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Mini-review

Patient-reported outcomes used actively in cancer patients undergoing antineoplastic treatment: A mini-review of the Danish landscape

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ABSTRACT

Introduction: Many studies using Patient-reported outcomes (PRO) data have been conducted to monitor symptoms and health-related quality of life during follow-up after cancer treatment. However new ways of using (e) PROs have emerged. We aimed to explore the Danish landscape of the use of PRO in a research setting, where PRO is used actively in cancer patients undergoing treatment, and give an overview of how it is embraced by patients and clinicians.

Methods and materials: A literature search was performed in June 2023, using the keywords Denmark, cancer, and patient-reported outcomes. An expert on literature searches identified the search terms, and double screening was performed at both abstract and screening levels and full-text stage. The software tool Covidence was used.

Results: 467 articles were retrieved and 19 studies were included. They described the type of ePRO instrument used and the application of active ePRO i.e. a dialogue tool in the clinical encounter, release of alerts to clinicians, and enhancement of self-management. Finally, a development in the use of active ePROs over time is elucidated and we show how it is embraced by patients and clinicians.

Conclusion: This mini-review gives an overview of how ePRO solutions are tested in oncological research in Denmark and embraced by patients and clinicians. ePRO solutions in a Danish setting seem well-suited for self-management. However, if more impact is warranted, clinicians need to engage in reviewing and using ePROs. Moreover, for successful implementation, the integration of ePROs in electronic health records must be supported by IT specialists and management.

1. Introduction

In the past decades, patient-reported outcomes (PROs) have frequently been collected in cancer trials to assess health-related quality of life (HRQoL) and capture the most common symptoms and treatment-related toxicities [1]. The PROs have been used in the passive sense on an aggregated level to generate population-based data to the advantage of future patients and have not benefitted the patients who report the PRO-data directly.

However, in recent years, the purpose of collecting PRO-data has changed. As the focus on patient involvement and patient preferences has intensified in the healthcare system, promoting self-management

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has become an important component of patient involvement. Following this development, many studies have been conducted internationally to monitor symptoms and HRQoL during follow-up after antineoplastic treatment [2–6]. This is in alignment with the trend in Denmark where PROs have been used for various cancer diagnoses to provide a complete picture of the patient's symptoms and problems, possibly leading to improvements in symptom management during follow-up care [7–10]. In some cases, PROs are used for resource purposes to design individual follow-up, prioritizing the patients most in need of a face-to-face consultation and reducing the number of consultations in a strained healthcare system [11,12].

During the last decade, there has been a growing interest in the use of real-time PRO in oncology for patients undergoing systemic antineoplastic treatment to improve symptom monitoring, HRQoL, and patient satisfaction [13]. This interest was enhanced by Basch et al. [14], who in 2016 showed that clinical benefits were associated with symptom self-reporting during cancer care.

The PROs are used actively on an individual level [15] i.e. as a dialogue tool in the clinical encounter, to trigger alerts for the clinician to react upon or to enhance self-management. Interventions that may reduce the severity of physical and emotional distress and improve quality-of-life outcomes [16]. Thus, PROs are used to inform clinical decision-making and enhance care for the individual patient, for example, by detecting physical or psychological issues that may otherwise be overlooked [17].

Specifically developed software systems and more advanced eHealth solutions have eased electronic data collection and enabled patient reporting, for example, symptom reporting, to be collected and used in real-time when the patient is seen at the clinic or contacted outside the planned visits to the hospital [18–22]. Data can be collected via the web, a handheld computer, a cell phone, or an interactive voice-response system.

According to ESMO "The use of electronic systems for administering PROMs to patients with cancer and communicating this information back to their clinicians has been shown to improve symptom control, physical function, QoL, adherence to treatment, reduction in emergency room and hospital admissions and survival." Further, ePRO may improve physical well-being and self-efficacy when used with self-management advice and clinical algorithms for management [23].

