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BRIEF COMMUNICATION

Recommended Patient-Reported Core Set of Symptoms to Measure in Prostate Cancer Treatment Trials

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The National Cancer Institute (NCI) Symptom Management and Health-Related Quality of Life Steering Committee convened four working groups to recommend core sets of patient-reported outcomes to be routinely incorporated in clinical trials. The Prostate Cancer Working Group included physicians, researchers, and a patient advocate. The group's process included 1) a systematic literature review to determine the prevalence and severity of symptoms, 2) a multistakeholder meeting sponsored by the NCI to review the evidence and build consensus, and 3) a postmeeting expert panel synthesis of findings to finalize recommendations. Five domains were recommended for localized prostate cancer: urinary incontinence, urinary obstruction and irritation, bowel-related symptoms, sexual dysfunction, and hormonal symptoms. Four domains were recommended for advanced prostate cancer: pain, fatigue, mental well-being, and physical well-being. Additional domains for consideration include decisional regret, satisfaction with care, and anxiety related to prostate cancer. These recommendations have been endorsed by the NCI for implementation.

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In September 2011, a National Cancer Institute Clinical Trials Planning Meeting was convened to develop recommendations regarding a core set of patient-reported symptoms and health-related quality of life (HRQOL) domains to be assessed in clinical trials (1). This brief communication summarizes the process and recommendations of the Prostate Cancer Working Group, which is composed of a multidisciplinary team of physicians, researchers, and a patient advocate, as well as discussions regarding these recommendations from the planning meeting. Recognizing that patients with localized prostate cancer (who commonly receive treatments targeting the prostate) vs those with advanced/metastatic disease (who commonly receive systemic therapy and experience symptoms from metastases) may experience different types of HRQOL impact, the working group made separate recommendations for these two groups of patients.

A systematic literature review was conducted to determine the prevalence and severity of symptoms and HRQOL domains across published studies. A PubMed search was performed using the search terms "prostate cancer" and "quality of life" and the following search filters: 1) published from January 1, 2001, to December 31, 2011; 2) English language; 3) human subjects; 4) adult: 19+ years; and 5) subjects: cancer. This resulted in an initial list of 1164 articles; 295 articles without prostate cancer patient-reported outcomes (PROs) data were excluded. Further, we excluded studies with less than 200 patients, those not of prospective design or lacking pretreatment PRO assessment, and those from a single institution (Figure 1), resulting in 77 articles included for review and providing the basis for the working group's considerations. The recommendations for core PRO domains were finalized through the multistakeholder planning meeting and subsequent consensus-building process, as described elsewhere (1).

Of 61 included articles for localized prostate cancer, 51 were prospective cohort studies, and 10 were clinical trials (references 43–88 are cited in Supplementary Table 1, available online). Studies reported PRO data in different formats, and those that reported the percentage of patients having each symptom in the different domains provided the level of detail needed by the working group.

In validated PRO instruments, urinary incontinence is measured as presence/absence of incontinence, incontinence frequency, and pad use (2–8). Incontinence is rare pretreatment, with less than 5% of patients using pads at baseline (9–11). Prostatectomy causes at least short-term incontinence in most men, with subsequent recovery over 1 to 2 years (9,10,12–14). At 2 months after operation, two-thirds of prostatectomy patients report pad use; this decreases to 20% by 2 years (9,14). However, up to 50% to 60% of patients report some degree of incontinence at 2 years after prostatectomy (10,13,15). The rates of pad use after external beam radiation and brachytherapy do not change dramatically with time, with 5% of patients reporting use at 2 years (9,10).

Urinary obstruction and irritation occur and change independently from incontinence; both domains should be assessed. In validated instruments, urinary obstruction and irritation is measured as ease/strength of urinary flow, nocturia, urinary frequency, urgency, and dysuria (2,3,5–8,16). At baseline, 10% to 15% of patients have weak urinary flow, and 15% report frequency (9). After prostatectomy, frequency is modestly more prevalent acutely (in one study, 17% to 24% of patients reported it at 2 months) (9), but obstructive symptoms improve, likely because of alleviation of benign prostatic hypertrophy (9). Up to one-third of external beam radiation patients and two-thirds of brachytherapy patients report acute obstructive and irritative symptoms (13,17), with resolution over 1 to 2 years to levels similar to baseline (9).

