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# Holistic Needs Assessment of Cancer Survivors—Supporting the Process Through Digital Monitoring of Circadian Physiology

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**Abstract**

The year 2022 could represent a significant juncture in the incorporation of mHealth solutions in routine cancer care. With the recent global COVID-19 pandemic leading a surge in both observation- and intervention-based studies predominantly aimed at remote monitoring there has been huge intellectual investment in developing platforms able to provide real time analytics that are readily usable. Another fallout from the pandemic has seen record waiting times and delayed access to cancer therapies leading to exhausting pressures on global healthcare providers. It seems an opportune time to utilize this boom in platforms to offer more efficient "at home" clinical assessments and less "in department" time for patients. Here, we will focus specifically on the role of digital tools around cancer survivorship, a relevant aspect of the cancer journey, particularly benefiting from integrative approaches. Within that context a further concept will be introduced and that is of the likely upsurge in circadian-based interpretation of continuous monitoring and the engendered therapeutic modifications. Chronobiology across the 24-hour span has long been understood to control key bodily aspects and circadian dysregulation plays a significant role in the risk of cancer and also the response to therapy and therefore progressive outcome. The rapid improvement in minimally invasive monitoring devices is, in the opinion of the authors, likely to advance introducing chronobiological amendments to routine clinical practices with positive impact on cancer survivors.

**Keywords**

cancer, survivorship, mHealth, digital, circadian, holistic, chronobiology, monitoring

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## Cancer Survivorship

Conceptual evolutionary analysis of medical literature first coined the term survivorship in the 1960s, but only by the 1980s was it linked to cancer.[1] As of 2022 the term cancer survivorship still lacks a unanimous and detailed definition. The most widely used definition describes cancer survivorship as 3 distinct phases, with each phase focusing on an aspect of the disease trajectory beginning at the point of diagnosis and continuing throughout life.[2] Although this phased concept is conventionally agreed upon, the definitions of cancer survivorship are subject to many interpretations dependent on the perspective of the patient, person and professional. Given that cancer doctrine is constantly evolving, the concept of cancer survivorship should adopt a universally accepted definition to ultimately capture, improve and ideally impact

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upon the health and wellbeing of those diagnosed with and treated for cancer.

More recently there has been a positive shift from defining cancer patients as victims to survivors, and one rarely hears the word victim associated with cancer anymore. Regardless of the phase in their journey of survivorship the patient reaches or is currently at, they are entitled to identify themselves as a cancer survivor and may often link this to the challenges they have had to overcome. How one refers to oneself is a personal decision but irrespective of the definition, cancer patients still have unmet physical and psychological needs and this can have a significant impact on quality of life for those living with, or after, a cancer diagnosis.[3,4]

Incremental improvements in diagnosis, prognosticating, and therapeutics are leading to a higher prevalence of cancer survivors; whilst objectively a positive improvement this is placing an increasing demand on already stretched healthcare services. Consequently, changes to the delivery of a service within a larger health organization are required to ensure needs are more effectively addressed.[5] Recently the National Institute of Clinical Excellence (NICE) has made recommendations in the United Kingdom of Great Britain that patients who have stable oncological disease should be offered primary care follow-up[6] thus allowing expert cancer care professionals the time to prepare a comprehensive care plan for patients whose disease needs active treatment changes. Theoretically, this approach would span the divide between primary and secondary care, utilizing the strengths of both sectors whilst producing a cohesive team within which the patient is front and center.

Unfortunately, primary and secondary care services are often fragmented for numerous reasons with the most common being poor communication, overwhelmed services and lack of co-ordination. As a result, patients often feel excluded from shared decision making regarding their care. Those living with and beyond cancer often report a desire to be actively involved and perception of self-efficacy is particularly important, as it is a critical feature of chronic disease management.[7]

## Holistic Needs Assessment

Crucially in the delivery of modern medicine it is important how healthcare professionals address the holistic needs of a cancer survivor regardless of phase of life and disease course. To succeed in maximizing the potential of this concept, it is therefore important to understand how to assess the differences between individual cancer patients and shared issues within tumor groups, whilst incorporating more generic cancer frameworks.