There exist a number of PRO measures to be used within oncology. The most widely used validated questionnaires are the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 [24], FACT [25], and the EuroQol EQ-5D Index questionnaire (EQ-5D) [26]. These questionnaires are generic and can be used across various cancer populations. Although some of these questionnaires have disease-specific modules, they are static, as they cannot be changed and adapted to a specific type of treatment or intervention for the patient population in question. Thus, there is a need for customized PRO measures [27], and various item libraries have been developed, such as the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE [28], the EORTC item library [29], and The Patient-Reported Outcomes Measurement Information System (PROMIS) [30]. Several Danish PRO studies have used these libraries, particularly the PRO-CTCAE, and carried out thorough item selection processes to determine the most suitable instruments before initiating new PRO studies [31–34].

Although evidence suggests that the use of active PRO during treatment is beneficial to patients and clinicians, it has not become a natural part of routine care in Denmark due to a number of barriers. It has primarily been examined in research studies but the extent has never been elucidated. Accordingly, this mini-review aimed to explore the Danish landscape of PRO studies in a research setting, where PRO is used actively in cancer patients undergoing antineoplastic treatment. Furthermore, we aim to give an overview of how it is embraced by patients and clinicians.

2. Methods and materials

A literature search was performed in June 2023 in PubMed using the Boolean logical operators to combine the search terms. A combination of keywords for Denmark (i.e. Denmark, Danish), cancer (i.e. neoplasm, cancer), and patient-reported outcomes (i.e. patient-reported outcome measures, patient-generated data, PROM) was used. An expert on literature searches identified the search terms (see supp. material). To supplement this search, a rough search was carried out in Google Scholar. To identify the relevant articles to include, a small project group was established, comprising an oncologist/professor in patient involvement and a nurse senior researcher. The online software tool Covidence was applied to streamline the process. Both group members did the title and abstract screening. Both members screened all the papers during the full-text review and extraction of articles. Thus double screening was performed at both abstract and screening level and full text stage.

A deductive approach was applied as preconceived themes were defined a priori to be used for data extraction. The categories were as follows:

- Clinical use of patient-reported outcome
- Patient and public involvement
- *PRO measures*
- Real-time feedback to patients and self-management
- Feedback from clinicians
- *Patient satisfaction*
- Patient and clinician compliance
- Development in the design and complexity of the use of PROs

2.1. Inclusion criteria

- Danish studies
- Studies written in English
- Studies including cancer patients receiving anti-neoplastic treatment $\geq$ 18 years
- Studies using or evaluating PROs actively during treatment, *or*
- Studies measuring HRQoL when PRO is used proactively

2.2. Exclusion criteria

- Review studies
- Studies with an exclusively hematological sample

3. Results

We retrieved 487 titles from the initial literature search in PubMed. One article was removed as it was a duplicate. The initial search included hematologic cancers to ensure that no studies with mixed populations of oncological and hematological patients were missed. However, mixed studies were not identified, and the hematological studies were excluded. In case of doubts (n = 10), the issue was resolved in collaboration. After title and abstract screening, 467 studies were excluded (see Fig. 1 for reasons), and 19 studies were assessed for eligibility. One study was excluded due to an inappropriate design as it was a pilot study using PRO in relation to radiation therapy, and one was identified through a search in Google Scholar and found eligible (Fig. 1 and Table 1).

3.1. Clinical use of patient-reported outcome

The papers included in this review describe the application of active PRO in a clinical setting within at least one oncological department in Denmark. The use of PRO in clinical oncology comprised a variety of cancer subtypes such as malignant melanoma (n = 4) [35–38], lung

