Associations Between Funding Source and Results of Cost Effectiveness Analyses of Drugs Used in Breast Cancer

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Abstract:

Background: Cost effectiveness studies are increasingly included in the regulatory decisions of many countries and in formulary decisions in the United States. Pharmaceutical company sponsorship of economic analyses of oncology drugs previously has been associated with reduced likelihood of reporting unfavorable results. Demonstrating persistence of this relationship may help enable better interpretation of study results and development of strategies to address potential bias.

Methods: Breast cancer was selected for analysis since it is the cancer with the largest number of cost effectiveness studies and the cost of recent drugs has caused questioning of their incremental cost effectiveness. Search of the Tufts Medical Center Cost Effectiveness Analysis Registry resulted in 105 studies published between 1991-2012 that evaluated the cost effectiveness of drugs used to prevent or treat breast cancer. Overall study conclusions regarding cost effectiveness of the investigated drugs were evaluated using three thresholds: $50,000 per quality adjusted life-year (QALY), $100,000 per QALY, and $150,000 per QALY. A logistical regression was performed to determine how study characteristics including funding source were associated with study findings.

Results: Overall, 65 studies were funded by industry (62%). Studies with pharmaceutical company funding were more likely than studies with other funding to report favorable cost effectiveness estimates (75.4% vs 40.0%, OR=4.07 CI=1.44-12.26 at the $50,000 threshold; 80.0% vs 57.5%, OR=3.15, CI=1.07-9.84 at the $100,000 threshold; and 87.7% vs 67.5%, OR=3.65, CI=1.02-14.66 at the $150,000 threshold).

Conclusions: Industry sponsorship continues to be associated with a higher likelihood of reporting favorable results. These findings suggest that steps are necessary to ensure that the cancer cost effectiveness literature is not biased by sponsorship. Expanding funding sources other than pharmaceutical companies for these studies or pre-registering cost effectiveness studies may help mitigate this potential source of bias.
Glossary of Acronyms:

ACA    Affordable Care Act
ACP    American College of Physicians
CEVR   Center for the Evaluation of Value and Risk in Health
CI     Confidence Interval
ESRD   End Stage Renal Disease
GDP    Gross Domestic Product
HER2   Human epidermal growth factor receptor 2
IV     Intravenously
JMP    “jump,” Statistical Program developed by SAS
NHS    National Health Service
NICE   National Institute for Health and Care Excellence
OR     Odds Ratio
p-value Probability Value
PCORI  Patient-Centered Outcomes Research Institute
QALY   Quality Adjusted Life Years
SAS    “Statistical Analysis System” Statistical Software Company
SD     Standard Deviation
Tufts CEA Registry Tufts Medical Center Cost Effectiveness Analysis Registry
U.K.    United Kingdom
U.S.    United States of America
VA     Veteran’s Health Administration
WHO    World Health Organization
Introduction

It is estimated that total world spending for health in 2010 was $6.5 trillion. In the United States we spend the highest amount per capita of any country, with an estimated $8,362 per person spent on health care in 2010. (1) In 2012, the health care spending in the U.S. was approximately $2.8 trillion which amounted to 18% of GDP. It is estimated that 11% of total health spending in the U.S. is paid out of pocket by individuals; the remainder is paid for primarily by private institutions and the government. (2) The government pays for 46% of health care in the country through expansive programs such as Medicare, Medicaid, the Veteran’s Health Administration (VA), the Public Health Service (including the Indian Health Service), and health care for federal employees including military service members. Health care costs at the state government level are significant due to state Medicaid programs. Outside of the government, corporations pay for a large portion of this country’s health care costs through employer sponsored health care. As members of society we pay directly or indirectly for health care through out of pocket expense, insurance premiums, taxes, reduced wages, and higher costs of services and products. In addition, large portions of the funds allocated to public services such as education, police, and defense are actually spent on health care. This has been popularized in the popular media including by Atul Gawande in the New Yorker when he described how his child’s school district, despite an increased budget, had to eliminate programs and employees due to health care costs. (3) As health care costs grow at a rate much greater than inflation or other sectors, even organizations whose focus is not health care such as the Department of Defense find health care spending taking up large portions of their budget. As the federal government attempts to reduce defense spending as it withdraws from two wars it finds that it is spending as much on health care as it is on military salaries and that 9.5% of the defense budget is spent on health care, which does not include the VA system. (4) This means that increased budgeting for public and private organizations is often spent on healthcare for employees or pensioners instead of strengthening the actual services provided by these organizations.

At levels ranging from individual through federal government, decisions about how to allocate limited funds are difficult and often contentious. At the family or individual level, money spent on health care is money that will not be spent on housing, entertainment, food, education, or other items. For the private employer, insuring employees and possibly retirees results in having to charge higher prices to the customer, providing reduced salary to employees,
and possibly reducing the number of employees. For federal and state governments, health care spending requires additional taxation and is money that is not spent on social welfare programs, infrastructure, education, or other programs. Many of the areas that appear to be in conflict with health programs in the budget actually affect the social determinants of health and play a large role in the health of citizens. This is important as it is estimated that 14.3% of American families were food insecure in 2013 (5) and an estimated 2.5 million American children are homeless every year. (6) In a world where resources are limited and tradeoffs between programs are a necessity, it is important to determine which health care costs are worth the benefit that they provide to the patient, payer, and society.

Cost effectiveness analyses are evaluations that are intended to help make the determination about what treatments are worthwhile by providing a cost to benefit value for medical interventions. Since such a calculation is more complex than it may appear on the surface, they often provide a cost per quality adjusted life year (QALY), which allows for different medical interventions to be compared to each other while taking into account difficult to measure costs and benefits, like loss of productive work time. While taking into account survival benefits, the use of QALYs also allows for comparing different states of health and quality of life. The QALY value cutoff that should be used to separate cost-effective from ineffective interventions depends on the payer and has not been formally established in most situations.

