Onwards and Upwards: A Systematic Survey of Economic Evaluation Methods in Oncology

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Abstract
Introduction The type of methods used in economic evaluations of health technology can lead to results that may influence decisions. Despite the potential impact on decision making, there is very little documentation of methods used in economic evaluation in oncology pertaining to key assumptions and extrapolation methods of survival benefits, especially in terms of survival analysis techniques and methods for extrapolation.

Objectives The primary objectives of this study were to identify, examine, and describe the methods used in economic evaluations in oncology over a 10-year period, while secondary objectives included examining the use of identified methods across different geographic regions.

Methods A systematic search of the published oncology literature was conducted to identify economic evaluations of advanced or metastatic cancers published between 2010 and 2019 using the PUBMED, Ovid MEDLINE, and EMBASE databases. A random sample was taken, and information on type of study, data source, modeling techniques, and survival analysis methods were abstracted and descriptively summarized.

Results A total of 8481 abstracts were identified and 76 economic evaluations were abstracted and assessed. Most identified studies were from North America (38%), East Asia (21%), continental Europe (18%), or the UK (16%), and most commonly focused on lung cancer (18%), colorectal cancer (16%), or breast cancer (13%). A large majority of studies were based on data from randomized controlled trials (82%), utilized a cost-utility approach (82%), and took a public healthcare system perspective (83%). Common model structures included Markov (49%) and partitioned survival (17%). Fitted parametric curves were the most commonly used extrapolation method (89%) for overall survival and most often utilized the Weibull distribution (64%). Secondary assessments showed modest regional variation in the use of identified methods, including the use of fitted parametric curves, testing of the proportional hazards assumption, and validation of results.

Conclusion A majority of papers in the study sample reported basic characteristics of study type, data source used, modeling techniques, and utilization of survival analysis methods. However, greater detail in reporting extrapolation methods, statistical analyses, and validation of results could be potential improvements, especially across regions, in order to support greater consistency in decision making. Future research could document the diffusion of novel modeling techniques into economic evaluation.

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1 Introduction

Economic evaluation in healthcare estimates the value for money of health technologies through assessment of the comparative costs and clinical impacts, the results of which can inform the value of a specified allocation of healthcare resources [1]. To increase transparency and reporting of economic methods of health technologies, several guidelines have been published. For example, the National Institute for Clinical and Care Excellence (NICE) in the UK publishes a series of practice guidelines to aid submissions from manufacturers seeking reimbursement of their health technologies. Similar guidelines have been published by the Canadian Association for Drugs and Technologies in Health (CADTH) in Canada, the 2nd Panel on Cost-Effectiveness in Health and Medicine in the US, the Research Group on Economic Evaluation for Japanese Public Medical Benefits in Japan, and the Health Insurance Review and Assessment Service (HIRA) in South Korea, among many others [2–7]. Despite widespread publication and availability of guidelines, documentation of the utilization of specific methods in economic evaluation in oncology remains limited. This is important as the last decade has seen many important methodological advances when conducting economic evaluations of oncologic treatments.

In addition to extrapolation and other survival analysis techniques, other quantitative methods (e.g. statistical testing, crossover adjustment techniques, alternative model structures) have been developed to overcome the limitations of previous methods. For example, clinical studies are finite in length, and in order for the results of clinical studies to be amenable to economic evaluation, it is often necessary to extrapolate clinical outcomes beyond the study duration through survival analysis techniques [2, 5, 6, 8, 9]. In addition, the analytical methods selected for economic evaluation in oncology have been shown to influence survival results [10], and therefore it is important for appropriate methods to be used when evaluating oncology products.

However, only two previous studies have detailed the use of survival analysis in economic evaluations in oncology [11, 12]. The first of these studies examined survival modeling and extrapolation techniques used in oncology submissions to the NICE in the UK before and after publication of the NICE Decision Support Unit’s Technical Support Document (TSD) on survival analysis [13]. The authors extracted data from 20 technology appraisals and reviewed information on model structure, data sources, extrapolation methods, and validation. The authors found that extrapolation techniques in practice have improved since the publication of the guidelines; some form of parametric extrapolation was used in almost all of the NICE submissions except one. However, nearly 30% of the submissions did not identify the source of overall survival (OS) data, and although the authors reported which parametric distributions were tested in the submissions, the specific distribution(s) chosen for extrapolation were not identified. Statistical testing methods used in the submissions were also documented but not disaggregated by type.

