A Review of Four Promising Digital Health Solutions in Oncology: Digital Therapeutics, Remote Monitoring, Clinical Decision Support and Wellness Applications

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ABSTRACT

Digital health (DH) is driving a paradigm shift in health care that is transforming the way in which health services are delivered and received. DH applications are creating significant opportunities for health care stakeholders to improve patient outcomes, reduce unnecessary costs, and create additional value. To reap the benefits, multiple organizations, including pharmaceutical companies, hospitals, public and private payers, patient advocacy groups, traditional technology companies, and health technology companies, among others, have sought to develop and incorporate DH tools. Although DH has great potential value in oncology, the adoption of DH solutions in this area has been relatively low compared with other disease areas, such as diabetes and cardiovascular disease. This report outlines definitions of four promising categories of DH solutions in oncology and presents in-depth analyses of the current state of each category of solution. By piecing together the fragmented oncology DH market, the key drivers of successful DH solutions are illuminated, along with the actions needed to more effectively realize their future impact and value within oncology.

INTRODUCTION

The size and revenue of the global digital health (DH) market are projected to increase from $84.08 billion in 2019 to $220.94 billion in 2026 at a 14.8% compound annual growth rate (CAGR) over the years 2021–2026.[1] Oncology is an area ripe for DH innovation and represents the fastest-growing area of health care spending in the United States.[2]

Despite advances in cancer treatment and growing survivorship, oncology remains a major public health concern globally.[3] The introduction of innovative therapeutics has transformed understanding of cancer pathways, improving outcomes for patients; however, there remain fundamental challenges that limit the efficiency and effectiveness of health care delivery, as well as new challenges introduced by new therapies. For example, self-administered oral formulations raise adherence challenges, long-term maintenance therapies heighten the risk for toxicities, new types of immunotherapies introduce novel adverse events (AEs), and strained health care systems can drive inefficient or insufficient follow-up.[4]

The opportunities for DH to address these challenges within oncology and create value for stakeholders are immense, but the goal of bringing these solutions to market in a scalable and sustainable way presents its own hurdles. In oncology, there is limited up-to-date literature providing comprehensive and robust insights on the current DH market and the key health care ecosystem dynamics that limit DH adoption. These are critical bottlenecks slowing down the speed at which technology-fueled patient care reaches the scale needed for significant impact.

The aim of this review is to illuminate a pathway through these barriers to DH implementation by offering a less fragmented picture of the oncology DH ecosystem. The first step to piecing together this fragmented landscape is outlining definitions of distinct categories of DH solutions and specifying the value and opportunities they offer across stakeholders. Case studies are also included to illustrate key success factors for the commercialization of DH within oncology.

Methodology

A mixed-methodology approach was adopted, comprising primary interview research with a variety of stakeholders across different countries and secondary desk research via PubMed and Google Scholar. For the RPM section of this report, 192 publications associated with oncology-specific RPM were identified through PubMed, Google and systemic reviews. Case reports (4), ongoing studies (5), thematic or systemic reviews (37) and publications considered not relevant (51) were left out of the analysis, leaving 95 papers on completed studies.

Defining DH and DH Solutions

The definition of DH varies globally, but the common consensus is that DH involves the use of digital technologies to facilitate health care via prevention, treatment, or management.[5-7] According to the U.S. Food and Drug Administration (FDA), if a medical device uses computing platforms, connectivity, software, or sensors to collect, store, process, or transmit health data to improve health care delivery or patient outcomes, it is considered DH.[6]

Our research suggests that DH solutions are best defined by four key parameters: (1) target user, (2) required clinical validation, (3) level of regulatory scrutiny, and (4) intended use-case. This review focuses on four distinct types of digital health solutions, each differing on these four parameters (Fig. 1).

Telehealth, enabling convenient virtual care, is another DH solution worthy of note, though it is not covered in this report because there are already extensive insights into its use and value. As of Q4 2020, many oncologists reported regular use of telehealth.[8] However, even with telehealth, health care providers (HCPs) struggle to objectively assess patient status while outside the clinic. The solutions evaluated in this report have the potential to address this area.

DH Solutions in Focus

Digital therapeutics

Working definition

A digital therapeutic (DTx) is a software as a medical device (SaMD) that delivers evidence-based therapeutic interventions to patients to prevent, manage, or treat a health condition. DTx solutions require rigorous clinical evidence of measurable therapeutic benefit and are reviewed and cleared by regulatory bodies that implement post-marketing requirements, distinguishing them from health and wellness applications.[9]

DTx solutions can be used to improve a health function, prevent a disease (e.g., by facilitating forward-looking lifestyle changes in patients before a disease develops), treat

a disease directly, or facilitate disease management (e.g., by collecting patient-reported data on symptoms or AEs).

Classification

A DTx can be categorized according to its relationship to pharmacological therapies and according to its intended use. At the time of this writing, several oncology DTx are in discovery and development by companies such as Kaiku Health, Blue Note Therapeutics, Voluntis, and Amalgam. Examples of different types and use-cases currently on the market are presented in Fig. 2.[4]

Stakeholder value

DTx have the potential to deliver distinct types of value to different stakeholders in oncology:

Patients: DTx solutions can improve outcomes for patients receiving pharmacological interventions. For example, a DTx can support patients with behavioral interventions or with symptom and AE monitoring that reduce the severity of complications from treatment or disease and thus decrease the need to permanently discontinue anticancer therapy. In oncology, DTx can also improve patient health-related quality of life (HRQoL), enhancing how patients manage and navigate the challenges of cancer with digitally enabled behavioral and psychosocial interventions.

HCP and health systems: DTx can improve efficiencies for health systems, extend clinicians' ability to care for patients beyond the clinic, and, with AE monitoring and

mitigation solutions, increase the confidence of health care providers (HCPs) to prescribe products.

Payers: DTx solutions can improve patient outcomes at a fraction of the cost of branded pharmacological interventions and may have the potential to be more cost-effective than pharmacological therapies because of this reduced cost.

Industry: Manufacturers can create DTx solutions to be used alongside existing products to improve outcomes for and differentiate their existing therapies. A DTx can also create a stand-alone, novel revenue stream; provide access to real-world data (RWD) for commercial and clinical insights; and elevate the public standing of a company. Furthermore, the DTx life cycle enables continuous iteration on therapeutic efficacy and adaptation to additional disease areas, with no decline in revenue or profitability when a patent expires.

Case study: Moovcare (Sivan Innovation)–a game changer for lung cancer follow-up

Unmet need: In standard lung cancer follow-up care, there can be lengthy gaps between oncologist appointments, leaving patients at risk of relapse, increased anxiety, and worse prognosis. The Moovcare Lung DTx—the first iteration of the Moovcare series—is indicated as a follow-up DTx for patients with a high risk of recurrence after lung cancer treatment.

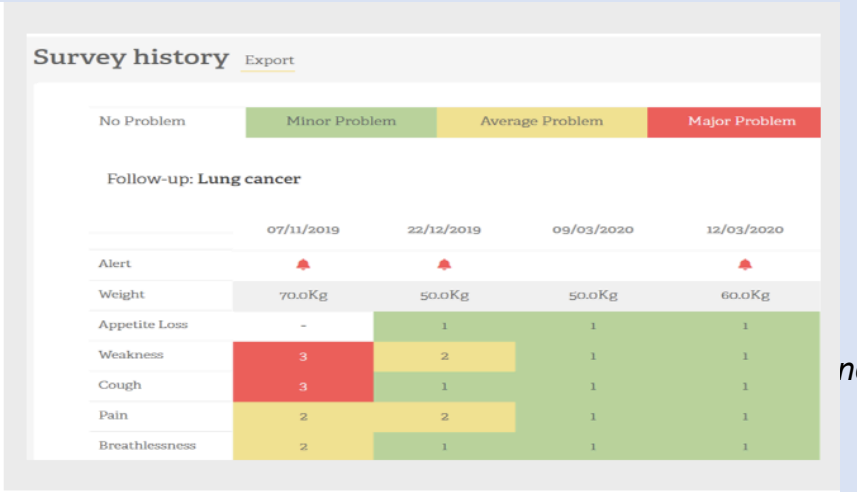
How it works: Moovcare enables patients to report their symptoms weekly with a simple survey. The algorithm analyzes symptoms, alerting HCPs to meaningful anomalies.[10] Moovcare has enabled earlier detection of relapses, resulting in treatment optimization, improved survival, and reduced anxiety, as demonstrated in randomized controlled trials (RCTs).[11-14] One study found the average annual cost of surveillance follow-up to be €362 lower per patient with Moovcare than in the control arm, and there was an incremental cost-effectiveness of €12,127 per life-year gained and €20,912 per quality-adjusted life-year gained.[13]

Sivan is a private prescription DTx company that developed Moovcare, the first digital platform for the early detection of disease recurrence. Their only marketed product at the time of writing this is Moovcare Lung.
In March 2020, Bristol-Myers Squibb (BMS) France agreed to support the promotion of Moovcare to all hospitals and HCPs treating lung cancer. BMS is mobilizing its field collaborators to present the solution to HCPs and hospitals throughout France. The pharma company cannot legally distribute the DTx, but if a hospital is interested, it will put them in contact with Sivan.[15]
The app is currently being used by 22 clinicians and 10 medical centers across France. Sivan intends to test the app in other cancers and make it available in other European countries, Israel, and the United States.