It has traditionally been thought that a cutoff of around $50,000/QALY in the U.S. should be used. This value has been thought to be set by the cost of dialysis for the treatment of End Stage Renal Disease (ESRD) in the 1970s, which was thought to be a worthwhile intervention. In the early days of dialysis there were not enough machines or funding to treat most of the patients dying of renal disease. In order to determine which patients to provide this experimental treatment, Seattle’s Swedish Hospital established a board of seven laypeople to select from the potential candidates. Decisions were often based upon a person’s value to society and social situation. This group which would be informally referred to as the “God Squad” was highlighted in a 1962 article in LIFE Magazine which shed light into how difficult these rationing decisions were to make and how they were often made based off of values that society as a whole may not deem appropriate such as age, sex, marriage status, likelihood of spouse being able to remarry, number of children, education, personal worth, and church participation. (7) This episode would prove important in the development of the field of bioethics. (8, 9) The Social Security Act was
amended in 1972 to have ESRD covered by Medicare. (10) This was the first time that a specific disease was covered by Medicare and has continued to this day. The willingness to have dialysis covered by the American taxpayer by Medicare would later be cited as to the origin of the $50,000/QALY threshold.

Interestingly, while this is a compelling story to explain the adoption of $50,000 as an appropriate QALY threshold value, the issue is far more complex than it appears. For starters, in the 1970s the cost for dialysis may have actually been closer to $25,000-30,000/LY. In addition, higher cost interventions were being funded at that time, suggesting that $50,000 was not the highest value deemed to be worthwhile. Perhaps most importantly, it was not until 1992 when a publication first used the $50,000/QALY cutoff. Looking objectively at why $50,000 was adopted, it may have been that it was selected arbitrarily due to it being a round number in the rough ballpark. (11) However, it has since been argued that in the U.S. a value closer to $100,000/QALY or $150,000/QALY may be more appropriate. (12) Even without a definite cutoff, cost effectiveness analyses and the cost per QALY that they provide gives a framework that allows for discussion of which interventions are worthwhile.

In some countries the value for a QALY threshold has been established in a more formalized fashion. For instance in the United Kingdom the National Institute for Health and Care Excellence (NICE) determines which health care interventions will be provided by the National Health Service (NHS) in England and Wales. While it does not use set cost effectiveness cutoffs to determine which interventions will be approved, cost effectiveness is one of the major determining factors for approval. Interventions that cost less that £20,000/QALY are normally considered cost-effective, while for those above that value the probability of acceptance in decreased. It has been shown that interventions that cost £40,000/QALY have had approximately a 50% chance of acceptance and interventions that cost £52,000/QALY have had approximately a 25% chance of acceptance. (13) The use of incremental cost effectiveness values to determine which interventions will be provided allows the NHS a means to attempt to provide effective care in a cost aware manner. The WHO has also provided guidelines for cost effectiveness by world region, and generally considers interventions that are less than per capita GDP as “very cost-effective,” interventions that are 1-3x per capita GDP as “cost-effective,” and interventions greater than three times GDP as “not cost-effective.” (14, 15)

In the United States, there is not a centralized funding source or performer of evaluations to determine which interventions are worthwhile economically. Since Medicare was created in
In 1965 it has been tasked with only providing care that is “reasonable and necessary,” however there has been controversy as to whether or not cost effectiveness should be included in determining which treatments meet this definition and concern that the government would ration care deemed to not be cost-effective. (16) A study looking at the national coverage determinations made by Medicare from 1999-2007 found that while Medicare decisions often mentioned cost effectiveness, there was no evidence of a threshold and it continued to cover numerous interventions which had been demonstrated to not be cost-effective. (17) However, insurers and payers factor in cost effectiveness when determining which interventions to provide as has been seen recently with the new treatments for Hepatitis C. (18) In addition, physicians are tasked with taking cost effectiveness into consideration as is made evident in the updated Ethics Manual of the American College of Physicians released in 2012 which says that,

“Physicians have a responsibility to practice effective and efficient health care and to use health care resources responsibly. Parsimonious care that utilizes the most efficient means to effectively diagnose a condition and treat a patient respects the need to use resources wisely....” (19)

Despite the importance of cost effectiveness studies, there is no centralized institution in the U.S. that funds or performs these studies. Perhaps one reason behind this is a lack of willingness to have a governmental or non-governmental organization determine what interventions a physician can prescribe for a patient. An aspect of this came to light during the debate that centered on the passing of the Affordable Care Act (ACA). In 2009, when the bill that would become the Affordable Care Act was being created there were provisions that would reimburse physicians for counseling patients about living wills, advance directives, and options for end-of-life care. Within the medical community, these are widely performed and respected discussions that are seen as important for patients and are rarely couched in terms of health care costs, with the intent of improving the end of life experience. However, in media and public debate these measures were depicted as “death panels” which would determine who should live and who should die. (20) While the original aspect of the proposed law, counseling patients about end-of-life care, had little to do with cost effectiveness, the surrounding issue centered strongly on it. Vice Presidential Candidate Sarah Palin is credited with starting the debate when she posted to Facebook,
“[G]overnment health care will not reduce the cost; it will simply refuse to pay the cost. And who will suffer the most when they ration care? The sick, the elderly, and the disabled, of course. The America I know and love is not one in which my parents or my baby with Down Syndrome will have to stand in front of Obama’s “death panel” so his bureaucrats can decide, based on a subjective judgment of their “level of productivity in society,” whether they are worthy of health care. Such a system is downright evil.” (21)

The imagined “death panels” which would play a major role in the health care reform debate would seem to harken back to the early days of dialysis and the “God Squad” combined with government bureaucracy.