People living with and beyond cancer are vulnerable to several physical, functional, practical, social, and psychological issues. A productive mechanism to help patients more easily identify and disclose their needs to healthcare professionals is the completion of an Holistic Needs Assessment (HNA) to fundamentally enable good quality person-centered care.[8] Yet, only 25% of cancer survivors in the UK receive a HNA and care plan.[9] In the UK, the charity Macmillan Cancer offer electronic forms as a way of completing their HNA, helping to identify and start conversations about the individual requirements of each patient.[10]

HNA is a checklist completed by the patient prior to the clinical consultation to support a structured discussion for the clinician to signpost more readily the individual's identified needs to facilitate better collaboration.[8] Guidance suggests that HNA should be delivered throughout the patient pathway. In practice this is not always the case for pragmatic reasons, which are paramount in the realistic clinical setting. Indeed, the needs related to the impact of the disease or its treatments on the patient's functioning or psychological state might be very different at diagnosis of a potentially curable disease versus on completion of aggressive multimodal palliative treatment.

The use of HNA is encouraged in cancer centers around the world, however, there is significant variability in its application, reflective of distinctly different healthcare systems with contrasting structures, funding, barriers, and cultures.[11] We believe that HNA conveys the right principles, but there needs to be an understanding of what effect variation in implementation has on the patient experience, outcomes and demand for service. Moreover, to ensure a dynamic assessment is accomplished, factors such as disease trajectory and individual clinical, social, cultural, and demographic features of each patient need to be considered.

We believe, from experience, that these factors can influence patient's needs considerably due to inequalities in outcomes, changing demographic and disease pattern, availability of new treatments and evolving expectations, thus the commitment from healthcare services needs to be robust, which in this current healthcare climate can be challenging.

Ideally, just like defining cancer survivorship, understanding the cohorts of patients in different tumor groups is paramount to being able to realize the full potential of HNA. In addition, knowing how to address changing needs and evolving expectations of patients is vital to be able to deliver patient-focused care. The utilization of technology to support these aims through collection and analysis of individual patient needs, and through facilitation of communication between the patient and their healthcare providers is becoming increasingly commonplace in modern cancer care.

## Electronic Patient-reported Outcomes (ePROs)

Approximately 10% of cancer patients have their symptoms underestimated during clinical consultations. Often the symptoms in question are subjective in nature, for example anorexia and fatigue.[12] This is alarming, particularly in a specialty where outpatient department decisions have potential wide ranging toxic consequences including prolonged admissions to hospital.

Modern society relies heavily on technology and modern healthcare is no exception: electronic records vastly improve accessibility of relevant information, documentation, efficiency, and safety.[13] Electronic prescribing can reduce the risk of serious medication errors and improve prescribing decisions[14]; and telemedicine consultations—the uptake of which has accelerated rapidly in the wake of the COVID-19 pandemic—offer a viable alternative option to a subset of patients when implemented appropriately.[15] An expanding body of evidence is documenting the benefits of using mobile devices to support this transition to technology-driven healthcare in a variety of ways, becoming known as mobile health or "mHealth."[16]

Patient-reported outcomes (PROs) are defined as "a measurement based on a report that comes directly from the patient about the status of a patient's health condition without amendment or interpretation of the patient's response by a clinician or anyone else."[17] PROs can be used to measure many facets of patient health, including clinical symptoms and quality of life. As a result, they are becoming an essential assessment tool in a variety of situations including postoperatively and in clinical trials.[18,19] Data they produce can be used to assess outcomes and experiences from the patient's perspective, in addition to more traditional outcome measures.

With the advent of mHealth and the ready availability of apps in general life, it has become easier for patients to document their outcomes electronically (ePROs). Patients can now report whenever they see fit, allowing real-time and longitudinal data collection and notification to the clinical team of any outcomes that may require intervention. In cancer patients specifically, ePROs have been shown to significantly increase health-related quality of life, reduce emergency hospital visits, encourage dialog between the patient and clinical team, prolong the duration of chemotherapy and increase survival by implementing simple questionnaires.[20-22]

There are, of course, challenges with implementing ePROs: they require sufficient patient motivation and education to take part; they require the development of an acceptable, usable interface; ensuring integration with existing clinical systems; and they also need to be adequately secure to protect patients' sensitive information. Additionally, the optimal analytical methodology of dense and long-term data can be challenging with regards to the relevant and actionable insight generated at a given point for the caring oncological team.[23,24] Finally, the optimal frequency, in terms of insight generated and compliance over time, is yet to be defined.[25]