Select clinical trial results

Study	**Results**
Phase 3 trial of self-reported symptoms transmitted via Moovcare versus conventional follow-up in patients with high-risk lung cancer (NCT02361099)[16]	Median overall survival was 22.5 months in the Moovcare group and 14.9 months in the usual care group, demonstrating greater overall survival of 7.6 months with Moovcare.
Subsequent analysis of phase 3 RCT (NCT02361099)	Demonstrated earlier detection of relapses and reduced anxiety[10,17,18] The average annual cost of surveillance follow-up was €362 lower per patient with Moovcare than in the control group, and an incremental cost-effectiveness of €12,127 per life-year and €20,912 per quality-adjusted life year were gained.[13]
Two-armed, controlled feasibility trial[19]	On average, relapses were detectable 5 weeks earlier than with planned visits. Sixty percent of patients self-reported less anxiety during the days before planned visits and imaging with the tool than without. Sensitivity and specificity, and positive and negative predictive values, provided by the tool's follow-up were high: 100% for Moovcare (84% for

	routine imaging), 89% (96%), 81% (91 %), and 100% (93%), respectively, and were well correlated with relapse ($P\chi 2 < 0.001$).



Screensh ncer patient

Key shortcomings

Despite their promise, the use of DTx systems in clinical practice is limited for several key reasons, including limited market access and related legislation, limited clinical validation, health system unwillingness to use DTx solutions, and lack of HCP trust and awareness of DTx.

Challenge 1: Market access and related legislation

Countries lacking central reimbursement regulations for SaMDs have poorer market access than those with central reimbursement frameworks. Although the United States has a framework for clearance of SaMDs via the FDA, there is no reimbursement framework, and the Centers for Medicare and Medicaid Services (CMS) have yet to formally recognize and reimburse DTx products, limiting overall access. In the European Union and the United Kingdom, reimbursement varies widely;[20] Germany (DiGA),[21]

Belgium (mHealth Validation Pyramid),[22] and France (PECAN)[23] lead the way with national coverage frameworks for DH, which includes DTx.

Challenge 2: Health system and other stakeholder buy-in

Health systems and hospitals are key stakeholders for any DTx requiring HCPs to monitor patient status. Most health systems require a clear cost benefit to permit the use of new digital solutions. Research indicates that there is more willingness in US academic hospitals and EU hospitals, although cost savings remains the primary value driver.[24] In addition, HCPs and health systems have indicated that they are unwilling to use solutions that are not already part of their workflow, making electronic medical record (EMR) integration crucial for a DTx requiring HCP oversight. Another challenge is payer concerns, as the greatest barriers to DTx coverage are price; inadequate clinical validation and peer review, payment models, and workflow integration;[25] and lack of coding standards and education.[26]

Challenge 3: HCP awareness and trust

The medical community has limited awareness of DTx solutions, especially in oncology. Of the small number of HCPs who are aware of existing DTx approaches, many have limited or no awareness of their clinical value and utility.[27] This is likely due to a confusion of DTx with other types of digital solutions, leading HCPs to assume that DTx solutions lack clinical evidence. Even in countries with robust payer coverage, such as Germany, uptake remains limited despite high user engagement.[28] According to a 2022 DiGA report, only 4% of HCPs had prescribed a digital health application since Q4 2020.[28] Since most prescriptions came from the location where DTx companies are situated, HCP awareness is the likely barrier.

Increasing the success and value of DTx solutions

Increasing the success and value of DTx solutions in oncology necessitates overcoming these challenges (Fig. 3) and finding the right commercial environment to deliver value.[25,29-31] Critically, companies must enter the oncology DTx landscape with end-in-mind clinical and technical development. The clinical development strategy should be designed with the end goal in mind and be focused not only on technical success, but with commercial, regulatory, market access, and end-user objectives considered. Ultimately, success hinges on the same variables as traditional drug interventions, but additional investment and forethought are required to develop the commercial model and ensure that the requirements associated with digital products are met.

Finding the right commercial environment

Finding the right commercial environment for oncology DTx solutions requires careful consideration of certain key parameters, including whether a prescription is required, who pays for the DTx, type of billing and payment, payment structure (e.g., subscription, volume-based, time-based, one-time fee), promotional model (e.g., business-to-business, business-to-consumer, business-to-business-to-consumer), and value for the manufacturer in terms of direct revenue from sales or indirect revenue by impacting pharmacological sales, out-licensing, and access to data.

Multiple payment models are available for DTx solutions, including the payer paying via medical benefit, pharmacy benefit, or direct investment; the institution paying; the patient paying; and innovative payment models such as value-based health care contracts and risk-sharing agreements. However, to date, no dominant payment model

has emerged. Medical benefit coverage is optimal for DTx solutions requiring HCP data oversight, pharmacy benefit coverage when no HCP data oversight is required, and direct payer investment and institution coverage when chronic management is required and large payers and academic health systems are more willing to pay directly. It is common for patients to pay for a niche DTx that is not covered by insurance. Some companies pursue multiple payment models simultaneously.[32]

The future of DTx solutions

Despite the vast functionalities of oncology DTx approaches and the extensive number of potential-use cases, there is limited market saturation and therefore huge future opportunity. Opportunities can be found in cancer prevention and screening; response, relapse, and adherence monitoring; AE detection and management; pharmacological response modulation; and HRQoL support. Currently, there are no DTx approaches for the detection or management of AEs or for modulation of pharmacological response, two key areas requiring intervention.[33] Currently, broader pan-oncology solutions are more common than solutions for specific disease indications. A tumor-specific model is needed for a personalized approach to cancer care, as different types of cancer may require specific treatment and management approaches due to variations in tumor biology, therapy responses, and psychological factors.[10] For even greater personalization, a move away from solutions focusing on cancer type to individual patient–driven solutions, informed by patient-specific data, is warranted.[10]

Remote patient monitoring

Working definition

Remote patient monitoring (RPM) is a method of health care delivery in which tailor-made software (and sometimes hardware) is used to gather and analyze patient data outside of traditional health care settings for use by HCPs. RPM solutions do not require clinical validation and subsequent regulatory review, though in many cases these are pursued; according to our definition, when an RPM system is clinically validated in a confirmatory study and earns a regulatory clearance for a specific indication, it can be deemed an RPM-based DTx. This distinction can be useful in distinguishing RPM systems with high-quality clinical evidence from those with little or no evidence of benefit (Fig. 4).

Functionality and use-cases

RPM solutions can be used to collect numerous types of data (Fig. 5). Commonly, RPM systems use electronic patient-reported outcomes (ePROs) to collect information on general and cancer-specific health, self-care behaviors, AEs, and adherence to treatment. RPM systems may also integrate data from wearable devices and sensors. Some RPM solutions make use of “symptom thresholds” to alert care teams of potential issues and send automatically triaged codes to HCPs. The HCP interface includes the option to examine trends within and between patients.

Stakeholder value

The primary value of RPM is its ability to capture a greater depth and breadth of patient information that can facilitate more personalized patient management. Indeed, up to half of cancer patients’ symptoms go undetected by providers, and RPM offers an opportunity to bridge this gap and create value.[17]

Most research evaluating oncology-specific RPM has comprised observational or feasibility studies, but of 28 identified RCTs (from 2010 to Q2 2021), 25 demonstrated statistically significant benefits for patients, caregivers, and health systems. Although the seminal study by Basch et al.[34] showed improvements in overall survival, the most common benefit of RPM is reduced symptom-related distress,[18,35-40] which is potentially attributable to early detection and intervention, bidirectional communication between patients and HCPs, and improvements in adherence, AE management, and care continuity.

Additional benefits of RPM include cost savings via reduced use of health care resources[13,34,41,42] and increased workflow efficiencies that facilitate the delivery of value-based care.[13] For manufacturers, RPM can be used to support patient adherence to pharmacological treatment, helping to detect AEs earlier so that they can be managed sooner, before severity escalates and permanent treatment discontinuation is required. RPM can also provide manufacturers with unique access to RWD insights, generate stand-alone commercial revenue of its own, and be paired exclusively with a single therapy to further differentiate a product from other treatments.

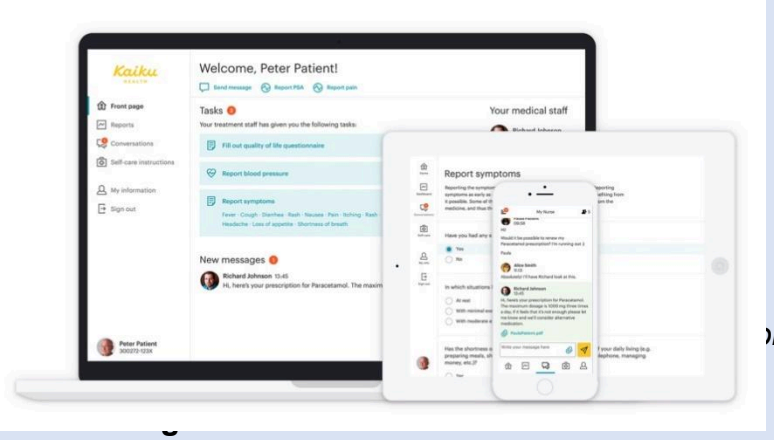
Case study: Kaiku Health—accelerating cancer care with a multi-partner ecosystem

Kaiku Health, acquired by Elekta in 2020, is a complementary digital platform that offers artificial intelligence– and machine learning (ML)–based RPM tailored to specific classes of anticancer therapies to facilitate disease management. It offers modules for more than 25 cancer types, covering various cancer care pathways. One key feature of the platform is its ability to integrate with EHRs, allowing HCPs to access patient data in real-time.[43]

Research has demonstrated that increased patient outcome data points enabled more precise monitoring, clearer lines of communication with care teams,[44] and customized HCP-patient interactions.[45] The technology was well incorporated into HCP clinical routines, enabling workflow optimization between physicians and nurses and saving time by reducing phone consultations and patient visits.[45]

Kaiku's commercial model is based on a multi-partner ecosystem comprising pharma and academic hospital partners. In 2019, the company joined forces with Amgen to roll out remote digital symptom tracking for multiple myeloma, which was developed in collaboration with the hematology unit of the Turku University Hospital in Finland.[46] By July 2020, Kaiku had entered a strategic long-term partnership with Roche to co-develop novel digital patient monitoring and management modules in oncology while also co-advocating for reimbursement.[47]

In 2021, Kaiku collaborated with Novartis to develop a therapy-specific module for patients with melanoma receiving dabrafenib (Tafinlar®) and trametinib (Mekinist®).[48] The success of the collaboration led to the expansion of their partnership in 2022 to provide better cancer care to a greater number of patients across multiple indications.



