# Do Value Thresholds for Oncology Drugs Differ from Nononcology Drugs?

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## ABSTRACT

**BACKGROUND:** In the past decade, many oncologic drugs have been approved that extend life and/or improve patients' quality of life. However, new cancer drugs are often associated with high price and increased medical spending. For example, in 2010, the average annual cost of care for breast cancer in the final stage of disease was reported to be $94,284, and the total estimated cost in the United States was $16.50 billion.

**OBJECTIVE:** To determine whether value threshold, as defined by the incremental cost-effectiveness ratio (ICER), differed between oncology and other therapeutic areas.

**METHODS:** The PubMed database was searched for articles published between January 2003 and December 2013 with calculated ICER for therapeutic drug entities in a specific therapeutic area. The search term used was "ICER" AND "United States." From 275 results, only those articles that reported ICERs using quality-adjusted life-years (QALY) were included. In addition, only those articles that used a U.S. payer perspective were retained. Among those, nondrug therapy articles and review articles were excluded. The mean ICER and value threshold for oncologic drugs and nononcologic drugs were evaluated for the analysis.

**RESULTS:** From 54 articles selected for analysis, 13 pertained to drugs in oncology therapeutics, and the remaining 41 articles addressed ICER for drugs in other therapeutic areas. The mean and median of ICERs calculated for cancer-specific drug intervention was $138,582/QALY and $55,500/QALY, respectively, compared with $49,913/QALY and $31,000/QALY, respectively, for noncancer drugs. Among the cancer drugs, 45.0% had ICERs below $50,000/QALY and 70.0% below $100,000/QALY. In comparison, 72.0% of noncancer drugs showed ICERs below $50,000/QALY, and 90.0% had ICERs below $100,000/QALY. When a specific threshold was mentioned, it was in the range of $100,000-$150,000 in cancer drugs, whereas drugs in other therapeutic areas used traditional threshold value within the range of $50,000-$100,000.

**CONCLUSIONS:** The average ICER reported for cancer drugs was more than 2-fold greater than the average ICER for noncancer drugs. In general, articles that addressed the relative value of oncologic pharmaceuticals used higher value thresholds and reported higher ICERs than articles evaluating noncancer drugs.


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### What is already known about this subject

- Although the incremental cost-effectiveness ratio (ICER), expressed as the cost per quality-adjusted life-year (QALY), has long been used as a standard metric in cost-effectiveness analyses, its use has been met with challenges both in the United States and abroad.
- In the United States, the 2010 Patient Protection and Affordable Care Act prohibits the Patient-Centered Outcomes Research Institute (PCORI) from the use of cost/QALY ICER as a threshold to make recommendations on what type of health care or intervention should be utilized.
- Other factors besides a drug's ICER influence the drug formulary decisions of insurers and third-party payers. Often, they need to consider factors such as available resources, existence of alternatives, and/or anticipated impact of the new drug being considered for the formulary.

### What this study adds

- This review of ICERs in oncology and other therapeutic areas documents wide variation in ICERs across disease states.
- Our systematic approach to make a side-by-side comparison of ICERs of cancer drugs and noncancer drugs from the literature within the past decade suggests that higher ICER thresholds for anticancer agents may exist.

The U.S. Food and Drug Administration (FDA) approves new anticancer drugs based on evidence for safety and efficacy, which often is demonstrated by extending progression-free survival or overall survival by weeks to months. Although research and development of new drugs are imperative for continued improvement of cancer therapy, many have questioned how sustainable it is for government and third-party payers to continue paying for the increasingly high price of contemporary cancer drugs for the incremental benefit they bring to the patients. The cost of a 1-year supply of these drugs typically reaches $100,000, and pricing for the new incoming agents have been on an upward trend. For example, in 2010, the average annual cost of care for breast cancer in the final stage of disease was reported to be $94,284, and the total estimated cost in the United States was $16.50 billion.[1] In order to assess the question of whether a new cancer drug holds adequate value for its price, cost-effectiveness analysis is often performed, which aids the health care decision makers with formulary listings or reimbursement policies.

