

Original Article  
Oncology & Hematology



# Should We Consider Value Frameworks for Cancer Drugs as Oncology's Landscape Evolves?; from an Oncologist Perspective in Korea

Do Yeun Kim ,<sup>1</sup> Hyerim Ha ,<sup>2</sup> SeungJin Bae ,<sup>3</sup> and Jin-Hyoung Kang <sup>4</sup>

<sup>1</sup>Department of Internal Medicine, Dongguk University Ilsan Hospital, Goyang, Korea

<sup>2</sup>Department of Internal Medicine, Inha University Hospital, Incheon, Korea

<sup>3</sup>Ewha Womans University, College of Pharmacy, Seoul, Korea

<sup>4</sup>Department of Internal Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, Korea



Received: Jan 8, 2021

Accepted: Jun 17, 2021

Address for Correspondence:

Jin-Hyoung Kang, MD, PhD

Department of Internal Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea, 222 Banpo-daero, Seocho-gu, Seoul 06591, Korea.

E-mail: oncologykang@naver.com

\*Do Yeun Kim and Hyerim Ha contributed equally to this work.

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ORCID iDs

Do Yeun Kim

<https://orcid.org/0000-0001-7265-1994>

Hyerim Ha

<https://orcid.org/0000-0001-8889-144X>

SeungJin Bae

<https://orcid.org/0000-0002-8993-8884>

Jin-Hyoung Kang

<https://orcid.org/0000-0002-3741-5168>

Funding

This study was supported by the Health Insurance Review and Assessment Service and supported in part by the Korean Cancer Study Group. This study was also supported

## ABSTRACT

**Background:** As the role of immunotherapies and personalized medicine grow, cancer patients have faced many choices in treatments and have suffered financial toxicity. These challenges brought the need for the value framework (VF) to guide treatment decision making.

**Methods:** A survey was taken to 102 oncologists about perception for VF. They were asked about priorities among several considerations when they prescribe cancer drugs. Their views on the need for development and potential implications of VF in Korea were assessed, also.

**Results:** The survey shows that 90% of the respondents choose clinical efficacy as the most important value in cancer drugs selection, and the cost of drug was more weighted value in immune checkpoint inhibitors (13.7%). Approximately half (53.9%) answered that they were aware of the existing VFs. Over 90% of respondents agreed with the need for development of a VF for cancer drugs based on Korean healthcare system and further usefulness for decisions about reimbursement issues. Seventy-one percent answered that two representative VFs (American Society Clinical Oncology-VF and European Society for Medical Oncology-Magnitude of Clinical Benefit Scale) should be reflected in value measurement of cancer drugs in Korea.

**Conclusion:** The Korean oncologists recognized the necessity for the clinical application of VF. Further discussion between the stakeholders should be followed to alleviate the financial burden through the value-based decision making of cancer drugs.

**Keywords:** Value Framework; Anticancer Drug; Korea

## INTRODUCTION

Recent advances in cancer treatment include development of targeted therapies and immune checkpoint inhibitors (ICIs). These chemotherapeutic agents offer clinical benefits such as prolonged survival, less toxicity and improved quality of life (QoL). However, it also entails financial burden for cancer patients and society.

Eight of the top 10 drugs based on total expenditure in 2012 by United State (US) Medicare were anticancer drugs. Approximately, \$87.5 billion was spent on cancer treatment in 2012

by a grant from the National R&D Program for Cancer Control, Ministry of Health and Welfare, Republic of Korea (1720150).

#### Disclosure

All authors have no potential conflicts of interest.

#### Author Contributions

Conceptualization: Kang JH, Kim DY. Data curation: Ha H, Bae S. Formal analysis: Ha H. Methodology: Kim DY, Bae S. Writing - original draft: Kim DY, Ha H. Writing - review & editing: Kang JH, Bae S.

and the estimated cost for 2020 is \$175 billion.<sup>1,2</sup> Among cancer types, lung cancer has the highest prevalence and the highest cost of treatment at \$2.9 billion, which is attributed to the use of expensive drugs such as ICIs in a variety of clinical scenarios.<sup>2</sup>

In addition to expanding the market for cancer treatment by adding new indications, ICIs are expected to have a profound effect on expenditure on anticancer drugs by patients as well as the government. Currently, with more than 3,300 new agents in the immuno-oncology pipeline and a wide array of combination regimens under investigation, it can be regarded as an innovation and represents a variety of options from a physician and patient perspective.<sup>3</sup> However, the annual cost of novel anticancer medications routinely exceeds \$100,000, which adds to the financial burden at the expense of clinical efficacy.<sup>3</sup>

