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HEOR in the Broader Context of HTA/CER

Health Technology Assessment Challenges in Oncology: 20 Years of *Value in Health*

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ABSTRACT

Background: Oncology treatments have changed from chemotherapies to targeted therapies and more recently immuno-oncology. This has posed special challenges in the field of health technology assessment (HTA): capturing quality of life (QOL) associated with toxicity due to chemotherapy, crossover upon progression in targeted therapy trials, and survival extrapolation for immuno-oncology drugs.

Objectives: To showcase 20 years of *Value in Health* (*ViH*) publications in oncology.

Methods: A review was undertaken of oncology articles published in *ViH* from May 1998 to August 2018. Full-length articles published in *ViH* with the keywords "oncology," "cancer," "h(a)ematology," and "malignancy" were included for review. Conference abstracts were excluded.

Results: Four major themes were identified: (1) QOL and the development of multiple functional assessment of cancer therapy tools and mapping instruments; (2) analysis of clinical evidence using indirect comparisons, network analyses, and adjustment for crossovers; (3) modeling, Markov models, partitioned survival models, and extrapolation methods; and (4) financial implications and how to deal with uncertainty, introduction of conditional reimbursement, managed entry, and risk share agreements.

Discussion: This review article highlights the important role *ViH* has played in disseminating HTA research in oncology. A few key issues loom on the horizon: precision medicine, further development and practical application of new QOL measures, methods for translating clinical evidence, and exploration of modeling techniques. For a better understanding of the complex interplay between access and financial risk management, *ViH* will no doubt continue to promote pioneering research in HTA and oncology.

Keywords: cost-effectiveness, cost-utility, health technology assessment, oncology, quality of life

VALUE HEALTH. 2019; 22(5):593–600

Introduction

Value in Health (*ViH*) is the flagship publication for the International Society of Pharmacoeconomics and Outcomes Research (ISPOR). The first issue was published in May 1998, and the journal's aim is to publish best applications of pharmacoeconomics and outcomes research.[1] The fields of pharmacoeconomics and outcomes research have seen many advances over the past 2 decades and the readership of *ViH* has grown to more than 10 000.[2]

An important therapeutic area that likewise has undergone significant evolution in the same time period is oncology, in which treatment options have changed from nonspecific chemotherapy to targeted therapy and more recently immuno-oncology (Figure 1).

Chemotherapies such as carmustine, docetaxel, and paclitaxel constituted major treatments in oncology until the start of this century,[1] but their effects on healthy cells led to adverse toxic profiles.[2] The impact of toxicities when assessing benefits and risks of chemotherapies became important and this stimulated research into quality of life (QOL).

In the 2000s, new classes of targeted therapies such as imatinib, gefinitib, and bevacizumab emerged and gained regulatory approval.[1] These drugs selectively target the growth of cancer cells[3] as demonstrated through superior progression-free survival.[4–6] Nevertheless, some of these trials allowed patients to switch from placebo/control to active treatment upon progression,[7,8] thereby making it difficult to translate the clinical evidence as overall survival was confounded.

