Wearables, sensors, and smart devices for the detection and monitoring of chemotherapy-induced peripheral neurotoxicity: systematic review and directions for future research

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Abstract

Background and aims. Chemotherapy-induced peripheral neurotoxicity (CIPN) diagnosis is largely based on patient reported outcomes. Wearables, sensors, and smart devices may potentially provide early detection and monitoring of CIPN. We systematically reviewed data on wearables, sensors, and smart devices to detect and/or monitor signs and symptoms of CIPN. Moreover, we provide directions and recommendations for future studies.

Methods. A literature search using PubMed/MEDLINE, Web of Science, IEEE Xplore and CINHAL databases was conducted from database inception until March 2021. The search was further updated in July 2022 to ensure currency of results.

Results. 1885 records were title-abstract screened, 33 full texts were assessed, and 16 were included. The retrieved papers were heterogeneous in terms of study design, sample size, CIPN severity, chemotherapy agents, type of wearable/sensor/device applied, parameters of interest and purpose.

Interpretation. Data are promising and provide preliminary evidence on wearables, sensors, and smart devices for CIPN detection and monitoring. There are several issues and knowledge gaps that should be addressed. We propose a framework for future studies.

Keywords. Chemotherapy-induced peripheral neurotoxicity (CIPN); evidence-based medicine; information and communication technology (ICT); sensors; telemedicine.

Introduction

Chemotherapy-induced peripheral neurotoxicity (CIPN) is the most common non-hematological dose-limiting toxicity during or after exposure to several widely used agents in the adjuvant and metastatic setting of several types of cancer [1-3]. CIPN can affect up to 70% of patients exposed to neurotoxic compounds [4,5], may improve after chemotherapy discontinuation, but can persist longer and be only partially reversible, particularly for platinums, because of the so-called "coasting" phenomenon [6]. A clinically significant grade 2 or treatment-emergent grade 3 CIPN may frequently cause treatment delay, dose reduction or even discontinuation [7], potentially affecting patients' survival, but also significantly downgrading quality of life and ability to walk independently [8].

CIPN is a predominantly sensory neuronopathy, mainly because of apoptosis in dorsal root ganglia neurons and other pathogenetic alterations, but occasionally motor and autonomic changes may occur and impose additional burden on long-term cancer survivors [1]. Common CIPN symptoms include numbness, tingling, burning, or shooting pain, impaired sensation in a stocking-and-glove distribution, and proprioception changes, while deep tendon reflexes are either reduced or abolished. Severely affected CIPN patients have unsteady gait, loss of balance and increased risk of falling, because of sensory ataxia [9,10].

There are no effective disease-modifying or symptomatic treatments for CIPN [1], probably because of the heterogeneity, number, and limited knowledge of pathogenetic mechanisms [11]. According to recently published guidelines, there is only a modest recommendation for the treatment of painful CIPN with duloxetine [12]. Rehabilitation, exercise, physical therapy, and other non-pharmacological approaches have been tested for CIPN, but studies are generally of low quality and data should be cautiously considered [13-15]. The only strategy to reduce CIPN symptoms is lowering the planned dose of chemotherapy or even discontinuation, which should consider cancer and patient factors and may have a negative effect on survival [7].

Delays in CIPN detection, leading to more severe neurotoxicity, increase the risk of irreversible effects that negatively influence long-term quality of life and health outcomes [16,17]. Accurate and early CIPN diagnosis during chemotherapy may reduce long-term or permanent neurotoxicity.

CIPN diagnosis is largely based on clinician impression of patient-reported symptoms, while an objective assessment of peripheral nerve damage is less frequently used [18]. Some patients may be unable or unwilling to describe CIPN symptoms, requiring objective assessment for CIPN detection [19]. Many potential objective measures have been proposed for CIPN assessment, including nerve conduction study (NCS), quantitative sensory testing, nerve excitability study, nerve imaging, skin biopsy, corneal confocal microscopy, laser-evoked and contact heat-related potentials, microneurography, and functional testing, such as, balance,

walking, strength, or manual dexterity [18]. Although not being able to fully assess the extent of small nerve fiber damage, NCS is the most applied objective technique to assess CIPN severity in the clinical setting. The other techniques are not routinely used, due to the need for specialized equipment, cost, trained personnel, and additional clinical time, combined with the lack of prospective confirmation that they may improve clinical outcomes.

Optimally, the ability of conducting remote assessment of CIPN would be particularly convenient, especially considering the healthcare changes during the COVID-19 pandemic [20]. In this setting, Information and Communication Technology (ICT) might be useful to detect early signs of CIPN through objective measures of nerve damage and monitor their course. Internet of Things (IoT), and more specifically, Internet of Medical Things (IoMT) have shown to be effective for the implementation of low-cost and ubiquitous solutions to promote healthy lifestyles and monitor patient's parameters and symptoms in various diseases. IoT and IoMT rely on smart devices (e.g., ambient and wearable sensors, actuators) and software applications, which are connected to the Internet, use artificial intelligence, and communicate with each other to cooperate with humans. While IoT generally uses consumer devices, being more suited for wellbeing, IoMT specifically adopts smart medical devices. As many devices may be wearable or portable, IoMT allows for remote monitoring at home, thus offering a more ecological view of patient's reports and performances, in comparison to the time-restricted traditional outpatient consultation. These solutions have been successfully applied for monitoring Parkinson's disease signs and symptoms [21-23], detecting atrial fibrillation [24,25] or managing diabetes-related complications [26] at home. Table 1 summarizes the definition of IoT, IoMT and related devices.

