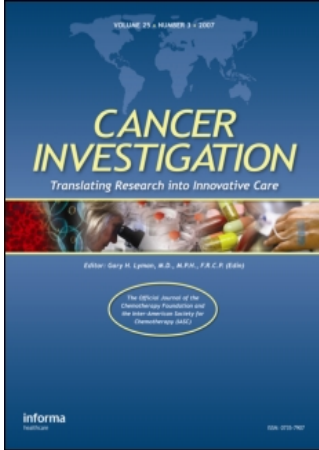


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What Are the Most Important Symptom Targets When Treating Advanced Cancer? A Survey of Providers in the National Comprehensive Cancer Network (NCCN)

David Cella^a; Diane Paul^b; Susan Yount^a; Rodger Winn^b; Chih-Hung Chang^a; Donald Banik^c; Jane Weeks^d

^a Northwestern University, Evanston, Illinois, USA

^b National Comprehensive Cancer Network, Rockledge, Pennsylvania, USA

^c Center on Outcomes, Research and Education, Evanston Northwestern Healthcare, Evanston, Illinois, USA

^d Dana-Farber Cancer Institute, Boston, Massachusetts, USA

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ORIGINAL ARTICLE

What Are the Most Important Symptom Targets When Treating Advanced Cancer? A Survey of Providers in the National Comprehensive Cancer Network (NCCN)

David Cella, Ph.D.,^{1,2,*} Diane Paul, M.S., R.N.,³ Susan Yount, Ph.D.,^{1,2}
Rodger Winn, M.D.,³ Chih-Hung Chang, Ph.D.,^{1,2}
Donald Banik, B.A.,¹ and Jane Weeks, M.D.⁴

¹Center on Outcomes, Research and Education, Evanston Northwestern Healthcare,
Evanston, Illinois, USA

²Northwestern University, Evanston, Illinois, USA

³National Comprehensive Cancer Network, Rockledge, Pennsylvania, USA

⁴Dana-Farber Cancer Institute, Boston, Massachusetts, USA

ABSTRACT

We derived a set of brief, clinically relevant symptom indices for assessing symptomatic response to chemotherapy for advanced bladder, brain, breast, colorectal, head and neck, hepatobiliary/pancreas, lung, ovarian, and prostate cancers. Questions were extracted from a multidimensional cancer quality of life (QOL) measurement system, the Functional Assessment of Cancer Therapy (FACT). Surveys of disease-related symptoms were presented to expert physicians and nurses at 17 National Comprehensive Cancer Network (NCCN) member institutions. In a two-step procedure, each expert narrowed the list to no more than five of the very most important to attend to when assessing the value of drug treatment for advanced disease. Symptoms endorsed at a frequency greater than chance probability were retained for the nine symptom indices. The resulting NCCN/FACT symptom indices are comprised of 6–15 items, depending on disease. Fatigue, pain, nausea, weight loss, worry about worsening condition, and contentment with current QOL were consistently selected by experts as priority symptoms across tumor sites. These nine tumor-specific symptom indices indicate the most important clinician-rated targets of chemotherapy for many advanced cancers. These results await validation in patient populations and examination of the extent to which changes in symptomatology translate into meaningful improvement to the patient.

Key Words: Cancer; Symptoms; Assessment; Quality of life.

*Correspondence: David Cella, Ph.D., Center on Outcomes, Research and Education, Evanston Northwestern Healthcare, 1001 University Place, Suite 100, Evanston, IL 60201; Fax: 847-570-1735; E-mail: d-cella@northwestern.edu.



INTRODUCTION

During the past 20 years, patient outcomes assessment in oncology drug development has evolved from consideration of more traditional endpoints, such as survival and tumor response, to broader, patient-reported well-being and quality of life (QOL).^[1,2] There has also been increased recognition that physiologic measures do not always correlate with health outcomes and that evaluation of new drugs should include, but not be limited to, outcomes such as clinical efficacy and toxicity.^[3] Recognizing these shifts in conceptualizing drug therapy outcomes, the U.S. Food and Drug Administration (FDA) has stated that, along with survival, benefit to QOL is one of two primary endpoints that could be considered for approval of new anticancer drugs.^[4]