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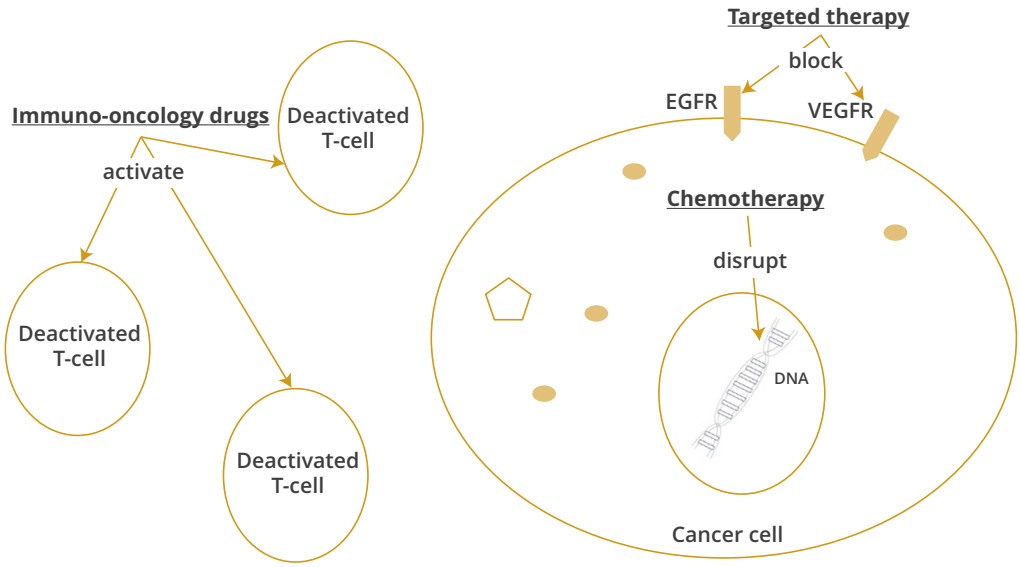
https://doi.org/10.1016/j.jval.2019.01.001

Figure 1. Modes of action: chemotherapy, targeted therapies, and immuno-oncology agents.



EGFR, epidermal growth factor receptor inhibitors; VEGFR, vascular endothelial growth factor receptor inhibitors.

More recently, immuno-oncology drugs have been developed (eg, ipilimumab, pembrolizumab, and nivolumab), which inhibit tumor-induced immunosuppression and enable the immune system to fight cancers.[9] These drugs often need time to work, which manifests in an efficacy profile in which there is seemingly no benefit in terms of progression-free survival despite a significant benefit in overall survival.[10,11] This has led to the focus on modeling techniques and especially on extrapolation of survival beyond the durations of clinical trials.

The proliferation of new medicines for cancer and the growing prevalence of cancer have meant that costs have threatened to spiral out of control.[12] As such, payers have actively looked at different types of market access agreements to manage the financial risks while ensuring that patients get access to the latest medication.

The aim of this article is to showcase the past 20 years of *ViH* publications in oncology over this period.

Methods

A search of every issue of *ViH* from May 1998 to August 2018 was performed using the *ViH* website. Full-length articles that were found using the keywords "oncology," "cancer(s)," "h(a)ematology," and "malignancy/malignant" were considered. Furthermore, ISPOR Task Force reports were reviewed. Conference abstracts were excluded. All articles were reviewed by a reviewer.

Results

A total of 147 issues of *ViH* were searched and 2628 publications were identified in the initial search. Of these, 2292 conference abstracts were excluded and the remaining 336 were full-length articles, review articles, correspondence, and editorials (Figure 2).

From these publications, 4 key themes were noted: (1) QOL and its measurement; (2) analysis of clinical evidence using indirect comparisons, network analyses, and adjustments for crossovers; (3) health economic modeling with respect to Markov models and partitioned survival models as well as extrapolation methods; and (4) financial implications and how to deal with uncertainty.

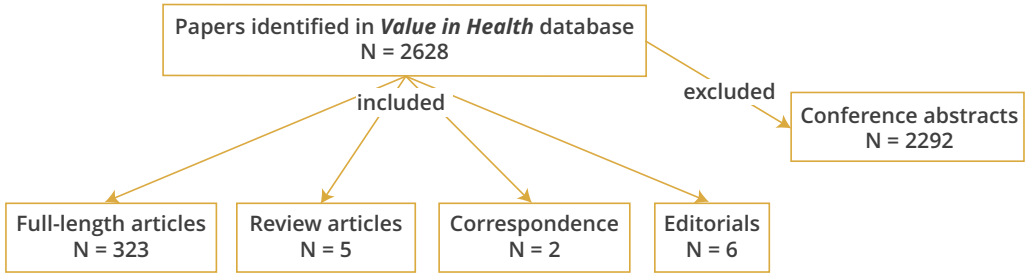
Quality of Life

The evolution of QOL in pharmacoeconomics and outcomes research in oncology is well documented in *ViH*. Twenty years ago, patients/physicians and payers were grappling with how to value chemotherapies despite severe toxicities. In this setting, QOL, which reflects the balance between benefits and harm to individuals, became an integral part of health technology assessments (HTAs) in oncology.