Wearable technology is another facet of mHealth where recent improvement potentially creates a path for significant benefits to patients. Such devices, often worn on the wrist like a watch but sometimes worn elsewhere, for example as a chest strap or a ring, are readily available for members of the public to purchase.[26] They come equipped with sensors capable of collecting continuously (ie, repeatedly at a variable epoch duration) a wide array of parameters that include locomotor activity tracking, heart rate, respiratory rate, peripheral oxygen saturation, and skin body temperature as detailed in the graphic (Figure 1). Lifestyle device use is rapidly increasing and by 2028 is predicted to by valued at 28 billion USD (this is compared to 3.7 billion USD in 2018).[27] The COVID-19 pandemic has accelerated the specific use in relation to diagnosis of medical conditions.[28]

The analysis of these multidimensional time-series, using validated or proprietary algorithms allow the computation of additional physiological parameters, such as heart rate variability, step count, sleep process, including its duration, efficiency and its cycle analysis, and even basic electrocardiograms.[29] Commercial devices from well-known manufacturers such as Apple, Samsung, Fitbit or Garmin have been shown to provide highly accurate results across these measured parameters.[30] On the face of it, the information provided by these devices is potentially invaluable for clinical teams to be able to remotely assess a patient's physical condition, activity levels, sleep-wake cycles, and biological rhythms. In this space should be a word of caution on designing protocols in relation to wearable devices by clarifying the level of market authorization the wearable is designed for. Medical grade devices often have undergone testing in situations of ill health where a clinician would be inclined to make clinical decisions and ensuring a validatory step is critical to ensure the device doesn't jeopardize patient-clinician confidence.[31]

The majority of trials conducted thus far focus on using wearable devices to monitor physical activity levels.[32] Higher physical activity levels have been shown previously to correlate with improved survival and lower cancer recurrence rates.[33,34] One observational study in patients undergoing chemotherapy showed a correlation between lower non-sedentary hours and higher average hourly metabolic equivalent of task (a measure of energy expenditure in relation to physical mass) with a reduction in unplanned healthcare encounters. In this study there were, however, marked issues with adherence of device use, particularly in patients over 60 years of age.[35] This highlights a possible fundamental flaw in its usability if it disenfranchises older patients. Another study in a cohort of 80 colorectal cancer patients reported that use of wearable devices in patients undergoing systemic therapy was acceptable to most patients with good adherence. They also found that a higher mean steps per day