Screenshot … oring with Kaiku

Select studies

Study	Findings
ePROs and ML in predicting immune-related AEs of immune checkpoint inhibitor therapies (NCT3928938)[49]	The Kaiku immuno-oncology module showed an accuracy score of 0.97, area under the concentration-time curve (AUC) of 0.99, F1 score of 0.94, and Matthew correlation coefficient (MCC) of 0.92. Prediction of immune-related AE (irAE) onset was slightly lower—accuracy score = 0.96, AUC = 0.93, F1 score = 0.66, and MCC = 0.64—but the model performance was still at a good level, suggesting that ML-based

	prediction models can predict the presence and onset of irAEs with high accuracy.
Retrospective analysis to investigate whether symptom information collected by Kaiku Health ePRO tool from cancer patients receiving immune checkpoint inhibitors (ICI) lines up with that reported in clinical trials and whether coupling of specific symptoms occurs[50]	Reported symptoms and severity were similar to those found in ICI clinical trials. Symptoms showed strong positive correlations between itching and rash; nausea and vomiting, decreased appetite or stomach pain; and cough and shortness of breath, showing an alignment with clinical data on ICI therapy. Correlations occurred between symptoms, potentially reflect therapeutic efficacy, side effects, or tumor progression.

Key shortcomings

The RPM market structure in oncology is fragmented, and use and adoption of this technology in oncology lags behind those of other therapeutic areas, such as diabetes. Solutions are often tied to specific indications, regions, therapies, or health systems. The adoption of RPM is mostly limited to academic centers, and there is minimal to no use in community settings.[24] It may be that smaller health systems and hospitals lack the resources to invest in RPM systems, highlighting the need for RPM providers to develop alternative commercial and pricing models that can accommodate smaller treatment centers.[51]

The state of RPM technology in oncology is also relatively rudimentary, with limited solutions syncing to EMR. Laborious manual input from patients and interpretation from HCPs is often required, reducing the time-saving value of solutions and hindering user

engagement. Few solutions take advantage of digital sensors and wearables that have the potential to more seamlessly measure activity, temperature, vital signs, and treatment adherence. There is also a lack of autonomous data analysis and artificial intelligence (AI) or machine learning (ML) to enhance the interpretation and alerting capabilities of RPM in oncology.[24]

Increasing the success and value of RPM

Increasing the success and value of RPM in oncology necessitates offering stakeholder-specific value propositions, selecting the right partnerships and commercial environment to deliver value, and creating customer-specific rollout strategies. In addition, because RPM providers cannot sustainably subsidize their health systems' upkeep of solutions, it is important to have a clear understanding of country-level regulations regarding RPM reimbursement, as well as a commitment to seeking payer coverage.

Designing user-oriented RPM solutions

An immediate opportunity is to integrate existing advanced technologies to create more user-friendly RPM solutions. For patients, the opportunity is to streamline their experience with passive wearables and sensors that monitor a broader range of physiological characteristics to complement ePROs. For HCPs, the opportunity is to enhance workflows with ML-based analysis of raw data, allowing for more intelligent alerts or continuous monitoring around issues of interest (e.g., specific AEs). Automation of data monitoring has been highlighted as crucial given that HCPs do not want to review additional data that are non-critical.

RPM rollouts should seek to build stakeholder insights into design, commencing with small pilots that enable iteration on RPM designs. RPM providers should consider starting with solutions that have narrow areas of focus, rather than generalized systems across oncology, to improve the relevance and beneficial impact of solutions. One approach that has shown promise is the creation of RPM solutions dedicated to a specific drug class or AE.

Selecting the right partners

Future RPM developers will need to select the right partners to successfully commercialize oncology RPM. These partnerships could be with EMR companies that can embed RPM solutions directly into an existing health system infrastructure[52] or with commercial health technology companies (e.g., Navigating Cancer[51]) that already provide broad RPM systems to end users via single or multiple health systems. RPM can also be delivered to end users through single large payers or employer plans or with government payers (e.g., the National Health Service in England). Market geography will guide the best partnership model. In primary research, US and UK stakeholders identified working with EMR companies and health technology companies with existing RPM systems as the optimal partnership approaches.[24] In the UK, working with government bodies and payers could also be valuable. Some companies may require a mix of partners or different partners for different markets.

Selecting the right commercial model

Since different customers (i.e., those paying or reimbursing RPM providers) have different needs and internal approval processes, RPM providers must tailor their commercial models to meet the needs of their target customers. For example, the

choice between a subscription versus an outcomes-based payment model depends on whether the company is serving the community or catering to well-funded academic institutions.

To select the right commercial model, market research and other assessments are needed to inform the financial viability, scale of opportunity, and feasibility of different approaches. Feasibility parameters include barriers to initiating partnerships, the time and cost required to launch, and technical and operational impediments. Financial viability and opportunity parameters include scale of reach, potential end-user uptake, and overall financial return. Ultimately, there is no single best commercial model, because all come with risks and rewards. Key differences between geographies and the RPM provider's goals will dictate the ideal model. For example, in the United States, hospitals have autonomy to buy into solutions, whereas in the UK, buy-in is required from both the National Health Service (NHS) and local NHS trusts. Manufacturers may see the primary financial rationale of RPM as supporting product adherence and thus sales, whereas health technology companies may rely exclusively on RPM sales to generate a return on RPM systems.

Customer-specific value proposition

Successful uptake of RPM is dependent on health systems, EMR providers, payers, and/or government bodies agreeing to invest in and deliver RPM to their end users (patients and HCPs). To gain buy-in from these stakeholders, RPM providers must convey a value proposition that demonstrates positive or direct impact on their bottom line. Initial customers of RPM solutions (i.e., those who will pay for the solution) need to

see cost savings or efficiencies before they agree to invest in or reimburse solutions. It is crucial to generate evidence to validate efficacy and value to stakeholders.

The future of RPM

The global RPM market is expected to grow at a CAGR of 19.7% from 2021 to 2028 and to reach $4.1 billion by 2028.[53] Although the North American region had the greatest share of the RPM market in 2022, accounting for 41.45% of overall revenue, the Asia Pacific region is expected to witness the fastest growth by 2028, owing to opportunities in India and China. Primary research with US and UK stakeholders shows an anticipation that RPM will 'explode' in the near future.[24] For this explosion to add growing value, the RPM market needs to gain maturity within oncology. Areas offering huge potential moving forward include geriatric oncology vis-à-vis the use of RPM to monitor and predict treatment tolerance and all-cause mortality and to help in the assessment of older patients.[54,55] Although there is limited evidence on the feasibility and utility of RPM in geriatric oncology, it is an area requiring investment as the elderly population is expands and cancer patients live longer.

Patient health and wellness apps (non-DTx)

Working definition

Patient health and wellness apps are software programs for mobile devices that process or provide health-related data for users.[56] These programs are designed for patient use only and do not require rigorous clinical validation or regulatory review before being released to the public.

Functionality and use-cases

Patient health and wellness apps aid in self-management, enabling patients to monitor their symptoms, organize appointments and medications, keep a diary, and learn about cancer-specific or holistic well-being and lifestyle choices (Fig. 6).

Stakeholder value

The effective use of patient health and wellness apps can empower patients to be more autonomous in how they manage their general and cancer-specific health, supporting them to take control over those aspects of their health that they can positively influence. This autonomy can create patient-HCP partnerships and reduce burden on health services.[57]

Case study: Pfizer's LivingWith app

Pfizer launched the free LivingWith app in 2017 to help cancer patients better manage life with cancer and its associated daily challenges.[58] The app is designed to help patients remain up to date on their treatment and health status, maintain a dashboard of daily tasks and coordinate assistance from loved ones, manage and remember important information from doctor's visits, and track their health and well-being. Key features of the app include:

User roles: The app can be used by both patients and the people who are supporting them. The user interface can be customized according to the role selected, and patients can also assign a proxy to handle the app on their behalf. Based on the level of access provided to them, the proxy can update tasks, track medicines, and respond to messages on the app.[59]

Health tracking: Patients can track their health and well being on the app with the MyWellbeing feature, rating their fatigue, pain, mood, and sleep. There is also the option to sync steps and sleep data from wearables like Google Fit (for Android devices), a FitBit tracker, or Apple Health (for iOS devices). MyWellbeing can provide better insight into the patient's current health status and how it might change over time. The MyWellbeing Stats tab allows the patient to view and download a customized graph of each health challenge and share it as a report with their physician.

Resources and tools: The app includes a resource tab with articles and videos on topics like finance, diet, fitness, and relationships. In addition, there is a host of behavioral tools to support the patient's well-being, which are presented based on the rating provided for specific health challenges.

Medication manager: This feature allows patients to add details about their medication, including name, dose, and schedule, and to set up reminders. The tracking feature shows doses that have been logged, skipped, or missed.

