Digital Follow-Up and the Perspective of Patient-Centered Care in Oncology: What's the PROblem?

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Keywords

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Abstract

There is accumulating evidence from randomized trials suggesting that digital patient-centered care allows a more reliable detection of tumour-related symptoms and adverse events – with a direct impact on overall survival. Consequently, a variety of unsynchronized approaches were kicked off to (electronically) measure patient-reported outcomes (PROs). Despite increasing evidence that PRO data are highly relevant for patient care, the data generated in these initial projects lack standardized processing pathways in order to impact clinical routine; therefore, potential future routine PRO assessments require adequate analysis, storage and processing to allow a robust, reproducible and reliable incorporation into routine clinical decision-making. Here, we discuss relevant challenges of digital follow-up that need to be tackled to render PRO data as relevant to physicians as laboratory or biomarker data.

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Introduction

One of oncology's great challenges is finding ways to cure both the disease and the patient. The great advances of molecular medicine carry the exciting promise to cure cancer but also the duty of listening more carefully to patients' needs and wishes and re-thinking strategies whenever side effects outweigh (often marginal) survival benefits.

A key challenge will be the ability to dedicate time to patients while facing narrowing budgets, shortage of medical resources and personnel, increasing costs of advanced drugs and the demographic changes [1]. The use of modern communication systems might hold the potential for improved access, enhanced quality and delivery of healthcare services, better distribution to patients (Table 1) and at the same time a dramatic reduction of healthcare costs [2].

For instance, an app-based monitoring system may effectively support general practitioners in rural areas, where a shortage in healthcare distribution is not only

Table 1. Comparison of PRO follow-up modalities

	Paper-based PRO	Web/App-based PRO
Frequency	Every 2–3 months	Ad libitum
Environment	Hospital/outpatient unit	Ad libitum
Device	None needed	Smart phone/tablet
Internet access	Not required	Required
Person answering questionnaire	Patient (ensured by care provider)	Anyone with password/access to device
Analysis	Delayed	Immediate
Time to response-to-problem	Very long	Short
Data storage	Local (binder)	Local (hard drive), mobile (USB) or global (cloud)
Responsible for data protection	Care team/hospital	Patient, provider of app and care team/hospital
Processing pathways	Healthcare providers	Healthcare providers/automatic algorithms

widespread in developing countries, but also in developed countries in Europe [3]. In addition to this, recent prospective trials indicated that telemedicine can help to detect critical symptoms and red flags more reliably than routine clinical care, thereby even causing impressive survival benefits that by far exceed those provided by many novel drugs [4].

There are various possibilities to implement telemedicine into clinical care and the rapid progression in technology has enabled medical staff to utilize a broad spectrum of communication tools [4–8]. It appears to be easier than ever to measure how a patient feels or functions – or, in short, to measure patient-reported outcomes (PROs). PROs have not only taken a prominent role in routine care, but they also gain importance in clinical trials where they are routinely measured as secondary outcomes [9–11].

Historically, a patient's well-being and function was assessed by a physician in an in- or outpatient environment, and reported symptoms were interpreted to fit the standardized assessment tools. Today, patients are given the possibility to report on all aspects of their health status without any external interpretation in a homely atmosphere; therefore PROs are to date considered a gold-standard regarding assessment of health-related quality of life (HRQL) and symptom monitoring, as they indicate the benefit that a patient subjectively perceives from any treatment [12].

In 2009, the FDA released guidance for the use of PROs to support labelling claims, stating that PROs should be included in trials that aim to assess properties that are best to be evaluated by the patient himself. In this context, the FDA defined PRO as “measurement based on a report that comes directly from the patient about the status of a patient's health condition without amendment

or interpretation of the patient's response by a clinician or anyone else” [13]. This may lead to problems in terminology, as not all PRO measures assess data depending on the patient's subjective impression of their health condition. PROs such as treatment adherence and satisfaction with care are both important outcomes used to evaluate quality healthcare, yet they do not directly assess “health-relevant” data. The choice of a definition leads to different ways of assessing measurement properties [14]. To address this problem, it was suggested that PROs may be further sub-divided into health-related PROs and other PROs (such as treatment compliance/adherence and satisfaction with care). In this context, health-related PROs can be seen as an umbrella term including the concept of HRQL, which is assessed by PRO instruments that were specifically designed to capture this multidimensional construct with high validity and reliability [15, 16].