Meanwhile, it has been argued that the value of cancer drugs is not properly measured during the economic evaluation.<sup>4,5</sup> Since active comparators are frequently lacking in the clinical trials of the cancer drugs, an indirect comparison is unavoidable. The clinical endpoints are often extrapolated based on several statistical techniques, which resulted in substantial uncertainty with the wide range of the Incremental Cost Effectiveness Ratio (ICER). These factors underlying clinical uncertainty and value-based clinical decision making led to the development and adaptation of several value frameworks (VFs), which quantify and evaluate the benefits, harms, and costs. In the past five years, several active discussions revolved around the clinical value of expensive anticancer drugs by diverse organizations and institutions. A few representative value evaluation tools are: European Society for Medical Oncology-Magnitude of Clinical Benefit Scale (ESMO-MCBS),<sup>6,7</sup> American Society of Clinical Oncology Value Framework (ASCO-VF),<sup>8,9</sup> National Comprehensive Cancer Network (NCCN) Evidence Block,<sup>10</sup> Drug Abacus Tool by Memorial Sloan Kettering Cancer Center (MSKCC),<sup>11</sup> and the ICER.<sup>12</sup> Incorporating these VFs in chemotherapeutic agent selection by physicians and patients is underway in several discussions of reimbursement issues.<sup>6-12</sup> These tools make us facilitate the identification of innovative access strategies to specific therapies under clinically diverse scenarios from the perspective of patients, physicians, payers, policymakers, and the pharmaceutical industry. The recent study insists that VFs help to identify therapies providing high clinical benefit and should be made rapidly available across countries.<sup>13</sup>

The issues about effective allocation of health resources and implications for value measurement of expensive cancer drugs has emerged from public hearings in Korea, also.<sup>14</sup> Many issues including methodological approaches and the value measurement from each stakeholder's view make it difficult to reach the consensus. To measure the value of expensive anticancer drugs, a thoughtful analysis by experts is required along with a broad discussion between multiple stakeholders including health insurance, pharmaceutical companies, physicians, and patients.

In this study, we surveyed to explore the perception and attitude for VFs from Korean oncologist's perspectives, so get insight for the possible implementation of VF for anticancer drugs, simultaneously.

## METHODS

### Survey development

We analyzed several existing evaluation tools such as ASCO-VF, ESMO-MCBS, NCCN evidence block, Drug Abacus Tool, and ICER, and reviewed the developmental process of these tools. Based on the review, a preliminary questionnaire (**Supplementary Table 1**) was developed with several rounds of feedbacks among researchers. The final questionnaire (**Supplementary Table 2**) was determined through discussion by all researchers based on the results of the pilot study. It consists of three parts except demographics. The first part includes a question regarding the values ranked according to physician priorities when prescribing anticancer drugs and ICIs. The most important parameters among efficacy, safety/tolerability, cost, and non-clinical factors such as convenience of administration, patients and preference were surveyed. The details of perception toward existing VFs were evaluated by asking whether oncologists were aware of any kind of VFs for anticancer drugs or whether VF can be used for reimbursement decisions at the Korean National Health Insurance (NHI) and re-evaluation of the reimbursement status. The final question pertained to a brief exploration of the parameters underlying the development of Korean VF based on which of the two evaluation tools, ESMO-MCBS and ASCO-VF, were more appropriate in the Korean context and which parameters should be incorporated based on the differences between these two VFs in Korea.

### Design and conduct of survey

A pilot study was conducted with a preliminary questionnaire addressed to 17 oncologists who attended the methodology workshop on July 6, 2019. The main survey was distributed to medical oncologists at one of the largest conferences of the Korean Society of Medical Oncology (KSMO), 2019 Best of ASCO, which was held on August 23–24. A paper-based, self-administered questionnaire was distributed to respondents who agreed to participate. The purpose of the survey and the details of the ASCO-VF and ESMO-MCBS were described by the Principal Investigator (JK) at the beginning of the survey.

To determine the perspective of hematologic oncologists, we collaborated with Korean Multiple Myeloma Working Party (KMMWP), which is the representative academic society of hematologic oncology. The survey was conducted with an online questionnaire using a google survey form because of the KMMWP's request for easy accessibility. The study protocol was the same except for the survey administration. We incorporated detailed descriptions of ASCO-VF and ESMO-MCBS parameters instead of providing a direct explanation by the researcher.