After its release, the LivingWith app was evaluated in a 3-month RCT comprising patients receiving chemotherapy who were randomized to either usual care or to using the app weekly for 3 months. Patients in the intervention group reported 0.74 fewer medical office visits (P = 0.043) and 0.24 fewer visits with a mental health professional (P = 0.061) during the 3-month period. However, there were no significant changes between the two groups in terms of HRQoL or visits to emergency departments and urgent-care facilities. In the intervention group, 75.3% of participants reported using the app an average of 11.7 times over the 3-month period.[60]

Key shortcomings

Five key challenges currently limit the use and value of patient health and wellness apps in oncology:

Challenge 1: Usability

Ease of use. Cancer apps often lack intuitive designs, user instructions, and glossaries to help users understand cancer-related information.[57,61] In one study investigating the use of Pfizer's LivingWith app, non-use was due to lack of time and interest in apps and usability challenges.[60]

Limited interactive features. Despite collecting vast amounts of valuable patient data, oncology patient health and wellness apps do not integrate with HCP workflows and do not offer the ability to easily share data with clinical teams. This can hinder joint decision-making and discourage patient-HCP partnerships.[57]

Accessibility and digital literacy. Lack of access to the internet, low socioeconomic status, old age, and lack of familiarity with mobile devices can impact accessibility to cancer apps.[57,62,63]

Challenge 2: Insufficient regulation and evidence of app quality and value

Few apps are supported by robust scientific evidence. In one review of oncology apps, only 42% were reported in scientific literature, 1% were evaluated in a feasibility study, and none were studied in RCTs.[57] In addition, many oncology apps do not provide reliable sources for their content.[57,61]

Challenge 3: Lack of stakeholder involvement

App development has primarily been led by web developers, who often lack direct involvement in oncology research or clinical care. Without the input of subject matter experts, developers run the risk of creating content that is neither beneficial nor accurate. There is a need for more oncology experts to participate in the development and deployment of oncology-specific wellness apps.[64] Critically, oncology patients need to be involved in app development to drive relevance and usability.[65]

Challenge 4: Lack of awareness

Health and wellness apps may not be adopted and used to their full potential due to limited patient awareness and understanding of their value.[66] In a study comprising participants with skin cancer, 98.9% reported never using skin cancer–related apps or could not recall doing so. In 49.7% of cases, patients expressed uncertainty regarding the usefulness of such apps.[67]

Challenge 5: Lack of commercialization

Few oncology-related apps exist commercially.[57,64] Of 54 studies that used oncology mobile apps, as identified via meta-analysis,[68] only two could be matched to commercially available apps, suggesting a substantial divide between investigation and product dissemination.[64]

Increasing the success and value of patient health and wellness apps

In addition to addressing the preceding challenges, the success and value of these apps in oncology can be increased via the following:

Targeting patient preferences: Apps require patients to be proactive and must incorporate features and functionalities preferred by patients. This requires further research on the functionality preferences of current apps and patient input into the design of future apps.[65]

Personalization: To empower patients to be proactive in their health care, apps must incorporate features that offer personalized treatment support based on the patient's specific cancer type, stage, treatment plan, and personal symptoms or AEs.[69]

Education: Choice overload can lead to inaction, especially when accompanied by decision aids such as information on the quality of different choices.[70] Patients should be educated on how to select the best app for their needs. To this end, HCPs could be provided with access to a continuously updated list of recommended apps for different purposes and patient segments.

Partnerships: Pharmaceutical companies, app developers, and patient advocacy groups can collaborate to create oncology-specific solutions that bring the best of

each world to create more valued and engaging solutions. Partnerships with behavioral scientists are also critical because successful app use is driven by personal motivation, user-centered design, and other psychological and behavioral factors for which the industry may require outside expertise.[71]

Tackling the digital divide: Variations in DH literacy need to be addressed via targeted app design and implementation, the latter of which can be facilitated by input from those at risk of low DH literacy, such as older patients and those from a lower socioeconomic status.[72] Access to DH could be facilitated by reimbursement of DH technologies and expenses related to implementation and maintenance, ensuring that apps are available to non–English-speaking patients, and making apps available at community oncology centers.[73]

The future of patient health and wellness apps

A 2021 analysis identified 794 oncology-specific English-language mobile apps,[64] most of which were being used for self-management activities.[74] With smartphone ownership on the rise and increasingly empowered patients who want to play a proactive role in their health and health care, the use of patient-facing apps is likely to increase.[75] However, the category of siloed patient health and wellness apps, as it is defined today, is unlikely to be the optimal approach for driving value in the future. These solutions will most likely need to move toward integration into EHRs to enable easy data sharing with HCPs, pushing these solutions into the category of RPM. Without this integration, patient self-management and HCP care will remain siloed, hindering the streamlined and coordinated model of care that many health systems are moving toward.[57] For this

future vision to occur, app quality and usage will need to be improved and valued over quantity.

Clinical decision support systems

Working definition

Clinical decision support (CDS) systems are software-based tools that assist HCPs in making informed clinical decisions by providing relevant, up-to-date, and patient-specific information at the point of care. CDS solutions require validation in a confirmatory study (or multiple studies) and must be cleared by regulatory bodies before reaching the market.

Functionality and use-cases

The FDA define CDS as “a software function that provides healthcare professionals and patients with knowledge and person-specific information, intelligently filtered or presented at appropriate times, to enhance health and health care.”[76] CDS devices can also provide risk scores, probability assessments, and time-critical outputs but do not provide the basis for recommendations; rather, HCPs must be able to interpret the data and make their own, informed decisions.

Stakeholder value

CDS has the potential to improve patient care and outcomes by furnishing HCPs with the data they need to make the most informed clinical decisions,[77] which in turn can decrease medical errors.[78] This can further translate into fewer hospital readmissions, minimizing health care costs.[77] CDS can also boost efficiency by enabling swifter

decision-making and ensuring that HCPs have access to the latest medical research and guidelines.[79]

Key shortcomings

Because CDS systems rely on the accuracy of the data entered, there is a risk of errors, which could have serious consequences for patients.[77] Additionally, CDS might not consider all relevant factors for a particular patient or condition, further increasing this risk.[80] Another potential risk is the possibility of bias. CDS algorithms are based on historical data, which can contain biases that lead to inappropriate recommendations for certain patient populations.[81] Therefore, it is perhaps not surprising that clinician trust can be one of the greatest barriers to the use of CDS systems. Some clinicians even believe that CDS is a threat to their clinical judgment.[82,83] Confounding these shortcomings are negative impacts on existing workflows, CDS systems that cannot adapt to local needs,[82] and high costs for initial set-up, integration, and training.[77]

Increasing the success and value of CDS

Five key areas of consideration drive success in CDS:

1. **Strategic implementation:** CDS can be integrated into workflows via EMRs at the level of the multidisciplinary tumor board to support treatment decisions (e.g., surgery versus radiotherapy) and at the specialist level to support the choice of treatment technique (e.g., whether to use a prostate spacer).[84]
2. **Data standardization and interoperability:** Lack of standardized data, along with issues around federated data access, data representation, and data mining approaches, pose significant obstacles to the effectiveness of oncology CDS

systems. Consensus data standards need to be developed within oncology as a requirement across EHR vendors and to require the adoption of Fast Healthcare Interoperability Resource application programming interface from all certified EHR vendors. This would facilitate the exchange of information among different CDS systems, enhance data quality, and enable more accurate CDS systems.[85]

3. **Multi-stakeholder involvement:** Collaboration among clinicians, researchers, technologists, insurers, patients, and patient advocacy groups is vital to ensure that CDS systems address the diverse needs of the oncology community. Establishing multidisciplinary working groups and involving stakeholders in the development, evaluation, and refinement of CDS tools would contribute to more effective and user-friendly solutions.[84]
4. **Education and training:** Stakeholders need to be empowered to obtain optimal value from CDS. This can be achieved by continuous education and training on CDS interpretation, which will also build acceptance and trust in these systems by maximizing their value in oncology. Additionally, ongoing educational programs should be designed to keep clinicians abreast of evolving evidence-based guidelines to help them confidently accept, reject, or adjust CDS output.[84]
5. **Clinical validation:** To facilitate stakeholders' trust in CDS, developers should seek to confirm CDS solutions in RCTs, similar in scale to what is expected from pharmacological interventions, showing improvements not just in decision-making accuracy but also in patient outcomes and cost savings.

navify®

Case study: Navify for intelligent decision-making by multidisciplinary teams

Roche's Navify suite of DH solutions utilizes a range of advanced technologies and data analytics to bridge the gap between the vast amount of data available to HCPs and the need for quick, patient-centric decision-making.[86] The Navify portfolio, which improves workflow efficiency and aids precision oncology,[87] includes:

Navify Oncology Hub—a single view of patient data, including clinical, genomic, and imaging data, enabling clinicians to make more informed decisions about treatment and to collaborate more effectively with other HCPs.

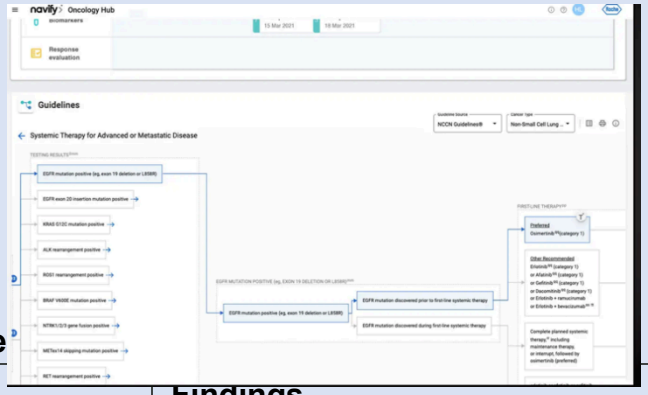
Navify Tumor Board—an online platform for clinicians to collaborate on and discuss cases and to more efficiently prepare for tumor board meetings. Studies have shown this solution to improve multidisciplinary tumor board workflows and user satisfaction, reduce case preparation time, decrease "failure-to-discuss" rates, and reduce the amount of time to match patients to clinical trials.[88-90]

Navify Mutation Profiler—a feature that helps clinicians to identify clinically relevant variants in cancer genomes via Sanger, next-generation, and transcriptome sequencing methods.

Navify Digital Pathology—a HIPAA-compliant environment for sharing digital pathology images and data. It includes a variety of tools to help pathologists and technicians analyze images, including image annotation, comparison, navigation, and sharing.

Navify Pass—a secure way to store and share test results.