The thought of a government payer or organization allowing individuals to die because it was not deemed cost-effective to treat them caused the portion of the ACA dealing with reimbursement for end of life conversations to be withdrawn and has affected much of the public debate surrounding medical therapeutic cost effectiveness. The ACA did succeed in creating an organization named the Patient-Centered Outcomes Research Institute (PCORI), which will be trusted with the task of performing comparative-effectiveness research of medical interventions. However, it prohibited PCORI from using cost-per-QALY thresholds to determine coverage of interventions—likely as a direct result of the controversial nature of “cost effectiveness.” This limitation has the capability to greatly reduce PCORI’s ability to evaluate medical interventions and is in sharp contrast to the UK’s NICE’s mandate. (22) This may reflect a deliberate intent to not replicate the cost effectiveness programs of some other nations and a tendency to not acknowledge the rationing decisions that must be made in a system with limited resources. In fact many of the aspects of the debate around the ACA focused on foreign examples. As supporters of health reform pointed to foreign examples of other systems with better outcomes at lower prices, their opponents talked about rationing, wait times, and worse treatment in the “socialist” systems abroad. In her article “My Drug Problem” in The Atlantic, Virginia Postrel made the argument that if she lived in New Zealand where Herceptin was not covered for early stage breast cancer, she would be dead if she was unable to travel and pay out of pocket. (23) These conversations exposed the unwillingness of many Americans to have a centralized organization determine which treatments are worth the cost.
Since there is no centralized institution responsible for performing or funding these studies, cost effectiveness studies are often funded by the pharmaceutical company that manufactures the drug. It is in their benefit to perform these studies because if they are able to demonstrate that their drug is cost effective then it is viewed as if the benefits outweigh the costs which may cause providers to increase prescriptions and payers to cover their cost. In a study previously performed by my co-authors 45% of the cost effectiveness studies evaluation cancer drugs were funded by industry. (24) With manufacturer funding being a large source of funding of these studies, it is possible that there is a conflict of interest that affects their outcomes. Financial conflicts of interest such as these have been identified as a major concern by the medical community. In 2009, the Institute of Medicine issued a comprehensive report on conflicts of interest in medical research, education, and practice and outlined a wide range of activities to reduce potential bias. (25) Some recommendations focused on reducing subconscious bias, including limiting pharmaceutical samples, (26, 27) acceptance of small gifts, (28, 29) and industry sponsorship of trainee lunches or continuing medical education. (27, 29) Other recommendations specific to research include mandatory disclosure (30) and institutional limits on relationships between researchers and industry. (31)

Conflicts of interest are particularly important for evaluating cost effectiveness of oncology pharmaceuticals. This is a class of treatments where great cost is spent on therapeutics that prolong life to an extent that may be of questionable value. It is also an area that is highly emotional and political—where withholding treatment due to cost or lack of evidence of efficacy can result in social and political outrage. In the past decade, the monthly cost of brand name oncologic drugs has doubled and these agents now account for the largest single therapeutic area in drug sales worldwide. (32) The cost of new oncology drugs has caused groups of oncologists to declare some new drugs to be unsustainably priced. (33) The importance of economic studies of oncology pharmaceuticals has increased, as some countries consider cost effectiveness estimates when reviewing applications for regulatory approvals for new oncology drugs (as well as for all drugs in general). Relative to other types of cancer, breast cancer accounts for the greatest share of published analyses in the cancer cost effectiveness literature (36%), (34) and the National Institute for Health and Care Excellence (NICE) has questioned the incremental value of recent new breast cancer drugs. (35)

In 1999, my co-authors analyzed cost effectiveness studies for drugs often used in cancer. They found 44 cost effectiveness articles published from 1988-1998 that analyzed hematopoietic
colony-stimulating factors, serotonin antagonist antiemetics, and taxanes. It was found that pharmaceutical company sponsored studies were less likely to report unfavorable cost effectiveness estimates for these drugs in cancer treatment. (24) This was followed in 2003 by two meta-analyses that both included original trials and cost effectiveness studies and found associations between industry sponsorship and pro-industry conclusions. (36, 37) Both of these systemic reviews were evaluating the biomedical research literature as a whole and were not focused on therapeutics or cancer specifically. In 2006 an analysis of 494 cost effectiveness studies published up to 2001 found that studies funded by industry were more likely than non-industry sponsored studies to report cost effectiveness ratios below three threshold values. (38) The studies included in that analysis were not limited to cost effectiveness studies of pharmaceuticals but rather included evaluations of any medical intervention. While it was also not specific to cancer, it may have indicated a general tendency at that time point for cost effectiveness studies funded by industry to be more likely to estimate that the intervention is cost-effective.

More recently, multiple other studies have shown that pharmaceutical company sponsorship is associated with favorable results in other areas of research. Favorable cost effectiveness conclusions for statin drugs, (39) endorsing the tested drug in cancer clinical trials, (40) and favorable conclusions despite non-supporting results in meta-analyses of antihypertensive drugs. (41) However, there have not been studies that have reexamined the relationship between sponsorship and cancer cost effectiveness outcomes for studies since 1999.

Since publication of my co-authors’ study in 1999, the number of published cost effectiveness studies published a year increased almost sevenfold (6.9 times from 1999 to 2011), with the percentage of studies pertaining to cancer remaining constant at 14%. (34) However, no study has examined the relationship between sponsorship and cost effectiveness assessments of oncology drugs in the recent era of increasing attention to cost effectiveness. Whether an association between industry funding and study findings in the cost effectiveness literature persists following incorporation of cost effectiveness assessments into regulatory decisions outside the United States as well as formulary decisions within the United States is unknown for cancer drugs in general and for therapies for breast cancer specifically.
Methods

Database of cost effectiveness studies

We obtained data on cost effectiveness studies from the Tufts Medical Center Cost Effectiveness Analysis Registry (Tufts CEA Registry, https://research.tufts-nemc.org/cear4/), which contains all English language, original studies of cost effectiveness found by searching MEDLINE by the key words QALYs, quality-adjusted, and cost-utility analysis. The database has a total of 4,007 cost-utility analyses which cover all diseases and treatments for which analyses have been published. It is well respected as has been used as a data source for fifty peer-reviewed publications. (42) Two reviewers with advanced training in decision analysis and cost effectiveness analysis extracted information from the articles using a standard auditing form. This form has three main sections: methodology, cost effectiveness ratios, and utility weights for a total of over 40 collected items. The process has been described in detail elsewhere. (43, 44)

We filtered the database for studies evaluating pharmaceuticals. A search was performed of these studies for those dealing with breast cancer, finding 110 studies published between 1991-2012. 1991 is the first year for which a cost effectiveness analysis for a breast cancer drug was in the registry despite the registry going back as far as 1976. The registry is currently in the process of inputting studies published in 2013. Studies are added to the registry in the order that they are indexed in PubMed which may be affected by what journal they are published in or their online release date. We therefore, decided to not include studies published in 2013 since there was a chance of bias in which papers would be included. We excluded 5 studies that evaluated drugs only in conjunction with specific clinical testing (eg. HER2 or radiological screening). This was done because these four studies were not purely focused on the cost effectiveness of the drug but evaluated different clinical testing protocols in combination with the evaluated drug. Excluding these studies yielded a final sample of 105 articles.