The incremental cost-effectiveness ratio (ICER) is used by many institutions to evaluate the value of a new drug in comparison with the established therapy from clinical efficacy and cost perspectives. The ICER is often expressed in the unit of

cost per quality-adjusted life-years (QALY), which incorporates components of quality of life as well as the duration to establish standardization in measuring health utility. It can be used in evaluating how much additional value a new drug can add compared with the current standard therapy at a measured cost. This is often performed with a predetermined threshold value that serves as the maximum ICER limit in deciding whether a drug is cost-effective. There are many factors in addition to the ICER that influence drug formulary decisions by institutions or third-party payers. The threshold value could be set based on an institution's financial budget, or it could also be taken from previous decisions, which are often variable across institutions and globally.[2] Currently, there is no uniformity in determination of a threshold across health care institutions, and a lack of standard exists.[3] In the United States, the use of ICERs in assigning value in health outcomes has faced challenges, since the Patient Protection and Affordable Care Act in 2010 prohibited use of cost per QALY as a threshold within the research sponsored by the Patient-Centered Outcomes Research Institute (PCORI). This prohibition was in response to long-standing public concerns that the use of ICER as a threshold would discriminate on the basis of age and disability.[4] Despite these concerns, ICER is often used in health care institutions and by third-party payers in private sectors and other countries as a valuable tool in the health care decision-making process. The objective of this study was to determine whether value threshold, as defined by the ICER, differed between oncology and other therapeutic areas.