Navify Algorithm Suite—a single platform hosting a library of digital medical algorithms that generate patient-centric insights and can aid earlier diagnosis.[91]



Select studies and re

Study	Findings
Evaluation of Navify Tumor Board (NTB) impact on tumor board	Showed significant reductions (30%) in overall preparation time across three tumor

preparation time across multiple user groups[89]	boards pre-NTB compared with the final post-NTB implementation phase
Evaluation of impact on case discussion time during tumor board meetings[88]	Demonstrated that NTB significantly decreased average discussion time per case at breast and gastrointestinal tumor boards and decreased postponement rates in ear, nose, and throat tumor boards
Evaluation of Navify Mutation Profiler accuracy[87]	Showed substantial agreement (Cohen κ = 0.62) for classifying actionable mutations, presented accurate targeted therapies across different regions, and remained up to date with evolving regional approvals and medical guidelines

The future of CDS

The global CDS market is expected to grow at a rate of 11.3% per year from 2020, reaching a value of $2.5 billion by 2026.[92] By 2030, the market is estimated to be worth $10.7 billion, with an annual growth rate of 10.4%. This growth is expected to be due to the increasing adoption of EHRs, the need to improve patient outcomes, and the growing focus on health care quality and safety.[77,93]

The CDS market is seeing increasing integration of AI and ML technologies, which enable the analysis of large amounts of data and the provision of real-time, personalized recommendations.[84,94,95] In oncology, a significant barrier to the use of precision medicine is human cognitive capacity, which is typically constrained to five variables for decision-making.[96] Continuously learning AI-based CDS systems have the potential to solve this problem by offering validated predictive models based on a range

of data (e.g., clinical, imaging, biologic, genetic, and cost) to guide HCP care and treatment decisions.[84] These systems can provide personalized probable outcomes related to toxicity, tumor control, HRQoL, and the cost-effectiveness of various pathway decisions to optimize care.

Another trend is the increasing use of mobile devices and cloud-based solutions, which allow HCPs to access CDS systems from anywhere, improving timely decision-making.[92] Finally, although CDS is currently used primarily by HCPs to make decisions, it is anticipated that CDS will enhance HCP-patient discussions and drive shared decision-making.[84]

DISCUSSION

The lag in the adoption of digital innovation in the field of oncology relative to other therapeutic areas is likely due to a number of challenges, including inadequate understanding of cancer care by DH developers; limited customer drive to adopt DH, which results from poor elucidation and comprehension of the full value of DH in oncology; unclear commercial opportunity and viability of DH in oncology; and lack of a standardized infrastructure to reimburse or implement digital innovations into the health care ecosystem.[97] There is a clear need for input by multiple stakeholders, combining clinical, technological, and commercial expertise, to realize the promise of DH.

Health care stakeholders who take the plunge into oncology DH will be faced with the following challenges, which currently limit its adoption in this field:

- An unclear and rapidly evolving DH regulatory and legislative environment makes it difficult for DH developers to plan their path to market.

- Lack of regulations and standards on reimbursement limits DH tools from consistent reimbursement.
- There is limited clarity and guidance on how regulators and payers should assess the efficacy and value of DH tools
- To date, many DH tools in oncology have had no or poor-quality clinical validation, contributing to HCP hesitancy or dismissal of DH; future DH solutions will require high-quality evidence to drive a shift in perception and gain trust.
- Community health systems and HCPs have shown less willingness to invest resources to adopt DH tools; future DH developers must clearly demonstrate the cost savings that DH tools can deliver to health care systems.
- The security of sensitive patient information is a growing concern due to the rising incidence of cyber attacks. Robust measures will be needed to protect patient information, comply with privacy regulations, and ensure secure data transmission.
- It is anticipated that DH will help to overcome health disparities in oncology by bringing care to patients' homes and communities, but caution is needed around widening health disparities, as levels of DH literacy and access to digital tools varies widely.[98] AI and ML might also perpetuate health disparities due to bias from data set training, which can lead to underestimating risk among underrepresented populations.[73,99]
- There is a potential for rapid disruption from large technology companies like Google and Amazon.

Several DH pioneers, such as Pear Therapeutics, have recently failed, and a winning model for success in DH has yet to be established; though future DH developers will be able to learn from recent failures.

Case study – Key learnings from the downfall of PEAR Therapeutics

Pear Therapeutics was a pioneer and one of the most well-known DTx companies from 2013 to 2022. They were the first prescription DTx company to receive FDA clearance to launch a prescription digital therapeutic (PDT), which in turn was the first PDT to receive Breakthrough Designation and the first to be cleared through the 510(k) pathway and FDA's Software Precertification Pilot Program. With a portfolio of three approved PDTs covered by multiple state Medicaid plans, the company went public in December 2021 in a $1.6 billion deal and successfully lobbied CMS to establish the first HCPCS Level II code for a prescription digital behavioral therapy.[100,101]

The company projected making $100–120 million in revenue in 2022 but earned just under $13 million in that year.[102] Despite its initial success, Pear Therapeutics filed for Chapter 11 bankruptcy protection on April 7, 2023 and was sold for $6 million on May 18, 2023.[102]

The CEO said the company failed because of denials from payers and poor funding conditions. Despite having direct contracts with certain state Medicaid providers, there was no statutory benefit category for Medicaid or Medicare to reimburse for PDTs. Although many of these forces fell outside of the company's power, one controllable variable that may have contributed to the limited acceptance and use of its solutions was its investment in clinical validation. Although Pear did generate high-quality empirical evidence of the benefit of its solutions, the magnitude of evidence pales in comparison to that of traditional pharmaceutical treatments, potentially underwhelming payers and others in the nascent field.

So, what are the implications for the future of DH as a whole? It primarily comes down to commercializing DH solutions:

- The optimal business model for DH remains unclear, but it is likely not one-size-fits-all.
- Payer reimbursement, and the regulations around it, will continue to be one of the biggest challenges.
- DH companies following the pharmaceutical model (i.e., reimbursement per prescription) are struggling more than other models, given limited capital to wait many years to break even; pharmaceutical companies will have a key advantage here.

- The funding environment is likely to be more constrained for DH due to investor skepticism.
- Investing in robust clinical validation is essential to gaining trust and buy-in from payers and prospective customers, especially as DTx remains a novelty.

Figures suggest that, despite growing pains, DH solutions such as DTx, patient health and wellness apps, RPM, and CDS will become mainstays of health care. As demonstrated in this report, the opportunities that DH solutions can provide to oncology care can make them a valuable addition to patient outcomes and health care efficiencies. Looking to the future, DH is expected to dramatically shift HCP practice, patient outcomes, and the model for delivering oncology health care from modest efficiencies to driving clinical decisions that improve outcomes. However, predicting the pace, timing, and the entities that will drive this evolution can be difficult.

Author contributions

DR and ND wrote the manuscript with support from AC, EN, TB and DB. AC and DR conceived the concept of the review paper. DR devised the main structure and flow of ideas, with support from TB, DB and EN. ND, TB, DB and EN conducted research, supported with case study development and figures. All authors read and approved the final transcript.

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Competing interests

DR, TB, DB, EN are employees of IDEA Pharma and may hold stock ownership, interests, or options in the company.

REFERENCES

1 Globe News Wire. Global report on digital health market size valuation will reach to USD 220.94 billion by 2026, according to Facts & Factors. https://www.globenewswire.com/en/news-release/2021/09/02/2290548/0/en/Global-Report-on-Digital-Health-Market-Size-Valuation-Will-Reach-to-USD-220-94-Billion-by-2026-According-to-Facts-Factors.html (2021). Accessed October 16, 2023.

2 Mariotto, A. B., Enewold, L., Zhao, J., Zeruto, C. A. & Yabroff, K. R. Medical care costs associated with cancer survivorship in the United States. *Cancer Epidemiol Biomarkers Prev* **29**, 1304-1312 (2020).

3 World Cancer Research Fund International. Global cancer data by country. https://www.wcrf.org/cancer-trends/global-cancer-data-by-country/#:~:text=Globally%2C%2018%2C094%2C716%20million%20cases%20of (2020). Accessed October 16, 2023.

4 Gussoni, G. *et al.* Digital therapeutics in oncology: findings, barriers and prospects. *Ann Res Oncol* **2**, 55 (2022).

5 European Commission. Overview. https://health.ec.europa.eu/ehealth-digital-health-and-care/overview_en#:~:text=Digital%20health%20and%20care%20refers. Accessed October 17, 2023.

6 U.S. Food and Drug Administration. What is digital health? https://www.fda.gov/medical-devices/digital-health-center-excellence/what-digital-health (2020). Accessed October 17, 2023.

7 World Health Organization. Digital health. https://www.who.int/europe/health-topics/digital-health#tab=tab_1 (2023). Accessed October 18, 2023.

8 Bogdan, B., Dahinden, A. T., Kurne, A. & Dietschy-Kuenzle, S. Empower oncologists, revolutionize biopharma. <https://www.accenture.com/_acnmedia/PDF-169/Accenture-Empower-Oncologists-Revolutionize-Biopharma-Report.pdf> (Accessed October 17, 2023.

9 Digital Health Therapeutics Alliance. Understanding DTx: a new category of medicine. https://dtxalliance.org/understanding-dtx/ (2023). Accessed October 18, 2023.

10 Vasudevan, S., Flashner-Abramson, E., Remacle, F., Levine, R. D. & Kravchenko-Balasha, N. Personalized disease signatures through information-theoretic compaction of big cancer data. *Proc Natl Acad Sci U S A* **115**, 7694-7699 (2018).

11 All.can. Moovcare: web-based follow-up care for lung cancer patients. https://www.all-can.org/efficiency-hub/moovcare-web-based-follow-up-care-for-lung-cancer-patients/ (2023). Accessed October 17, 2023.

12 Denis, F. *et al.* Randomized trial comparing a web-mediated follow-up with routine surveillance in lung cancer patients. *J Natl Cancer Inst* **109** (2017).