It was recommended in 1999 at the ISPOR Inaugural European Conference that quality-adjusted life-years (QALYs) be used instead of healthy-year equivalents when conducting health economic evaluations.[3] At the same conference, it was noted that current databases did not usually contain QOL data[4] and, as such, economic evaluations of cancer interventions did not necessarily focus on QALYs but rather on life-years gained.[5] Many challenges of QOL were identified by Leidy et al[6] who highlighted the need for rigorous study design and for more research into methodology, development of new instruments, and interpretation in the field of health-related quality of life (HRQOL). Later the same year, Wan et al[7] published an analysis on the demographic, social, and clinical factors that have an impact on the HRQOL of patients with 4 different types of cancer (breast, colon, head/neck, and lung) at different disease stages using the Functional Assessment of Cancer Therapy—General (FACT-G) instrument. This study not only showed that multiple factors influence patient assessments of HRQOL, but also showed that the management of cancer was diverse and that there were significant differences in functional well-being among people with different types of cancer. Several articles were published subsequently on FACT instruments specific to advanced kidney cancer,[8] metastatic hormone-refractory prostate cancer,[9] stage I-IV melanoma,[10] acute and chronic leukemia,[11] stage III/IV breast cancer,[12] and advanced brain cancer.[13]

Typically, utility values are not generated by authors of oncology economic evaluations and have been taken from separate published studies using standard gamble or time trade-off

Figure 2. Flowchart of the review.



(TTO).[14–17] Nevertheless, with increased use of the QALY as the key reported outcome, mapping tools were developed to allow the derivation of utilities from HRQOL instruments, such as the FACT-G mapping by Cheung et al[18] and the mapping of the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) by Pickard et al,[19] both of which were used by patients at different stages of various cancers. Direct measurements were also undertaken. For example, a TTO study involving 50 oncology nurses was performed by Brown et al[20] as part of an economic evaluation in head and neck cancer, with the health state values being based on EQ-5D health states rather than on cancer-specific health states. The broader general EQ-5D instrument became more popular over time but was not without issues. In 2009, Norman et al[21] highlighted variation in EQ-5D utility values across the United Kingdom, the Netherlands, Denmark, and Germany. This variation meant that economic evaluations in Germany using UK weights would underestimate utility, because Germans generally valued each EQ-5D health state higher than did people in the United Kingdom. Viney et al[22] published Australia-specific EQ-5D TTO weights in 2011 and did a further comparison with Japanese and Spanish data. Around the same time, important contributions to the discussion surrounding important clinical differences of QOL were also published in *ViH*. Cella et al[9] reported estimates of meaningful difference in metastatic hormone-refractory prostate cancer, and Askew et al[10] published estimates of meaningful difference in stage I-IV melanoma. A review by Tosh et al[23] of economic models reviewed by the UK National Institute for Health and Care Excellence reported that the EQ-5D was the most common tool extracted from clinical trials for economic evaluation. Mapping, systematic reviews, and elicitation studies were and still are the basic techniques used when utility data are not measured alongside efficacy data in a clinical trial setting. A recent initiative to move toward an EORTC QLQ-C30–derived disease-specific utility in cancer called EORTC Quality of Life Utility Measure-Core 10 dimensions[24] has recently been revealed. The reliability of this tool was recently published in *ViH* by Gamper et al[25] who showed that it is more likely to measure health state preferences rather than mood-specific or condition-specific judgments. This is potentially a significant advance because it enables researchers not only to measure cancer-specific issues with respect to utilities, but also to apply it retrospectively to old studies in which EORTC QLQ-C30 was administered.

Table 1 lists key publications of QOL instruments in *ViH* published between 1998 and 2018.

