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Symptom Monitoring in Pediatric Oncology Using Patient-Reported Outcomes: Why, How, and Where Next

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Abstract Symptom monitoring using patient-reported outcomes (PROs) is not common in pediatric oncology, despite interest from stakeholders—including patients, families, clinicians, and regulatory organizations—and proven clinical benefit in adult oncology. This article examines the foundational data for patient-reported symptom reporting in this population and posits the next investigative steps toward the implementation of patient-reported symptom monitoring in the care and research of pediatric oncology patients. The reasoning behind, and feasibility of, monitoring symptoms in pediatric oncology patients using PRO measures are discussed, as well as specific tools that have been developed to track symptoms in this population, including innovative electronic self-reporting platforms built to engage children in the symptom reporting process. Aspects of engaging both patients and clinicians in the symptom self-report process are reviewed, as are the experiences of "early adopters" of this process in pediatric oncology and across pediatrics. It is clear that there are key issues that remain regarding the use of PROs for symptom monitoring, including selection of specific outcomes to monitor, how to resolve discrepant reports, and determination of benefit. The next steps for investigation of these issues are discussed. Unanswered questions notwithstanding, work should continue to make patient-reported symptom monitoring an established, evidence-based part of routine and research practice in pediatric oncology.

Key Points for Decision Makers:

Patient-reported outcomes (PROs) in pediatric oncology are not commonly used despite evidence that collecting them is feasible and that patients, families, and physicians are interested in their use.

Specific symptom-monitoring PRO tools exist for use in the pediatric oncology population, and innovative electronic reporting platforms have been developed to engage children in the self-report process.

Using PROs as dynamic, clinically actionable data has the potential to improve outcomes of children with cancer, but more work must be done to study their implementation and use.

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1 Introduction

For children with cancer, both the cancer and the treatment generate symptoms and adverse events [1]. Accordingly, the US National Academy of Medicine and the American Cancer Society have called the integration of patient-reported outcome (PRO) measures into pediatric research and care "essential" [2]. Similarly, the National Cancer Institute named symptom management "a priority for accelerated funding" aimed at deploying PRO measurements to all cancer patients in an effort to optimize patient outcomes and decrease costs associated with poorly controlled symptoms [3]. In adult oncology, the practice of tracking symptoms and toxicities using PROs has increased and correlates with increased survival [4]. PRO use in pediatric oncology, however, is not yet common [5]. In this commentary, we make eight recommendations to remedy this situation, discussing the current state of PRO use for children with cancer and outlining the rationale and path toward the implementation of patient-reported symptom information in the care of all pediatric oncology patients.

2 "Patient-Side" Barriers to Reporting Symptoms Addressed Using Patient-Reported Outcomes (PROs)

Data suggest that children and their families believe that experiencing side effects from chemotherapy is necessary to cure their cancer [6], despite evidence that good symptom management decreases treatment-related complications and increases quality of life [1]. Children under-report their symptom severity during the clinical interview to avoid complaining or "bothering" the physician with a symptom perceived as inherent in the treatment, or in an effort to protect their family from worry. Qualitative work has demonstrated that children can feel "silenced" by their healthcare providers [7, 8].

These "patient-side" barriers can, in part, be surmounted by the use of PROs. Standardized patient-elicited assessments can normalize the symptom-reporting process, reassure the child that the physician values their experience, and generate more reliable symptom data [9]. This, in turn, enables better control of those symptoms. The use of symptom self-reporting increases patient engagement in care, enhances communication with the treating team [10], and allows symptom management to be custom tailored to the patient. In adults, better symptom management has resulted in less emergency room utilization, improved patient engagement, and a significant survival benefit [4, 11]. In this era of personalized medicine and customized healthcare, hearing and using the child's voice will advance our ability to alleviate pain and distress, and to improve outcomes.

3 Feasibility of Monitoring Symptoms with PRO Measures

A scientifically rigorous foundation supports the collection of PROs in pediatric cancer, with studies highlighting the feasibility of the practice and providing useful descriptions of symptom burden at all stages of treatment.