In validated instruments, bowel-related symptoms include diarrhea, bowel

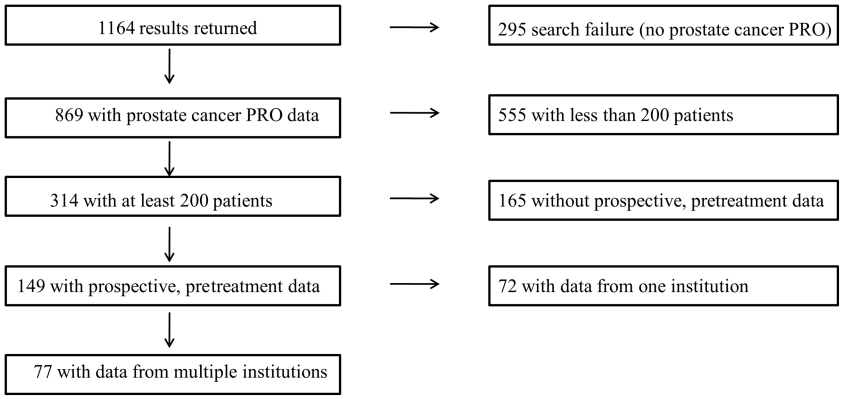

Figure 1. Flowchart of the selection process of articles for the literature review.

urgency, incontinence, frequency, pain with bowel movements, hematochezia, abdominal cramping, and tenesmus (2–8,16). Most bowel symptoms are uncommon pretreatment, except diarrhea (up to 15%) (10,14). Both external beam radiation and brachytherapy can cause symptoms: approximately 15% to 40% of patients report increased urgency, frequency, or diarrhea acutely after radiation (9,10,15), with recovery in brachytherapy patients (<10% report these symptoms at 2 years) and less so in external beam radiation patients. Five percent of external beam patients and 3% of brachytherapy patients report hematochezia at 2 years (9). Bowel incontinence is rare (13).

In validated instruments, sexual function is measured as libido, frequency of sexual activity, quality of erection, ability to get and keep an erection, and ability to achieve orgasm and ejaculation (2–8,16,18). In the literature, fewer prostatectomy patients than radiation patients have baseline sexual dysfunction (19,20), likely because of age and comorbidity differences in patients selected to undergo these different treatments. Approximately 15% of prostatectomy patients report baseline poor erections, compared with 30% to 40% of radiation patients (9). Acutely after prostatectomy, 80% to 90% of patients report difficulty with erections (9,10), but this proportion decreases to approximately 60% by 2 years (9,19,21). After radiation, erectile dysfunction increases with time and is reported by 50% to 60% of external beam radiation patients and 20% to 50% of brachytherapy patients at 2 years (9,10,13,19,22). Those who received radiation alone (without androgen deprivation therapy) had better outcomes (9). Most existing studies have not consistently captured use of sexual dysfunction therapies and how these therapies affect PROs.

In validated instruments, hormonal-related symptoms include hot flashes, breast tenderness or enlargement, depression, fatigue, and weight change (3,5–7). Depression and fatigue are reported by approximately 10% of patients at baseline. After external beam radiation or brachytherapy, fatigue affects 21% to 23% of patients at 2 months, but this rate decreases to 12% to 16% by 2 years (9). Hot flashes (1%), breast problems (1%), and weight change (4%) are uncommon at baseline and for patients who do not receive hormonal therapy (9).

PROs in advanced prostate cancer are less well studied. Of 16 included articles, two were prospective cohort studies, and 14 were clinical trials (references 89–98 are cited in Supplementary Table 2, available online).

In validated instruments, pain is measured as presence of pain, bother, and pain interfering with activities (18,23–25). Pain is common in advanced prostate cancer patients, reported by more than 70% in some studies (26–28). With systemic therapy or zoledronic acid, one-third or more of patients can experience a pain response (27–29).

In validated instruments, items in the fatigue domain include experiencing tiredness, or lack of energy or vitality (18,23–25). Items in the mental well-being domain include feeling depressed, trouble sleeping, difficulty with concentration, feeling tense, worry, feeling irritable, and difficulty remembering things (18,23,25). Items in the physical well-being domain include ability to perform activities of daily living, instrumental activities of daily living, and physical functioning. Some instruments include specific examples of these, including ability to work, perform strenuous activities, and take a walk (18,23,25).

The prevalence of symptoms in these domains is difficult to ascertain from existing literature. Studies that have reported PRO data in patients with advanced prostate cancer commonly include these measures and describe changes in domain scores (30) but do not report the prevalence of each symptom.