A second study from 2019 reviewed 58 NICE technology appraisals and examined the extent to which recommendations made in the NICE Decision Support Unit’s TSD on survival analysis have been followed since its publication [11]. The authors found that while there were increases in validation of the results using data and/or clinical opinion following publication of the TSD, the proportion of submissions that adhered to the TSD recommendations did not change substantively over time. The authors concluded that despite publication of the guidelines, survival analysis conducted as part of NICE technology appraisals remains suboptimal [11]. The study was limited to assessment of survival analysis and did not examine other characteristics of the NICE submissions. While these two UK studies are informative, their generalizability may be limited outside of the UK, and the results are not necessarily reflective of economic models found in the published oncology literature.

2 Objectives

To fill a gap in the literature, the present study aims to identify, examine, and describe the analytical methods used in economic evaluations, including study characteristics and model structure, although a systematic survey of the published oncology cost-effectiveness literature over a 10-year period between 2010 and 2019 using commonly cited
English language databases for economic evaluations in oncology. This approach allows a wider range of analytical techniques to be catalogued over a longer period of time than has been presented in previous studies. Secondary objectives of the study include examining the use of identified methods across different geographic regions.

3 Methods

A systematic search of the published oncology literature was conducted to identify economic evaluations of advanced or metastatic cancers published between 2010 and 2019 using the PUBMED, Ovid MEDLINE, and EMBASE databases. The Population, Intervention, Comparison and Outcomes (PICOS) method was followed for determining literature search criteria; identified studies were limited to English-language economic evaluations of advanced or metastatic cancer among adult populations, both treatment(s) and comparator(s) had to be explicitly reported, and outcomes of interest included incremental cost-effectiveness ratios (ICERs) and/or cost-utility effectiveness ratios (ICURs). The literature search was limited to economic evaluations, and duplicates and published abstracts were excluded. All eligibility criteria were defined a priori.

The following keywords were used in the database search queries: ‘cost-effectiveness analysis’, ‘cost-benefit analysis’, ‘cost-utility analysis’, ‘quality-adjusted life-years’, ‘metastasis’, ‘advanced cancer’, ‘advanced neoplasm’, ‘metastatic neoplasm’, ‘economics’, ‘cost’, ‘health economics’, ‘budget’, ‘costing’, ‘price’, ‘pharmacoeconomic’, ‘expenditure’, ‘expenses’, ‘statistical model’, ‘economic model’, ‘probability’, ‘Markov’, ‘Monte Carlo method’, ‘decision theory’, and ‘decision tree’. Refer to the Appendix for specific search strategies for each database.

Initial screening of titles and abstracts for relevance to the study objectives was conducted according to the stated eligibility criteria by the primary author. Full-text articles meeting all of the inclusion criteria and none of the exclusion criteria were reviewed by the primary author, and for each included study, data were extracted (see the electronic supplementary material [ESM] for a complete list of extracted studies) to describe study characteristics (i.e. disease area, patient population, type of cancer, source of clinical data, type of economic evaluation, study perspective, overall conclusions, funding source, validation methods, software used), key assumptions and modeling techniques (model structure, number of modeled health states, time horizon, intervention, comparator, treatment line, discount rates, outcomes of interest, types of analyses, key study results, total costs, base-case ICER, sensitivity analyses, willingness to pay [WTP] threshold, data sources), and extrapolation methods (i.e. statistical techniques used for fitting curves, type of distribution, crossover adjustment, digitization method use).