There remain significant barriers to incorporating QOL assessment into drug trials and clinical practice. These include the uncertainty reported by clinicians and researchers about how to use QOL information and translate it into treatment decisions^[5–10] and how to interpret and derive clinical meaning from QOL scores.^[11–14] Practical barriers include time and resource constraints and the perceived lack of a suitable^[13,15,16] or standardized QOL assessment tool.^[3,10,17] For many of these same reasons, regulatory agencies also struggle with QOL assessment issues. The FDA has been confronted with the need to develop stricter standards for assessing an increasing number of new drug approval submissions that include, or are even based on, QOL claims.^[18]

The concerns of the clinical and regulatory communities about the interpretability and relevance of multi-item, multidimensional QOL instruments have suggested there would be value to a more symptom-focused approach to QOL assessment, whereby the disease symptoms measured by these multidimensional QOL questionnaires are aggregated in a way that is clinically relevant and psychometrically acceptable.^[19] This is particularly true for patients with advanced disease, where life expectancy is reduced, there is no cure, and relief of physical symptoms and maintenance of function become primary objectives of medical intervention.^[2,15,20] Disease-specific measures offer the advantages of being more likely to be sensitive to the impact of drug therapy,^[1] underscoring the importance of developing tumor-specific symptom lists, as opposed to a generic symptom list, to assess drug efficacy across the broad spectrum of tumors.

Most recently validated measures of cancer-specific QOL incorporate an assessment of certain prevalent

symptoms, such as pain and fatigue, within the multidimensional assessment.^[21–23] More broad-based cancer-specific QOL questionnaires, such as the EORTC QLQ-C30^[21] and the FACT-G,^[22] assess a few common cancer symptoms such as pain, fatigue, and nausea, adding more detailed, tumor-specific symptom assessment to the “core” general questionnaire. For example, in lung cancer, nine questions are added to the FACT-G to assess specific concerns related to lung disease, including lung cancer symptoms.^[24] As a result, while there are many questionnaires that have been developed and tested to assess tumor-specific symptoms, many of them have been nested within larger multidimensional QOL questionnaires. This creates an opportunity to derive clinically appropriate and precise evaluation of symptomatology in specific cancer populations.

There are two prerequisites to deriving symptom lists for evaluating response to chemotherapy in advanced cancer. The first is information from patients on the presence and relative importance of the wide array of symptoms and concerns associated with a given cancer. The second is input from clinicians as to those symptoms and concerns that are most likely to be ameliorated by chemotherapy and would therefore comprise reasonable criteria for evaluating its benefit. The first of these prerequisites was met by the procedures used to develop the questions on the FACT-G and its site-specific subscales. Existing FACT item composition was determined by a standardized procedure in which patients and experts—usually in a 3:1 (patient:expert) ratio—were asked to nominate and prioritize important symptoms and concerns of each disease.^[22,24,25] This created an opportunity to present these prioritized questions again to expert clinicians to evaluate the second prerequisite: the extent to which each symptom or concern is a target of palliative chemotherapy. To accomplish this, investigators at the Center on Outcomes, Research and Education (CORE) and the National Comprehensive Cancer Network (NCCN), an alliance of 19 cancer centers across the United States, sought to derive nine tumor-specific indices of the most important symptoms and concerns to monitor in evaluating treatment for advanced bladder, brain, breast, colorectal, head and neck, hepatobiliary/pancreas, lung, ovarian, and prostate cancers. This article describes the procedures employed in developing these indices and the potential future research applications. In this article, the term *symptoms* will be used to reflect not only actual symptoms but also other specific concerns identified to be associated with any of these advanced cancers.

**METHODS****Measures****Study Design and Overview**

The symptom indices were constructed in a two-step process: (1) a list of symptoms related to cancer in general as well as each of nine specific tumors were independently extracted from the FACT and its tumor-specific subscales by a panel of co-authors; (2) these lists of symptoms for each of the nine tumor sites were presented to experts at 17 NCCN member institutions for their selection of the five most important symptoms to address in treating patients with these types of cancer.

Participants

Participants consisted of 223 physicians and 232 nurses at 17 NCCN member institutions. For each of the nine tumor sites, at least two physicians and two nurses from each institution were asked to complete a symptom survey specific to their area of specialization (i.e., tumor site). Participants were identified through NCCN guideline panels, NCCN board membership, NCCN physician database, and personal contacts. Participating physicians and nurses were required to have a minimum of 3 years experience treating patients with advanced disease in the specified tumor. The overall response rate for both experts was 68%, with a response rate of 64% for physicians and 73% for nurses. Table 1 displays the number of experts who were contacted and responded for each of the specified diseases.