## Methods

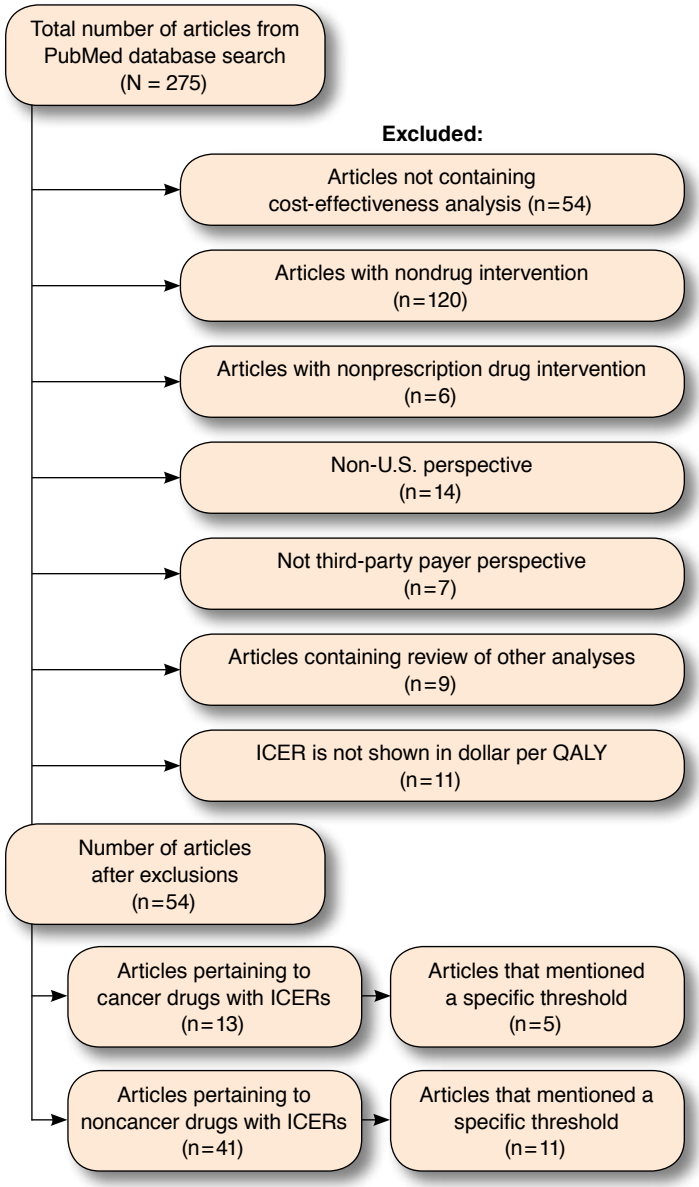
### Data Collection

The lead author conducted searches and pulled data, which were reviewed by the coauthor. The PubMed electronic database was searched, using the search term "ICER" AND "United States." Results were restricted to articles in English. Time frame was limited to the 11 years from January 1, 2003, to December 31, 2013, and focus was on the treatments developed during the recent advancement in cancer research. With these criteria, we were able to obtain 275 articles from the search results. Articles that addressed cost-effectiveness of nondrug therapy were excluded. Articles that reported ICER of nonprescription drugs were also excluded from the list. Included articles were those that assumed a U.S. payer perspective and reported ICER in unit of dollar per QALY. If a study reported ICERs from review of multiple independent studies, it was excluded (Figure 1).

### Analysis

All articles were sorted into either an oncology-related drug group or a nononcology-related drug group. Drugs used for treatment of cancer or reducing the risk of cancer were categorized into the oncology-related drug group. Individual values of ICER were obtained from the articles and analyzed for the mean and median in each group. If an article presented multiple ICERs of 1 drug to several comparators, each ICER was entered separately into the analyses. A similar method of analysis was employed for threshold values stated for the evaluation of ICER in some of the articles. The mean value thresholds obtained from each group of articles were compared for the analysis. If an article mentioned 1 value threshold and

**FIGURE 1** Article Selection Process for Analyses of Average ICERs and Value Thresholds




*ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.*

**TABLE 1** Reported ICERs and Value Threshholds for Oncologic Agents

| Disease State | Drug | Comparison | ICER ($/QALY) | Value Threshold ($) |
|---|---|---|---|---|
| Prostate cancer[9] | Abiraterone | Placebo | 94,000 | N/A |
| | Mitoxantrone | Placebo | 101,000 | |
| | Abiraterone | Mitoxantrone | 91,000 | |
| Colon cancer[10] | FOLFOX | 5-FU/LV | 54,000 | N/A |
| | 5-FU/LV | Observation group | 14,000 | |
| Stage IV lung cancer[11] | Erlotinib | Platinum-containing chemotherapy | 110,644 | 100,000 |
| Cervical cancer[12] | Gemcitabine/cisplatin | Cisplatin | 33,000 | 100,000 |
| Pancreatic cancer[13] | Everolimus | Sunitinib | 41,000 | N/A |
| Breast cancer[14] | Denosumab | Zoledronic acid | 697,000 | N/A |
| Breast cancer[15] | Bevacizumab | Standard care | 745,000 | 150,000 |
| Ovarian cancer[16] | Carboplatin/paclitaxel and additional paclitaxel cycle | Carboplatin/paclitaxel | 13,000 | 100,000 |
| | Carboplatin/paclitaxel/bevacizumab | Carboplatin/paclitaxel | 326,000 | N/A |
| Breast cancer[17] | Peg-filgrastim | Filgrastim | 31,000 | N/A |
| Non-Hodgkin lymphoma[18] | Peg-filgrastim | Filgrastim | 6,000 | N/A |
| Breast cancer risk reduction[19] | Tamoxifen | Standard care | 190,000 (low risk with uterus) | 100,000 |
| | | | 72,000 (low risk without uterus) | |
| | | | 57,000 (high risk with uterus) | |
| | | | 37,000 (high risk without uterus) | |
| Breast cancer[20] | Adjuvant trastuzumab | Standard care | 39,000 | N/A |
| Breast cancer[21] | Anastrozole | Tamoxifen | 20,000 | N/A |
| **Total: 13 articles** | **Total: 20 interventions** | | **Mean: 138,582** | **Mean: 110,000** |

*FOLFOX = leucovorin, fluorouracil, oxaliplatin; 5-FU = fluorouracil; ICER = incremental cost-effectiveness ratio; LV = leucovorin; N/A = not available; QALY = quality-adjusted life-year.*

presented more than 1 ICER for a particular drug, it was counted for each of the ICERs. We also assessed whether the article compared the reported ICER with the value threshold ICER. Because the prices of therapeutic agents, as well as ICERs, are likely to be higher in more recent years, we examined ICER thresholds of the historical benchmark of $50,000/QALY and the more contemporary benchmark of $100,000/QALY.