Analytical methods identified in each included study were extracted and documented in the extraction sheet, and similarities and differences were descriptively assessed. Economic evaluations sponsored by industry have been observed to utilize longer time horizons than those conducted by health technology assessment (HTA) agencies [14]. Previous observations have also suggested that industry-sponsored studies are more likely than academic-sponsored studies to report favorable conclusions of cost effectiveness [15]. In addition, since novel approaches have been suggested to model immunotherapy (IO) [16, 17], a comparison of the model structure between IO and non-IO drugs was conducted. Chi-square tests were used to probe relationships between categorical variables in order to substantiate these previous observations. Identified studies were also grouped according to geography in order to capture potential variation across regions. Statistical testing was performed in Microsoft Excel 2019 (Microsoft Corporation, Redmond, WA, USA).

A large number of studies was anticipated to be identified through the search strategies. Based on the number of studies reported in previous publications, it was determined that a sample size approximately equal to that reported by Benedict and Muszbek [12] (n = 58), and three times larger than the sample size of n = 20 studies reported by Bell Gorrod et al. [11], would be an appropriate and representative snapshot of the large number of studies captured in the literature search. It was initially assumed that a 20% random sample of all eligible studies over the 2010–2019 timeframe, conducted in Microsoft Excel using a combination of RAND, INDEX, and MATCH functions, would yield at least 60 studies. Prior to knowing the exact number of studies that would meet the inclusion criteria, the random sample size of 20% was to be increased to reach a total of 60 studies if necessary. This desired sample of 60 studies was based on previous studies on methods [Benedict and Muszbek (N = 58) and Bell Gorrod et al. (N = 20) [11, 12]]. To validate the representativeness of our sample, we took another random sample of 20% of the studies and compared the two samples in terms of type of economic evaluation and model structure.

4 Results

4.1 Results of a Systematic Survey

A total of 8481 abstracts were identified through the literature search and 1671 duplicates were removed (Fig. 1); 5907 studies were excluded in level 1 screening (according to the PICOS criteria), and the remaining 903 full-text studies were
assessed using a predefined eligibility form. Of these studies, 538 were removed through level 2 screening (according to the PICOS criteria) and a total of 378 met the eligibility criteria (Fig. 1). The 20% random sampling of the 378 studies meeting the inclusion criteria resulted in 76 studies being included in the abstraction set (see the ESM for a complete list of the included studies).

4.2 Study Characteristics

A detailed description of the study characteristics is presented in Table 1. Briefly, close to half of the included studies originated from North America (38%), and the most commonly assessed cancer types were lung (18%), colorectal (16%), and breast cancers (15%). Approximately half of the studies were published within the last 4 years. A majority (82%) of identified papers were based on clinical data from phase III randomized controlled trials, while another 16%
utilized observational data from real-world evidence studies. The remaining 3% of studies were based on data from random-effects network meta-analyses, including one study employing a network of five trials [18] and the other comprising a network of 16 studies [19]. The real-world studies were overwhelmingly retrospective in nature (92%), comprised of predominantly database analyses (67%) or based on registry data (25%). Several of the real-world studies (17%) conducted propensity score matching to balance prognostic factors between treatment arms, and 33% utilized Cox models.

Funding sources of the identified studies were relatively well-balanced between industry sponsorship (33%), public grants (32%), and no declaration of funding (28%). Cross-referencing the time horizon selected by study authors with the source of funding revealed that industry-sponsored studies were more likely to use longer time horizons. Of the 32 included studies that used a time horizon of 10 + years (including lifetime), 47% were industry-sponsored, whereas 16% were funded through public grants. Conversely, for the studies using shorter time horizons of ≤ 5 years, funding sources were more evenly distributed, with 39% sponsored by industry and 39% funded through public grants; however, no statistically significant relationship was identified between funding sources and time horizon (Chi-square test: $p = 0.2939$).

### 4.3 Key Assumptions and Modeling Techniques from Identified Studies

Over three-quarters of all included studies (82%) were cost-utility analyses and 83% were conducted from a public healthcare system perspective. The most common model structure was the Markov model (47%) followed by the partitioned survival model (17%). More than half (57%) of all included studies concluded that the intervention under investigation was cost effective and this proportion was higher for industry-sponsored studies (76%; Chi-square test: $p = 0.0054$). Details are presented in Table 2.