The survey tool was designed by reviewing comprehensive lists of symptoms, problems, and concerns raised by patients with advanced cancer and by health providers with expertise in managing each of the nine cancer types. This list was derived from the FACT measurement system questionnaires for each of the nine specific diagnoses.^[22,24–33] Each FACT questionnaire is comprised of 27 core questions that are common to all nine diseases, plus an additional number of items specific to each type of tumor, with the number of additional items ranging from 9 to 18. For example, 12 prostate-specific items are added to the 27 items of the FACT-G to comprise the FACT-Prostate (FACT-P^[29]).

The selection of symptoms to be included in the tumor-specific expert surveys first involved a review of symptoms that were felt to be related to cancer and were susceptible to amelioration by drugs. Questions that were obviously related to treatment side effects (e.g., hair loss) were excluded. The 27 items on the FACT-G were independently reviewed by two medical oncologists with subspecialties in health services research and policy (JW, RW) and by a clinical psychologist specializing in QOL assessment (DC) to determine if the items were “always, usually, rarely, or never” disease-related symptoms. Items rated as “always” or “usually” disease-related symptoms by two or more of the three raters were retained. The remaining items on each tumor-specific subscale were then subjected to the same rating process by the above three raters. Any items that did not receive a consensus rating were discussed in a conference call.

Table 1. Descriptive statistics on initial pool of symptoms and expert samples.

Advanced tumor type	No. of candidate symptoms	No. of symptoms excluded	No. of symptoms on survey ^a	No. surveys distributed to nurses	No. surveys returned by nurses (%)	No. surveys distributed to physicians	No. surveys returned by physicians (%)
Bladder	39	12	27	48	31 (65)	48	28 (58)
Brain	46	10	40	50	35 (70)	46	34 (74)
Breast	36	14	23	46	36 (78)	44	34 (77)
Colorectal	36	12	24	56	36 (64)	48	30 (63)
Head and neck	38	13	26	42	32 (76)	46	33 (72)
Hepatobiliary/pancreas	45	10	35	38	31 (82)	54	30 (56)
Lung	36	12	25	44	35 (80)	50	31 (62)
Ovarian	37	10	27	39	30 (77)	48	30 (63)
Prostate	39	10	29	48	33 (69)	55	33 (60)
Overall response rate ^b				411	299 (73)	439	283 (64)

^aNumber of items on survey includes new symptoms added to brain (4), breast (1), head and neck (1), and lung (1) surveys.

^bTotal number of surveys received (582) exceeds the actual total number of experts participating in the study (N = 455) because some experts completed more than one survey.

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As a result of this consultation among experts, changes were made to several items. Specifically, "fatigue" was added in parentheses after the question "I have a lack of energy" on all nine surveys. "Bone pain" was added as clarification in parentheses on the prostate survey after the question: "I have certain areas of my body where I experience significant pain." Bone pain was added as an item on the breast and lung surveys. "I have pain in my face and neck" was added as an item to the head and neck survey. The questions "I have headaches," "I have weakness in my arms or legs," "I have trouble with coordination," and "I have trouble feeling sensations in my arms, hands, or legs" were added to the brain survey.

Procedure

Tumor-specific surveys containing 23 (breast) to 40 (brain) items were distributed to participants via email, fax, or conventional mail. To control for effects due to order of presentation of items in the surveys, four versions of each survey were created by dividing items into approximate quartiles and rotating each quartile into a different order on each version of the survey. Versions were randomly distributed to participants. Each survey asked the participant to "select no more than 10 that you consider to be the most important symptoms or concerns to monitor when assessing the value of drug treatment for advanced (site) cancer." Of the 10 symptoms they had nominated as "the *most* important," respondents were then asked to select up to 5 as "the very most important symptoms or concerns to monitor when assessing the value of drug treatment for advanced (site) cancer." Space was provided for

respondents to write in symptoms that had not been listed. Respondents were compensated (\$75) for their time spent completing the survey.

Analysis Plan

Returned surveys were tabulated according to the expert category (physician versus nurse) and by the frequency with which experts selected a particular symptom/concern as one of the five most important. The most frequently endorsed items were retained in the final symptom indices. The criterion for item retention was the probability of chance endorsement as one of the top five symptoms, calculated by dividing five (the allowable number of "very most important symptoms") by the total number of items in each tumor-specific survey. In addition, using the total combined expert sample, 2×2 Chi-square analyses (endorsed/not, early/late presentation in survey) were conducted on each tumor-specific survey to determine if the order of presentation of the symptoms had any systematic influence on experts' selection of the 10 "most important" symptoms.