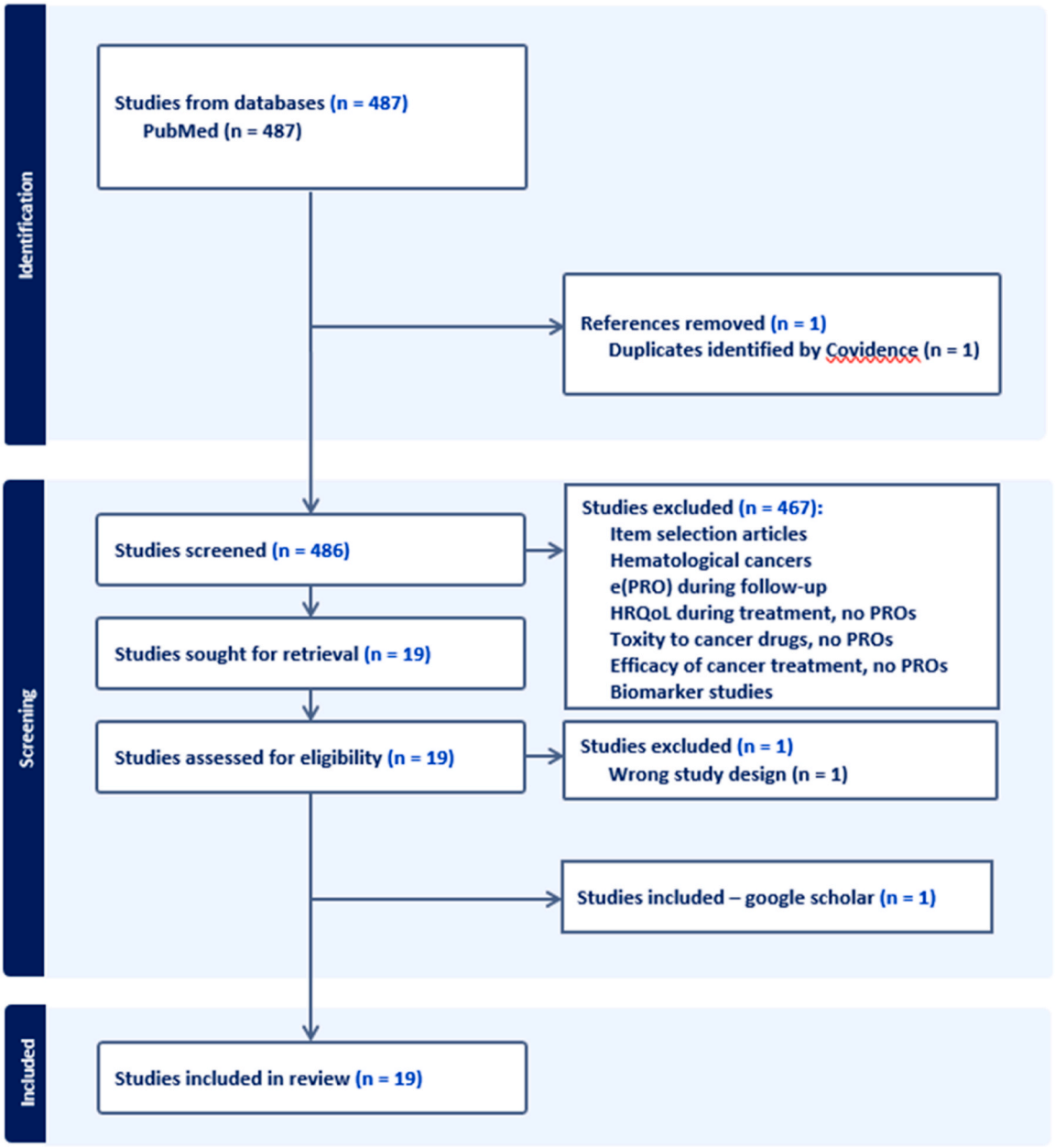

Fig. 1. Flow diagram of the articles selected in the mini-review.

(n = 1) [53], ovarian and endometrial (n = 1) [49], head and neck (n = 1) [50], breast (n = 4) [45–48], prostate (n = 2) [43,44], kidney (n = 2) [51,52] (n = 2), or bladder cancer (n = 4) [39–42].

3.2. Patient and public involvement

Patient and public involvement (PPI) was described in five studies [35,39,46,49,53]. PPI contributed to the development of a patient-reported experiences measure [46], a screening tool and intervention content [53], and content for a future app [39]. Patients were members of patient advisory boards involved in all stages of the research in two studies [35,49].