HRQL is a multidimensional concept describing patients' subjective perception of the impact of their disease and its treatment(s) on their daily life, physical, psychological and social functioning and well-being [13]. Hence, the influence of different symptoms on a patient's psychological and physical well-being can be evaluated, and the treating physician can lay more emphasis on alleviating particular symptoms that have been reported to be most stressful for this individual patient [17, 18]. HRQL has even been shown to be a more reliable prognostic marker for survival than the performance status [19–21]. It may also decide about a preferred treatment strategy if 2 available treatments that are almost indistinguishable in cost and efficacy exhibit a significantly different impact on a patient's subjective well-being [22]. Instruments such as the EORTC-QLQ-30 questionnaire can measure HRQL by asking single-item questions, which are then combined into health domains; the evaluation of these

particular domains then leads to the overall status of the patient's HRQL.

As many HRQL tools also assess symptoms, adverse event monitoring (AEM) is frequently mistaken as a sub-form of HRQL. Yet, while HRQL tools are usually employed to evaluate efficacy or the overall clinical benefit of an individual treatment, AEM reporting specifically aims to counteract treatment-related toxicities [12]. Therefore, HRQL monitoring remains purely observational, whereas AEM triggers interventions, depending on the severity of the reported symptoms. This implies that AEM may have direct impact on the clinical course of a patient. Two recent clinical trials have impressively shown that AEM has a direct and tremendous influence on patient survival [4, 8]. In both studies, researchers used a web-based weekly symptomatic adverse-event monitoring, based on either NCI-PRO-CTCAE or self-developed symptom grading, generating automated alerts if the measured symptom burden surpassed a pre-defined threshold [12, 23]. Both PRO-based AEMs detected symptoms much earlier (and more reliably) than routine care. In the reported trial, the e-FAP tool was able to detect relapsing lung cancer patients on average 5 weeks earlier than standard imaging-based follow-up, thereby enabling earlier interventions at a commonly much better performance status and, in consequence, much more frequent salvage therapies [4, 23]. Moreover, “red flags” (i.e., classical life-threatening complications such as pneumonia or pulmonary embolism) were detected earlier in patients with access to AEM tools. With a median gain of 7 months in overall survival (19.0 months with e-FAP vs. 12.0 with standard care), PRO-based AEM appears to be considerably more beneficial for patients that any recently approved novel drug or other treatment strategy for lung cancer.

However, despite the reported improvements in patient outcomes through PRO evaluation, there are several pitfalls and challenges both for patients and health care providers that need to be taken into consideration.

What's the Problem?

Tackling the Great Unknown: Capability versus Willingness

The compliance of both patients and health care providers remains a key issue to be resolved before PROs can be assessed in the routine clinical context. A survey among 108 oncologists and nurses reported that more than 80% of health care providers deemed app-based PRO reporting as useful as part of complimentary oncological surveillance

[24]. Patients seemed slightly more reluctant to share their medical data with between half and two thirds of patients willing to report PROs online [25, 26]. Only few clinical factors seem to influence the willingness of patients to use mobile device-based PRO reporting, including a younger age and a reduced performance status while gender, tumour stage, histology and type of treatment did not have any significant effects [26]. Early feasibility studies confirmed overall compliance levels of around 50% in cancer patients using mobile PRO reporting, although adolescents and patients from countries with an advanced technological infrastructure have been found to exhibit higher rates of up to 80% [27–29]. Additional trials are currently underway to assess compliance rates for specific oncologic patient cohorts and additional feasibility issues such as time consumption, completion rates of PRO instruments and cost-benefit analyses [30, 31]. However, several patient-specific characteristics that may influence the willingness for mobile PRO reporting such as the familiarity with mobile devices will require further investigations, and the long-term compliance rates regarding the often protracted course of oncologic diseases remain to be elucidated.