RESULTS

Expert Endorsement of Symptoms, Total Sample

Table 2 displays the number of symptoms presented and the number endorsed with a probability greater than chance. Table 3 displays the frequency of items endorsed by the experts for the total sample by disease

Table 2. Effect of presentation order on symptom endorsement.

Advanced tumor site	No. of symptoms presented on survey	No. of symptoms endorsed > chance ^a	No. of symptoms with order effects
Bladder	27	7	1
Brain	40	15	2
Breast	23	8	0
Colorectal	24	9	0
Head and neck	26	10	1
Hepatobiliary/pancreas	35	10	1
Lung	25	6	1
Ovarian	27	8	1
Prostate	29	7	0

^a Probability of chance endorsement was calculated by dividing five (the allowable number of "very most important symptoms") by the total number of items in each tumor-specific survey.

Table 3. Rankings of symptoms/concerns^a by expert group and by advanced tumor site.

Advanced tumor site	Overall rank	% Endorsed (top 5)	Symptom or concern	Nurse ranking	Physician ranking
Bladder	1	85	Pain	1	1
	2	58	Fatigue ("lack of energy")	2	2
	3	39	Weight loss	4	2
	4	36	Nausea	6	2
	5	25	Feel ill	12	5
	5	25	Worry condition will get worse	3	11
	7	20	Urinary incontinence	10	6
Brain	1	39	Headaches	1	4
	1	39	Seizures	3	3
	1	39	Weakness in extremities	5	1
	4	38	Unable to care for self	6	1
	5	36	Fatigue ("lack of energy")	2	5
	6	26	Difficulty expressing thoughts	3	9
	7	25	Trouble with coordination	7	6
	8	19	Frustrated that can't do usual things	11	7
	9	17	Nausea	9	13
	9	17	Word finding	7	16
	11	16	Losing hope	11	13
	12	14	Trouble meeting needs of family	15	9
	13	13	Worry condition will get worse	18	9
13	13	Afraid of having seizure	9	21	
13	13	Able to enjoy life	23	7	
Breast	1	67	Fatigue ("lack of energy")	1	2
	2	64	Pain	3	1
	3	43	Nausea	2	7
	4	34	Bone pain	4	4
	5	33	Shortness of breath	5	4
	6	26	Worry condition will get worse	7	9
	6	26	Content with present QOL	11	3
	8	23	Trouble meeting needs of family	6	11
Colorectal	1	65	Fatigue ("lack of energy")	1	3
	2	62	Pain	3	1
	2	62	Weight loss	2	2
	4	47	Diarrhea	4	4
	5	36	Nausea	5	5
	6	26	Abdominal swelling/cramps	6	6
	7	21	Appetite	9	6
	7	21	Able to enjoy life	7	11
Head and neck	7	21	Content with present QOL	8	8
	1	58	Pain	1	1
	2	48	Fatigue ("lack of energy")	1	3
	2	48	Able to swallow naturally/easily	3	2
	4	43	Face or neck pain	5	3
	5	42	Trouble breathing	3	6
	6	38	Able to communicate with others	8	3
	7	26	Nausea	6	9
	8	22	Able to eat solid foods	9	7
9	20	Worry condition will get worse	7	16	
9	20	Content with present QOL	9	8	

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Table 3. Continued.

Advanced tumor site	Overall rank	% Endorsed (top 5)	Symptom or concern	Nurse ranking	Physician ranking	
Hepatobiliary/pancreas	1	64	Pain	1	2	
	2	57	Weight loss	2	1	
	3	41	Fatigue ^b (“lack of energy”)	3	3	
	4	31	Nausea	3	7	
	4	31	Fatigue ^b (“feel fatigued”)	6	4	
	6	28	Abdominal discomfort/pain	5	7	
	7	26	Jaundice	6	5	
	8	23	Abdominal swelling/cramps	8	5	
	9	15	Back pain	15	9	
Lung	9	15	Itching	15	9	
	1	74	Shortness of breath	1	3	
	2	68	Fatigue (“lack of energy”)	2	1	
	3	62	Pain	3	2	
	4	47	Weight loss	3	4	
	5	45	Coughing	5	4	
	6	27	Bone pain	6	6	
	Ovarian	1	63	Fatigue (“lack of energy”)	1	1
		2	60	Vomiting	2	1
3		53	Pain	2	3	
4		38	Nausea	4	3	
5		32	Stomach swelling	4	6	
5		32	Worry condition will get worse	8	5	
7		30	Content with present QOL	6	6	
8		23	Stomach cramps	7	8	
Prostate	1	59	Fatigue (“lack of energy”)	2	1	
	2	50	Bone pain	1	4	
	3	47	Pain	3	2	
	4	42	Pain limits performance	4	5	
	5	29	Weight loss	9	2	
	6	24	Able to enjoy life	6	6	
	7	21	Difficulty urinating	5	11	

