Managing Immune-related Adverse Effects

of Immune Checkpoint Inhibitors through ePROs

Executive summary

Immune checkpoint inhibitor (ICI) therapies have radically transformed the treatment of certain advanced cancers. While ICIs result in remarkable efficacy in some patients, they have also introduced an assortment of new and unpredictable toxicities known as immune-related adverse effects (irAEs).

These toxicities can affect almost any organ in the body and they vary in frequency and severity, making them challenging for healthcare professionals (HCPs) to predict and manage. Because irAEs have a highly disparate profile, empowering patients to self-monitor and self-report their symptoms could improve treatment safety and overall patient quality of life.

Electronic patient reported outcomes (ePROs) are a practical tool for oncology care. They consist of health-related questionnaires completed by the patients themselves and can capture symptoms and overall well-being on any given day.

As value-based care reimbursement models mature, ePROs can give pharma companies a competitive edge as companies are able to assess their therapies in a real-word setting, and optimize their products from a place of deeper consumer understanding.

Your companion guide

This deep dive focuses on the value of ePROs in managing irAEs and the impact this has on patient well-being and outcomes. It also considers the value and potential of the real-world data collected within the context of patients' environments, and how this longitudinal view of patient well-being and treatment progression gives pharma companies a competitive advantage within the market.

Consider this a companion guide for the possibility of ePROs, and the way in which their clinical integration can optimize the management of the wide range of irAEs associated with ICI therapies.

Immune-related adverse effects

Immune checkpoint inhibitors (ICIs) are profoundly revolutionizing the field of oncology. In 2011, when the first ICI (CTLA-4) was authorized by the FDA, the stage was set for a transformational shift in treatment possibilities for cancer patients. With eight checkpoint inhibitors now approved by the FDA, and more than 3,000 active clinical trials evaluating T cell modulators[1] underway, it's safe to say that innovation is at the core of cancer therapy.

Immunotherapy relies on the activation of a body's immune system to destroy the cancer cells, but this ICI action mechanism can lead to off-target effects resulting in immune-related inflammation in any organ of the body, regardless of where the tumor is located. These atypical responses, referred to as immune-related adverse effects (irAEs), can look like autoimmune diseases and they can be severe, especially when anti-CTLA and anti-PD1 are used in combination.[2]

Clinical management of irAEs is uniquely challenging as they are random and vary considerably between patients, cancer types, and treatment plans.[5] As an example, colitis occurs more frequently in CTLA-4 treated patients while thyroid disorders are more frequently seen during PD-1 therapy.[6]

This varied clinical presentation makes it difficult to distinguish from alternative diagnoses such as infection or tumor progression, often leading to a delay in diagnosis and treatment. Because early detection of irAEs can improve patient outcomes and overall chances of survival, there is an urgent need for careful and regular patient monitoring.

Unsurprisingly, this new spectrum of side effects is radically different from those associated with previous cancer treatments, cytotoxic, or targeted therapies. Chemotherapy-related toxicities are more predictable than irAEs and are often dependent on organ reserve and cumulative dose, so preventative measures and pre-treatment assessments of target organ function can be implemented to assuage specific toxicities.[7]

Severe irAEs occur in (apprx.)

10—27%
of CTLA-4 treated patients.

7—20%
of PD-1 treated patients.

55%
of patients receiving combined CTLA-4 and PD-1 treatments.[3]

The frequency of irAEs can, amongst other things, depend on the ICI treatment, with any irAE occurring in:

57—85%
of PD-1 treated patients.

60—85%
of CTLA-4 treated patients.

95%
of patients receiving combined CTLA-4 and PD-1 therapies.[4]

Hope and the need for remote patient monitoring

ICIs have given cancer patients substantial hope for a cure. This is especially true for about

20% of melanoma patients

who achieve a complete response and have a less than 10% risk of relapse after six months of ICI treatment.[8]

But in many ways, ICIs are a victim of their own success, as they have emerged as an appealing route for cancer patients, when in fact, at the time of writing, the majority of cancer patients do not respond to this form of treatment.