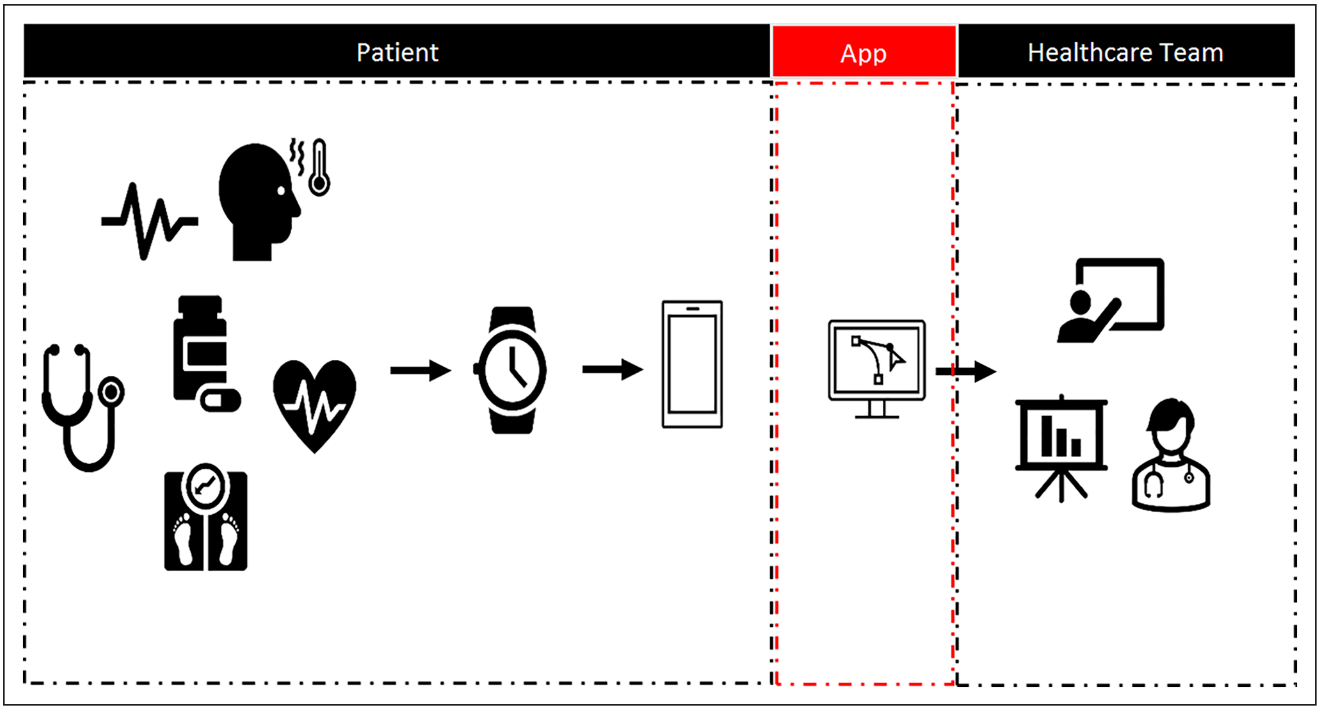

**Figure 1.** A generalized simplistic work plan of mHealth incorporates the collection of a specific health data point from the patient often displayed for example on a smart watch and stored in their smart phone. Moving to the next stage the data is collated in a safe manner into user friendly analytics that are then analyzed by the healthcare team to target areas of improvement for that specific patient.

was associated with fewer high-grade toxicities and although this was not statistically significant it certainly suggests a potential biomarker of risk.[36] If these results can be validated in larger randomized controlled trials, the use of wearable devices in patients currently undergoing chemotherapy may significantly reduce the number of emergency admissions by allowing clinical teams to formulate more individualized plans for toxicity prevention, set realistic targets for activity levels, and avoid a significant number of unplanned admissions and therefore bed-days. These studies highlight both the strengths and weaknesses of wearable devices at this present time.

In terms of key weaknesses adherence can be a significant issue, particularly amongst older patients. A report from Age UK found that there are nearly 2 million over-75s in the UK who remain digitally excluded—the same age group in which the incidence of cancer diagnoses peaks in the UK.[37] This is a significant hurdle to overcome if use of these devices is to become routine.[38] Another issue noted among the trials that have been conducted thus far is the lack of consensus on how to define and measure physical activity, as demonstrated in the contrasting methods in these 2 studies. The data, while immature at present, does show promise for a role for passive patient-generated data from wearable devices in cancer patients, and as more data becomes available and devices become more reliable, the potential benefits will become clearer.

Whilst noting success within observational studies transitioning to using mHealth to deliver clinical interventions is more limited and time consuming as validation and comprehensive planning is necessary. A cohesive combination of apps and wearables could potentially proactively allow a platform to provide a complete HNA. This is not only by collecting personalized data for clinical decisions but by also empowering the patients in terms of planning future therapy and communicating explicatory information at a time of high anxiety.

## Circadian Phenotyping

The aforementioned "snapshot" behavioral and physiological digital data and the ecological momentary assessments in free-living conditions[39] that can be unobtrusively extracted from the signals collected by wearable biosensors have proven clinical interest in oncology, as discussed earlier. Nevertheless, the intrinsic characteristic of these devices of being continuously worn, day and night alike, allows the estimation of biological rhythms along different timescales, the most clinically relevant of which is the 24-hour one.[40] Although some earlier studies in cancer patients wearing wrist accelerometers had focused on either day-time physical activity or night-time sleep, the integration of both behaviors over the 24-hour span has been able to provide further characterization of patient's physiology.[41,42] Indeed,