Analytic variables

For each article in our analysis information was extracted from the Tufts CEA Registry with the abstract or full article being referenced as necessary. The result for each cost effectiveness estimate determined in a paper was recorded. Therefore, it was possible for each paper to have multiple cost effectiveness evaluations associated with it. There was data gathered for each individual evaluation and for the papers as a whole.
The treatments given to the intervention and comparator arms of the study were extracted to determine what the cost effectiveness estimate was comparing. Drugs were categorized into five groups: hormonal therapy, chemotherapy, bisphosphonates, hematopoietic growth factors, and targeted therapies. The purpose of the treatment was characterized as prevention, first-line, adjuvant, second-line, or complication. The complication category included treatments aimed at addressing complications of the disease or treatment such as anemia, neutropenia, bone pain, or pathologic fractures. The stage of disease was determined as being primary prevention, early (stage IIIA or below), or late (above stage IIIA). The country used in the analysis was also extracted.

Tufts registry reviewers assigned each study a quality score from 1 (lowest quality) to 7 (highest quality) using the following criteria: whether the authors correctly computed the incremental cost effectiveness ratios, performed a sensitivity analysis, correctly used and specified the health economic assumptions used in the study, and if they appropriately and explicitly estimated the utility weights. (42) We considered studies that met or exceeded the median quality score of 4.5 to be “high quality.”

We identified study funding source from author affiliations and funding or disclosure information, if provided. For 13 studies, the funding source was not clearly stated in the original publication, and we determined study sponsorship by contacting the first or last authors, receiving responses in all cases. We categorized a study as having pharmaceutical company funding if it explicitly received funding from a pharmaceutical company or if at least one author was an employee of a pharmaceutical company.

Analyses

We converted the cost per QALY for each cost effectiveness estimate in a study using purchase power parities and adjusting for inflation to 2013 U.S. dollars, if necessary. Many of the studies included more than one cost effectiveness analysis. For example, if a study compared two separate drugs to the standard of care or only one drug but for multiple patient populations then it had multiple cost effectiveness estimates. Each of these was compared to 3 values: (1) $50,000/QALY, (2) $100,000/QALY, and (3) $150,000/QALY. For each of our evaluated cutoffs, we classified a study’s overall results as “cost-effective” if all of its analyses produced
cost effectiveness estimates equal to or more favorable than the threshold. We classified a study’s overall results as “not cost-effective” if none of its estimates were equal to or more favorable than the threshold. If there was a mixture of cost-effective and non-cost-effective results at a given cost effectiveness threshold, we classified the study as “mixed” at that threshold.

We used Fisher’s exact tests or Wilcoxon rank sum tests, as appropriate, to analyze associations between funding source and other study characteristics: (1) category of drug, (2) purpose of drug as evaluated in the study, (3) stage of disease, and (4) overall cost effectiveness results at the 3 cut-off thresholds. To assess if there was a difference related to the authors of the studies, papers were cross-referenced to determine if authors had more than one paper in this study. Papers where divided into three groups: (1) having only authors that had one article, (2) at least one author with two papers, or (3) at least one author with more than two papers in the breast cancer drug cost effectiveness literature. Fisher’s exact test was used to assess for differences based on authorship with multiple papers.

An analysis was performed to determine if the country that was used for the model was associated with cost effectiveness results. The location for the model was characterized as the United States, United Kingdom, Europe (other than U.K.), Canada, or other. An analysis was performed with country specific cutoffs of Canada: C$50,000, UK: £30,000, Europe (other than UK): €50,000, and everywhere else: US$50,000 to determine if using cost effectiveness thresholds typical for the countries modeled in the studies would result in different results from using $50,000/QALY for every study.

To assess for heterogeneity, a multivariate analysis via logistical regression was performed. A model was created to assess the variables of sponsorship, drug class, primary prevention, prospective design, paper quality, country, and number of publications by the authors in the data set. A 2-sided p-value less than 0.05 was considered to be statistically significant. All data analysis was performed using JMP Pro 11.0.0 (SAS Institute).

As a secondary analysis of previously published research findings, this project did not meet the definition of human subjects research. (45) It was approved by the Institutional Review Board of Brigham and Women’s Hospital.
Results

Of the 105 articles reporting on cost effectiveness of breast cancer drugs, 65 were funded by industry (46-110) and 40 had other funding. (111-150) [Figure 1] Consistent with trends in the cost effectiveness literature in general,(42) there has been a large increase in the number of articles published yearly with the peak being fifteen articles published in 2007. For most years, studies with pharmaceutical sponsorship have made up the majority of studies. The number of studies in general and pharmaceutical studies specifically, has decreased since the peak in 2007. [Figure 2] The number of studies published with funding other than from industry has remained relatively level. [Figure 3]

Overall, 42 (40.0%) of studies evaluated hormonal therapies, 37 (35.2%) evaluated chemotherapy, 9 (8.6%) evaluated bisphosphonates (including denosumab), 8 (7.6%) evaluated hematopoietic growth factors, and 16 (15.2%) evaluated targeted therapies (trastuzumab and lapatinib). [Table 1] All of the studies funded by a pharmaceutical company assessed a drug that the sponsoring company produced. There was a significant difference in which drug classes were evaluated by industry and other funded studies (p-value = 0.04). Pharmaceutical sponsored studies were more likely to analyze hormonal therapies (46.2% vs. 30.0%), bisphosphonates (12.3% vs. 2.5%), and hematopoietic growth factors (9.2% vs. 5.0%). Studies with other than industry sponsorship were more likely to evaluate chemotherapies (42.5% vs. 30.8%) and targeted therapies (25.0% vs. 9.2%).

There was a significant difference in the purpose of treatment for hormonal and chemotherapy drugs between the two groups. For hormonal therapies non-industry sponsored studies were more likely to evaluate the drugs for primary prevention while industry studies were more likely to focus on first line, adjuvant, or second line treatment (p-value <0.001). Among chemotherapy drugs non-industry funded studies primarily focused on adjuvant therapies while industry studies also evaluated first and second line treatments (p-value = 0.02).