Beyond patient compliance, patient ability to access and use mobile technology may also pose a major challenge for mobile PRO reporting. The availability of mobile devices among cancer patients has been reported to range between 70 and 80% [25, 26]; however, this patient cohort contains a considerable percentage of elderly patients that may not have access to mobile technology. In order to accommodate these patients, web-based platforms and the recruitment of family members and relatives for the collection and reporting of PROs have been used as alternative means in prospective trials [4, 8]. Nevertheless, differences between web/computer-based and mobile device-based reporting strategies remain to be tested regarding both compliance and accessibility. Additionally, further analyses are needed to clearly differentiate between compliance issues and ability/access issues in cases of underreported PROs in order to determine optimized strategies for collecting disease- and treatment-related PRO data from cancer patients.

Where Is the Line between Normo- and Hyperreporting?

With the first trials reporting dramatic improvements in overall survival by a more personalized, patient-centered follow-up (specifically AEM), physicians and other health care providers have been repeatedly accused of providing an insufficient standard of care with a high risk of *underdetecting* critical symptoms. The opposite posi-

Table 2. Selection of recent initiatives on measuring PRO

Area of interest/PRO instrument	Purpose	Reference
COSMIN <i>Consensus-based standards for the selection of health measurement instruments</i>	This initiative provides a checklist for clinicians that have only little expertise with regard to PRO measures Checklists are proposed depending on what should be measured in which circumstance/disease	[14]
SPIRIT-PRO <i>Standard protocol items: recommendations for interventional trials in patient reported outcomes</i>	SPIRIT-PRO represents a first attempt trying to summarize existing PRO-specific-protocol-guidelines, creating easier access and working towards a more consensus-based guidance	[39]
CONSORT-PRO <i>Consolidated standards of reporting trials in patient-reported outcomes</i>	CONSORT was established to enable transparent and complete reporting of clinical trials The PRO extension was introduced by a task force of the International Society for Quality of Life Research (ISOQOL) to give recommendations on how PRO-related findings should be reported	[40, 41]
SISAQOL <i>Setting international standards in analyzing patient-reported outcomes and quality of life endpoints data</i>	This EORTC-led multidisciplinary consortium specifically aims to establish standards for definition, analysis and interpretation of HRQL endpoints in RCTs	[10]
PROMIS <i>Patient-reported outcomes measurement information system</i>	As a part of the National Institutes of Health Roadmap Initiative, this network aims to improve appreciably how PROs are selected and assessed in clinical research, including clinical trials	[42]

tion would be to assume *underreporting*, meaning that patients for whatever reason do not report the full spectrum or the adequate intensity of signs and symptoms that occurred between the FU intervals, for example, due to the inability to remember, pre-defined short time slots for clinic visits or other reasons. Both increased usage of computers, tablets and smartphones and novel digital PRO monitoring carry the promise to tackle both issues: in 2015, roughly 65% of the American adult population owned a smartphone or other mobile devices, with an approximate annual increase of 5–6%/year. Capturing PROs with a patient's own electronic device ("bring your own device" strategy) may not only diminish the risk of data entry errors but also serve to increase patient compliance, resulting in more comprehensive PRO reports [32].

Although bring-your-own-device strategies may bear greater possibilities for patients to report and physicians to detect critical signs and symptoms, the mere number of reports each patient may cumulate in different clinics and hospitals will challenge healthcare providers. PROs are entirely subjective, and the absence of any validation tool for each report may prompt physicians to define individual thresholds for interacting with a specific patient, with the evident risk of misunderstanding reports especially for patients they have never met in person. This in turn may result in ignoring the daily PRO reports as some form of

medical "spam." Therefore, it will be of huge importance to introduce validation tools such as point-of-care sensor systems to collect correlate markers parallel to PRO reports. Examples may include "wearable" motion sensors to objectify mobility, or temperature probes and gyroscopes to identify fevers and seizures (reviewed in [33]).

Challenges of Data Collection, Storage and Analysis

The market for mobile applications in the healthcare sector has grown strongly in recent years, especially in the United States, but this development is also becoming more and more visible in Europe; to date, almost all major software manufacturers in the healthcare market offer mobile solutions.

The range of applications is diverse and covers almost all conceivable scenarios (e.g., collecting vital data, exchange of administrative information, answering specific patient questions or support for dedicated clinical trials). In particular, survey portals are available on a large scale, which so far have their main focus outside the healthcare market but are increasingly used for clinical applications.

In addition to direct integration into the respective hospital information systems, several online platforms have been developed that allow direct interaction with other patients or practitioners, for example, for the management of blood glucose levels or pain management [34].