This uncertainty of outcomes coupled with the inherent risk and unpredictability of irAEs during and after treatment has given rise to the need for long-term, personalized supervision of patients' symptoms.

In the absence of clinically-validated biomarkers enabling individualized assessments of the risks of irAEs, remote patient monitoring and management via ePROs has emerged as a strong contender for HCPs to track patient well-being as well as recognize and respond to worsening symptoms in real time.[9]

What are ePROs?

The value of ePROs in managing irAEs

ePROs come directly from the patient and include information on the status of their health and well-being. They are a standardized and often clinically-validated tool, and are usually in the form of an electronic questionnaire delivered via an app or webpage.

When compared to paper-administered PROs which patients would typically answer in a clinical setting on an ad hoc basis, ePROs integrated into a digital therapeutics solution like Sidekick are considered more efficient as patients and HCPs are able to identify and manage symptoms as they occur.

This is particularly relevant in immuno-oncology as ICIs are administered intravenously in an outpatient setting. With HCP visits often several weeks apart, serious adverse effects can develop in the interim. It is also arguable that the information patients provide is more accurate and detailed as they are able to respond to questions within the familiarity of their homes, and in real time, thus minimizing recall bias.[10]

Sidekick: ePRO best practices

Patients accessing the Sidekick digital therapeutics (DTx) platform via their smartphone through an app receive daily questionnaires as well as automated reminders which can help HCPs detect the serious side effects of the ICI therapy, while also helping to boost adherence and therapy completion rates. Typically, the questionnaire can be tailored to the cancer type and treatment plan by including questions relating to a physical function symptom (e.g. energy levels), a social function, or a mental health symptom.

If patients miss a scheduled self-report, a reminder prompt can be triggered automatically through the app or by the monitoring HCP. Equally, when a worsening or severe symptom is self-reported, an electronic alert is triggered to the care team to inform potential intervention. Self-care advice can be delivered instantly and automatically to the patient via the app.

Sidekick intends to conduct clinical studies in collaboration with a National Oncology Rehabilitation Centre and University Hospitals which will explore the benefits and potential of ePROs and remote patient monitoring in the early recognition and management of irAES during an ICI treatment journey.

No one is ever prepared to be diagnosed with cancer, but as oncologists we can help patients and their families prepare for their ICI treatment journey and any irAEs they may experience.

Remote patient monitoring and ePROs can support patients and give them comfort knowing that they are connected to their team at all times. I look forward to seeing Sidekick's clinical results in this space.

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PRO-CTCAE
(Common Terminology Criteria for Adverse Events)

ePROs add most value when they are specific to a patient's unique experience and ICI therapy, and allow for measurement of individual outcomes. The National Cancer Institute developed the Common Terminology Criteria for Adverse Events (PRO-CTCAE) as a standardized patient-centred method to help patients identify and capture symptoms and health-related issues throughout their treatment journey.