### Ethics statement

The study protocol was reviewed and approved by the Institutional Review Board of The Catholic University of Korea (Approval No. KC19QIDI0791). All studies were conducted according to guidelines for biomedical research and the Declaration of Helsinki. The requirement for participants' informed consent was waived because this study was a survey.

### Statistical analysis

The data of the responders were evaluated using descriptive statistics. Continuous variables are expressed as means  $\pm$  standard deviation (SD) and categorical variables as numbers and percentages.

## RESULTS

### Perception for VF

#### Demographics

Respondents were predominantly medical oncologists (82 of 102, 80.4%), in their forties (52 of 102), and 54.9% were female. The median duration of clinical experience of respondents was 16.3 years (mean, SD; 90.1 months) (Table 1).

#### Relative priority of values and awareness of VFs

Ninety-two of 102 respondents (90.2%) selected the clinical efficacy, including improved overall survival and progression-free survival, as the most important factor when prescribing chemotherapeutic drugs, followed by safety/tolerability ( $n = 6$ , 5.9%) and the cost of drugs ( $n = 1$ , 1.0%). When prescribing ICIs, clinical efficacy was also considered as the highest priority (76 of 102, 74.5%). However, several respondents (14 of 102, 13.7%) replied that the cost of drugs was the most important (Fig. 1).

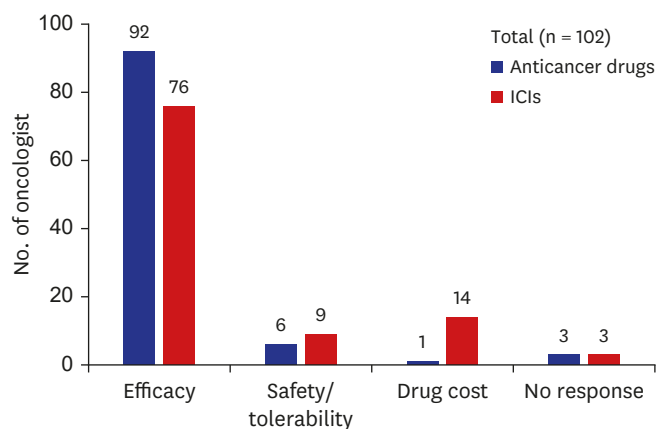
**Table 1.** Demographics of respondents

Demographics	Values (n = 102)
Subspecialty	
Medical oncologist	82 (80.4)
Hematologic oncologist	20 (19.6)
Sex	
Male	46 (45.1)
Female	56 (54.9)
Age, <sup>a</sup> yr	
30–39	28 (27.5)
40–49	52 (51.0)
50–59	16 (15.7)
Over 60	5 (4.9)
Duration of work as oncologist (mean $\pm$ SD)	16.3 $\pm$ 7.5 yr

Values are presented as number (%).

SD = standard deviation.

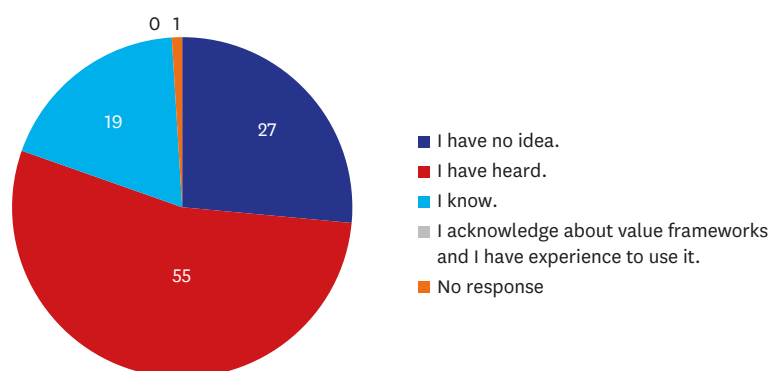
<sup>a</sup>Nonresponder: 1.



**Fig. 1.** Summary of consideration when prescribing anticancer drugs and ICIs.

In final survey, we asked what factor is most considered when prescribing anticancer drugs and ICIs. Most medical oncologist and hematologist considered efficacy than any other factors. However, they considered cost when prescribing ICIs than anticancer drugs.

ICI = immune checkpoint inhibitor.



**Fig. 2.** Awareness of value evaluation tools.

Approximately 55% of medical oncologist and hematologist had heard of the value framework for anticancer drugs, however none of the respondents had experience in using the value frameworks practically.