Clinical Evidence

Direct head-to-head evidence provides an unbiased estimate of efficacy, safety, and QOL and is therefore considered the criterion standard criterion in HTA.[37] It is, however, not always possible to perform head-to-head trials. One reason is that interventions are developed in parallel, which makes it impossible to predict what the standard of care will be even in the short term. Another complicating factor may be the lack of an alternative effective treatment available. This means that patients are reluctant to join trials if they risk being randomized to placebo. These issues are well recognized in oncology by regulators[38] and researchers[39] and, as a consequence, single-arm trials are becoming common in the development of cancer drugs.

As the treatment landscape of cancer moved from chemotherapy to targeted therapies to immuno-oncology agents, several issues emerged that related to identifying, describing, and accounting for uncertainty as a result of lack of head-to-head evidence and economic evaluations based on evidence from single-arm trials.

Two ISPOR Task Force reports[37,40] have been published on indirect comparisons and network meta-analysis. The first report[37] provided guidance on the interpretation of indirect comparisons and network meta-analysis to assist policy makers and healthcare professionals in decision making. The second report[40] set out best practices for HTA practitioners who perform these types of analyses. A review of HTAs in endocrine early breast cancer[41] revealed that methods such as indirect comparisons are common. Nevertheless, Casciano et al[42] noted in an economic evaluation of metastatic renal cell carcinoma the inherent limitation of indirect comparisons arising from differences in baseline characteristics of groups being compared, which could confound the results. Exploring the use of propensity scoring to adjust baseline differences in a cohort of elderly patients with non-Hodgkin lymphoma was undertaken by Gruschkus et al.[43] An in-depth article extending this method to naive comparisons to perform matching-adjusted indirect comparisons for newly diagnosed patients with chronic myeloid leukemia was published by Signorovitch et al[44] (Figure 3).

Another significant issue with respect to patients switching treatment upon progression in a clinical trial was highlighted by Hoyle et al[45] for advanced renal cell carcinoma. This was typically done for ethical reasons, that is, to ensure that all patients have a chance of receiving potentially optimal treatment when participating in a clinical trial, regardless of whether they were randomized to control or intervention. Nevertheless, this meant that the impact of the intervention on overall survival would be confounded by treatment switching when progression occurred. Adjustment to postprogression survival using a calibration term so that the resulting median overall survival time was equal to that derived from advanced multiple myeloma trial data was presented by Ishak et al[46] and methods such as inverse of censoring weighting and rank preserved structural failure time became popular, as described by Jönsson et al[47] in a literature review. This

Table 1. Key publications of QOL instruments in *Value in Health* published between 1998 and 2018

Instrument	Cancer type	Reference
FACT—biological response modifiers	Not tumor-specific	Yost 2005[26]
Mapping of Functional Assessment of Cancer Therapy—Prostate and EORTC QLQ-C30 onto EQ-5D	Metastatic hormone-refractory prostate cancer	Wu 2007[27]
Functional Assessment of Cancer Therapy—Kidney Symptom Index	Kidney cancer	Cella 2007[8]
Functional Assessment of Cancer Therapy—General	Not tumor-specific	Dobrez 2007[28]
Cancer Therapy Satisfaction Questionnaire	Not tumor-specific	Trask 2008[29]
TTO and EQ-5D Australian weights	Not tumor-specific	Viney 2011[22]
Utility-Based Questionnaire—Cancer derived using TTO	Not tumor-specific	Grimison 2009[30]
Mapping of EORTC QLQ-C30 onto TTO utility scores	Not tumor-specific	Pickard 2009[19]
Mapping of EORTC QLQ-C30 onto EQ-5D, SF-6D, and 15D	Gastric cancer	Kontodimopoulos 2009[31]
Functional Assessment of Cancer Therapy—Melanoma	Melanoma	Askew 2009[10]
Mapping of Functional Assessment of Cancer Therapy—General onto EQ-5D	Not tumor-specific	Cheung 2009[18]
Mapping of EORTC QLQ-C30 onto EQ-5D	Esophageal cancer	McKenzie 2009[32]
Estimate utility scores and treatment preferences using VAS and TTO	Early-stage cervical cancer	Jewell 2011[33]
National Comprehensive Cancer Network-Functional Assessment of Cancer Therapy-Breast Cancer Symptom Index	Breast cancer	Garcia 2012[12]
Functional Assessment of Cancer Therapy—Leukemia	Leukemia	Cella 2012[11]
Functional Assessment of Cancer Therapy—Cognitive Function	Not tumor-specific	Cheung 2013[34]
FACT in advanced kidney cancer	Advanced kidney cancer	Rothrock 2013[35]
Mapping of FACT onto EQ-5D	Metastatic castration-resistant prostate cancer	Skaltsa 2014[36]