## Results

For the analysis, we included 13 articles that addressed cancer treatment and 41 articles that related to treatment of other diseases or conditions. From these articles, we obtained 20 ICERs that were related to cancer treatment and 50 ICERs that were related to treatment of noncancer conditions.

The range of ICERs reported for oncologic agents was $6,000-$745,000. The mean in this group was $138,582/QALY and the median was $55,500/QALY (Table 1). Among these values, 45.0% (9 of 20) were below $50,000/QALY, and 70.0% (14 of 20) were less than $100,000/QALY. As for noncancer-related drugs, the range of ICERs reported in the articles was $-54,000-$332,309, and the mean and median were $49,913/QALY and $31,000/QALY, respectively. In this group, 72.0% (36 of 50) fell below $50,000/QALY, and 90.0% (45 of 50) were below $100,000/QALY (Table 2).

Sixteen articles mentioned a specific value threshold for the evaluation of ICER. Of those 16 value thresholds, 5 were from the oncologic drug group, and 11 were from the nononcologic drug group. In the oncologic drug group, the range of value thresholds was $100,000-$150,000 with the mean of $110,000. In comparison, the range of thresholds used in the nononcologic drug group was $50,000-$100,000, and the mean was $68,181.

## Discussion

The data showed that the mean ICER of oncologic drugs was higher than the mean ICER of nononcologic drugs by more than 2-fold. Among the articles that mentioned specific value threshold in the analysis, all oncologic drugs were evaluated in context of thresholds between $100,000-$150,000, whereas the thresholds for nononcologic drugs were in the range of $50,000-$100,000. The results confirmed that oncologic drugs are often evaluated with value thresholds higher than the traditional range to adjust to high ICERs reported for these agents.

A high range of ICERs is also observed in some specialty drugs, such as biologics—drugs made of biological rather than chemical properties—along with many of the cancer therapy drugs. These specialty biologic drugs are often approved for life-threatening illnesses, such as multiple sclerosis, hemophilia, cancer, human immunodeficiency virus, and diabetes.