^aIncludes only those symptoms exceeding chance probability of endorsement by total sample.

^bTwo different fatigue items were endorsed for hepatobiliary/pancreas cancers.

(only items endorsed >chance probability are shown). The resulting NCCN/FACT symptom indices are comprised of 6–15 items, depending on tumor site. Symptoms receiving the most consistent endorsement across the tumor-specific surveys included pain, lack of energy (fatigue), nausea, and weight loss.

Symptoms within each disease that exceeded the chance probability of endorsement were examined for possible order effects, and these results are displayed in Table 2. There were no systematic effects noted. Symptoms displaying significant order effects were observed in the brain (“difficulty expressing thoughts,” $\chi^2(1) = 5.22, p < .05$; “able to enjoy life,” $\chi^2(1) = 4.22, p < .05$), head and neck (“trouble breathing,” $\chi^2(1) = 4.28, p < .05$), hepatobiliary/pancreas

(“lack of energy,” $\chi^2(1) = 6.04, p < .05$), lung (“coughing,” $\chi^2(1) = 4.22, p < .05$), and ovarian (“vomiting,” $\chi^2(1) = 7.63, p < .01$) cancer surveys.

Endorsement of Symptoms by Expert Group

The pattern of endorsement of symptoms was also examined by expert groups. The respective rankings by physicians and nurses of the symptoms within each tumor site that exceeded chance probability of endorsement are displayed in Table 3. Although the relative ranking of symptoms varied somewhat between the two groups of experts within each tumor site, physicians and nurses agreed more than they disagreed on the relative importance

Table 4. Expert “write-in” nominations.^a

Advanced tumor site	Symptom	Number of times symptom was endorsed
Bladder	Hematuria	7
Brain	Lethargy	3
Colorectal	Fever	3
	Constipation	3
Head and neck	Bleeding	5
	Weight loss	5
Hepatobiliary/pancreas	Loss of appetite	4
	Edema	3
Lung	Hemoptysis	8
	Difficulty swallowing	4
	Headache	3
Ovarian	Constipation	8
	Edema	5
	Difficulty breathing	4
	Dyspepsia	4
Prostate	Weakness in legs	3
	Hematuria	3

^aOne hundred and thirty-four nominations were excluded, either because they were endorsed by fewer than three experts (76 nominations), could only be due to treatment (e.g., hair loss, mucositis; 52 nominations), or were related to financial concerns (6 nominations).

of these symptoms. On five of the nine disease-specific surveys, physicians and nurses agreed on the top three symptoms.

Expert “Write-In” Nominations

Physicians and nurses were allowed to write-in additional symptoms that were not on the survey. Those items contributed by at least three experts are displayed in Table 4.

DISCUSSION

The objective of this project was to identify the highest priority symptoms and to determine whether or not physicians and nurses could agree on the symptoms that are a priority to attend to when evaluating chemotherapy for advanced cancer. The amount of rater agreement and symptom consistency across tumor sites suggest it is feasible to construct brief symptom indices for advanced bladder, brain, breast, colorectal, head and neck, hepatobiliary/pancreas, lung, ovarian, and prostate cancers. Appropriate measurement of these high-priority symptoms can, in turn, be applied to

evaluate the effectiveness of noncurative therapy in these diseases.