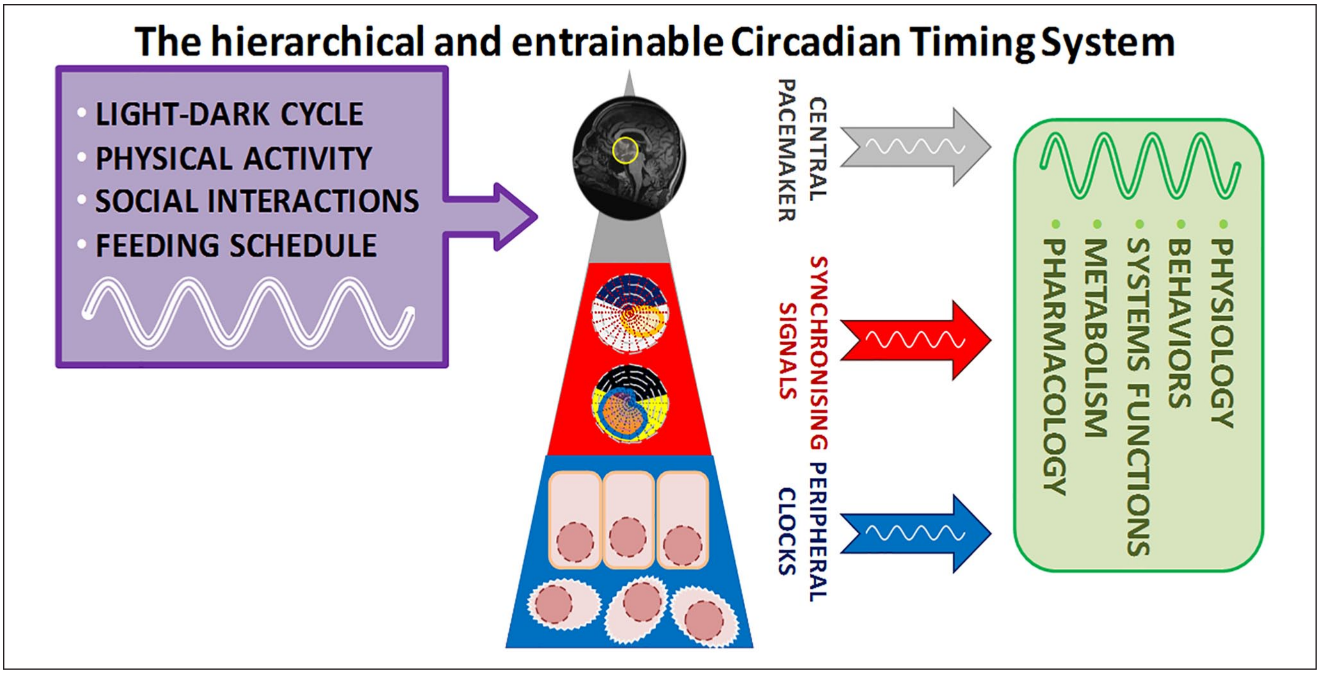

**Figure 2.** Schematic representation of the Circadian Timing System with its hypothalamic master pacemaker (Suprachiasmatic Nuclei, yellow circle), synchronizing signals (here depicted cortisol and core body temperature rhythms) and the myriad of peripheral molecular clocks. The main external synchronizing cues for humans are listed.

the multidimensional and longitudinal digital phenotyping that can be performed with modern wearable biosensors[43,44] should not overlook the biologically-paramount oscillations that occur across the day and night cycle.[45,46]

Thus, locomotor activity, as well as heart rate and skin temperature, frequently continuously measured by wearables,[26,47] all display physiological variations across the 24-hour span.[48,49] These rhythms, whose period is called circadian (ie, of about 24 hours), are endogenously generated and controlled by a hierarchical system, whose central pacemaker, the suprachiasmatic nuclei, is located in the hypothalamic region in the brain[50] (Figure 1). These paired nuclei convey periodical time cues to the rest of the body through neuronal, endocrinological and physiological rhythms[51] (Figure 1). These signals synchronize the molecular clocks ticking spontaneously in each nucleated cell of the body,[52] which in turn drive the oscillatory transcription of a significant proportion of the genome.[53,54] As a consequence of this, multiple aspects of physiology, behavior, apparats functions, metabolism, and pharmacology display robust circadian rhythms[45,46,54,55] (Figure 1). This endogenous circadian timing system can be further entrained through external cues, such as bright light or darkness, physical exercise, social interactions or feeding and fasting schedules[56,57] (Figure 2). Closely linked and temporally influenced by the circadian timing system is sleep process.[58,59] Thus, digital tools, especially wearable biosensors, allow the assessment of both circadian rhythms and sleep, alongside physical activity.[60-63]

The features of a circadian rhythm (assuming the period of 24 hours is sustained through social entraining cues) that can be extracted from the continuously-recorded time-series include the extent of variability within the 24-hour span (ie, the amplitude of the rhythm), the degree of reproducibility from day to day (ie, the robustness of the rhythm), the time of its highest (zenith) or lowest (nadir) points (ie, the phase of the rhythm), the presence or not of rhythms with shorter (ultradian) or longer (infradian) periods, and the coherence or not of different rhythms within the same individual (internal synchronization or desynchronization, respectively).[64-74]

Circadian physiology, as well as sleep and physical exercise, are relevant in cancer, especially in case of disturbance. Thus, circadian disruption has been associated with increased risk or increased severity of a plethora of illnesses, including cancer.[75,76] Indeed, circadian disruption has been classified as probably carcinogenic to humans.[77,78] Additionally, disruption of the function of the circadian timing system, as assumed from the alteration in surrogate biomarker rhythms, is associated with worse overall survival, independently from other prognostic factors, in various cancer types.[79] Moreover, even anticancer treatments, and the associated support medications, could alter the function of the circadian timing system as an undesired or a sought-after effect.