**TABLE 2** Reported ICERs and Value Thresholds for Nononcologic Agents

| Disease State | Drug | Comparison | ICER ($/QALY) | Value Threshold ($) |
|---|---|---|---|---|
| Chemoprevention in Barrett's Esophagus[22] | Aspirin + statin | Aspirin | 158,000 | 100,000 |
| Osteoarthritis[23] | Duloxetine | Naproxen | 47,678 | N/A |
| Chronic hepatitis C[24] | Boceprevir | Standard dual-therapy: peginterferon alpha and ribavirin | 29,184 | 50,000 |
| | Telaprevir | | 44,247 | |
| Glaucoma[25] | Nitroglycerin | Standard care to all patients | 34,000 | N/A |
| Neurogenic detrusor overactivity[26] | OnabotulinumtoxinA | Best supportive care | 24,000 | N/A |
| Knee osteoarthritis[27] | Disease-modifying osteoarthritis drugs | Standard care | 57,000 | N/A |
| Chronic low back pain[28] | Duloxetine | Naproxen | 59,473 | N/A |
| Human immunodeficiency virus[29] | Generic-based antiretroviral therapy | No antiretroviral therapy | 21,000 | 100,000 |
| | Branded antiretroviral therapy | Generic-based antiretroviral therapy | 114,000 | |
| Type 2 diabetes[30] | Exenatide | Insulin glargine | 15,000 | N/A |
| ADHD[31] | Guanfacine XR + stimulant | Stimulant monotherapy | 31,000 | 50,000 |
| Anticoagulation in cancer patients[32] | Low molecular-weight heparin | No prophylaxis | 90,893 | N/A |
| Stroke prevention in atrial fibrillation[33] | Rivaroxaban | Warfarin | 27,000 | 100,000 |
| Multiple sclerosis[34] | Fingolimod | IFN beta-1a | 73,000 | 100,000 |
| S. aureus vaccine in hemodialysis patients[35] | Vaccine (1% colonization rate) | No vaccine | 25,217 | N/A |
| Schizophrenia[36] | Olanzapine ODT | SOT | 19,000 | N/A |
| | Olanzapine ODT | Risperidone SOT | 39,000 | |
| End-stage renal disease[37] | Erythropoietin stimulating agents | Routine blood transfusions | 873 | N/A |
| Hyperlipidemia[38] | Atorvastatin | Simvastatin | 45,000 | N/A |
| Acute coronary syndrome[39] | Ticagrelor | Genotype-driven treatment | 10,000 | 50,000 |
| Human immunodeficiency virus[40] | Atazanavir – ritonavir | Lopinavir – ritonavir | 26,000 | 50,000 |
| Type 2 diabetes[41] | Liraglutide | Exenatide | 40,000 | N/A |
| Human immunodeficiency virus[42] | Darunavir – ritonavir | Lopinavir – ritonavir | 23,000 | N/A |
| Macular degeneration[43] | Bevacizumab | Ranibizumab | -54,000 | N/A |
| Cardiovascular disease[44] | Rosuvastatin (20-year horizon) | Placebo | 10,000 | N/A |
| | Rosuvastatin (10-year horizon) | | 44,000 | |
| Psoriasis[45] | Adalimumab | Etanercept | 5,000 | 50,000 |
| | Infliximab | Etanercept | 293,000 | |
| Asthma[46] | Omalizumab | Usual care | 172,000 | N/A |
| Influenza during pregnancy[47] | 2-dose influenza vaccine | No vaccine | 6,787 | 50,000 |
| Osteoporosis[48] (ages 75-79) | Bisphosphonates | No bisphosphonates | 87,853 | N/A |
| Cardiovascular disease[49] | Clopidogrel/aspirin | Aspirin | 36,000 | N/A |
| Type 1 diabetes[50] | Continuous subcutaneous insulin injection | Multiple daily injection | 16,000 | N/A |
| Type 2 diabetes[51] | Pioglitazone | Rosiglitazone | 20,000 | N/A |
| Peripheral artery disease[52] | Urokinase | Alteplase | 332,309 | N/A |
| Human immunodeficiency virus[53] | Tipranavir – ritonavir | Protease inhibitor – ritonavir | 56,000 | N/A |
| Alzheimer's disease[54] | Olanzapine | No treatment | 50,000 | N/A |
| Type 2 diabetes[55] | Exenatide | Standard care | 35,000 | N/A |
| Osteoarthritis[56] | Celecoxib | NSAID | 31,000 | N/A |
| Chemotherapy-induced nausea and vomiting[57] | Aprepitant | Standard care | 96,000 | N/A |
| Type 2 diabetes[58] | Exenatide | Insulin | 13,000 | N/A |
| Diabetic peripheral neuropathy[59] | Duloxetine | Standard care | -342 | N/A |
| | | | -429 | |
| Parkinson's disease[60] | Pramipexole | Levodopa | 42,000 | N/A |
| Hepatitis C[61] | Boceprevir (response-guided therapy) | Peginterferon-ribavirin | 30,200 | 50,000 |
| | Boceprevir (fixed-duration 48 weeks) | Boceprevir (response-guided therapy) | 91,500 | |
| Hepatitis B prophylaxis[62] | HEPLISAV – diabetes patients | Engerix – B | 12,613 | N/A |
| | HEPLISAV – health care workers | Engerix – B | 11,062 | |
| | HEPLISAV – travelers | Engerix – B | 5,564 | |
| **Total: 41 articles** | **Total: 50 interventions** | | **Mean: 49,913** | **Mean: 68,181** |

*ADHD = attention deficit hyperactivity disorder; ICER = incremental cost-effectiveness ratio; IFN = interferon; NSAID = nonsteroidal anti-inflammatory drug; ODT = orally disintegrating tablet; QALY = quality-adjusted life-year; SOT = standard oral tablet; XR = extended-release.*

This is one of the elements that keeps the prices of these drugs just as high as cancer drugs. Their high prices are also derived from the extended exclusivity protection of the patent for biologic drugs that is separated from regular pharmaceuticals that allowed the monopolistic pricing for these drugs. It is only recently that the patent for some of the earlier biologics expired allowing development of generic versions of these biologics, often referred to as biosimilars.[5] However, the regulation of these products is expected to meet with challenges, since the different manufacturing process of biopharmaceuticals may affect the activity of the product. It is reasonable to expect the prices of these drugs to become more affordable as the knowledge of the production technology for biosimilars becomes more standardized in the future.