13 Lizée, T. *et al.* Cost-effectiveness of web-based patient-reported outcome surveillance in patients with lung cancer. *J Thorac Oncol* **14**, 1012-1020 (2019).

14 Moovcare. What is Moovcare? https://www.moovcare.com/. Accessed October 18, 2023.

15 Zirar, W. Lung cancer: partnership between BMS France and Sivan to depoly the Moovcar remote monitoring software. http://esalut.umanresa.cat/?p=238. Accessed October 17, 2023.

16 Denis, F. *et al.* Two-year survival comparing web-based symptom monitoring vs routine surveillance following treatment for lung cancer. *JAMA* **321**, 306-307 (2019).

17 Basch, E., Leahy, A. B. & Dueck, A. C. Benefits of digital symptom monitoring with patient-reported outcomes during adjuvant cancer treatment. Editorial. *J Clin Oncol* **39**, 701-703 (2021).

18 Berry, D. L. *et al.* Electronic self-report assessment for cancer and self-care support: results of a multicenter randomized trial. *J Clin Oncol* **32**, 199-205 (2014).

19 Denis, F. *et al.* Detection of lung cancer relapse using self-reported symptoms transmitted via an internet web-application: pilot study of the sentinel follow-up. *Support Care Cancer* **22**, 1467-1473 (2014).

20 Chawla, V. Where is the money in digital health? The roadmap to digital health app reimbursement in Europe. https://research2guidance.com/where-is-the-money-in-digital-health-the-roadmap-to-digital-health-app-reimbursement-in-europe/ (2020). Accessed October 17, 2023.

21 German Market Access. Digital treatments and medical applications (DiGA)—assessment process in Germany. https://germanmarketaccesssimplified.com/digital-treatments-and-medical-applications-diga-assessment-process-in-germany/. Accessed October 17, 2023.

22 MHealth. Validation pyramid. https://mhealthbelgium.be/validation-pyramid. Accessed October 17, 2023.

23 GNIUS. Early access to reimbursement for digital devices (PECAN). https://gnius.esante.gouv.fr/en/financing/reimbursement-profiles/early-access-reimbursement-digital-devices-pecan. Accessed October 17, 2023.

24 IDEA Pharma. IDEA Pharma post-Dx digital health database, 2019–Q2 2021.

25 Syneos Health. Digital therapeutics at the crossroads. https://www.syneoshealth.com/insights-hub/digital-therapeutics-crossroads (2020). Accessed October 17, 2023.

26 Avalere Health. Survey shows potential, challenges, and solutions for broad PDT access. https://avalere.com/insights/survey-shows-potential-challenges-and-solutions-for-broad-pdt-access. Accessed October 17, 2023.

27 Dang, A., Arora, D. & Rane, P. Role of digital therapeutics and the changing future of healthcare. *J Family Med Prim Care* **9**, 2207-2213 (2020).

28 Die Techniker. DiGA report 2022. https://www.tk.de/presse/themen/digitale-gesundheit/digitaler-fortschritt/diga-report-2022-2125138?tkcm=aaus (2022). Accessed October 17, 2023.

29 U.S. Food and Drug Administration. Enforcement policy for digital health devices for treating psychiatric disorders during the coronavirus disease 2019 (COVID-19) public health emergency. Guidance for industry and Food and Drug Administration staff. Rockville, MD: U.S. Department of Health and Human Services, 2020. https://www.fda.gov/media/136939/download. Accessed October 17, 2023.

30 Pear Therapeutics. Pear prescription digital therapeutics (PDT) digest. https://www.amcp.org/sites/default/files/2022-02/Pear_Digest_Final_10-26-21.pdf (2021). Accessed October 17, 2023.

31 U.S. Food and Drug Administration. Requests for feedback and meetings for medical device submissions: the Q-Submission Program. Guidance for industry and Food and Drug Administration staff. Rockville, MD: U.S. Department of Health and Human Services, 2021. https://www.fda.gov/media/114034/download. Accessed October 17, 2023.

32 Keeler, G. DTx part I: identifying optimal payment methods for digital therapeutics. https://veranex.com/2019/12/03/dtx-part-i-identifying-optimal-payment-models-for-digital-therapeutics/?source=bostonhealthcare (2019). Accessed October 17, 2023.

33 Bossi, P., De Luca, R., Ciani, O., D'Angelo, E. & Caccialanza, R. Malnutrition management in oncology: an expert view on controversial issues and future perspectives. *Front Oncol* **12**, 910770 (2022).

34 Basch, E. *et al.* Overall survival results of a trial assessing patient-reported outcomes for symptom monitoring during routine cancer treatment. *JAMA* **318**, 197-198 (2017).

35 Berry, D. L., Blonquist, T. M., Patel, R. A., Halpenny, B. & McReynolds, J. Exposure to a patient-centered, Web-based intervention for managing cancer symptom and quality of life issues: impact on symptom distress. *J Med Internet Res* **17**, e136 (2015).

36 Børøsund, E., Cvancarova, M., Moore, S. M., Ekstedt, M. & Ruland, C. M. Comparing effects in regular practice of e-communication and web-based self-management support among breast cancer patients: preliminary results from a randomized controlled trial. *J Med Internet Res* **16**, e295 (2014).

37 Kolb, N. A. *et al.* Chemotherapy-related neuropathic symptom management: a randomized trial of an automated symptom-monitoring system paired with nurse practitioner follow-up. *Support Care Cancer* **26**, 1607-1615 (2018).

38 Pfeifer, M. P. *et al.* Impact of a telehealth intervention on quality of life and symptom distress in patients with head and neck cancer. *J Community Support Oncol* **13**, 14-21 (2015).

39 Ruland, C. M. *et al.* Effects of an internet support system to assist cancer patients in reducing symptom distress: a randomized controlled trial. *Cancer Nurs* **36**, 6-17 (2013).

40 van den Berg, S. W. *et al.* BREATH: web-based self-management for psychological adjustment after primary breast cancer—results of a multicenter randomized controlled trial. *J Clin Oncol* **33**, 2763-2771 (2015).
41 Pritchett, J. C. *et al.* Association of a remote patient monitoring (RPM) program with reduced hospitalizations in cancer patients with COVID-19. *JCO Oncol Pract* **17**, e1293-e1302 (2021).
42 Ruland, C. M. *et al.* Effects of a computer-supported interactive tailored patient assessment tool on patient care, symptom distress, and patients' need for symptom management support: a randomized clinical trial. *J Am Med Inform Assoc* **17**, 403-410 (2010).
43 Kaiku Health. Kaiku Health home page. https://kaikuhealth.com/ (2023). Accessed October 28, 2023.
44 Peltola, M. K., Lehikoinen, J. S., Sippola, L. T., Saarilahti, K. & Makitie, A. A. A novel digital patient-reported outcome platform for head and neck oncology patients—a pilot study. *Clin Med Insights Ear Nose Throat* **9**, 1-6 (2016).
45 Schmalz, O. *et al.* Digital monitoring and management of patients with advanced or metastatic non-small cell lung cancer treated with cancer immunotherapy and its impact on quality of clinical care: interview and survey study among health care professionals and patients. *J Med Internet Res* **22**, e18655 (2020).
46 Kaiku Health. Kaiku Health and Amgen roll out digital patient support for multiple myeloma. https://kaikuhealth.com/press/kaiku-health-and-amgen-roll-out-digital-patient-support-for-multiple-myeloma/ (2019). Accessed October 17, 2023.
47 Kaiku Health. Kaiku Health expands collaboration with Roche in digital patient monitoring and management. https://kaikuhealth.com/kaiku-health-expands-collaboration-with-roche-in-digital-patient-monitoring-and-management/ (2020). Accessed October 17, 2023.
48 Kimber, E. Novartis and Kaiku Health expand digital health monitoring partnership. https://www.pmlive.com/pharma_news/novartis_and_kaiku_health_expand_digital_health_monitoring_partnership_1454205 (2022). Accessed October 17, 2023.
49 Iivanainen, S., Ekstrom, J., Virtanen, H., Kataja, V. V. & Koivunen, J. P. Electronic patient-reported outcomes and machine learning in predicting immune-related adverse events of immune checkpoint inhibitor therapies. *BMC Med Inform Decis Mak* **21**, 205 (2021).
50 Iivanainen, S. *et al.* ePROs in the follow-up of cancer patients treated with immune checkpoint inhibitors: a retrospective study. *J Cancer Res Clin Oncol* **145**, 765-774 (2019).
51 Navigating Cancer. Digital health solutions that improve the lives of cancer patients. October 28, 2023 (2022). Accessed October 18, 2023.
52 Pierce, E., Stott, C. & Larned, Z. Ochsner Health System's Chemotherapy Care Companion: technology for monitoring outpatient oncology patients at home. Clinical poster JL913. Journal of the Advanced Practitioner in Oncology (Live Virtual), October 7–17, 2021.
53 Globe News Wire. Remote patient monitoring system market size, share & trends analysis report by product, by application, by end-use and segment forecasts, 2021–2018. https://www.globenewswire.com/news-release/2021/02/16/2175987/0/en/Remote-Patient-Monitoring-System-Market-Size-Share-Trends-Analysis-Report-By-Product-By-Application-By-End-use-And-Segment-Forecasts-2021-2028.html (2021). Accessed October 17, 2023.
54 Fallahzadeh, R., Rokni, S. A., Ghasemzadeh, H., Soto-Perez-de-Celis, E. & Shahrokni, A. Digital health for geriatric oncology. *JCO Clin Cancer Inform* **2**, 1-12 (2018).
55 Shahrokni, A., Loh, K. P. & Wood, W. A. Toward modernization of geriatric oncology by digital health technologies. *Am Soc Clin Oncol Educ Book* **40**, 1-7 (2020).
56 Maaß, L. *et al.* The definitions of health apps and medical apps from the perspective of public health and law: qualitative analysis of an interdisciplinary literature overview. *JMIR Mhealth Uhealth* **10**, e37980 (2022).
57 Vercell, A., Gasteiger, N., Yorke, J. & Dowding, D. Patient-facing cancer mobile apps that enable patient-reported outcome data to be collected: a systematic review of content, functionality, quality, and ability to integrate with electronic health records. *Int J Med Inform* **170**, 104931 (2023).
58 Pfizer. Pfizer launches novel programs to put important support services at the fingertips of cancer patients. https://www.pfizer.com/news/press-release/press-release-detail/pfizer_launches_novel_programs