3.3. PRO measures

As for PRO measures, the EORTC QLQ-C30 is the most commonly used static questionnaire in the PRO studies (n = 9) [35,39–42,49–52], and most commonly applied to measure the outcome of a PRO intervention. In some of these studies, disease-specific EORTC questionnaires have been added, i.e. QLQ-BLM (n = 4) [39–42], QLQ-OV28 [49], and QLQ-EN24 [49]. The Functional Assessment of Cancer Therapy (FACT-G) has been used in two studies, including the melanoma-specific module (FACT-M) (n = 2) [35,37]. EQ-5D-5 L was used in three studies [37,50,53], and The Hospital Anxiety Depression Scale (HADS) in five studies [35,40–42,49]. The Self-Efficacy for Managing Chronic Disease 6-Item Scale (SES6G) [49], the Cancer Behavior Inventory–Brief Version (CBI-B) [49], and the Perceived efficacy in patient-physician interactions (PEPPI) [35] were used in one study each. Most customized questionnaires were derived from the PRO-CTCAE library (n = 17) [36–52]. Items from the EORTC library were used in two studies [50,53].

3.4. Real-time feedback to patients and self-management

Five papers describe the active use of PRO between visits with real-time feedback to the patients on how to adjust their supportive care or

Table 1
Description of the articles selected in the mini-review, including aims, study type, PRO intervention, and outcomes.