There was a significant difference in the stage of disease assessed in industry versus other funded studies (p-value < 0.001). Non-industry studies were more likely to evaluate drugs for primary prevention (20.0% vs. 1.5%) and early stage disease (65.0% vs. 56.9%) while industry studies were more likely to evaluate late stage disease (40.0% vs. 12.5%).
There was not a significant difference in the quality of papers based on funding (p-value = 0.087). However, industry sponsored studies trended towards being of higher quality with a mean of 4.78 vs. 4.43.

Overall, 65 (61.9%) of studies were cost effective at a $50,000/QALY threshold, 75 (71.4%) at $100,000/QALY threshold, and 84 (80.0%) at $150,000/QALY threshold. [Table 2] Studies sponsored by industry were significantly more likely to find the intervention cost effective at all three thresholds (75.4% vs. 40.0%, p-value = 0.001 at $50,000/QALY; 80.0% vs. 57.5%, p-value = 0.037 at $100,000/QALY; 87.7% vs. 67.5%, p-value = 0.044 at $150,000/QALY). There was not a significant difference in drugs evaluated for primary prevention (p = 0.99). Treatments for early stage and advanced disease were significantly more likely to be found cost effective in studies sponsored by industry at a threshold of $50,000/QALY (early stage: 78.4% vs. 53.8%, p-value = 0.037; advanced disease: 73.1% vs. 0.0%, p-value = 0.005). There remained a significant difference among the 71 studies that were considered “high quality” and met or exceeded the median quality value of 4.5 (75.5% vs. 45.5%, p-value = 0.040). When drugs were evaluated at country specific cutoffs of Canada: C$50,000, UK: £30,000, Europe (Other than UK): €50,000, and everywhere else: US$50,000 there was no change from evaluating all studies at $50,000/QALY.

There was not a significant difference in cost effectiveness estimate based on country of study (p-value = 0.072). [Table 3] However, there was a trend towards significance with studies performed in the U.K. (80.0%) and Canada (82.4%) having a higher percentage of studies being cost effective when compared to those performed in the U.S (46.2%) or Europe (62.5%). The percentage of studies funded by industry greatly differed between countries with a high proportion of studies performed in the U.K. (85.0%) and Canada (76.5%) being industry funded while only 51.3% of those in the U.S., 58.3% in Europe, and 20.0% performed elsewhere were. [Table 4]

26 (24.8%) studies did not share any authors with other studies in this series. 79 (75.2%) had at least one author that had been an author for another paper. 54 (51.4%) had at least one author that had been on at least two other of the studies. [Table 5] There was a significant difference among these three groups in likelihood of favorable cost effective estimate (p-value = 0.049).

A breakdown of study outcome by pharmaceutical company sponsor was revealing. [Table 6] For two companies every study funded was found to be cost effective (Sanofi and
Bayer/Rhone Poulenc). Two companies also had very high rates of cost effective findings (AstraZeneca with 90.0% and Novartis with 93.8%). However, some companies had much lower rates like Amgen (33.3%) and GlaxoSmithKlein (33.3%).

The multivariate model found industry sponsorship to be significant at all three cost effectiveness cutoffs (OR 4.07, 95%CI: 1.44-12.26 at $50,000/QALY; OR 3.15, 95%CI: 1.07-9.84 at $100,000/QALY; OR 3.65, 95%CI: 1.02-14.66 at $150,000/QALY). [Table 7] Paper quality was significant at the $100,000/QALY threshold with an odds ratio of 0.52 per increase of 1 in paper quality (95%CI: 0.27-0.94). Having at least one shared author was significant for at least one other publication at the $50,000/QALY threshold (OR 4.51, 95%CI: 1.05-21.59) and for at least one author with more than one other paper at the $150,000/QALY threshold (OR 0.05, 95%CI: 0.00-0.60). None of the other variables were significant.

Discussion, Conclusions, and Suggestions for Future Work

We undertook this study to determine if the outcomes of cost effectiveness studies for breast cancer drugs are associated with funding source. This is important since these studies help inform policy makers’ decisions regarding drug coverage, providers’ prescription of these drugs, and the willingness of payers to pay for them. We found that pharmaceutical company sponsored studies were more likely to reach favorable cost effectiveness conclusions than studies funded by other sources at three different commonly used thresholds ($50,000/QALY, $100,000/QALY, and $150,000/QALY). Funding source remained significant in sub analyses specific for different stages of disease, high quality papers, and country specific cutoffs.

There are several factors that could cause this to be the case. One possibility is that there are differences in the types of evaluations that are undertaken. This is supported by there being significant differences in the characteristics of the studies based on funding source. Industry funded studies were more likely to evaluate hormonal therapy, bisphosphonates, and hematopoietic growth factors while other funded studies were more likely to evaluate chemotherapies and targeted therapies. Non-industry sponsored studies were more likely to focus on prevention and early stage disease while industry funded studies were more likely to focus on advanced disease. While these differences may be expected to have an effect on cost effectiveness results, neither agent nor stage of disease were significant variables in the multivariate analysis. There remains a chance that there are other background aspects of the
studies that are not captured in our analysis but that contribute to the significant differences in results.

Another possible cause of a difference in results is varying study quality. The average quality of industry sponsored studies was higher than that of other studies which is consistent with prior findings (151), however this was not statistically significant. While study quality was significant in the multivariate analysis at the $100,000/QALY threshold, it was not significant at the two other thresholds. It is not certain if this represents a genuine effect that contributes to difference in outcomes.

Another variable that was significant in the multivariate analysis was having an author that had more than one publication in our study. This could be important because it could point towards a tendency for authors that are active in the literature to produce multiple evaluations showing favorable cost effectiveness. It is possible that there would be a cadre of researchers that receive funding or support due to their tendency to have positive findings. Contrarily, it is possible that authors with multiple publications would have higher quality papers than authors with a single publication and that this could play a role.

The country of study was not statistically significant in the multivariate analysis. However, as countries such as the United Kingdom and Canada are more likely to have industry-sponsored studies and studies with cost effective results, it is possible that country of origin could have an effect. It could be that studies are more likely to be cost effective in those countries because companies know approximately what the cutoff of is required to gain approval and price their drug accordingly. It is also possible that the cost effectiveness literature in those countries is dominated by studies intended to gain drug approval while in the United States and Europe the literature is intended to answer more academic questions.