In approximately 9% of studies, methods for crossover adjustments were reported to have been used. Of these seven studies, some of which reported more than one crossover adjustment method, the most commonly cited methods were Cox regression with crossover as a time-dependent covariate (29%), rank-preserving structural failure time (29%), and inverse probability of censoring weights (29%); however, three of the seven studies (43%) did not report the specific crossover adjustment method used.

### 4.4 Extrapolation Methods

Forty-nine percent of studies reported extrapolation of survival endpoints and 19% of these studies reconstructed Kaplan–Meier curves using digitization techniques (Table 3). When reported, the average number of months of extrapolation beyond the clinical study duration was approximately 90 months. Among the 49% of studies that extrapolated results, 89% reported extrapolation using fitted parametric curves. Hybrid models combining both Kaplan–Meier trial data and extrapolated data were relatively rare (5%), and only two studies (5%) used solely the hazard ratio method to extrapolate over time (both based on patient-level observational data). Other non-common methods used for extrapolation included use of a simple average monthly transition probability applied across years (3%), and transition probabilities calibrated to minimize mean squared differences between trial survival endpoints and model-generated curves (3%). Less than 20% of the extrapolated studies reported testing the proportional hazards assumption to
Half of these used the log-cumulative hazards plot to assess proportional hazards, while the other half did not report the method of assessment used.

Overall, 28 studies (37%) reported which distributions were used for extrapolation, and among these 28 studies, the Weibull distribution was the most commonly used parametric distribution for both treatment and comparator model arms in modeling progression-free survival (PFS; 39%, 36%) and OS (64%, 61%), followed by the log normal distribution for PFS (18%, 21%) and the log-logistic for OS (14%, 14%). Distribution selection for PFS was reported in 21 studies, 27 studies reported distribution selection for OS, and the Akaike Information Criterion (AIC) was the most commonly reported method for identifying best statistical fit (32%). The majority of identified studies did not validate the results of their analyses and extrapolations; only 21% of the identified studies performed a validation procedure, and validation was more commonly performed in studies published in later years compared with earlier years. The most common validation techniques reported were clinical experts (44%), comparison with previous studies (31%), comparison with real-world evidence (13%), and creation of a separate validation model (13%).

### 4.5 Additional Analyses

The greatest number of identified studies were from North American countries (38%), followed by countries in East Asia (21%), continental Europe (18%), and the UK (16%). A majority of the North American studies (59%), European studies (64%), and UK studies (58%) found the treatment under investigation to be cost effective at the WTP threshold cited by the authors, while this proportion was 50% for studies from East Asia. Among studies that reported conducting validation exercises, some small geographic variation was noted: 11% of studies from North America reported validation, compared with 6% of studies from East Asia, 5% of studies from the UK, and 4% of studies from continental Europe. In addition, a much higher proportion of studies from the UK (100%) and North America (93%) reported use of probabilistic sensitivity analysis than studies from other geographic regions (continental Europe: 71%; East Asia: 69%). Comparable trends were observed for utilization of deterministic sensitivity analysis, scenario analyses, and use of cost-effectiveness acceptability curves. Sensitivity analyses were also reported in some studies from South America, Australia, and Africa, but the number of studies included for each of these regions was too low to draw clear inferences or conclusions.

Some regional variation was also observed when analyzing survival extrapolation methods across jurisdictions. The use of fitted parametric curves for extrapolation was frequently reported in studies from the UK (83%), about twice
as often as reported in studies from other geographic regions (East Asia: 44%; North America: 38%; continental Europe: 29%). Additional variation between regions included the number of studies reporting adjustment for crossover, which was higher in the UK (25%) than in other regions (0–7%), and testing of the proportional hazards assumption, which was consistently rare across most regions (between 7% and 17%) but was not reported at all in studies from East Asia. Other methods were broadly similar across regions. Results of the analysis comparing IO ($n = 19$) and non-IO ($n = 57$) economic evaluations indicated that while approximately half of both IO (58%) and non-IO studies (46%) used Markov models, a greater proportion of IO-focused studies used partitioned survival models (32%) compared with non-IO studies (12%).