Study	Aim	Study type	PRO-intervention/ Software	Outcomes
Melanoma				
Skovlund et al. [35]	To investigate the potential of using PRO as a dialogue-based tool in consultation with patients with metastatic melanoma.	Prospective non-randomized controlled trial	QLQ-C30/ Ambuflex	HRQoL (FACT-M) Self-efficacy (CBI-B) Patient-Physician interaction (PEPPI) Patient activation (PAM)
Tolstrup et al. [36]	To investigate the reduction of irAEs and number of reported irAEs, telephone consultations, out-patient visits, days in hospital, days in steroid treatment	Randomized controlled trial	PRO-CTCAE/ Ambuflex	Reduction of irAEs (CTCAE)
Tolstrup et al. [37]	To examine group differences in HRQoL and associations between irAEs severity and HRQoL.	Randomized controlled trial	PRO-CTCAE/ Ambuflex	HRQoL (FACT-M, EQ-5D-5 L)
Tolstrup et al. [38]	To examine patients' and clinicians' experiences with an eHealth intervention for weekly monitoring of side effects during treatment with immunotherapy.	Mixed methods study	PRO-CTCAE/ Ambuflex	Patient Satisfaction Clinician satisfaction (Patient Feedback Form)
Bladder				
Tolstrup et al. [39]	Testing how symptoms measured using ePRO in a multimodality app are correlated to HRQoL	Study protocol	PRO-CTCAE/ Mit Sygehus, Journl,	HRQoL (QLQ-C30, QLQ-BLM30) Patient Satisfaction (Patient Feedback Form)
Taarnhøj et al. [40] 2020	To investigate which PRO-CTCAE symptoms correlate with quality of life domains. Collection of PROs in prospective study during treatment of bladder cancer	Prospective observational study	PRO-CTCAE/ Paper	HRQOL (QLQ-C30, QLQ-BLM30, HADS)
Taarnhøj et al. [41] 2020	To investigate the feasibility of ePRO completion for bladder cancer patients during treatment	Prospective observational study	PRO-CTCAE/ Ambuflex	HRQOL (QLQ-C30, QLQ-BLM30, HADS)
Taarnhøj et al. [42]	To collect ePROs and QoL assessments for bladder cancer patients during chemo- or immunotherapy To determine the rate of hospital admissions and treatment completion	Randomized controlled trial	PRO-CTCAE/ Ambuflex	HRQOL (QLQ-C30, QLQ-BLM30) Treatment completion Hospital admission
Prostate				
Stormoen et al. [43]	Comparing findings with toxicity data from relevant phase 3 registration trials	Sub-analysis of the feasibility trial	PRO-CTCAE/ Ambuflex	Toxicity monitoring compared to the literature
Bæksted et al. [44]	To examine the feasibility, acceptability, and clinical utility of electronic symptom surveillance with clinician feedback	Feasibility study	PRO-CTCAE/ Ambuflex	Patient Satisfaction Clinician satisfaction Technical and clinical barriers and acceptability
Breast				
Bæksted et al. [45]	To explore any differences in the documentation of symptomatic adverse events and the handling of those when patients used ePRO compared to usual care	Randomized controlled trial	PRO-CTCAE/ Ambuflex	Documentation of symptomatic adverse events Prescription of medication Referrals
Bæksted et al. [46]	To examine patient-reported experience measure (PREM) regarding communication and handling of side effects/symptoms	Mixed methods study	Patient Reported Experience Measure (PREM)/ Paper	Patient Satisfaction
Pappot et al.[47]	To describe the design of a national study, which examines the effect of using patients' electronic PRO-CTCAE reporting with real-time feedback to clinicians on treatment events for breast cancer patients receiving adjuvant chemotherapy	Study protocol	PRO-CTCAE/ Ambuflex	Treatment adjustment Hospitalizations
Pappot et al.[48]	To reduce treatment adjustments and hospitalizations in breast cancer Patients cluster-randomized immediately before initiating six cycles of standard adjuvant chemotherapy	Randomized controlled trial	PRO-CTCAE/ Ambuflex	Treatment adjustment Hospitalizations
Ovary				
Christiansen et al.[49]	To develop a model for systematic nurse-led consultations based on ePRO facilitating symptom management and to examine whether nurse-led consultations can be integrated into a multidisciplinary treatment regimen for women with ovarian or endometrial cancer receiving chemotherapy.	Study protocol	PRO-CTCAE/ Kaiku Health	HRQoL (QLQ-C30, OV28/EN24, HADS, SES6G). Toxicity registration (CTCAE) Patient and clinical satisfaction (Patient Feedback Form)
Head and neck				
Holländer-Mieritz et al. [50]	To investigate the active use of PRO during radiotherapy for patients with HNC compared to standard management	Study protocol	PRO-CTCAE and EORTC item library/ Ambuflex	HRQoL (QLQ-C30, EQ-5D-5 L) Toxicity-monitoring Patient satisfaction (Patient Feedback Form)
Kidney				
Rasmussen et al. [51]	To investigate whether adding weekly monitoring of patient-reported symptoms can improve physical function in patients with metastatic renal cell carcinoma	Study protocol (RCT)	PRO-CTCAE/ Journl	Physical function (QLQ-C30) Patient satisfaction (Patient Feedback Form)
Rasmussen et al. [52]	To improve the treatment of patients with non-clear cell renal cell carcinoma by individualizing the medical treatment and use of PRO to monitor symptoms and QoL	Study protocol (prospective feasibility study)	PRO-CTCAE/ Journl	Overall response rate (RECIST) and time to treatment failure. HRQoL (QLQ-C30) Patient satisfaction (Patient Feedback Form)
Lung				

(*continued on next page*)

Table 1 (*continued*)

Study	Aim	Study type	PRO-intervention/ Software	Outcomes
Langballe et al. [53]	To investigate the effect of the intervention on survival, lung cancer treatment adherence, HRQoL and other psychosocial outcomes, as well as health costs and process evaluation	Study protocol	EORTC items/ Electronic platform	Survival (months), HRQoL (QLQ-C30, QLQ-LC13, ^{5}Q–^{5}D-5 L)

References 47 and 48 represent the same study, where reference 47 is the protocol article and reference 48 includes the results

with alerts advising them to contact the hospital [36,39,49,51,52]. The advice was based on algorithms linked to the severity of the symptoms reported by the patient. The patients also received feedback from clinicians at the following consultation. In total five studies described advice to contact the hospital that was actively used in clinical encounters [35,39,49,51,52]. Most were protocol studies (n = 4), describing how patients would receive self-management advice when reporting symptoms in an ePRO platform [39,49,51,52]. In a non-randomized clinical trial, Skovlund et al. [35] investigated whether a PRO-based dialogue tool aided patients with metastatic melanoma in self-management and found no statistically significant effect. None of the studies included a full integration of patient reporting in the electronic health record (EHR).