_to_put_important_support_services_at_the_fingertips_of_cancer_patients (2017). Accessed October 17, 2023.
59 Pfizer. This is living with cancer: FAQs. https://www.thisislivingwithcancer.com/faqs (2017). Accessed October 17, 2023.
60 Graetz, I. *et al.* Mobile application to support oncology patients during treatment on patient outcomes: evidence from a randomized controlled trial. *Cancer Med* **12**, 6190-6199 (2023).
61 Charbonneau, D. H. *et al.* Smartphone apps for cancer: a content analysis of the digital health marketplace. *Digit Health* **6**, 2055207620905413 (2020).
62 Dhar, E. *et al.* A scoping review and a taxonomy to assess the impact of mobile apps on cancer care management. *Cancers (Basel)* **15**, 1775 (2023).
63 Moon, Z. *et al.* Disparities in access to mobile devices and e-health literacy among breast cancer survivors. *Support Care Cancer* **30**, 117-126 (2022).
64 Upadhyay, V. A., Landman, A. B. & Hassett, M. J. Landscape analysis of oncology mobile health applications. *JCO Clin Cancer Inform* **5**, 579-587 (2021).
65 Vaffis, S. *et al.* Features of cancer mHealth apps and evidence for patient preferences: scoping literature review. *JMIR Cancer* **9**, e37330 (2023).
66 Lu, D. J. *et al.* Evaluation of mobile health applications to track patient-reported outcomes for oncology patients: a systematic review. *Adv Radiat Oncol* **6**, 100576 (2021).
67 Steeb, T. *et al.* Patient attitudes and their awareness towards skin cancer-related apps: cross-sectional survey. *JMIR Mhealth Uhealth* **7**, e13844 (2019).
68 Ana, F. A. *et al.* Mobile applications in oncology: a systematic review of health science databases. *Int J Med Inform* **133**, 104001 (2020).
69 Beutter, C. N. L., Martens, U. M. & Fegeler, C. From patient-generated data to precision medicine: an example of a patient-centered application in oncology. American Society of Clinical Oncology Annual Meeting, Chicago, IL, June 3–7, 2022.
70 The Decision Lab. Why do we have a harder time choosing when we have more options? https://thedecisionlab.com/biases/choice-overload-bias (2023). Accessed October 17, 2023.
71 Hamel, L. M., Thompson, H. S., Albrecht, T. L. & Harper, F. W. Designing and testing apps to support patients with cancer: looking to behavioral science to lead the way. *JMIR Cancer* **5**, e12317 (2019).
72 Kemp, E. *et al.* Health literacy, digital health literacy and the implementation of digital health technologies in cancer care: the need for a strategic approach. *Health Promot J Austr* **32 Suppl 1**, 104-114 (2021).
73 Parikh, R. B., Teeple, S. & Navathe, A. S. Addressing bias in artificial intelligence in health care. *JAMA* **322**, 2377-2378 (2019).
74 Nasi, G., Cucciniello, M. & Guerrazzi, C. The role of mobile technologies in health care processes: the case of cancer supportive care. *J Med Internet Res* **17**, e26 (2015).
75 Pew Research Center. Mobile fact sheet. https://www.pewresearch.org/internet/fact-sheet/mobile/ (2019). Accessed October 17, 2023.
76 U.S. Food and Drug Administration. Step 6: Is the software function intended to provide clinical decision support? https://www.fda.gov/medical-devices/digital-health-center-excellence/step-6-software-function-intended-provide-clinical-decision-support#:~:text=Clinical%20decision%20support%20(CDS)%20is,enhance%20health%20and%20health%20care (2022). Accessed November 1, 2023.
77 Sutton, R. T. *et al.* An overview of clinical decision support systems: benefits, risks, and strategies for success. *NPJ Digit Med* **3**, 17 (2020).
78 Helmons, P. J., Suijkerbuijk, B. O., Nannan Panday, P. V. & Kosterink, J. G. Drug-drug interaction checking assisted by clinical decision support: a return on investment analysis. *J Am Med Inform Assoc* **22**, 764-772 (2015).
79 Akalin, B. & Veranyurt, Ü. Artificial intelligence-based clinical decision support systems in health sciences. *Gevher Nesibe J Med Health Sci* **7**, 64-73 (2022).
80 Rahim, H. Tackling racially biased health care algorithms. (2023). <https://blog.petrieflom.law.harvard.edu/2023/10/05/tackling-racially-biased-health-care-algorithms/>. Accessed October 24, 2023.

81 Larrazabal, A. J., Nieto, N., Peterson, V., Milone, D. H. & Ferrante, E. Gender imbalance in medical imaging datasets produces biased classifiers for computer-aided diagnosis. *Proc Natl Acad Sci U S A* **117**, 12592-12594 (2020).
82 James, B. Utility of evidence-based clinical decision support in reducing unwarranted variations in diagnosis and treatment of breast and lung cancer. *Eur Med J* **7**, 28-37 (2022).
83 Klarenbeek, S. E., Schuurbiers-Siebers, O. C. J., van den Heuvel, M. M., Prokop, M. & Tummers, M. Barriers and facilitators for implementation of a computerized clinical decision support system in lung cancer multidisciplinary team meetings: a qualitative assessment. *Biology (Basel)* **10** (2020).
84 Walsh, S. *et al.* Decision support systems in oncology. *JCO Clin Cancer Inform* **3**, 1-9 (2019).
85 Osterman, T. J., Terry, M. & Miller, R. S. Improving cancer data interoperability: the promise of the minimal Common Oncology Data Elements (mCODE) initiative. *JCO Clin Cancer Inform* **4**, 993-1001 (2020).
86 Roche Diagnotics. Navify. https://usinfo.roche.com/SimplifyOncology.html. Accessed October 17, 2023.
87 Yaung, S. J. *et al.* Assessment of a highly curated somatic oncology database to aid in the interpretation of clinically important variants in next-generation sequencing results. *J Mol Diagn* **22**, 1356-1366 (2020).
88 Hammer, R. D., Fowler, D., Sheets, L. R., Siadimas, A. & Guo, C. A digital tumor board solution impacts case discussion time and postponement of cases in tumor boards. *Health Technol* **11**, 525-533 (2021).
89 Hammer, R. D. *et al.* Digital tumor board solutions have significant impact on case preparation. *JCO Clin Cancer Inform* **4**, 757-768 (2020).
90 Krupinski, E. A., Comas, M., Gallego, L. G. & Group, G. A new software platform to improve multidisciplinary tumor board workflows and user satisfaction: a pilot study. *J Pathol Inform* **9**, 26 (2018).
91 Roche Diagnotics. Roche introduces navify algorithm suite, a digital library of medical algorithms that enhances clinical decision-making to optimise patient care. https://diagnostics.roche.com/global/en/news-listing/2023/roche-introduces-navify--algorithm-suite--a-digital-library-of-m.html (2023). Accessed October 18, 2023.
92 Ghosh, S. Clinical decision support systems market outlook. https://www.futuremarketinsights.com/reports/clinical-decision-support-market (2022). Accessed October 18, 2023.
93 Mordor Intelligence. Market trends of clinical decision support industry. https://www.mordorintelligence.com/industry-reports/clinical-decision-support-systems-market/market-trends (2023). Accessed October 18, 2023.
94 Cuocolo, R., Caruso, M., Perillo, T., Ugga, L. & Petretta, M. Machine learning in oncology: a clinical appraisal. *Cancer Lett* **481**, 55-62 (2020).
95 Mahajan, A. & Chakrabarty, N. Editorial: The use of deep learning in mapping and diagnosis of cancers. *Front Oncol* **12**, 1077341 (2022).
96 Halford, G. S., Baker, R., McCredden, J. E. & Bain, J. D. How many variables can humans process? *Psychol Sci* **16**, 70-76 (2005).
97 Patel, S. *et al.* Advancing digital health innovation in oncology: priorities for high-value digital transformation in cancer care. *J Med Internet Res* **25**, e43404 (2023).
98 Parikh, R. B. *et al.* Digital health applications in oncology: an opportunity to seize. *J Natl Cancer Inst* **114**, 1338-1339 (2022).
99 Obermeyer, Z., Powers, B., Vogeli, C. & Mullainathan, S. Dissecting racial bias in an algorithm used to manage the health of populations. *Science* **366**, 447-453 (2019).
100 Nussey, S. *SoftBank-backed Pear Therapeutics agrees $1.6 billion SPAC deal*. Reuters, June 22, 2021. https://www.reuters.com/article/us-pear-therapeutics-spac-idUSKCN2DY158. Accessed October 18, 2023.
101 Devs, S. *Pear Therapeutics announces new CMS HCPCS code for prescription digital behavioral therapy inclusive of its commercial products*. BusinessWire, February 24, 2022. https://www.businesswire.com/news/home/20220224005355/en/Pear-Therapeutics-Announces-New-CMS-HCPCS-Code-for-Prescription-Digital-Behavioral-Therapy-Inclusive-of-All-of-Its-Commercial-Products. Accessed October 18, 2023.

102 Jennings, K. *Pear Therapeutics files for bankruptcy as CEO blames shortfalls on insurers*. *Forbes*, April 7, 2023. https://www.forbes.com/sites/katiejennings/2023/04/07/pear-therapeutics-files-for-bankruptcy-as-ceo-blames-shortfalls-on-insurers/?sh=677dcdf02bd6. Accessed October 18, 2023.