Around half of respondents (55 of 102, 53.9%) answered that they already had heard of the VFs for anticancer drugs, while 27 of 102 (26.5%) were not aware of VFs at all. None of the respondents had experience in the practical use of VFs (**Fig. 2**).

#### *Need and possible implications of VFs in Korea*

More than 95% of respondents agreed on the need for development of a value evaluation tool for anticancer drugs in Korea (97 of 102). Most respondents agreed on the need for an assessment tool as a criterion for determining reimbursement (84.3%) as well as re-evaluation of the reimbursement status after registering with the Korean NHI (89.2%) (**Table 2**).

#### *Factors underlying development of Korean VFs for anticancer drugs*

With regard to the representative two VF tools, ASCO-VF and ESMO-MCBS, 70.6% of respondents suggested that it would be better to refer to both evaluation tools in the Korean context (**Table 3**). In addition to common characteristics of ASCO-VF and ESMO-MCBS, the highly ranked parameters reflecting Korean VF based on the respondents' perspective were: bonus points in QoL, symptom palliation or treatment-free interval (45.3%) from ASCO-VF, followed by stratified scoring for toxicity penalty according to the primary outcomes based on ESMO-MCBS (29.3%) (**Table 4**).

**Table 2.** Summary of awareness and need for value framework

Questions	Values
Q1. Do you think we need a value framework of anticancer drug in Korea?	
1) Yes	97 (95.1)
2) No	5 (4.9)
Q2. Do you think it is necessary to use a value evaluation tool that reflects clinical effects, toxicity and quality of life as a criterion for determining reimbursement for anticancer drugs? <sup>a</sup>	
1) Yes	86 (84.3)
2) No	15 (14.7)
Q3. Do you think it is necessary to use a value evaluation tool that reflects clinical effects, toxicity and quality of life in the re-evaluation post-reimbursement? <sup>a</sup>	
1) Yes	91 (89.2)
2) No	10 (9.8)

Values are presented as number (%).

<sup>a</sup>Nonresponder: 1.

**Table 3.** Summary of comparison of ASCO-VF and ESMO-MCBS

Questions	Values
Q1. Considering the domestic clinical situation, which of the two tools do you think would be more appropriate for the evaluation of anticancer drug?	
1) ESMO-MCBS	5 (4.9)
2) ASCO-VF	20 (19.6)
3) Both	72 (70.6)

ASCO-VF = American Society of Clinical Oncology Value framework, ESMO-MCBS = European Society for Medical Oncology-Magnitude of Clinical Benefit Scale.

<sup>a</sup>Non-responder: 5 (4.9%).

**Table 4.** The ranked parameters among ESMO-MCBS and ASCO-VF relevant to Korean value evaluation tool

Parameters	Values (n = 95)
Bonus for QoL, symptom palliation and treatment-free interval <sup>a</sup>	43 (45.3)
Stratified approach to toxicity penalties according to primary outcomes (less toxicity penalty when outcomes is cure or OS instead of PFS) <sup>b</sup>	28 (29.5)
Toxicity assessment incorporates penalty for low-grade toxicity <sup>a</sup>	3 (3.2)
Toxicity assessment incorporates only abnormal laboratory finding <sup>b</sup>	8 (8.4)
Downgrades for PFS scores not associated with improvement in OS or QoL <sup>b</sup>	6 (6.3)
Separate scale for single-arm studies <sup>b</sup>	5 (5.3)
Credits QoL gains <sup>b</sup>	2 (2.1)

OS = overall survival, PFS = progression-free survival, QoL = quality of life.

<sup>a</sup>Parameters from ASCO-VF; <sup>b</sup>parameters from ESMO-MCBS.

## DISCUSSION

This study showed that the majority of Korean oncologists insisted on the development of VF and its practical application in Korea.

In Korea, total healthcare expense increased between 2015 and 2018, which was mainly attributed to drug acquisition cost.<sup>15</sup> In this proportion, the anticancer drug claim in 2016 was about 1.39 trillion KRW (which equates to US \$11.6 billion), accounting for 6.8% of the total drug cost. Additionally, the increase rate was doubled for cancer drugs compared to all drugs and this has been gradually increasing since 2014.<sup>16</sup> The compound annual growth rate (CAGR) of anticancer drug expenditure from 2015 until 2017 was 11.2%, whereas the CAGR for the general pharmaceutical expenditure was 8.2%.<sup>15</sup> These drugs increase the financial burden, which amounted to 233.9 billion KRW (which equates US \$194 million) in 2010, increasing annually to 578.5 billion KRW (which equates US \$482 million) in 2016.<sup>17</sup>