In order to retrieve the most informative and potentially actionable insight from the multidimensional and longitudinal time-series derived from patient-generated subjective and objective data, a truly multidisciplinary team is required

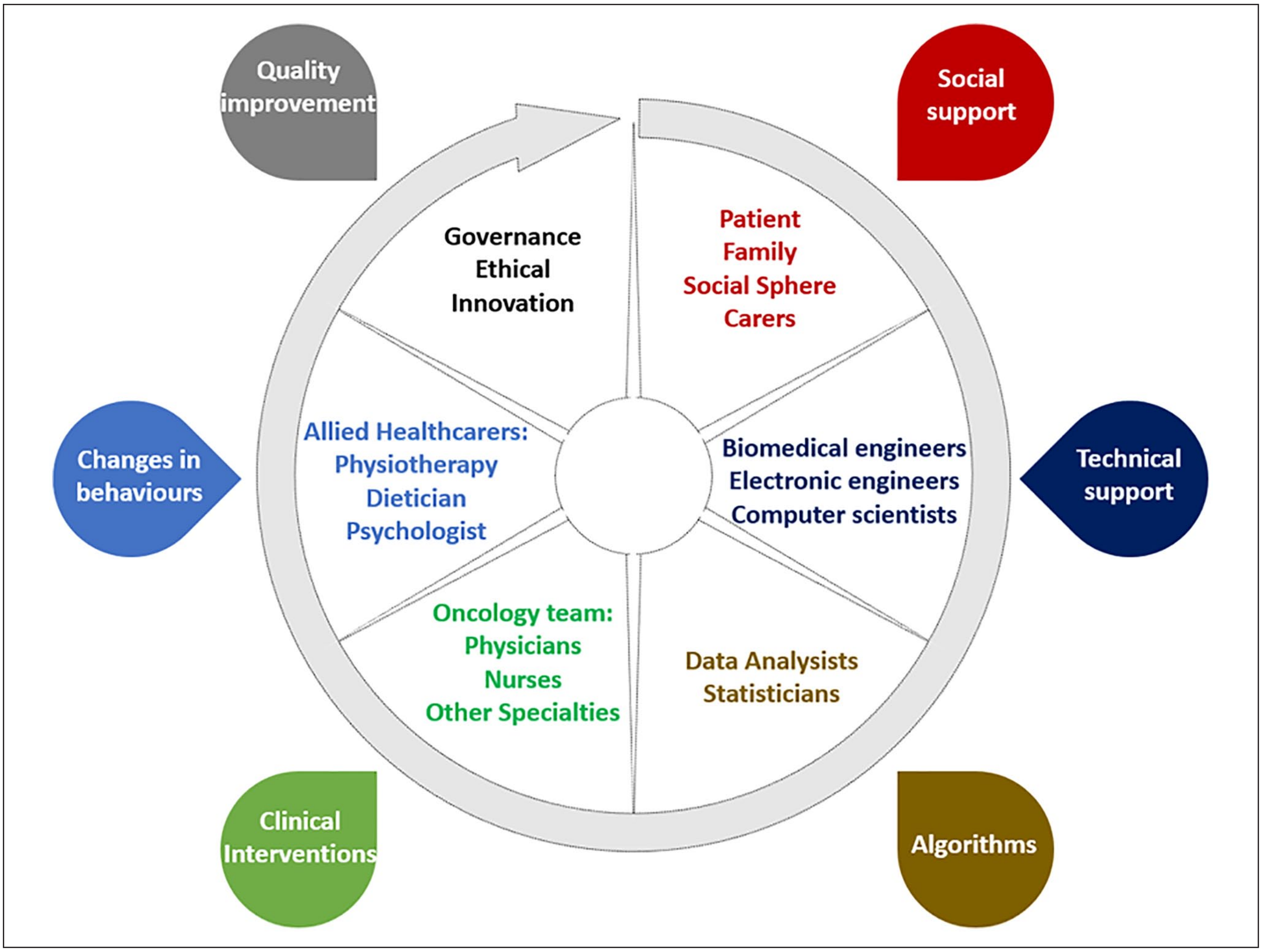

**Figure 3.** The circle of key players and multidisciplinary teams potentially implicated in digital health studies in oncology, with their chief aims; a wide overlap obviously exists.