3.1 Cross-Sectional Symptom Reporting with No Feedback to the Clinical Team

Pediatric self-reported symptom burden has thus far been elicited primarily using cross-sectional designs. Children's reports typically confirm the expectations of oncologists: known side-effects of chemotherapy, like pain and vomiting, are experienced throughout treatment [12–17]. Other, less obvious treatment comorbidities have also been identified, such as insomnia [13–15], numbness [16], and itch [13, 16], and psychological symptoms [12, 15]. Further, symptoms generating the most distress for children are not the most clinically evident ones, but rather symptoms such as nausea, feeling sad [14, 17], insomnia [13], lack of appetite, and pain [13, 14, 18]. These studies support the feasibility of eliciting self-reported symptom information from children between the ages of 8 and 18 years at single time points during treatment. Each reported high enrollment and completion rates with good "ease of use," indicating that children can, and will, self-report symptom information. Additionally, they suggest that self-report of the less visible sequelae of treatment, both physical and emotional, will help us to better understand a child's experience with cancer treatment and provide opportunities for enhanced supportive care.

3.2 Longitudinal Symptom Reporting with No Feedback to the Clinical Team

The feasibility of longitudinal symptom collection suggests that PROs can be used as a dynamic clinical tool to optimize symptom management. Children are able to complete symptom assessments in multiple domains at multiple time points during chemotherapy, with excellent enrollment rates and minimal attrition [19, 20]. Trials with longer surveillance periods (greater than 3 months) show lower enrollment rates, with less adherence to repeated measures [18, 21], but demonstrate, nonetheless, the viability of the concept and illustrate essential aspects of the childhood cancer experience: symptoms fluctuate over the duration of treatment, different chemotherapy regimens result in different symptoms, and the individual response to treatment is widely variable. The theme of "invisible" symptom prevalence is again noted [18, 20], lending importance to

providing a standard method for patients to provide this information directly to their healthcare team.

3.3 Symptom Reporting with Feedback to the Clinical Team

Three studies have examined the effect of providing pediatric patient-reported symptom information to their healthcare provider in real time. Investigators in the Netherlands developed the Quality of Life in Childhood Oncology (QLIC-ON) PROfile and tracked four health-related quality of life (HRQoL) domains in children who had completed treatment for their cancer. In a sequential cohort design, three clinic encounters were captured, with information from the QLIC-ON PROfile provided to treating oncologists. Findings included enhanced identification of emotional problems, with sub-group analysis that demonstrated overall improvement in HRQoL for children aged 5–7 years. Given the promising results, the authors called for the exploration of longitudinal reporting and study of the tool in children actively receiving treatment [22].

The Symptom Monitoring & Systematic Assessment in Young Survivors (SyMon-SAYS) was an 8-week feasibility study that captured self-reported fatigue from children and young adults who had received chemotherapy in the preceding 6 months. Fatigue information was relayed to clinicians prior to each visit and when participants' fatigue met certain severity thresholds. Notably, both clinicians and patients felt that self-reporting fatigue had no perceivable impact on treatment strategies [23], highlighting the imperative that PROs should be selected according to patients' needs, treatment goals, and clinical actionability.

The Pediatric Quality of Life and Evaluation of Symptoms Technology (PediQUEST) study was a longitudinal self-report study that relayed information to the treatment team for clinical decision making. The population was limited to children with advanced cancer, with reports collected at least monthly. Symptom reports and email alerts were provided to the treatment team, without guidance on how to respond [24]. The perceived benefits from self-reporting included helping the parent understand what the child was feeling and the use of symptom reports as a "communication enhancer" in discussions with the doctor. No significant change in the child's symptoms or HRQoL was seen, but post hoc subgroup analysis revealed benefit to emotional HRQoL and improved scores on a total sickness measure [25].

These results merit further investigation of patients on active therapy. Successful integration of symptom monitoring via PRO measures requires demonstrating the clinical usefulness of the information and should focus on symptoms that are thought to be clinically actionable or meaningful to patients [26–28]. Future directions may also include investigation of clinical decision support to aid clinician response.

4 Developing Pediatric Oncology-Specific Symptom-Monitoring Tools

Several noteworthy measures have been used to monitor symptoms in pediatric oncology patients. Select pediatric Patient-Reported Outcomes Measurement Information System (PROMIS) measures have been validated for children undergoing chemotherapy, including pain interference and fatigue [19, 29, 30]. Similarly, the Memorial Symptom Assessment Scale (MSAS) has been validated [12, 13] and is used frequently to characterize pediatric symptom burden, including in longitudinal studies such as PediQUEST [31].