A survey result of 185 cancer patients reported that a total of 28.77 million KRW (which equates US \$2.4 thousand) was spent on cancer treatment and anticancer drugs accounted for the highest proportion (60.5%) of the total cost of treatment.<sup>18</sup> When the difficulty of the treatment process is identified, the financial factor was 37.3%, ranking first followed by psychological factor 31.9%, and physical factor 27.6%. The financial burden had worsened while the physical and psychological hardship resolved by passing treatment time.<sup>18</sup>

The need for measuring the true value of anticancer drugs is emerging as expensive anticancer drugs, such as ICIs are introduced in clinical field. The Korean scenario is no different than that of the US based on the data of cancer drug expenditure. In fact, our review confirmed the anticancer drugs were the main driver of escalating pharmaceutical expenditure in Korea.

With the introduction of various schemes for enhanced access to expensive anticancer drugs in Korea, such as risk sharing agreement (2014) or waiver of the cost-effectiveness analysis



dossiers (2014), it has been reported that the accessibility of the cancer drugs has improved.<sup>19</sup> Nevertheless, the value of expensive anticancer drugs is still uncertain, which underscores the need for VFs in Korea.

ASCO published a VF in 2015 in an effort to incorporate value discussion in the shared decision making between patients and physicians. Briefly, the three variables are clinical benefit, toxicity or side effects of the treatment, and out-of-pocket costs.<sup>6,7</sup> NCCN evidence blocks were developed by analyzing the scores of NCCN expert panels by plotting onto a 5 × 5 matrix of the panel member's response.<sup>10</sup> As fore mentioned, ICER and MSKCC's Drug Abacus are tools<sup>11,12</sup> available for value measurement. These four tools were developed in the US. ESMO-MCBS is unique in that it aims to cover several European nations.<sup>6,7</sup> Generally, compared with ICER VF tool and Drug Abacus, ASCO-VF and NCCN evidence blocks have been regarded as useful and rated favorably for clinical application by physicians.<sup>2</sup> The key element is that the used or weighted variables differed among these tools. Given the difficulty to estimate the total cost, all the listed VFs do not offer (might not be able to offer) the affordable at the individual patient level. Despite this limitation, VFs provide a comparative assessment of various treatment options available and their relative financial implications for patients.

Which parameter does an oncologist usually rank as the highest in priority? More than 90% of respondents gave the answer that improved clinical efficacy such as prolongation of overall survival and/or progression-free survival are the most important factor for determining the drug selection, and only 1% replied that drug cost was the critical factor. Regarding to ICIs, 74.5% replied that clinical efficacy is the top priority and 13.4% responded that drug cost is the key factor. Invariably, improved clinical efficacy was the primary parameter dictating drug selection by medical oncologist and was considered by all VFs as the highest priority despite differences in methodology. Clinical efficacy was also ranked as the highest priority by US physicians, which is consistent with our study.<sup>20</sup> The interviewed US physicians acknowledged that cost/economic factors, system/organization, and social values played a limited role in influencing drug value assessment. However, at the same time, 83% of participants indicated that a patient's affordability was a key determinant of their perception of drug value. We found that our responders heavily considered drug costs associated with ICIs. It appears that Korean oncologists face a conflict between their professional responsibility to provide effective healthcare based on ethical principles of quality and cost-effective medicine.<sup>21</sup> Our findings suggest that the introduction of novel immunoncology drugs with increase of drug price might have influenced the perceived value of the oncology landscape in Korea.

Even though half of the respondents answered that they had heard of VFs previously, none of them experienced clinical use of the VF tools. We compared our findings with two studies conducted with US physicians in 2016 and 2018.<sup>22,23</sup> In 2016, 85% of the surveyed respondents (n = 93, medical or hematologic oncologists in community or academic settings) were aware of VFs; however, 46% of survey respondents did not use these tools, which is similar to our finding. A variety of reasons were listed: 'not mandatory by institution or payer' (28%), 'too early to adapt' (17%), complicated (14%), and 'don't worry about cost' (11%). However, the experience of using VFs increased with 76% (N = 200) of the oncologists in the US using them in 2018<sup>23</sup>. The increased usage across two years suggests the need for value measurement and collaboration with key stakeholders in order to adapt VFs to Korean conditions.