In the field of oncology, mobile PRO data reporting systems “Cancer Care” (Kaiku Health, Helsinki, Finland), Careonline (Oncare, Munich, Germany) or CompanionRT (OPASCA, Mannheim, Germany) have been clinically evaluated [11, 30, 35]. To date, all available systems lack common standards; hence, the cross-platform exploitation of data and the integration of these mobile solutions into higher-level systems, for example, hospital or oncology information systems remain challenging.

With the shift from paper-based instruments to electronic data collection, the considerable efforts associated with providing safe and fast data storage, handling and analysis tools are a major reason why institutions are still reluctant to acquire PROs in routine practice. Although a body of evidence supports equivalence between electronic and paper-based PRO measures and, for some instances (such as the EORTC questionnaires), clear recommendations are at hand how to migrate from paper to electronic formats (available online at <http://www.eortc.org/app/uploads/sites/2/2018/03/ePRO-guidelines.pdf>), PROs were evidently not regarded to be similarly important as laboratory values or medication data, and thus efforts to digitalize PRO were limited to clinical trials where questionnaires were either manually transferred or scanned into parallel databases [36]. Since recent studies showed that PROs (specifically AEM) may trigger interventions that provide better symptom control and improved survival rates, they will have to be considered highly relevant data.

Yet, similar to processing raw laboratory data, PRO data analysis (potentially complemented by sensor information, see above), novel tools need to be designed to provide a numeric or visual output that will allow physicians to detect medical abnormalities and to justify subsequent intervention. As reported above, Denis et al. [4] have used an unspecified dynamic analysis algorithm to trigger alerts, pointing towards a novel possibility of efficient PRO data analysis in their prospective randomized trial. Future PRO analysis will need to incorporate methods derived from computerized clinical decision-support systems, which resemble electronic toolboxes that match individual patient information and data with knowledge bases or repositories [37, 38].

Lack of Standardization

Patient-centered care with mobile devices could not only improve provider-to-patient but also provider-to-provider communication, making referrals and interdisciplinary care coordination simpler and more cost efficient. However, a prerequisite for this would be a somewhat standardized or comparable data collection and

analysis system [10]. Mostly with the aim to standardize PROs in clinical trials, there have been initiatives and groups that generated a plethora of suggestions on which PROs and how PROs should be collected. Depending on the settings that PROs are planned to be used in, one may consider corresponding initiatives specifically designed to fit the purpose (Table 2). Hence, a variety of initiatives on *why*, *how*, *where* and *which* PROs should be measured have been proposed. Nevertheless, the list is evidently not exhaustive, and several initiatives have considerable overlaps. Therefore, it remains unclear as to which of those will take the lead and define a potential future common standard. It seems conceivable that with the inclusion of mobile devices and the establishment of apps into PRO measurements, the patients will have the final say for or against a specific method.

Conclusion

Telemedicine might help to tackle several challenges of modern cancer care, such as more reliable and earlier detection of critical symptoms, and it carries the promise to improve survival. Specifically the use of patient-owned mobile devices to collect PRO data is promising, as it may help to establish a more patient-centered healthcare. Nevertheless, large amounts of data need to be harnessed, which implies that PROs are not only complemented/validated with sensor data but also adequately analyzed and reported to allow their incorporation into clinical decision-making. However, as multiple independent activities and initiatives are launched, PROs are still collected in a generally uncoordinated fashion. A major challenge along the way to consider PRO data similarly relevant as laboratory data will be the use of a common terminology and common standards in assessing and analyzing PROs. After solving these challenges, it is conceivable that PRO data will make their way not only into oncological clinical trial protocols but eventually also into the clinical routine.

Disclosure Statement

F.A.G. is consultant and speaker for Carl Zeiss Meditec AG, NOXXON Pharma AG, MSD Sharp and Dohme, Roche Pharma AG, ONCARE GmbH and holds patents related to Carl Zeiss Meditec AG. F.W. is an advisor, consultant and/or speaker for Celgene GmbH, Roche Pharma AG, Eli Lilly and Company, Ipsen Pharma GmbH, receives travel and research grants from Carl Zeiss Meditec AG and Elekta AB, is on the Carl Zeiss Meditec AG speaker's bureau, holds patents related with Carl Zeiss Meditec AG.

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