Based on the input of a sample of expert physicians and nurses, nine tumor-specific NCCN/FACT symptom indices were constructed by tabulating only those that were endorsed more often than chance. The number of symptoms on eight of the indices ranged from 6 to 10 items, with the brain index containing 15 items. One could reasonably assign all of the items endorsed more often than chance to a testable index. However, it may also be possible to further shorten the tumor-specific “short lists” by including only symptoms that exceed a confidence interval (CI) above chance probability. If one were to do this using a 95% CI, it would shorten the lists of symptoms to the top four bladder, seven brain, five breast, five colorectal, six head and neck, seven hepatobiliary/pancreas, five lung, seven ovary, and five prostate cancer symptoms listed in Table 3. The best approach to refining these symptom lists and enhancing targeted symptom assessment is a matter for further study.

Across all nine indices, the symptoms and concerns endorsed most frequently (the majority of tumor sites) were fatigue, pain, nausea, weight loss, and worry. Each of the indices also included tumor-specific items. The candidate items presented to the experts for selection were drawn from the FACT QOL measurement system



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and, as such, were derived from a list of symptoms identified by patients with that disease and expert clinicians as being significant to their QOL. Experts were provided with the opportunity to “write in” items not appearing on the surveys. The results suggest that the FACT QOL instruments specific to the above diseases contain most, but not all, of the disease-related symptoms that physicians and nurses believe are important to monitor in these patient populations. Experts’ responses in some instances were influenced by the order of presentation of symptoms on some of the disease surveys, but no systematic pattern of order effects was detected.

The prevalence of pain, lack of energy (fatigue), and nausea, in particular, has been highlighted in a number of studies of symptom assessment in medical oncology populations.^[23,34,35] The report of one symptom can be considered a marker for the presence of other symptoms, as most oncology patients experience multiple symptoms.^[34] Because symptoms tend to be underreported by patients,^[36] the presence of these multiple symptoms may not be brought to the attention of the health care professional without formal assessment, highlighting the need for comprehensive systematic symptom assessment.^[34]

Despite the documented high prevalence and adverse impact of physical and psychological symptoms in oncology populations,^[23,37] systematic symptom assessment of cancer patients is rarely implemented. Symptom measurement has historically been used in clinical investigations to determine the impact of disease-focused therapies or symptom-focused palliative treatments and to improve the accuracy of prognosis estimation.^[38] In evaluating the efficacy of new chemotherapeutic agents, the ability to demonstrate the amelioration of symptoms specific to a given tumor may represent efficacy in achieving a meaningful patient outcome. A recent example of this orientation was a pivotal trial in pancreatic cancer, which demonstrated the clinical benefit of gemcitabine in this disease, based on its effectiveness in improving symptoms specifically related to this tumor (e.g., pain, weight loss, and weakness^[39]). Thus, the use of brief tumor-specific tools to assess symptomatology has the potential to play a key role in evaluating patient-related endpoints in clinical trials.

The assessment of global QOL is important, and many widely used multidimensional QOL instruments assess a limited number of symptoms. However, the use of global QOL scores may obscure important and significant changes in disease-related symptoms,^[35] underscoring the importance of measures for the assessment of specific disease-related symptoms. The FDA Oncology Drug Advisory Committee (ODAC) subcommittee on QOL has advanced the position that

overall claims of QOL benefit cannot be made from one or two domain measurements and that claims made about “QOL” need to be specific to the domain that was measured.^[19] An abbreviated, symptom-focused assessment would not be considered sufficient for a broadly worded QOL regulatory claim but it could lend support to the use of more narrowly worded claims such as “clinical benefit,” “symptom relief,” or “delay of onset of tumor-related symptoms.”

The results of this project demonstrate that experts in the management of particular cancers can reach consensus about the symptoms that are most important to monitor when treating patients with these advanced diseases and that are applicable to the assessment of drug efficacy. While some symptoms are consistent across disease sites, others are specific to the particular disease. Furthermore, we have shown that most of the symptoms identified by experts as the most important to assess in treating patients with advanced cancer can be derived from a well-established multidimensional QOL questionnaire. Although the symptom indices described in this study represent the constellation of symptoms endorsed by our sample of experts, the ultimate selection of questions remains the discretion of the investigator and may be dictated by preferred length of scale, weighting of symptom category, or particular cluster of symptoms of interest.

Pending further studies examining the performance of these indices with patient populations, we present these nine NCCN/FACT symptom indices as starting points for describing the most important symptoms that represent the target of chemotherapy for advanced cancer. Future work can compare these clinician-rated priorities to those of patients and test related symptom indices in patient populations. It will be useful to examine the extent to which changes in these high-priority symptoms translate into meaningful changes in patient function or quality of life.

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