3.5. Feedback from clinicians

In half of the papers, PROs were used by the clinicians after being filled out electronically by the patient either at home or in the waiting area and sent to the hospital staff (n = 9) [35,45,47–53]. In two papers, the clinicians could review the PRO prompt and contact the patient to initiate supportive care if needed [49,52]. In most cases, the PRO was used at the following clinical encounter to systematically address the most troublesome symptoms for the patient, thereby functioning as a dialogue tool (n = 15) [35,36,39–42,44,45,47–53]. In five papers, the clinicians who reviewed the PRO and provided patient feedback were specified as either physicians [40–42] or nurses [49,53].

3.6. Patient and clinician compliance

The research conducted by Pappot et al. [48] found that patient compliance in the ePRO arm was 87%, with 63% of the electronic PRO questionnaires reviewed by a healthcare professional at least once. Taarnhøj et al. [41] reported lower physician compliance with the ePRO system at 35% despite high patient adherence (70–94%) over six cycles of oncological therapy. Similarly, Baeksted et al. [44] reported that 52% of questionnaire completions were reviewed by an oncologist with a patient compliance rate of 97%. Interestingly, a higher response rate for the PREM questionnaire was observed in the usual care arm than in the ePRO arm (74% vs. 55%), as per Bæksted et al. [46]. Tolstrup et al. [37] reported that most melanoma patients (78%) complied with the ePRO intervention weekly for an average of 17 weeks. Lastly, completion rates for HRQoL questionnaires remained relatively high over time, with no significant differences observed between the intervention and control groups (Table 2).

3.7. Patient satisfaction

Of the 19 studies, eight explored the level of patient satisfaction with completing PROMs [38,39,44,46,49–52]. Six studies [38,39,49–52] used the Patient Feedback Form (PFF) adapted by Snyder et al. in 2014 [54] consisting of 13 items, measuring patient satisfaction with an electronic PRO intervention. The study by Tolstrup used a mixed-methods approach combining the PFF with patient interviews [38]. Baeksted et al. (n = 2) [44,46] used patient interviews and non-validated patient evaluation questionnaires developed with patient representatives. Five of the eight studies, including PREM, are study protocols [39,49–52]. Results from PREMs in the completed studies showed high satisfaction with the PROMs and that the PROs were used during most consultations, thus improving the discussion with clinicians (n = 3) [38,44,46]. Furthermore, the ePROs helped the patients be more aware of their symptoms (n = 2) [38,44].

Table 2
Studies reporting patient adherence to respond to questionnaires, or clinician compliance to review the patient reporting.

Study	Clinician Compliance to review PROMs	Patient Adherence to PROM/PREM completion	Interpretation
Pappot et al. [48]	63%	87% of questionnaires answered	Clinician compliance is lower than patient adherence.
Taarnhøj et al. [41]	0–52%	70–94% over six treatment cycles	
Baeksted et al. [44]	52%	97% of questionnaires answered	
Bæksted et al. [46]	-	74% (usual care arm) vs 55% (ePRO arm)	Higher adherence in normal care arm vs. intervention arm
Tolstrup et al. [37]	-	78% of patients answered questionnaires	

3.8. Development in the design and complexity of the use of PROs

The complexity and ways of how PROs can be used are increasing over time which is displayed in Fig. 2. In the studies from 2015 (n = 4) [44–47], PRO focuses on improving the dialogue between patients and clinicians whereas in 2021 PRO is extended to be used in five different ways (n = 2) [49,53]. Examples of this are self-management advice to patients or alerts to clinicians based on the severity of the patient-reported information.