EORTC QLQ-C30 indicates European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D, EuroQol 5-dimensional questionnaire; FACT, Functional Assessment of Cancer Therapy; QOL, quality-adjusted life-year; SF-6D, 6-dimensional health state short form; SG, standard gamble; TTO, time trade-off; VAS, visual analogue scale.

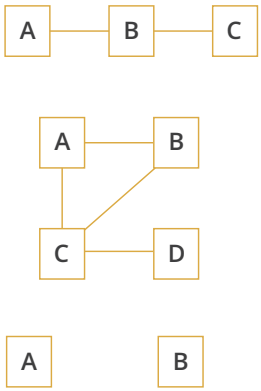
is still a hotly debated topic, with Bennett et al[48] publishing an article in 2018 highlighting issues with uncertainty of rank preserved structural failure time estimates when applied to parametric survival models. Isbary et al[49] reported that oncology medicines with switching received better additional benefit ratings, but were assigned lower evidence levels in Germany, reflecting the uncertainty associated with adjustment methods.

Modeling

The ISPOR Task Force Report on modeling good research[50] states that specifications of health states should generally reflect the disease condition modeled. This is well accepted in oncology, and Frederix et al[41] concluded in a review of breast cancer models that the underlying biological processes were taken into account to a large extent. Markov models with disease-/progression-free and progressive/recurrence health states are common across tumor types from adjuvant therapy to advanced stages of cancer.[14,17,51,52] Another popular method that was explored by Hoyle et al[53] in metastatic colorectal cancer was to estimate the proportion of patients in each health state (nonprogressive disease, progressive disease, and death) using the area under the survival curves. This type of modeling was later coined as "partitioned survival" modeling and several HTAs adopting the approach have been published in *ViH*, with recent examples in advanced ovarian cancer[54,55] and advanced melanoma.[55] Discrete event simulation (DES)[56] is also common in oncology because it enables models to take into account heterogeneity in baseline characteristics as well as to reflect the complexity of real-world treatment pathways. Other advantages of DES include tracking of health status, treatment history, and treatment switches over the course of the disease to improve accuracy and efficiency. Multiple examples have been published in *ViH* for testing of ovarian cancer,[57] chemotherapy-naive patients with prostate cancer,[58] follicular lymphoma,[59] and a surveillance program for melanoma.[60] Tappenden et al[61] even used DES to model the whole disease of colorectal cancer (Figure 4).

A hotly debated topic in oncology modeling is the extrapolation of survival curves. The issue is highlighted in the ISPOR Task Force Report on modeling good research[50] and relates to challenges with respect to transforming trial data, such as estimating survival curves on the basis of published summary data to extrapolate beyond trial durations. A practical implementation of these methods was outlined by Coyle et al,[62] who performed a cost-effectiveness analysis of systemic therapies in advanced pancreatic cancer. A lifetime horizon is frequently considered, and although for many cancer types the duration is short, a time horizon of 60 years was used by Johal et al[63] in a cost-effectiveness analysis of adjuvant treatments for osteosarcoma. Different time horizons are often applied, such as by Hsu et al,[64] who considered 3, 4, 5, and 10 years for their cost-effectiveness analysis of treatments for stage III colon cancer. Pure trial-based economic evaluations have also been published in *ViH*. For example, Goulart and Ramsey[16] showed that in stage III/IV non–small cell lung cancer, a trial-based evaluation for bevacizumab added on to chemotherapy would result in an incremental cost-effectiveness ratio of

Figure 3. Methods for dealing with lack of head-to-head data and practical examples published in *Value in Health*.



ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; NMA, network meta analysis.

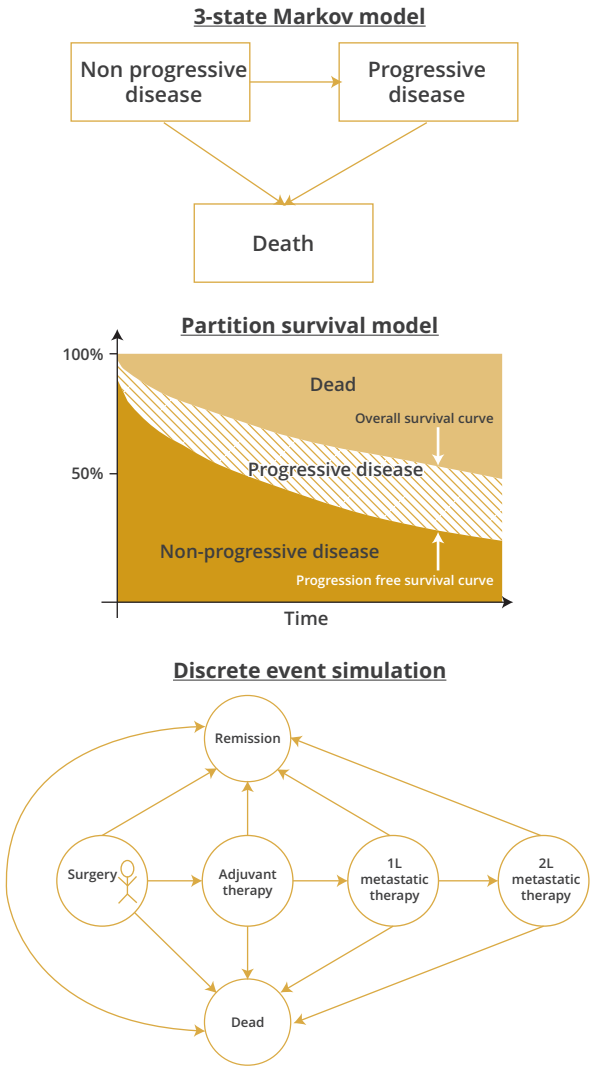
$500 000 per QALY gained. When extrapolating survival curves to longer time periods, the choice of distribution is most commonly justified using Akaike and Bayesian information criteria, as exemplified by models in chronic lymphocytic leukemia and ovarian cancer published by Woods et al[65] and Fisher and Gore,[66] respectively. Bohensky et al[52] used Akaike and Bayesian information criteria, as well as made sure that the selected function matched the underlying biological assumption with respect to the drug under investigation in stage IIIb/IV melanoma.

Financial Implications and How to Deal With Uncertainty

Cipriano et al[67] reported that the price of lung cancer treatment across all stages is approximately $10 000 per month for the first 6 months and up to $2000 thereafter. The high cost of cancer drugs and budget implications have been well highlighted in *ViH* over the years. A recent study by Leopold et al[68] looking at media coverage on high drug prices in the United States found that launch prices of cancer drugs have increased about 10% per year between 1995 and 2013. Nevertheless, drug prices are only a part of the equation. Tan et al[69] highlighted that inpatient hospital costs for patients with cancer are more than 50% higher than the average inpatient costs in the Netherlands. Félix et al[70] showed that the costs associated with common skeletal-related events for metastatic breast and prostate cancer were between €5700 and €6000 per patient in the Portuguese health system.