(Figure 3). Thus, the patients and their social sphere are the main stakeholders for their health,[80] and their unmet needs, identified with the support of the clinical team in an holistic way, drive the digital solution development. The choice and integration of appropriate wearables and PRO measures, and the definition of their frequency of sampling will require abiding by clinical needs, feasibility, acceptability, usability and attrition, patients' preferences, and technical constraints.[25,31,81-83] The analytical algorithms that provide the most relevant insight to the clinical team and the patient need to be developed, tested and improved, and ideally coupled with predictive and interpolative algorithms to maximize the potential benefit to the patients.[84-86] The caring team at large, both hospital- and community-based, should integrate not only the nursing and physician actors, but also the allied healthcare staff who could promote effective and safe behavioral interventions on patient's physical and psychological domains.[87,88] Any integrative solution would need to be overseen from the ethical, governance and cost-effectiveness viewpoints, but also to undergo reiterated cycles assess-plan-do-review, in order to provide constant quality improvement (Figure 3).

Thus, the integration of all these multidisciplinary skills is required for a potentially impactful digital phenotyping of cancer patients, and most of ongoing projects worldwide in this domain rely on such broad teams. In particular, with regards to the holistic assessment of cancer patient's needs, we believe that the combination of repeated-measure subjective data on symptoms and health-related quality of life, captured with ePROs and the physiological and behavioral data passively, unobtrusively and continuously collected with the appropriate wearable provide the most valuable insight into cancer patient's unmet needs, that could be intervened upon in a personalized and timely manner. For this, the assessment of circadian function is relevant for its impact on several domains of wellbeing and on symptoms.

Thus, circadian disruption in healthy subjects caused by night- or rotating- shift work[89,90] or long haul transmeridian