4. Discussion

In this mini-review, we identify 19 Danish scientific reports describing PRO studies. These studies actively employed PROs for cancer patients undergoing antineoplastic treatment to improve symptom monitoring, HRQoL, patient management, and patient satisfaction. One of the study protocols [47] describes a study on which results are later reported [48]; one study is a sub-analysis of another primary outcome report [43]. Apart from one study, all studies use software systems (ePROs) for their questionnaires, generally based on validated preexisting questionnaires or item libraries. The patients' perspectives on ePRO during cancer therapy seem limited to four studies reporting patient involvement and six using PREM to describe the patient-s´experiences with ePRO. However, more recent studies might have more focus on this. Concerning healthcare professionals, a somewhat disappointing result appears across studies, with only 35–63% of PRO questionnaires being reviewed by clinicians. Newer studies seem to have more focus on the health care professionals' and patients' perspectives

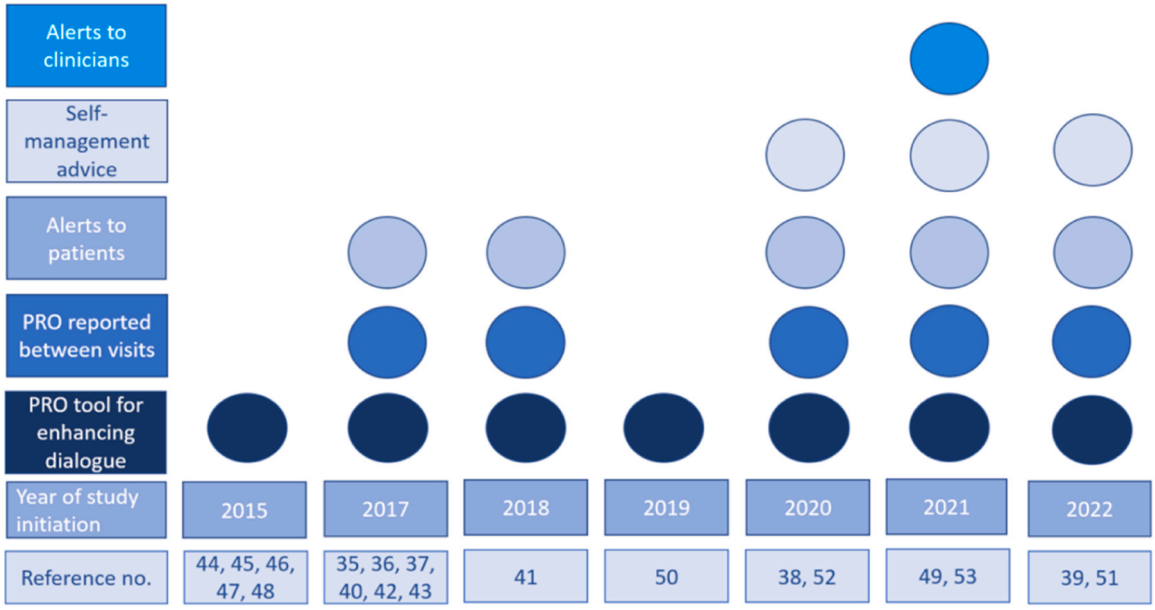

Fig. 2. Change in ways of incorporating PRO across time for 19 scientific reports included in this review (references 47 and 48 represent the same study, where reference 47 is the protocol article and reference 48 includes the results).

working with alerts to clinicians and self-management advice to patients in between visits. Comparable findings of patients' compliance with ePRO reporting during cancer treatment have been observed elsewhere [2,14,23] (U.S., France, UK). In a randomized trial assessing electronic symptom reporting during treatment with chemotherapy in patients with colorectal, breast, or gynecological cancer, average adherence to weekly reporting of 64.6% was observed. Compared to the previously mentioned Danish studies, relatively high clinician compliance was observed, with 81.4% of reports being reviewed by a clinician while 59.9% of expected clinician feedback forms were completed [23]. Further, clinicians' use of information from the patient reporting as a dialogue tool was positively associated with patient outcomes.

As in several Danish studies [38,39,44,46,49–52], Mody et al. examined patients' experience using ePRO [55]. They received positive feedback from patients with lung cancer in treatment with chemotherapy, with 87% stating they would recommend the system to other patients. About two-thirds of the participants experienced that the PRO data improved discussion with the clinician and that the clinician used the information [55].