	Target user	Clinical validation	Regulatory scrutiny	Common use-cases
Digital therapeutics (DTx)	• Patients • May include Healthcare Providers	Requires confirmatory clinical study	Always regulated and reviewed as **software-as-a-medical device** (SaMD) by FDA	• Directly treat disease • Serve as adjunct to complement pharmacological treatment • Provide supportive care (e.g., psychological)
Patient health & wellness apps (PHW)	• Patients	Does not require clinical validation	None	• Support lifestyle and wellness • Enable self-monitoring of disease and treatment • Provide consumer health information
Remote patient monitoring (RPM)	• Patients • Healthcare Providers	May have some degree of clinical validation, but not required	Dependent on risk associated with intended use and setting of solution; can be classified as a DTx if regulatory review required	• Collect and transmit patient data (reported outcomes, activity, vital signs etc.) to HCPs • Alert to medical anomalies while patient is outside clinic • Monitor patient adherence
Clinical decision support (CDS)	• Healthcare Providers	Requires confirmatory clinical study	Always regulated and reviewed as **software-as-a-medical device** (SaMD) by FDA; requires confirmatory clinical study	• Analyze and interpret data on behalf of HCPs in support of clinical decision making • Enable workflow to reinforce use of evidence-based clinical guidelines at the point of care

Fig 1 Types of DH solutions by end user, clinical validation, regulatory scrutiny, and common use-cases.

	attune™	CANKADO	moovcare By Sivan	oleena®
	Attune (Blue Note Therapeutics)	**Cankado PRO-React Onco** (Cankado)	**Moovcare** (Sivan Innovation)	**Oleena** (Voluntis)
Oncology indication	Invasive or infiltrating (e.g. bladder, testicular, breast)	Breast	Lung	Pan-oncology
Intended use-case	**Disease management:** Cancer-related anxiety and depression	**Disease management:** Symptom monitoring	**Disease prevention:** Relapse and complication detection	**Disease management:** Symptom management and progress monitoring
Classification, as related to pharmacological therapies	**Standalone** (functions independently from pharmacological interventions)	**Complementary** (indicated for use in combination with potential therapies)	**Standalone** (functions independently from pharmacological interventions)	**Complementary** (indicated for use in combination with potential therapies)
Regulatory approval	 US	 US, EU	 France, EU	 Germany

Fig 2 Examples of DTx products with oncological indications.

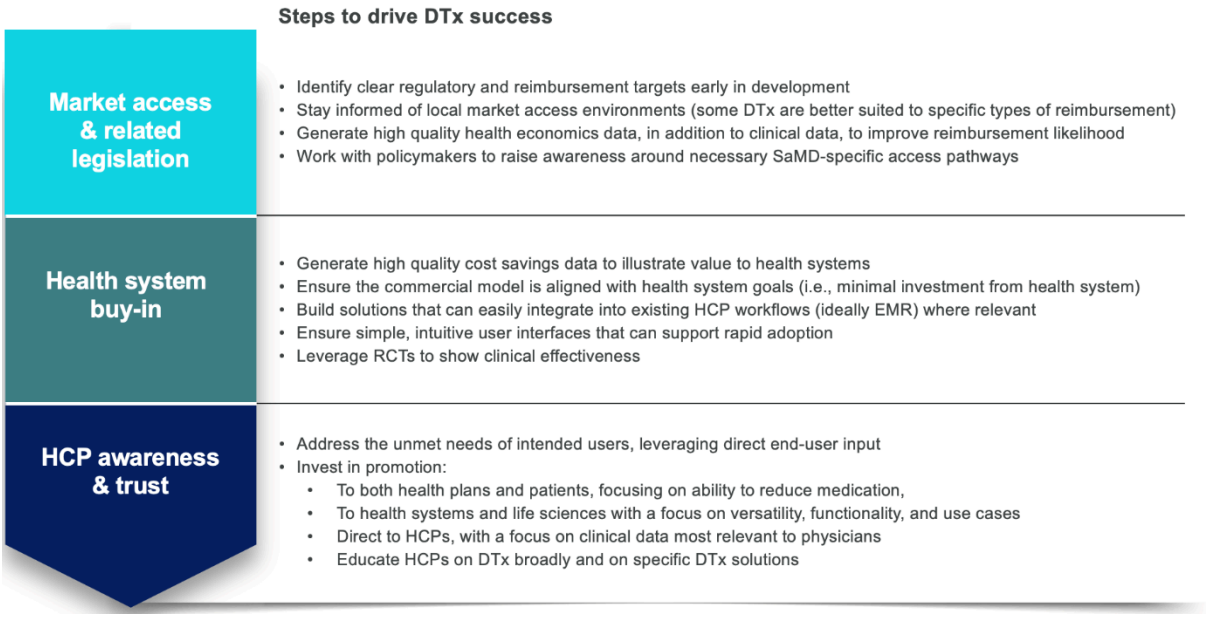

Fig. 3 Challenges with recommended steps to drive DTx success and value.[25,29-31]

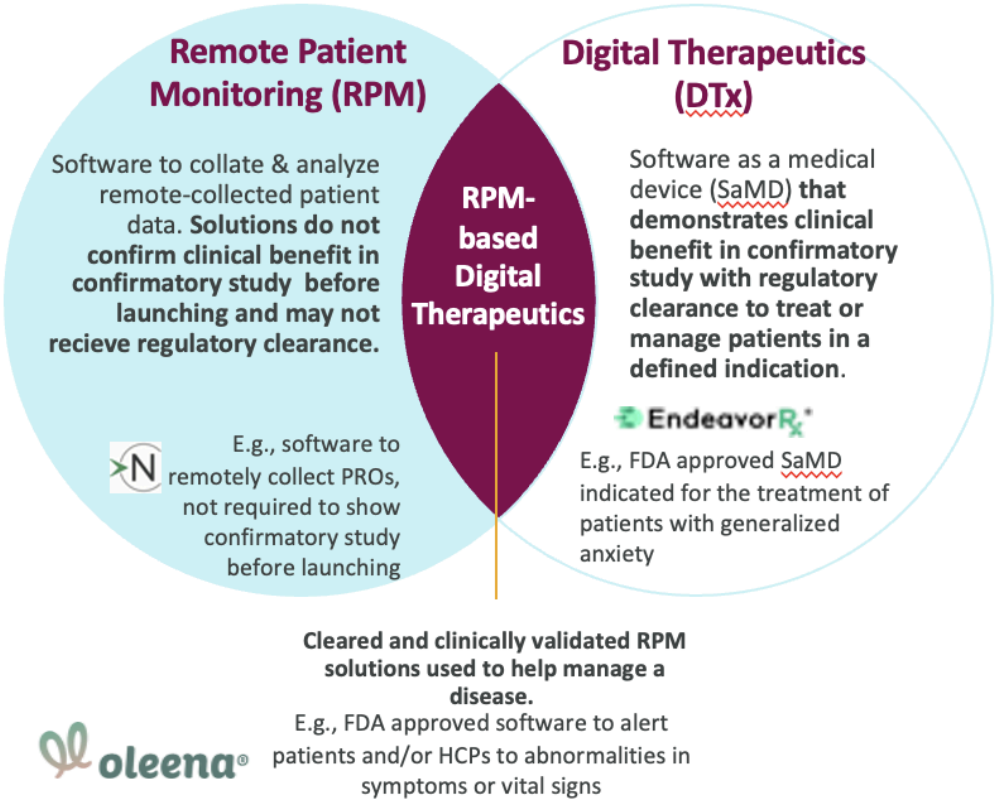

Fig. 4 Differences and overlap between RPM and DTx products.

	Kaiku Health	Navigating Cancer Care	Careology	Current Health
Oncology indication	Pan-oncology	Pan-oncology	Pan-oncology	Pan-oncology
Intended use	• Provides patient-reported outcome monitoring and intelligent symptom tracking to help clinics optimize care. • Split into modules for specific AEs related to classes of therapy	• Optimizing workflows to triage, and alert providers to at-risk patients with ePRO-based patient monitoring • Patient module enables viewing of visit summaries, recording of Tx details, reminder and calendar scheduling, and side effect recording	• Enables virtual rounds, provides real-time visibility across patient populations and better-informed consultations, allowing physicians to understand how patients are tolerating treatment. • Patient-facing app equips patients to feel more in control of their disease management	• Remote care management platform that combines connected health devices, telehealth and patient engagement into a single solution that enables customizability when it comes to alerts for specific patients • Includes an FDA-cleared wearable medical device that monitors vital signs, a home hub that integrates with other monitoring devices and connection to patients' health records
Confirmatory clinical trial before launch?	No	No	No	No

Fig. 5 Examples of RPM products with oncological indications.

	LivingWith (LivingWith Ltd.)	Cancer.Net Mobile (American Society of Clinical Oncology)	Osara Health (Formerly CancerAid)	Dave – Belong AI Mentor (Belong.Life)
Indication	Pan-oncology	Pan-oncology (more than 120 types of cancer)	Pan-oncology	Pan-oncology
Stage of journey	Diagnosis, treatment and survivorship	Diagnosis, treatment and survivorship	Diagnosis, treatment and survivorship	Diagnosis, treatment and survivorship
Use case	• Helps users manage life with cancer via options to track components of health such as mood, pain, steps, and sleep. • Reports can be shared with HCPs and support networks. • Enables organization of test results, medication details, and insurance information. • Holistic information on lifestyle, inspirational stories, motivational quotes, clinical trials, and community support.	• Multiple tools to self manage cancer care, including symptom and medication tracking, contact details of providers, and appointment reminders. • Latest oncologist-approved information.	• Multiple tools and resources to self manage cancer care, including personalized educational content, symptom tracking, medication reminders, and appointment management.	• Conversational AI oncology mentor named Dave. • Provides personalized, oncology-specific information to educate and guide patients throughout the clinical journey.

Fig. 6 Examples of health and wellness apps with oncological indications.