More cancer patients benefit from continued advancement in cancer treatment research that allows patients to live longer. However, there has yet to be a cure for cancer. Current therapy includes drugs that delay cancer progression and extend overall survival as much as possible. Patients are treated with each approved agent sequentially or in combination over the course of the disease, since the effectiveness of the drugs is overcome by resistance, which requires a change in therapy. This need to continuously change treatment plans is the reason that prices of cancer drugs remained high in the past. The use of 1 drug did not invalidate the need for the other drug, creating a virtually monopolistic pricing scheme.[6] When a new and improved version of a drug becomes available, the older drug is often viewed as substandard treatment and over time becomes an obsolete option rather than used in establishing a competitive pricing scheme.

Many argue that it is unsustainable for the current health system to continue to pay for expensive cancer drugs that provide modest incremental benefits in therapy. The current task remains for society and payers to draw the line and decide when a life-saving drug is "too expensive." The FDA approved Zaltrap (ziv-aflibercept) in 2012 for second-line treatment of advanced colon cancer based on a phase III clinical trial that showed ziv-aflibercept extended median overall survival by 42 days. However, ziv-aflibercept received disapproval for cost-effectiveness by Memorial Sloan-Kettering Cancer Center in New York and the National Institute for Health and Care Excellence (NICE) in the United Kingdom, based on the conclusion that ziv-aflibercept was no more effective than Avastin (bevacizumab), a similar drug already on the market, but was twice as expensive—priced at $10,000 for a month supply, compared with $5,000 a month for bevacizumab. The reported ICER for ziv-aflibercept by NICE was between $97,000-$102,656/QALY. This may also suggest that with persistent entry of similar cancer drugs into the market, the prices will decline over time, and the ICER of cancer drugs will also decrease in the future.[7]

Cancer drugs are not the only drugs that historically have high prices. Drugs that treat serious illnesses also tend to enter the market with prices in the higher ranges. Correspondingly, we have observed drugs being compared with different thresholds based on the seriousness of the disease they treat. For example, lifestyle drugs are often compared with a lower threshold, while life-saving drugs, such as orphan drugs, are compared with a much higher threshold. This practice raises the question of whether it is valid to have fixed $50,000/QALY or $100,000/QALY thresholds across all payers, types of care, and populations.[8] Because of the variations among the types of third-party payers in the United States, it is reasonable that the threshold acceptance should also be based on those factors unique to the insurer and the care given.

## Limitations

First, the reported ICERs included in our analyses are not in direct reference to what is being accepted in the real-world formulary decisions. The value thresholds used in the reports analysed have been chosen by the authors performing the cost-effectiveness analyses, and while it may indicate a general trend of higher value thresholds in oncology drugs, it is not directly attributed by the actual value thresholds utilized by insurers and third-party payers. Second, some of the articles included in our analysis addressed the cost-effectiveness of an old drug, for example, as an added therapy to standard care. Finally, the comparator drug in the cost-effectiveness analyses was not required to be the most appropriate standard therapy for the disease state by the practice guidelines or the most cost-effective choice in current practice. The reported ICERs can vary significantly based on the value of the comparator drug.

## Conclusions

The results of our analyses indicate that cancer drugs are associated with higher ICERs in comparison with ICERs reported for noncancer drugs. On average, the ICER for cancer drugs was more than 2-fold higher than other therapeutic areas, with the majority of cancer and noncancer ICERs falling in the $100,000-150,000 and $50,000-100,000 ranges, respectively.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## DISCLOSURES

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Bae and Mullins contributed equally to concept and design of this study. Bae collected the data, which were interpreted by both authors. The manuscript was written primarily by Bae, assisted by Mullins, and revised by both authors.

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