Finally, to investigate the representativeness of the 20% random sample, a second 20% random sample was taken. Comparing the types of models in the second random sample with the original random sample, the proportion of studies reporting the primary analysis as cost utility, cost effectiveness, or ‘other’ were 84%, 13%, and 2% in the second random sample, and 82%, 17%, and 1% in the original random sample, respectively. A high degree of concordance between the two random samples was also observed for the proportions of studies reporting common model structures: Markov models (58% vs. 49%), partitioned survival (17% vs. 17%), decision tree (8% vs. 7%), ‘other’ (7% vs. 5%), and not reported (9% vs. 9%). A small degree of variation was seen for less commonly used model structures: combination (0% vs. 7%), discrete event simulation (0% vs. 3%), and microsimulation (1% vs. 4%).

### Table 3 Extrapolation techniques and methods reported in the articles included in the random sample

| Characteristic                                      | Number of studies [n (%)] |
|----------------------------------------------------|---------------------------|
| Extrapolation [$N = 37$]                           |                           |
| Kaplan–Meier curves included                       | 2 (5)                     |
| Fitted curves only                                 | 35 (95)                   |
| Extrapolation method [$N = 37$]                    |                           |
| Fitted parametric curves                           | 33 (89)                   |
| Hazard ratio method                                | 2 (5)                     |
| Other methods [$n = 1$]                            | 2 (5)                     |
| Statistical fit [$N = 37$]                         |                           |
| Akaike information criterion                      | 12 (33)                   |
| Bayesian information criterion                     | 7 (19)                    |
| Digitization of survival curves [$N = 37$]         |                           |
| Yes                                                | 7 (19)                    |
| No                                                 | 19 (53)                   |
| Not reported                                       | 10 (28)                   |
| Proportional hazards assumption [$N = 37$]         |                           |
| Tested                                             | 6 (16)                    |
| Validation [$N = 76$]                              |                           |
| Study results validated (e.g. using RWE, etc.)     | 16 (21)                   |
| Distributions used for extrapolation [$N = 37$]    |                           |
| PFS [$N = 21$]                                     |                           |
| OS [$N = 27$]                                      |                           |
| Treatment                                          |                           |
| Weibull                                            | 11 39% 18 64%             |
| Log-logistic                                       | 2 7% 4 14%                |
| Log-normal                                         | 5 18% 1 4%                |
| Exponential                                        | 1 4% 1 4%                 |
| Generalized gamma                                  | 2 7% 3 11%                |
| Comparator                                         |                           |
| Weibull                                            | 10 36% 17 61%             |
| Log-logistic                                       | 1 4% 4 14%                |
| Log-normal                                         | 6 21% 1 4%                |
| Exponential                                        | 2 7% 2 7%                 |
| Generalized gamma                                  | 2 7% 3 11%                |

OS overall survival, PFS progression-free survival, RWE real-world evidence
5 Discussion

5.1 Summary of Main Results

This 20% random sample of published economic evaluations over the past decade has shown that many advances in economic evaluation methods have diffused into common usage. These methods included deterministic and probabilistic sensitivity analysis, extrapolation of outcomes beyond the duration of clinical trials, utilization of cost-effectiveness acceptability curves, both Markov and partitioned survival model structures, and the cost-utility analytical framework. Less frequently or inconsistently utilized methods included testing of the proportional hazards assumption (for those studies in which it would have been appropriate to do so), assessing statistical fit of survival extrapolations, and validating study results. Looking at the study sample across geographic regions, heterogeneity was observed in the use and reporting of procedures for validating results, statistical curve fitting techniques, testing of proportional hazards assumption, and adjustment for crossover. While new methods may be developed over time, uniform uptake across regions is not guaranteed, even when supported by the publication of economic evaluation guidelines.