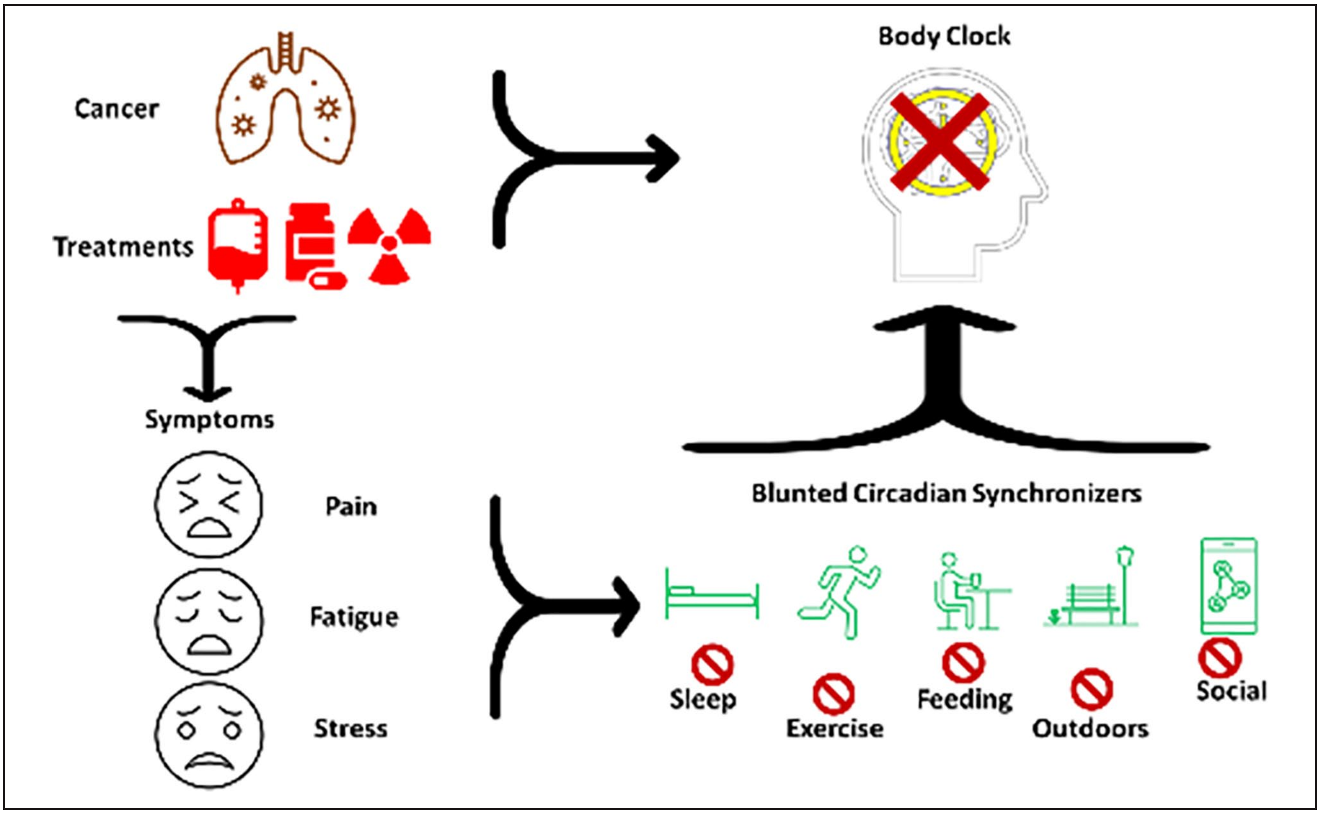

**Figure 4.** The impact of cancer processes and anticancer treatments on the circadian timing system includes direct mechanisms and indirect ones, mediated by blunted synchronizers as a consequence of symptoms.

flights (jet-lag)[91,92] has been associated with a plethora of symptoms related to multiple holistic compartments elicited by the internal desynchronization.[59,76,93] Interestingly, these same symptoms are also the most prevalent complaints of patients with cancer, on or off treatment.[94-98] As one example, the clustering of constitutional symptoms (such as fatigue, insomnia, anorexia) and psycho-emotional ones (mood alterations) has been frequently described in patients with cancer and in subjects intolerant to jet-lag or shift work alike,[55] raising the possibility that a common shared mechanism, circadian disruption, might be implicated.[99] Indeed, altered circadian rest-activity rhythm has been shown to correlate not only with constitutional symptoms (fatigue, anorexia), but also with physical and emotional domains of health-related quality of life and general well-being.[100] Altered physical and emotional characteristics driven by circadian irregularities can impact a patient's holistic needs in a multitude of ways ranging from relationships to physical performance. Elevated levels of circulating pro-inflammatory cytokines, induced by both cancer processes and anticancer treatments, which can alter the circadian coordination centrally, have been indeed shown to be associated with the clustering of fatigue and anorexia in cancer patients.[41] Circadian disruption could also account for digestive complaints,[101] sleep troubles,[102] and altered metabolism.[103] Thus, the accurate evaluation of circadian function through remote monitoring of cancer patients[83] could represent a biomarker of physiological and behavioral alteration,[75] a surrogate of symptom burden and of subjective complaints,[100,104,105] as well as a potential novel target of intervention, both pharmacological and behavioral.[79]

In addition, the behaviors resulting from the experience of fatigue, pain and psychological distress, such as poor sleep, lack of physical exercise, reduced time outdoors, erratic feeding patterns, and social isolation, generated by both the cancer itself and the anticancer treatments, can all negatively impact on the circadian coordination (Figure 4). Indeed, regular sleep patterns and feeding schedules, bright light exposure, and robust interpersonal relationships all act as entraining cues of the circadian system[56,57] and, when blunted, such as often in cancer patients, could result in even weaker circadian synchronization (Figure 4). This highlights the relevance of a true holistic and long-term assessment in cancer patients in order to grasp the instances of co-occurring and concomitantly evolving symptoms and physiological alterations. Appropriately validated and purposely developed modern digital tools, therefore, including mobile applications and wearable biosensors, as well as dedicated clinically-oriented analytical algorithms, can be harnessed to help clinicians better understand the physical and emotional burden of cancer patients, and develop personalized, precise, and timely interventions.

In summary, 2022 and onward marks an opportunity to embrace comprehensive clinical monitoring with daily proactive ePROs collected in conjunction with well validated wearable devices to improve the concordance of patients and clinicians' interpretation of cancer symptoms with a view to improving delivery of cancer therapy and reducing toxic effects, as well as to increasing patients' wellbeing and experience with care. There is widespread interest in the topic, with multiple projects ongoing to improve the tools and the understanding of the novel big data generated. These technological advances are likely to foster and blend the key understandings from chronobiology and chronotherapeutics research to improve personalized cancer care.

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