The design of this study does not allow for determination of the exact cause for the association between industry funding and favorable cost effectiveness findings. To the extent that this difference in findings reflects differences in researchers’ tendencies to conduct and publish cost effectiveness studies, such differential tendencies could bias the overall body of published cost effectiveness research, misleading policy makers. A total of 12 (8.0%) of the cost effectiveness studies evaluated were prospectively designed studies that included economic data collected alongside the clinical data. The retrospective nature of the majority of the cost effectiveness studies could allow potential study sponsors to make initial estimates of cost effectiveness results and only fund studies likely to report favorable findings. While prospective
clinical trials must be registered on clinicaltrials.gov in order to reduce the censoring of negative results, there is no such requirement for registering prospective economic studies. Retrospective analyses, clinical or economic, are not required to be registered anywhere.

A large portion of the cost effectiveness studies published in Canada (76.5%) and the U.K. (85.0%) are sponsored by industry. Also, these countries have a much higher proportion of studies with favorable cost effectiveness estimates (Canada: 82.4%; U.K.: 80.0%). These are countries where regulatory approval of drugs is much more tied to proof of cost effectiveness. It is possible that the cost effectiveness literature in these countries is mainly used by industry to prove cost effectiveness and gain approval of their therapies. A similar phenomenon that could explain the difference in results based on funding source would be if favorable studies are more likely to be modified for different country settings and republished. This would result in a cost effectiveness literature that is heavy in favorable studies that are repeated in multiple countries and light in unfavorable studies which are not repeated.

Our study has limitations. First, we examined only one cancer diagnosis (breast cancer), and the relationships we observed may be different for drugs targeting other types of cancer. Second, we considered only one type of economic relationship between pharmaceutical companies and researchers: direct funding of the reported analyses. Other types of financial and non-financial conflicts of interest are possible. Third, unmeasured variables such as patient population including severity of disease could confound our results. Another limitation in our methods is the way that the results of the studies were characterized. Studies were deemed cost effective, not cost effective, or mixed based the combination of the individual cost effectiveness estimates that were included in the study. This leaves some room for mischaracterization. For instance if a study funded by a pharmaceutical manufacturer compared their drug and their competitor’s drug to the standard of care and found their drug but not the competitor’s cost effective, then the study would be categorized as “mixed.” In actualty this is a favorable study for the sponsor since it does not only show their drug to be cost effective but also is unfavorable for their competition. This does not appear to be a factor in the vast majority of the papers included in this analysis and not attempting to identify these cases is the more conservative approach. If these papers were identified and characterized this would most likely make the effect due to sponsorship only greater.

Another weakness is that we did not take into consideration the number of evaluations that a study performed. The Cochrane Handbook suggests extreme caution in attempting to
perform meta-analyses of cost effectiveness studies. (152) Due to the way that we have characterized studies, studies that had several cost effectiveness estimates such as a wide range of patient populations or treatment options would be more likely to have at least one intervention not be cost effective and to be characterized as “mixed.” However, this would affect both industry and other funded studies.

The cancer cost effectiveness literature has expanded greatly over the past decade and is now incorporated into regulatory filings for pharmaceutical approvals in many countries. The associations we observe between the funding source and findings of cost effectiveness analyses of drugs used to prevent and treat breast cancer raise the possibility of bias in this important research literature. To rebalance this body of research and give policy makers the best possible information, health care purchasers, government agencies, and non-profit groups could increase their support for high-quality prospective pharmacoeconomic studies. (153) Also, encouraging registration of cost effectiveness studies at the initiation of phase III clinical trials may help address any bias due to non-publication of results unfavorable to drug manufacturers.

Suggestions for Future Work:

Our findings warrant further investigation into what is causing the difference in results based on funding source. One method would be to characterize the studies in greater detail in order to determine if there is a difference in the models used in industry versus other funded studies. For instance different patient populations could play a role. Characteristics such as age, time since diagnosis, and comorbidities could affect outcome. Sicker patients may receive the benefit of certain drugs for a reduced amount of time. If a patient is treated as an inpatient or outpatient greatly affects the cost of treatment. Another factor could be the treatment and screening protocols used. For instance if a drug is delivered intravenously (IV) whether or not a study coordinates its infusion with an already scheduled infusion visit (eg. IV bisphosphonate at time of chemotherapy administration) could affect the cost of treatment. Whether or not a study factors in travel time, loss work, and how it estimates quality of life weights would also affect its final cost estimate. Further research into the exact differences in the models used for analysis in these studies could help clarify the differences in how they are performed.

Other potential research could extend our project to make it more international. This would include articles not printed in English. This would allow for better analysis of what is going on in the literature as a whole. As mentioned previously, it is possible that favorable
studies are modified with industry funding and then published in other countries in order to get the drugs into wider use in those countries. This would not be replicated in studies with unfavorable cost effectiveness estimates. Comparing studies, their authorship, funding, and timeline could help elucidate if studies are being replicated in this manner.

Ideally, a formalized, non-industry source of funding would be made to strengthen this literature. This would help combat the preferential funding of projects that are anticipated to be favorable. This could also help to ensure that studies are performed in a more uniform manner which may eliminate possible cofounders and could allow for more accurate cost effectiveness estimates and a better understanding of the literature.
Summary

We evaluated 105 cost effectiveness studies for breast cancer drugs and found that industry sponsorship was associated with an increased likelihood of favorable results at three different cost effectiveness thresholds (75.4% vs 40.0%, OR=4.07 CI=1.44-12.26 at the $50,000 threshold; 80.0% vs 57.5%, OR=3.15, CI=1.07-9.84 at the $100,000 threshold; and 87.7% vs 67.5%, OR=3.65, CI=1.02-14.66 at the $150,000 threshold). This finding is consistent with previous findings from over a decade and a half ago. Since that previous study, the importance of cost effectiveness studies has increased as they are factored into regulatory and formulary decisions. Providers also make treatment decisions based off the benefit to cost associated with the treatment. If funding source produces a bias in this important literature then it is important to find ways to reduce this effect. This could be accomplished through increased funding for cost effectiveness studies from non-industry sources or registration of cost effectiveness studies in a way similar to clinical trials to prevent the preferential publication of favorable findings or the funding of retrospective analyses that are anticipated to be favorable. Further research is warranted to better characterize the differences between industry funded and other studies in order to determine what causes the difference in outcome. Also a more international review of the literature may provide a better understanding of how studies are funded, modified, and performed which will allow for better interpretation of results.
Acknowledgement

I would like to thank Peter Neumann, Sc.D. and the Center for the Evaluation of Value and Risk in Health (CEVR) at Tufts University for their work in establishing and maintaining the Cost effectiveness Analysis Registry and for allowing us to use the Registry.