5.2 Explanation of Findings and Comparison with Other Studies

Previously cited reviews of economic evaluations in oncology have examined data over a very limited period or have been focused on a specific jurisdiction [11, 12]. An additional study from late 2019 examined modeling approaches in 100 NICE technology appraisals and 124 published studies, finding that the state transition model (41.0%, 82.3%) and partitioned survival model (54.0%, 12.1%) were the most commonly utilized model structures in NICE submissions and published oncology literature, respectively [20]. However, this study was limited to a 5-year period and investigated model structure exclusively and did not review, for example, the model assumptions regarding PFS or survival extrapolations. To the authors’ current knowledge, the present analysis provides the first examination of published English-language economic evaluations in oncology across a 10-year period, focused on multiple modeling methods across multiple jurisdictions and cataloguing trends in methods uptake across geographies.

Comparing the study characteristics observed in the present study based on published economic evaluations in oncology between 2010 and 2019 with the results of previously conducted studies reveals a number of similarities. First, Markov models and partitioned survival models appear to be the most commonly utilized model structures across most geographic regions, which suggests that these methods have been broadly accepted and integrated into economic evaluation processes. Comparisons between UK studies included in the present analysis and previous studies (also UK studies) demonstrates further similarities in terms of average model duration (time horizon), use of fitted parametric curves and extrapolation techniques, the use of procedures to validate results, and testing of the proportional hazards assumption. For example, the use of fitted parametric survival curves was found to be similar between previous publications and the UK subset from the present study (76% [12], 91% [11], and 83%, respectively).

Insights beyond those presented in previous studies include results presented across more than a single geography. For example, while the use of partitioned survival models has been extensively observed by Benedict and Muszbek (61%) [12], Bullement and colleagues (54%) [20], and UK studies included in the present analysis (42%), this model structure was seldomly observed in studies from North America (17%), continental Europe (7%), and East Asia (6%). Studies from jurisdictions outside the UK tended to favor the use of Markov models (24%, 43%, and 56%, respectively). In contrast to the results from previous UK studies, fitted parametric survival curves were also much less frequently reported in studies from East Asian countries (44%), North America (38%), and continental Europe (29%). These observations suggest that there may be important differences in uptake of economic evaluation methods across geographic regions, and these could potentially lead to differences in decision making.

5.3 Limitations

The present study is associated with a number of limitations. Search parameters were limited to articles published in English, exhibiting a bias towards studies from countries that have English as a first language. Second, not all economic evaluations in oncology require or report extrapolation of survival endpoints, and thus the total number of studies from which inferences may be drawn around survival outcomes may be limited. In addition, while the 20% random sample taken was assumed to be representative of the entire 378 identified studies that met the inclusion criteria, there is no guarantee that the studies not included in the random sample would provide similar or corroborative results, although this may be an intuitively plausible conjecture. To address this limitation, a second 20% random sample was taken in which the analysis type and model structure characteristics were found to be similar to the proportions observed in the original 20% random sample, providing some reassurance.
regarding its representativeness. It was also assumed that if study authors did not mention extrapolation, it was assumed that study results were not extrapolated. In some cases, absence of this evidence may not be evidence of its absence, although the number of studies to which this applies might be expected to be small. Comparisons between regions were also limited by the relatively small number of studies per group.

This study was focused on published literature exclusively, and thus there is a potential for publication bias since oncology models built for reimbursement submissions were not included in the study. The study results also do not directly capture the impact of the evolution of methods on oncology models submitted to HTA agencies or the subsequent reimbursement recommendations made based on those models. Conference abstracts were also excluded, implying the potential for not having captured some of the most up-to-date economic evaluation methods in use, and this may in turn affect the external validity of this study. However, since the content of conference abstracts is necessarily limited and may differ from the content included in full publications, excluding them in the present study may be justifiable for the purposes of comparison with published economic evaluations.