The Prostate Cancer Working Group recommends five domains for studies of localized prostate cancer patients (urinary incontinence, urinary obstruction and irritation, bowel-related symptoms, sexual dysfunction, and hormonal symptoms [if relevant for patients receiving hormonal therapy]) and four domains for advanced cancer (pain, fatigue, mental well-being, and physical well-being). Table 1 summarizes existing validated PRO instruments that can be used for these assessments. These recommendations are in addition to those from the cross-cutting group, which apply to all cancer patients (1). Several points of discussion during the planning meeting deserve mention:

1. In the context of these recommendations, PRO incorporation in clinical trials should be hypothesis-driven and should measure symptoms appropriate for the treatments being assessed.
2. Symptoms experienced by patients with localized and advanced cancers

Table 1. Validated prostate cancer–specific patient-reported outcome instruments*

First author (reference)	Instrument	Domains
Clark (2)	Prostate Cancer Symptom Indices (31 items)	- Urinary incontinence (3 items) - Incontinence bother (1 item) - Obstruction (5 items) - Obstruction bother (5 items) - Bowel problems (6 items) - Bowel problems bother (4 items) - Sexual dysfunction (5 items) - Sexual problems (2 items)
Litwin (4)	UCLA Prostate Cancer Index (20 items)	- Urinary function (5 items) - Urinary bother (1 item) - Sexual function (8 items) - Sexual bother (1 item) - Bowel function (4 items) - Bowel bother (1 item)
Wei (3)	Expanded Prostate Cancer Index Composite (EPIC) (50 items)	- Urinary incontinence (4 items) - Urinary irritation/obstruction (7 items) - Overall urinary (1 item) - Sexual function (9 items) - Sexual bother (4 items) - Bowel function (7 items) - Bowel bother (7 items) - Hormonal function (5 items) - Hormonal bother (6 items)
Szymanski (6)	EPIC–26 (26 items)	- Urinary incontinence (4 items) - Urinary irritation/obstruction (4 items) - Overall urinary (1 item) - Bowel (6 items) - Sexual (6 items) - Vitality or hormonal (5 items)
Chang (5)	EPIC–Clinical Practice (16 items)	- Urinary incontinence (3 items) - Urinary irritation/obstruction (3 items) - Overall urinary (1 item) - Bowel (3 items) - Sexual (3 items) - Vitality or hormonal (3 items)
van Andel (7)	EORTC QLQ-PR25 (25 items) Use with QLQ-C30 (30 items)	- Urinary symptoms (8 items) - Incontinence aid (1 item) - Bowel symptoms (4 items) - Hormonal symptoms (6 items) - Sexual active (2 items) - Sexual function (4 items)
Esper (23)	FACT-G + FACT-P (47 items)	- Physical well-being (8 items) - Social/family well-being (8 items) - Relationship with doctor (3 items) - Emotional well-being (7 items) - Functional well-being (8 items) - Additional items: weight loss, appetite, pain (4 items), feel like a man, difficulty bowel, urinary (3 items), erection, QOL.
Yount (24)	FAPSI-6 (6 items) FAPSI-8 (8 items) – designed for advanced prostate cancer	FAPSI-6 - Pain (3 items) - Fatigue/lack of energy - Weight loss - Worry FAPSI-8 = FAPSI-6, plus… - Urination (2 items)
Victorson (25)	NCCN/FACT-P Symptom Index (17 items) – designed for advanced prostate cancer	Items are: lack of energy, fatigue, leg weakness, pain (3 items), difficulty urinating, weight loss, appetite, worry, sleep, nausea, trouble moving bowels, satisfied sex life, treatment side effects, enjoy life, QOL
Stockler (41)	PROSQOLI (10 items) – designed for advanced prostate cancer	Present pain intensity (1–5) Linear-analog (0–100): pain, fatigue, appetite, constipation, passing urine, physical activity, mood, family/marriage/relationships, overall well-being

(Table continues)

Table 1 (Continued).

First author (reference)	Instrument	Domains
Farnell (16)	LENT (22 items) – designed for radiation-related symptoms	- Rectum/Bowel (10 items) - Bladder/Urethra (9 items) - Sexual Function (3 items)
Cleary (18)	(30 items) – designed for advanced prostate cancer	- Pain (4 items) - Emotional well-being (5 items) - Social functioning (2 items) - Vitality (5 items) - Physical capacity (6 items) - Sexual interest (3 items) - Sexual Functioning (4 items) - Overall health (1 item)
Rodrigues (8)	Prostate Cancer Radiation Late Toxicity (29 items) – designed for radiation-related symptoms	- Bowel (12 items) - Urination (11 items) - Sexual function (6 items)
Ritvo (42)	Prostate Outcomes Record of Psychometric and Utility Self-Report (PORPUS; 10 items)	- Pain/disturbing body sensations - Energy - Family/friend support - Communication with doctor - Urinary frequency - Urinary incontinence - Sexual function - Sexual interest - Emotional well-being - Bowel problems