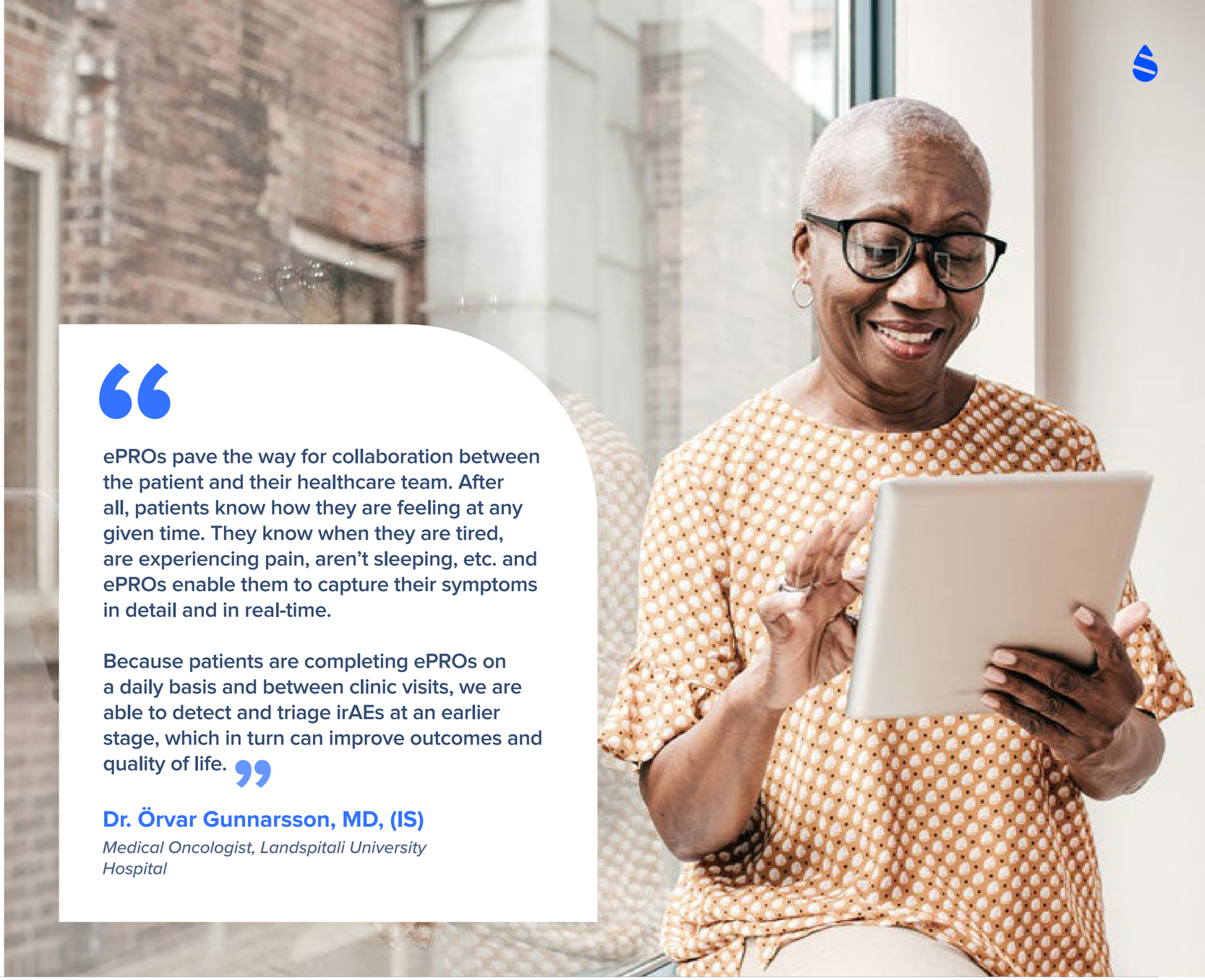
The development of the PRO-CTCAE is significant as a growing body of evidence[11] suggests that patients rank symptoms

up to 40% higher

compared with HCPs, and these discrepancies result in a substantial number of symptoms going undetected by the care team.

Science supporting ePROs

A recent study conducted at Memorial Sloan Kettering attempted to address the gap between patient-reported symptoms and HCP-reported symptoms. In this study, 766 cancer patients receiving chemotherapy for advanced solid tumors were randomly divided into two groups: each person in one group was given a tablet computer to remotely report twelve common symptoms, while the other group received the usual cancer care delivered by the hospital.



> ePROs pave the way for collaboration between the patient and their healthcare team. After all, patients know how they are feeling at any given time. They know when they are tired, are experiencing pain, aren't sleeping, etc. and ePROs enable them to capture their symptoms in detail and in real-time.
>
> Because patients are completing ePROs on a daily basis and between clinic visits, we are able to detect and triage irAEs at an earlier stage, which in turn can improve outcomes and quality of life.

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Patients with home computers received weekly email prompts to report between visits. Treating HCPs were given symptom printouts at visits, and nurses received email alerts when patients reported severe symptoms or a decline in well-being. At the end of the study, it was concluded that

34% of the group

that were self-reporting symptoms showed an improved health-related quality of life compared with 18% of the control group.

In addition, self-reporting patients were also less frequently admitted to the ER or hospitalized.