For this project I was supervised by Dr. Mark Friedberg (RAND Corporation, BWH General Medicine, Harvard Medical School) and Dr. Charles Bennett (University of South Carolina, Hollings Cancer Center). They initially devised the project and provided guidance throughout as to how to best perform the data collection and analysis. They also critically edited a separate manuscript that has been submitted for publication-- aspects of which appear in part in this thesis.

I assisted in designing the study. I performed all data collection and analysis, drafted and revised the manuscript submitted for publication (as first author), and wrote this thesis.

Dr. Bennett receives financial and material support from the National Cancer Institute (1R01CA165609-01A1), the South Carolina SmartState Program, and the Doris Levkoff Meddin Medication Safety Center.
References:


60. Marchetti M, Carughi M, Colombo G. Cost utility and budget impact of third-generation aromatase inhibitors for advanced breast cancer: a literature-based model analysis of costs in the Italian


Figure 1: Number of Breast Cancer Pharmaceutical Cost Effectiveness Studies Published a Year

![Bar chart showing the number of papers published by industry and academia from 1991 to 2012. The chart indicates a significant increase in the number of papers published from 2007 onwards, particularly in the industry category.]
Figure 2: Breakdown of Cost Effectiveness Studies Sponsored by Industry by Year Evaluated at $50,000/QALY Threshold

Figure 3: Breakdown of Cost Effectiveness Studies Sponsored by Other Than Industry Sources by Year Evaluated at $50,000/QALY Threshold
Table 1: Characteristics of Published Cost effectiveness Analyses of Drugs for Breast Cancer

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pharmaceutical Company Sponsored (n = 65)</th>
<th>Other Sponsorship (n = 40)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agent</td>
<td>N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hormonal Therapy</td>
<td>30 (46.2%)</td>
<td>12 (30.0%)</td>
<td></td>
</tr>
<tr>
<td>Primary Prevention</td>
<td>1 (3.3%)</td>
<td>8 (66.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>First Line</td>
<td>6 (20.0%)</td>
<td>1 (8.3%)</td>
<td></td>
</tr>
<tr>
<td>Adjuvant</td>
<td>21 (70.0%)</td>
<td>3 (25.0%)</td>
<td></td>
</tr>
<tr>
<td>Second Line</td>
<td>2 (6.7%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>20 (30.8%)</td>
<td>17 (42.5%)</td>
<td>0.04***</td>
</tr>
<tr>
<td>First Line</td>
<td>3 (15.0%)</td>
<td>1 (5.9%)</td>
<td></td>
</tr>
<tr>
<td>Adjuvant</td>
<td>9 (45.0%)</td>
<td>15 (88.2%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Second Line</td>
<td>8 (40.0%)</td>
<td>1 (5.9%)</td>
<td></td>
</tr>
<tr>
<td>Bisphosphonate*</td>
<td>8 (12.3%)</td>
<td>1 (2.5%)</td>
<td></td>
</tr>
<tr>
<td>Hematopoietic Growth Factor</td>
<td>6 (9.2%)</td>
<td>2 (5.0%)</td>
<td></td>
</tr>
<tr>
<td>Targeted Therapy**</td>
<td>6 (9.2%)</td>
<td>10 (25.0%)</td>
<td></td>
</tr>
<tr>
<td>Cancer Stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preventative</td>
<td>1 (1.5%)</td>
<td>8 (20.0%)</td>
<td></td>
</tr>
<tr>
<td>Early (Stage IIIA or below)</td>
<td>37 (56.9%)</td>
<td>26 (65.0%)</td>
<td></td>
</tr>
<tr>
<td>Advanced</td>
<td>26 (40.0%)</td>
<td>5 (12.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Both Early and Advanced</td>
<td>1 (1.5%)</td>
<td>1 (2.5%)</td>
<td></td>
</tr>
<tr>
<td>Average Quality Rating of Paper ± SD</td>
<td>4.78 ± 0.79</td>
<td>4.43 ± 0.98</td>
<td>0.087</td>
</tr>
<tr>
<td>Prospective Design of Study</td>
<td>8 (12.3%)</td>
<td>4 (10.0%)</td>
<td></td>
</tr>
</tbody>
</table>

All p-values determined using Fisher Exact tests except Average Quality Rating which was calculated using Wilcoxon Rank Sum test.

* Includes denosumab
** Includes trastuzumab and lapatinib
***P-value for difference in type of agent evaluated (hormonal, chemotherapy, bisphosphonate, hematopoietic, targeted) between pharmaceutical company sponsored and other sponsorship
Table 2: Cost effectiveness Rating of Drugs for Breast Cancer in Studies with Pharmaceutical Company and Other Funding