5.4 Future Directions

As economic evaluation becomes increasingly embedded in decision making, a subsequent increase in the aggregate number of published studies can be expected. This increase will provide opportunities to re-evaluate the uptake of methods in the light of the development of new guidelines, survival analysis techniques, and other methods. While our study found that Markov and partitioned survival models were the most common structures used among our sample of studies published between 2010 and 2019, future research could focus on the use of novel modeling techniques such as discrete event simulation [20–24], multistate modeling [20, 25, 26], and mixture cure models [27, 28], which are more frequently used to overcome specific limitations inherent in more rudimentary analytical approaches. Discrete event simulation, for example, is typically used when the implementation of a defined model structure is not manageable as a cohort-based state transition model, or when baseline heterogeneity, continuous disease markers, time-varying event rates, and the influence of prior events on subsequent event rates are of relevance to decision making [22]. Recent advances in the development of anticancer therapies have led to the advent of therapeutics that may be curative for certain patients, leading to recommendations of using mixture cure modeling [29]. Since we might expect to see more frequent use of newer modeling methods [20], and given that these novel methods have not (yet) been incorporated into current guidelines, it could be helpful and informative for future research efforts to track and document the diffusion of these newer methods into use over time, both in the published oncology literature and in technology appraisals from health technology assessment bodies.

6 Conclusion

This review of published economic evaluations in oncology has shown that over the past decade a majority of the identified papers reported basic characteristics of study type, data source used, modeling techniques, and utilization of survival analysis methods. However, greater detail in reporting extrapolation methods, statistical analyses, and validation of results could be potential improvements. Regional variation observed in the use of these methods warrants further examination in order to support greater consistency in decision making. Future research efforts could be dedicated towards documenting the diffusion of novel modeling techniques into economic evaluation.

Appendix

Search strategies
Ovid Medline

1  exp Cost-Benefit Analysis/ec [Economics]  1557
2  quality adjusted life years.mp. or exp Quality-Adjusted Life-Years/  14480
3  (cost-effectiveness or cost-utility or cost-benefit or economic or cost or costs or quality adjusted life years or quality-adjusted life years or qaly or qalys).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]  756701
4  1 or 2 or 3  756701
5  exp Neoplasm Metastasis/ec  18
6  (advanced cancer or advanced neoplasm or metastases or metastasis or metastatic or metastatic cancer or metastatic neoplasm).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]  527874
7  5 or 6  527885
8  4 and 7  6867
9  Economics/  27052
10  exp "Costs and Cost Analysis""/  225854
11  Economics, Nursing/  3986
12  Economics, Medical/  9019
13  Economics, Pharmaceutical/  2865
14  exp Economics, Hospital/  23657
15  Economics, Dental/  1902
16  exp "Fees and Charges"/  29773
17  exp Budgets/  13530
18  budget*.ti,ab,kf.  27665
19  (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kf.  214269
20  (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2  265345
21  (cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kf.  148552
22  (value adj2 (money or monetary)).ti,ab,kf.  2200
23  exp models, economic/  14209

△ Adis
24 economic model*.ab,kf.  3048
25 markov chains/    13474
26 markov.ti,ab,kf.  20624
27 monte carlo method/  26847
28 monte carlo.ti,ab,kf.  46006
29 exp Decision Theory/  11495
30 (decision* adj2 (tree* or analy* or model*)).ti,ab,kf.  21379
31 or/9-30  683448
32 8 and 31 4503
33 limit 32 to (humans and yr="2010 -Current") 1916
34 (cost or costs).tw. 501891
35 33 and 34  1457
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 Declarations

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 Conflict of interest Graeme Ball is an employee of Gilead Sciences, Inc. (Canada). Jean-Eric Tarride, Mitch Levine, and Lehana Thabane have no conflicts of interest that are directly relevant to the content of this article.

 Availability of data and material The authors declare that all data used in this study are derived from the publicly available published oncology literature. The Excel spreadsheets used for the analysis can be provided upon reasonable request.

 Code availability Not applicable

 Author contributions GB collected and analyzed the data, and drafted the manuscript. JET contributed to the design of the study, and the analysis and interpretation of the data. JET, ML, and LT conceptualized the study and contributed to the revision of the manuscript. All authors gave final approval for the version to be published.

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