* EORTC = European Organization for Research and Treatment of Cancer; FACT = Functional Assessment of Cancer Therapy; FAPSI = FACT Advanced Prostate Symptom Index; LENT = Late Effects in Normal Tissues; NCCN = National Comprehensive Cancer Network; PROSQOLI = Prostate Cancer Specific Quality of Life Instrument; UCLA = University of California—Los Angeles. Instruments that measure pain, fatigue, mental well-being, and physical well-being can be considered in clinical trials assessing advanced prostate cancer treatments. Instruments that measure urinary incontinence, urinary obstruction and irritation, bowel-related symptoms, sexual dysfunction, and hormonal symptoms (for patients receiving hormonal therapy) can be considered in clinical trials assessing localized prostate cancer treatments, including radical prostatectomy, radiation therapy, and other local therapies. Patient-reported outcome assessment in clinical trials should be hypothesis-driven, and patients with localized and advanced cancers may have overlapping symptoms depending on their disease status and prior treatments.

Table 2. Validated prostate-cancer specific patient-reported outcome instruments measuring decisional regret, satisfaction with care, and anxiety

First author	Instrument	Number of items
Decisional regret		
Clark (99)	Clark 3-question	3
Clark (100)	Clark 5-question	5
Satisfaction with care		
Lubeck (101)	CaPSURE* satisfaction scale	9
Prostate cancer anxiety		
Roth (102)	Memorial Anxiety Scale for Prostate Cancer	18

* CaPSURE = Cancer of the Prostate Strategic Urologic Research Endeavor.

may overlap. For example, localized cancer patients can experience fatigue and physical well-being changes while receiving treatment. Similarly, advanced cancer patients may experience symptoms relating to their local (prostate) cancer or residual symptoms from prior treatment, as well as hormonal therapy symptoms. If appropriate, these additional domains can be included.

3. Longitudinal PRO measurement is important because of the time-dependent nature of symptom development and resolution after treatment. Investigators need to consider not only relevant domains and symptoms for inclusion but also appropriate measurement time points.
4. PRO measurement burden needs to be considered because substantial overburden may increase missing data. Among the attendees, there was general feeling that the working group's recommended domains are not overly burdensome because validated instruments measuring these domains have been successfully incorporated in prior trials.
5. PRO use in clinical trials is changing over time. Not only are PROs commonly incorporated in current trials (31), but they have also been used as primary endpoints. For example, a randomized phase II trial (RTOG 0938) is comparing two different doses of stereotactic body radiation therapy for early prostate cancer. The primary goal is to assess the safety and tolerability of this treatment, as assessed by patient-reported bowel and urinary symptoms. Similar approaches can be applied to trials examining future surgical, radiation, and other treatment technologies.

The working group recognizes the rich literature in prostate cancer PROs and important methodologic advances over the past 20 years. However, the current literature is based mainly on cohort studies, which are limited by differential patient selection into treatment groups. Patients treated by prostatectomy are often younger, healthier, and have higher baseline sexual, bowel, and urinary function than those treated by radiation (9,10,32–36), thus making comparisons across groups

difficult. More PRO incorporation in trials and publication of PRO results simultaneously with the mortality and disease control outcomes (31) will help mitigate this limitation and provide important new information to patients and physicians.

Because the working group's recommendations are based on a systematic literature review, they may not incorporate all possible side effects from newer systemic therapies. Hypothesis-driven additional measures may be needed in trials that use these therapies.

A continued challenge is interpretability of PRO data (19,37,38). Most published studies report average scores of symptom domains, usually ranging from 0 to 100 points, but the exact meaning of higher vs lower scores is unclear. The proportion of patients experiencing symptoms and severity of these symptoms cannot be ascertained from average scores. Further, a commonly used threshold of one-half standard deviation signifying clinically meaningful change (39) appears limited in that a statistical threshold is used to derive clinical meaning; however, few alternatives have emerged. Reporting the prevalence of individual symptoms in addition to summary scores (9) provides important and more tangible information. In addition, some studies have classified patients into different levels of function (eg, normal, intermediate, poor) (19,33,40), which can facilitate interpretation of "meaningful change" as a move from one clinical level to another. Further methodologic development is needed.

Although not included in the official recommendation, other PRO measures that investigators may consider include decisional regret, satisfaction with care, and anxiety or worry related to prostate cancer (Table 2). Further, although the charge of the working group was to make recommendations for clinical trials, these same considerations may also apply to observational studies.

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Notes

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