These findings were further endorsed by a multisite randomized trial in France. Studies like these underscore the importance of implementing a tool that enables patients to track symptoms in real-time, which in turn gives HCPs insight into symptom trends, disease progression, and patient engagement with the treatment plan.

> **Symptom management is a cornerstone of high-quality cancer care. There is a substantial discrepancy between what people experience and what we pick up and act on.[13]**

> **Patients possess a body of knowledge about themselves that we can never hope to master, and we have a body of knowledge about medicine that they can never hope to master. Our job is to bring these two groups together so we can serve each other well.[15]**

ePROs and the value proposition for pharma

The value of ePROs to pharma

Because ePROs are instruments used to assess a patient's individual symptoms, quality of life, and health status, the data that is generated from these interactions provides distinctive insight into all irAEs regardless of severity, and ultimately gives deeper insight into the underlying pathogenesis, kinetics of appearance, and clinical presentation of irAEs. This bigger picture understanding can support research and help pharma companies understand what works and what needs improvement, as well as identify where more investment is needed. By harnessing the power of real-world data gathered through ePROs, pharma companies can leverage the advanced analytics to enrich and more effectively personalize and target care.

Real-world data

ICIs are a powerful tool in the fight against melanoma and non-small cell lung cancer, and they are continuing to show promising responses across many different cancer subtypes.[16,17] As ICIs settle into an oncologist's treatment arsenal, we can expect them to be prescribed in a larger number in the future. As a consequence, more people will be exposed to ICIs and the number and type of irAEs will also dramatically increase. The frequency, spectrum, toxicity profile, and variations in time needed to resolve irAEs are challenging traditional understanding of adverse effects, and effective clinical management is not well-defined.[18]

It is for this reason that real-world data generated through ePROs is essential to develop a longitudinal view of disease patterns and trends, as well as possible symptoms and irAEs. This data could help pharma to learn more granular-level information on irAEs which in turn could inform the development of new biomarkers for predicting ICI efficacy and toxicity in patients, as well as identify and optimize ICI regimens and new combinations.

Increased collaboration and partnerships

Partnerships with DTx companies like Sidekick are a cost-effective approach for pharma companies to either incorporate or remain active in the ePRO space without the burden and expense of setting up the complex organizational structures and processes in-house. Sidekick offers pharma companies a solution that can facilitate improvements in patient experience, medication adherence, and overall disease management.

Conclusion

Cancer treatment has taken a huge leap forward with immunotherapies, but a lot of ground still needs to be covered to prepare for and effectively manage irAEs that complicate these otherwise transformative drugs. The toxicity spectrum of ICI therapies remains a major challenge in clinical care and is a barrier for developing even more active combinations.

Optimal management of irAEs relies on early recognition to limit the need for treatment interruptions, preserve quality of life, and avoid or minimize the risk of rare fatal outcomes. The symptom variety, incidence, and grading collected via ePROs could help manage symptoms and predict the presence and onset of irAEs with a high accuracy.

The real-world data collected throughout the treatment could in turn be used by pharma companies to better understand how the ICI therapy interacts with the disease, paving the way for further innovation.

Sidekick believes that a DTx solution offering 360-degree support for cancer patients will further augment improvements in cancer therapy. By empowering and motivating patients, and helping them to manage any irAEs that may occur during and after a therapy plan, pharma companies and Sidekick can make cancer care personal and more effective.

About Sidekick Health

Sidekick is built on a tech-enabled clinical platform that uses evidence-based behvaioral science principles to transform disease management globally, improving health outcomes and the use of healthcare resources.

The platform empowers patients and clinicians to better manage chronic diseases, improving patient symptoms and quality of life, managing underlying risk factors (preventing disease deterioration), and facilitating remote patient monitoring and treatment adherence.

Sidekick's digital care platform transforms disease management and remote patient monitoring by providing a bridge into the clinical setting while reducing the total cost of care and improving workflows.

If you would like to learn more about how we can help your company with digital therapeutics and digital therapy management solutions, please connect with us at **partners@sidekickhealth.com**

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Resources

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