The issues implicating the VFs are linked to which VF should be mainly adapted. Even though value-based prescribing is emphasized, physicians responded not to adopt VF until

mandatory regulation.<sup>22</sup> Except for clinical decision making between patients and physicians regarding chemotherapeutic agents, the reimbursement list and evaluation of the listing status post-reimbursement are major issues in Korea. In fact, current VFs are increasingly tied to reimbursement strategies, and two VFs, ESMO-MCBS and ICER, are representative because these tools aim for government policy making.<sup>6,7,12,23,24</sup> Generally, the government approves drugs based on clinical trial data, but the setting and design of clinical trials are very different from the real world. We frequently face situations that raise concerns about the clinical efficacy of even high priced drugs. The VFs can be used for reliable analysis of real world data and effective allocation of health resources.

In our analysis, only ASCO-VF and ESMO-MCBS were presented in the survey because the two tools were initiated by global academic societies and are considered clinically representative. According to the survey reported from the ASCO 2016 annual meeting, ASCO-VF are one of the most frequently used VF in the US with 38% response, followed by the NCCN evidence blocks.<sup>22</sup> Because ASCO-VF was intended for use by oncologists as part of the treatment decision-making process, we may consider this tool as the most useful for clinical application. However, the score with meaningful net clinical benefit is confusing since the score is a continuous variable and no clear cut-off information is available. The ESMO-MCBS was acceptable to a multidisciplinary task force from a public health perspective, and its use in reimbursement decisions leads us to benchmark the allocation of health resources in Korea.<sup>25</sup> Our respondents' answer that both VFs should be reflected for developing Korea VF suggests the consideration for covering the purpose of different uses of the two VFs at the same time. We tried to identify the specific parameters by briefly summarizing the ASCO-VF and ESMO-MCBS for the participants. We focused on the different characteristics of these two VFs because the common parameters are supposed to be included in the Korean context with no doubt. Nearly half of responders selected bonus point as the most important factor when the drug is evaluated based on improved QoL, symptom palliation or treatment-free interval using ASCO-VF. The scoring system of existing VFs is complicated and prevents analysis of our scope using only a one-time survey. Moreover, these tools have their unique shortcomings and methodological limitations of their own.<sup>25,26</sup> Despite their intrinsic differences, the two revised versions of VFs, ESMO-MCBS version 1.1 (updated in 2017) and the ASCO-VF version 2.0 (updated in 2016), demonstrated good agreement in scores.<sup>27</sup> Both societies remain committed to refining their framework. The ASCO Value in Cancer Care Task Force composed of physicians sought inputs from an advisory committee that included oncologists, patient advocates, payers and the biopharmaceutical industry, followed by public comments.<sup>28</sup> Suggestions to adjust the inputs or outputs of parameters based on individual patient preferences and consideration for years of life gained or even gain in quality-adjusted life expectancy are being discussed in ASCO.<sup>9,29</sup> It is unclear how this methodology will ultimately be developed, but we can adapt it by incorporating parameters to conduct further studies to measure the value of cancer treatment reflecting the Korean situation.

This study has some limitations. First, the response was acquired from a proportion of participants in the Best of ASCO and KMMWP study group. Although the opinions of additional oncologists may result in different findings, the response of 100 oncologists was substantial in exploring our study aim. For references, the US studies involved less than 200 oncologists<sup>22,23</sup> of approximately 13,000 practicing medical oncologists, with another 500 graduates joining the workforce annually.<sup>30</sup> Second, nearly half of responders never heard of VFs, suggesting that they may not have understood the concept of ASCO-VF and ESMO-MCBS correctly even though we provided a short introduction to the two VFs. Nonetheless,



this study is significant in demonstrating the need for value measurement of anticancer drugs from an oncologist perspective with background data of financial burden in Korea for the first time.

In conclusion, we explored the oncologist's perception for possible development and adaptation of VF for anticancer drugs in Korea. In the face of escalating anticancer drug expenditure, VF might represent an appropriate option to relieve financial toxicities occurring from expensive anticancer drugs. Further studies are warranted to get insight into which VF is acceptable or whether an evidence-based VF reflecting the healthcare system can be developed in Korea. Taken together, VF-based strategy is needed to address the needs of multiple stakeholders. We should ensure that cancer patients receive the highest value care within the limited health resources.

## ACKNOWLEDGMENTS

This study was conducted as part of a research about drug value evaluation in HIRA. The authors are indebted to questionnaire respondents, as well as to all members of the KSMO and KMMWP.

## SUPPLEMENTARY MATERIALS

### Supplementary Table 1

Pilot study questionnaire

[Click here to view](#)

### Supplementary Table 2

The final survey

[Click here to view](#)

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