New PRO measures have also been recently developed. The Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) was developed for use in adults to evaluate symptomatic toxicity as a companion to the CTCAE [32, 33], the standardized language of symptom severity applied in US clinical trials. A pediatric version, the pediatric PRO-CTCAE, has been designed to assess symptomatic adverse events via child self- or proxy-report [27, 28] and is currently being validated [34, 35]. Specific symptom items may be selected from a bank to develop a questionnaire that elicits only symptoms of interest and includes the attributes of presence, frequency, severity, and interference [34]. An electronic version has not yet been created.

The Symptom Screening in Pediatrics (SSPedi) was developed by a Canadian group to provide unidimensional symptom screening in pediatric oncology patients [26, 36]. An electronic version is currently being validated [37, 38]. Designed as a symptom screen, only a child form exists, without a proxy version. The instrument includes 15 items, with selection based on expert opinion [26] and confirmed in cognitive interviews [37]. In contrast to the pediatric PRO-CTCAE, SSPedi captures symptom interference ("bother") without symptom prevalence or severity.

5 Developing and Investing in Self-Reporting Platforms

A handful of programs developed for symptom reporting by children with cancer have been published, each highlighting needed aspects of future program development [23, 39, 40].

The first, SyMon-SAYS, discussed previously, found a strong preference for internet-based reporting [23]. Two others, Pain Squad [39] and Pain Buddy, utilized a

"gamified" approach, including the use of avatars [40] and an adherence-based rewards system [39], with excellent participation and patient satisfaction. In Pain Buddy, a report of pain automatically triggered electronic skill training in evidence-based pain management techniques, teaching children how to use guided imagery, progressive muscle relaxation, diaphragmatic breathing, mindfulness, and distraction. This innovative feature empowers children in the self-management of their symptoms, a critical next step in this field. Pediatric participants found the skill training useful and the program desirable to recommend to friends [40]. Construct validity and reliability for Pain Squad was assessed, but was not for Pain Buddy. This raises the question as to whether the game-like approach could alter a child's self-reported symptoms through distraction or improvement in mood, particularly as some studies suggest that playing certain health-related video games can be used for that purpose [41]. This should be explored in further investigations of these methods.

6 Engaging Stakeholders to Facilitate the Use of PRO Symptom Information

Integrating PROs into practice requires engagement of patients and their clinicians.

6.1 Optimizing Patient Engagement

Patients require platforms that are convenient and easy to use, capture information that is of concern to the patients and their families, and is felt to be meaningfully used by their care team. The high retention rates and reported usefulness in the PediQUEST study show the investment in longitudinal symptom reporting that pediatric patients and their families have if they feel it is of benefit [24]. Further, nearly three-quarters of participants reported that they would "very much" like to continue reporting following study conclusion [25]. This suggests that caregiver engagement in patient-reported symptom monitoring may be achieved by the recognition that it enhances communication with the treating team and aids in understanding what their child is feeling. Children, particularly younger ones, though, need to be engaged in other ways. The gamification of tools described above may be an important method to engage this audience.

Increasingly, a "bring your own device" design is being used for PROs, in which patients enter data into clinical and research databases on their own tablets and smartphones [42]; the same approach should be pursued in pediatrics. The rising presence of technology and internet access in children's lives [43] should be leveraged to make symptom reporting convenient for patients and their families.

6.2 Optimizing Clinician Logistics

While a survey revealed that the overwhelming majority (94%) of pediatric oncologists in international cooperative groups saw value in the routine collection and use of PROs, barriers to implementation were felt to be mainly logistic, namely, the time required and disruption of the clinical workflow [5]. The advancement of symptom monitoring via PROs must address these concerns. The data must be easy to interpret and be linked to evidence-based supportive care interventions. Effective methods to present PRO data to clinicians and patients have been detailed [44–46]. This includes a preference for a line graph, with clear delineation of what is "good" and "bad" descriptive labels in addition to numerical scores, and parsimonious use of colors. More work is needed to enhance point-of-care symptom management decision support.