Previous studies showing the effect of PROs on the chosen endpoints have applied different elements of PRO interventions used actively during the patients' course of treatment [23,56,57]. Mooney et al. showed how every unique component of PRO interventions has an impact on symptom relief and that fewer interventional components result in less benefit for the patient in terms of symptom relief [56]. These findings suggest that single-component PRO interventions may be less effective and that it is recommendable that PRO interventions include sufficient components and that matching resources are allocated. The diversity of PRO interventions may to some degree be a reflection of the resources and logistical setup in different hospital systems. These differences may be a determining factor in how efficiently PROs are implemented as part of routine care [58,59]. Foster et al. [60] emphasized that organizations need to invest time and resources to train and involve clinicians in the design process addressing potential problems before the clinical implementation of PROs.

Our mini-review demonstrates the importance of PRO questionnaires being reviewed by a healthcare professional on patient compliance. Accordingly, we suggest consolidating this as a workflow in routine care with the integration of PRO data into the electronic health record (EHR). Healthcare systems should integrate PROs into routine care, as there seems to be a high impact of using PROs in the EHRs, particularly for outpatient monitoring of symptoms [61]. This integration brings different sources of patient information together which may improve symptom management for patients, patient-centered care, shared decision-making, and self-management [62]. Girgis et al. also stress the importance of integrating ePRO systems into future models of routine care to the benefit of healthcare systems as well as patients, for example by automated alerts within existing workflow [6]. However, the integration of PRO data into EHRs can be challenging [63], and barriers to the integration and workflow around the implementation of PROs in existing EHRs can potentially affect the effectiveness of implementation [63,64]. Most importantly, the integration of PRO has to be supported by IT specialists and driven by the management of the health system [65]. Challenges in implementation may be a lack of resources, user-friendly EHRs for PRO integration, and time to manage PROs in the clinic [66]. Despite this, several studies find that the integration of PRO-based symptom management in EHRs has many advantages such as consolidation of workflows [61,67,68]. The implementation of PRO-data into EHRs can be guided by either the companion guide to the ISOQOL User's Guide on implementing patient-reported outcome measures in clinical practice [69] or Best Practices User Guide for Patient-Centered Outcomes Research Teams Engaging Online [70]. This mini-review gives an overview of how ePRO solutions are tested in oncological research protocols in Denmark and welcomed by patients and clinicians. At present, ePRO solutions in a Danish setting seem well suited for self-management offering advice to patients based on scientifically developed algorithms. However, if more impact is warranted, healthcare professionals need to be engaged in reviewing PROs and using them in clinical care. Moreover, for successful implementation, the integration of PRO in EHRs must be supported by IT specialists and driven by the management of the health system.

CRediT authorship contribution statement

Lærke K. Tolstrup: Conceptualization, Project administration, Methodology, Literature search, Analysis, Writing - Original Draft, Writing - review and editing. **Helle Pappot**: Conceptualization, Project administration, Methodology, Literature search, Analysis, Writing - Original Draft, Writing - review and editing. **Gry Assam Taarnhøj**: Methodology, Analysis, Writing - Original Draft, Writing - review and

editing. **Line Bentsen:** Methodology, Analysis, Writing - Original Draft, Writing - review and editing. **Rasmus Blechingberg Friis:** Methodology, Analysis, Writing - Original Draft, Writing - review and editing. **Christina Bæksted:** Methodology, Analysis, Writing - Original Draft, Writing - review and editing. **Mille Guldager Christiansen:** Methodology, Analysis, Writing - Original Draft, Writing - review and editing. **Cecilie Holländer-Mieritz:** Methodology, Analysis, Writing - Original Draft, Writing - review and editing. **Pia Krause Møller**: Methodology, Analysis, Writing - Original Draft, Writing - review and editing. **Ida Marie Lind Rasmussen**: Methodology, Analysis, Writing - Original Draft, Writing - review and editing. **Trine Lund-Jacobsen:** Methodology, Analysis, Writing - Original Draft, Writing - review and editing. **Dag Rune Stormoen:** Methodology, Analysis, Writing - Original Draft, Writing - review and editing.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.csbj.2023.11.054.

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