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pharmaceutical Company Funding (n = 65)</th>
<th>Other Funding (n = 40)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost Effective</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$50,000/QALY Cutoff</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>49 (75.4%)</td>
<td>16 (40.0%)</td>
<td>0.001</td>
</tr>
<tr>
<td>No</td>
<td>8 (12.3%)</td>
<td>14 (35.0%)</td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>8 (12.3%)</td>
<td>10 (25.0%)</td>
<td></td>
</tr>
<tr>
<td>$100,000/QALY Cutoff</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>52 (80.0%)</td>
<td>23 (57.5%)</td>
<td>0.037</td>
</tr>
<tr>
<td>No</td>
<td>4 (6.2%)</td>
<td>7 (17.5%)</td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>9 (13.8%)</td>
<td>10 (25.0%)</td>
<td></td>
</tr>
<tr>
<td>$150,000/QALY Cutoff</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>57 (87.7%)</td>
<td>27 (67.5%)</td>
<td>0.044</td>
</tr>
<tr>
<td>No</td>
<td>3 (4.6%)</td>
<td>4 (10.0%)</td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>5 (7.7%)</td>
<td>9 (22.5%)</td>
<td></td>
</tr>
<tr>
<td>Prevention at $50,000/QALY Cutoff</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1 (100.0%)</td>
<td>2 (25.0%)</td>
<td>0.99</td>
</tr>
<tr>
<td>No</td>
<td>0 (0.0%)</td>
<td>3 (37.5%)</td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>0 (0.0%)</td>
<td>3 (37.5%)</td>
<td></td>
</tr>
<tr>
<td>Early Stage at $50,000/QALY Cutoff*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>29 (78.4%)</td>
<td>14 (53.8%)</td>
<td>0.037</td>
</tr>
<tr>
<td>No</td>
<td>2 (5.4%)</td>
<td>7 (26.9%)</td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>6 (16.2%)</td>
<td>5 (19.2%)</td>
<td></td>
</tr>
<tr>
<td>Advanced Stage at $50,000/QALY Cutoff*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>19 (73.1%)</td>
<td>0 (0.0%)</td>
<td>0.005</td>
</tr>
<tr>
<td>No</td>
<td>6 (23.1%)</td>
<td>4 (80.0%)</td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>1 (3.8%)</td>
<td>1 (20.0%)</td>
<td></td>
</tr>
<tr>
<td>High Quality Studies at $50,000/QALY Cutoff**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>37 (75.5%)</td>
<td>10 (45.5%)</td>
<td>0.040</td>
</tr>
<tr>
<td>No</td>
<td>5 (10.2%)</td>
<td>7 (31.8%)</td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>7 (14.3%)</td>
<td>5 (22.7%)</td>
<td></td>
</tr>
<tr>
<td>Country Specific Cutoff***</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>49 (81.7%)</td>
<td>16 (40.0%)</td>
<td>0.001</td>
</tr>
<tr>
<td>No</td>
<td>8 (13.3%)</td>
<td>14 (35.0%)</td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>8 (13.3%)</td>
<td>10 (25.0%)</td>
<td></td>
</tr>
</tbody>
</table>

All p-values were calculated using Fisher’s Exact Test.

*Early Stage considered Stage IIIA or below, advanced stage considered above Stage IIIA.

**For studies that met or exceeded the median quality rating of 4.5.

***Canada: C$50,000, UK: £30,000, Europe (Other than UK): €50,000, and Everywhere Else: US$50,000
Table 3: Cost Effectiveness of Studies Evaluated by Country at $50,000/QALY

<table>
<thead>
<tr>
<th></th>
<th>U.S.</th>
<th>U.K.</th>
<th>Europe*</th>
<th>Canada</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>18 (46.2%)</td>
<td>16 (80.0%)</td>
<td>15 (62.5%)</td>
<td>14 (82.4%)</td>
<td>0.072</td>
</tr>
<tr>
<td>No</td>
<td>13 (33.3%)</td>
<td>1 (5.0%)</td>
<td>4 (16.7%)</td>
<td>2 (11.8%)</td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>8 (20.5%)</td>
<td>3 (15.0%)</td>
<td>5 (20.8%)</td>
<td>1 (5.9%)</td>
<td></td>
</tr>
</tbody>
</table>

P-value calculated using Fisher’s Exact Test

*Europe calculated other than the UK

Table 4: Breakdown of Sponsorship By Country of Study

<table>
<thead>
<tr>
<th></th>
<th>U.S.</th>
<th>U.K.</th>
<th>Europe*</th>
<th>Canada</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Industry</td>
<td>20 (51.3%)</td>
<td>17 (85.0%)</td>
<td>14 (58.3%)</td>
<td>13 (76.5%)</td>
<td>1 (20.0%)</td>
</tr>
<tr>
<td>Other</td>
<td>19 (48.7%)</td>
<td>3 (15.0%)</td>
<td>10 (41.7%)</td>
<td>4 (23.5%)</td>
<td>4 (80.0%)</td>
</tr>
</tbody>
</table>

Table 5: Cost effectiveness for papers based off of number of papers in analysis published by authors at $50,000/QALY

<table>
<thead>
<tr>
<th></th>
<th>At Most One Publication</th>
<th>At Least One Author With Two Publications</th>
<th>At Least One Author &gt;2 Publications</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>10 (38.5%)</td>
<td>55 (69.6%)</td>
<td>38 (70.4%)</td>
<td>0.049</td>
</tr>
<tr>
<td>No</td>
<td>9 (34.6%)</td>
<td>13 (16.5%)</td>
<td>8 (14.8%)</td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>7 (26.9%)</td>
<td>11 (13.9%)</td>
<td>8 (14.8%)</td>
<td></td>
</tr>
</tbody>
</table>

P-value calculated using Fisher’s Exact Test. Number of publications is the number of papers that an author has among the cost effectiveness papers in this study.
Table 6: Cost Effectiveness of Studies by Pharmaceutical Company Sponsor at $50,000/QALY

<table>
<thead>
<tr>
<th>Company</th>
<th>Yes</th>
<th>No</th>
<th>Mixed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AstraZeneca</td>
<td>10 (90.9%)</td>
<td>0 (0.0%)</td>
<td>1 (9.1%)</td>
</tr>
<tr>
<td></td>
<td>US</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>UK</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Europe</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Canada</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Novartis</td>
<td>15 (93.8%)</td>
<td>1 (6.3%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td></td>
<td>US</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>UK</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Canada</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Hoffman-La Roche/Genentech</td>
<td>6 (66.7%)</td>
<td>1 (11.1%)</td>
<td>2 (22.2%)</td>
</tr>
<tr>
<td></td>
<td>US</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>UK</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Europe</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Sanofi</td>
<td>8 (100.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td></td>
<td>UK</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Canada</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Europe</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Other(Johnson&amp;Johnson, Abraxis,Bristol-Myers Squibb, Eli Lilly)</td>
<td>2 (40.0%)</td>
<td>3 (60.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td></td>
<td>US</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>UK</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Canada</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>
Table 7: Adjusted Odds Ratios (OR) that Study is Cost Effective at Three Thresholds for Study Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>$50,000/QALY</th>
<th></th>
<th></th>
<th>$100,000/QALY</th>
<th></th>
<th></th>
<th>$150,000/QALY</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
<td>p-value</td>
<td>OR</td>
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*OR is per increase of Paper Quality score by 1.

**Not including the United Kingdom.

***All of the papers in this study were cross-referenced to determine if they had authors that had published other papers in the study.