Different measures have been put in place around the globe to control the spending of cancer drugs, from setting up a special cancer fund independent of the drug reimbursement authority in the United Kingdom[71,72] to issuing government drug licenses to local manufacturers for patented drugs in Thailand.[73] Kircher et al[74] discussed whether legislation on parity can help reduce the cost burden of anticancer medications, but it remains unclear what an optimal plan would look like. Boersma et al[75] argue that a reduction in drug expenditure can be achieved with the introduction of a decision threshold using examples in non–small cell lung cancer and leukemia. In line with this, Wilson and Cohen[76] showed that in a comparison between Australia and the United States, implementing processes for cost-effectiveness assessments did indeed restrict budget and use of cancer medicines. Nevertheless, Franken et al[77] reported that economic evaluation has had limited impact in restricting access for controversial high-cost drugs such as cancer drugs in England, Germany, the Netherlands, and Sweden.

Figure 4. Common health economic models used in oncology.



A framework for coverage with evidence development to facilitate paying for use of new drugs in areas such as lung cancer and colorectal cancer despite uncertain evidence was put forward by Walker et al.[78] Wonder et al[79] described the Australian process in which the price of a drug was justified by the existing evidence, pending the availability of more conclusive evidence of cost effectiveness to support continued listing of, for example, anticancer medicine at a higher price.

New trial evidence for anticancer medicines is not always going to be available. Instead, real-world evidence (RWE) has been used to cover the evidence gaps, and *ViH* has published an ISPOR Task Force Report on the subject.[80] Several articles on the use of RWE in oncology have been published. Mohseninejad et al[81] showed how the use of registries could improve the follow-up for conditional approval of oxaliplatin in stage III colon cancer, and Lakdawalla et al[82] showed that real-world data generation can be used to predict overall survival and progression-free survival of chemotherapies using data from breast, colorectal, lung, ovarian, or pancreatic cancer. Nevertheless, RWE generally showed lower efficacy when compared with trial evidence. RWE can be used not only to prove that a drug works, but also to build pay-for-

performance schemes such as cost sharing and payment by results as reported by Navarria et al.[83] They reported on a so-called success fee scheme in Italy, where an anticancer drug is provided by the company at no initial cost and the payer provides payment only for those treatments that have shown effectiveness in a predefined period. Nevertheless, RWE is still considered lower level of evidence compared with randomized clinical trials by HTA agencies (Swedish TLV, UK National Institute for Health and Care Excellence, German IQWiG, French HAS, and Italian AIFA) around the world, as pointed out by Makady et al.[84]

Discussion

Over the last 20 years, as new treatments have emerged in oncology, they have brought new challenges to pharmacoeconomics and outcomes research. Regarding QOL, the inability of general instruments such as the EQ-5D to capture outcomes specific to chemotherapy led to the development of new instruments such as the EORTC QLQ-C30. Issues related to clinical data and lack of active comparators led to methods such as indirect comparisons, network analysis, and matching-adjusted indirect comparisons. Common to oncology, modeling beyond the trial horizon has generated numerous articles on extrapolation and non-Markov modeling techniques. The high costs of oncology medicines and the impact they have on budgets have stimulated research into risk share agreements, conditional reimbursement, and managed entry schemes.

It is not easy to predict what the future of pharmacoeconomics and outcomes research in oncology will look like. There seems to be room for further research into the practical application of disease-specific QOL instruments such as the newly created EORTC Quality of Life Utility Measure-Core 10 dimensions by King et al.[24] Translation of clinical evidence in the absence of head-to-head trial data is also becoming increasingly relevant as new biomarkers are discovered. Further exploration of extrapolation methods is also on the cards considering that trial evidence will need to be assessed well beyond the durations of clinical trials. Finally, it is predicted that the complex interplay between access and financials will be front and center of it all because payers will have to balance pressure from the public to get reimbursement with the ability to pay.

The limitation of an anniversary article such as this is obviously that contributions in other journals are not presented, but this article has outlined the rich heritage that *ViH* has in disseminating research in the areas of pharmacoeconomics, outcomes research, and oncology. Continued development of pharmacoeconomics and outcomes research methods in oncology is likely to continue well into the future, and *ViH* will hopefully continue to be an important platform for researchers to publish best applications in these fields. This was the explicit wish of the inaugural editor of *ViH*, James E. Smeeding, as outlined in the first editorial of the journal.

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