Porter PL, Malone KE. Breast tumor proliferation in relation to breast cancer risk factors. Poster Presentation, Society for Epidemiologic Research Annual Meeting, Seattle, WA, June 2000.

DeRoo L, **Oestreicher N**, Shaw C. Birth outcomes of women with neoplastic conditions. Poster Presentation, American Public Health Association Annual Meeting, Chicago, IL, November 1999.

Oestreicher N, Nakamura H, McTiernan A. The PATH Study: Effects of Exercise on Endogenous Sex Hormones in Postmenopausal Women. Poster Presentation, National Action Plan on Breast Cancer Workshop on Physical Activity and Breast Cancer, Albuquerque, NM, November 1997.