7 Learning from the Experience of Early Adopters

Symptom monitoring using PROs in routine care can be guided by the experience of early adopters. In pediatric oncology, an international study found that 27% of responders reported that their institution obtained PROs as part of their clinical practice [5]; however, there remains little in the literature describing that experience. Based on the implementation of the QLIC-ON PROfile experience in the Netherlands, a practical guide was generated to help guide implementation of PRO interventions in clinical settings [47] and to posit future directions [48].

Experience in other areas of clinical practice is also relevant. For example, one children's hospital in the USA has adopted PROs in rheumatology, cardiomyopathy [49], inflammatory bowel disease and cystic fibrosis clinics [50]. Published reports suggest that patients and clinicians have been receptive to these initiatives and, in some cases, self-reported data has been hypothesis-generating for more traditional research questions [49].

8 Employing Symptom-Monitoring PROs in Treatment Trials

As new classes of cancer therapeutics are developed, novel toxicity profiles have emerged [51]. Utilizing symptom-monitoring PROs in the evaluation of these agents is important, given emerging evidence that traditional adverse event reporting underestimates patient symptoms [52]. Further, from the patient perspective, when treatment options offer similar survival rates, differences in the types or degree of symptoms posed by new therapeutics could aid in treatment selection. In the future, longitudinal PRO

symptom measurement in clinical trials could enhance adverse event monitoring and more accurately capture the patient experience with novel regimens.

9 Investigating Key Questions About Symptom-Monitoring PROs

Advancement of symptom-monitoring PROs will require ongoing research in at least three areas.

First, we must determine the most important outcomes to collect in the clinically heterogeneous pediatric oncology population. When patients experience highly bothersome symptoms such as pain or dyspnea, they likely always matter. The prevalence of such symptoms, though, varies across different forms of pediatric cancer. Other symptoms, even if they occur with similar intensity, may bother some patients more than others. Thus far, selection of symptom-monitoring PRO measures has been driven by expert oncologist opinion and generalized patient input, with limited stratification based on diagnosis type, treatment phase, or availability of effective symptom prevention or amelioration interventions.

Second, we need to study discrepancies between a physician's interpretation of a child's symptoms and a child's own report. In adults, oncologists have higher symptom-grading thresholds [53] and underestimate symptom severity in comparison to patient self-report [54, 55]. In children, agreement in symptom severity is more concordant for visible symptoms, such as immobility, than for "invisible" symptoms, such as pain or feelings [12, 13]. This may indicate that the clinician fails to understand the severity of a child's symptoms, but other factors may be at play. In some cases, children over- [56] or under-report [57] their symptom severity for secondary gain, or because they do not want to cause worry, or they feel that they cannot be helped. Feelings of anxiety or depression may drive symptom scores higher or undercut the ability to accurately report. Moving beyond simple identification of these discrepancies, we need to understand what psychological or social factors generate them and how to manage clinical care when clinician assessment and patient PRO symptom reports diverge.

Third, we do not yet know whether the routine use of symptom-monitoring PRO measures will benefit patients. Because small sample sizes and heterogeneous populations limit the statistical significance of single-institution trials, the evaluation of clinical outcomes associated with patient-reported symptom information must be pursued in a collaborative, multi-institutional manner. Suitable designs would include a pragmatic, clustered, randomized control trial approach or a step-wedge evaluation.

10 Conclusion

We now have the knowledge and technical capacity to make the child's voice a formal part of the clinical encounter as a dynamic, important, actionable piece of data. Given the availability of well-developed PRO tools, as well as the ethical imperative to measure our patients' experiences, and evidence of benefits, what will facilitate wider implementation of PROs in pediatric oncology? First, PROs need to be integrated into clinical trials, since so many pediatric patients are treated on protocol. Second, technologies for collecting this information need to be seamlessly integrated into practice—likely through the electronic health record system at the clinic or hospital. Third, the culture needs to change. We need to come to expect this information as a part of routine practice, like blood pressure or heart rate. Clinical champions need to advocate for patient-centered care and enlist administrative leaders to facilitate implementation. Substantial strides have been made in the methods of PROs, and now is the time to focus on implementation.

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Compliance with Ethical Standards

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