The aims of this paper are threefold. The first is to perform a systematic review on wearables, sensors, smart devices, and related applications for detecting and monitoring CIPN in cancer patients undergoing neurotoxic chemotherapy. The second is to extend the search to devices that have been applied to CIPN and may be engineered and integrated in IoT/IoMT architectures. The third is to provide directions for future studies aimed to assess the role of IoMT-based solutions for CIPN detection and monitoring.

Methods

Systematic review. The systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations [27,28]. The review protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD42021246784).

Eligibility criteria. Inclusion/exclusion criteria: a) feasibility/pilot, cross-sectional, case-controlled, cohort,

prospective clinical trials aimed to detect and monitor sensory, motor and autonomic symptoms and/or signs in patients at risk of developing CIPN (i.e., patients receiving any neurotoxic chemotherapy), or with overt CIPN; b) studies published in English; c) no restrictions on the publication date; d) full text available (i.e., conference proceedings excluded if only in abstract form); e) no reviews, editorials, commentaries, abstracts, f) no studies on animal models, healthy subjects or aimed to assess CIPN-related pathophysiology; g) articles excluded if they did not report data derived from the use of any form of wearable, sensor, or other devices that can be engineered and integrated in IoT/IoMT architectures. All electronic technologies designed to be worn on the body or embedded into wearable devices (e.g., smart-watches, bracelets), as well as medical devices allowing the objective assessment of CIPN-related parameters were considered eligible.

PICo model. *Patients* (P) were cancer patients of any age with CIPN or receiving treatment with neurotoxic anticancer agents tested at different timepoints (i.e., before/after CIPN development and/or during CIPN worsening/improvement); the variable of *Interest* (I) was related to wearables, sensors, and other devices applied to detect and/or monitor the presence and/or changes in the signs or symptoms related to CIPN, i.e., spatiotemporal parameters of gait and balance (e.g., gait speed, area of ankle sway), and manual dexterity (e.g., amplitude of the movement to remove pegs in the dominant hand), pain, paresthesia, sensory or motor symptoms, autonomic changes; the *Context* (Co) included home-based, laboratory, hospital or outpatient clinic settings. Being aware that the number of studies on wearables and sensors was limited, we extended the search to devices for the assessment of CIPN [18] that could be engineered into novel wearable/portable systems and integrated with IoT/IoMT architectures to detect or remotely monitor CIPN symptoms and signs. However, for the purpose of this systematic review, we included the main devices, instruments and systems that were tested to objectively assess the main features of CIPN, and not any existing device that could be conceivably adapted to monitor CIPN remotely via IoT/IoMT.

Search Strategy. The PubMed/MEDLINE, Web of Science, IEEE Xplore and CINHAL databases were searched on March 24th 2021 for peer-reviewed papers published from database inception with the following search string: (Paclitaxel OR docetaxel OR taxane OR oxaliplatin OR cisplatin OR platinum OR vincristine OR vinca OR vinblastine OR thalidomide OR lenalidomide OR pomalidomide OR bortezomib OR ixazomib OR carfilzomib OR ixabepilone OR cabazitaxel OR eribulin OR carboplatin OR chemotherap*) AND (chemotherapy induced peripheral neuropathy OR CIPN OR neuropath* OR neurotoxic* OR neuropathic pain OR neuralgia OR peripheral neuropathy OR peripheral nervous system diseases) AND (wearable OR wearable technology OR sensor OR device OR tracker OR accelerometer OR gyroscope OR smartphone OR magnetometer OR smartwatch OR “inertial sensors” OR machine learning OR deep learning OR signal

processing OR artificial intelligence OR “e-health” OR “electronic health” OR internet of things OR telemedicine). Additional searches identified papers on devices for the assessment of CIPN that could be engineered and integrated for CIPN early diagnosis and remote monitoring. The following keywords were combined with those related to CIPN: “sympathetic skin response”, “autonomic testing”, “heart rate variability”, “quantitative sensory testing”, “microneurography”, “small nerve fiber function”, “nerve excitability”, “nerve conduction”. The literature search was rerun on July 20th 2022 to ensure currency of results. Each database was searched separately. References from retrieved papers were hand-searched for other relevant studies potentially missed in the literature search and gray literature (i.e., reports not controlled by commercial publishers, including non-peer-reviewed academic papers, theses, conference papers, etc.) [29] was consulted for additional relevant reports.

Study selection. Search results were uploaded to Rayyan software, a web-based application to facilitate collaborations among reviewers during the selection of the studies [30]. Two authors (EM, CT) independently screened titles and abstracts. Any disagreement was solved by consensus or consulting two other authors (FD, ST).

Data collection. Two authors (EM, CT) independently extracted the following data from the included papers: study design, population (gender, age, sample size), CIPN severity, cancer type, chemotherapy agent, time since chemotherapy completion/last chemotherapy cycle (for studies on cancer patients at risk of developing CIPN), data source (i.e., wearable/device/sensor type), wearable/device/sensor purpose, assessment protocol, features extraction and selection, main results.

Data analysis. A systematic and descriptive analysis of the results was reported in the text and tables were generated to summarize the characteristics and findings of the included studies. A meta-analysis was not feasible due to the small number and heterogeneity of the included studies.

Risk of bias. Risk of bias in the determination of whether the sensor could detect or monitor CIPN was assessed independently by two authors (EM, ST) using the Quality Assessment of Diagnostic Accuracy Studies, version 2 (QUADAS-2) tool, which examines the following domains: patient selection, index test, reference standard, flow, and timing [31]. The potential risk of bias associated within each domain was rated as “low”, “high”, or “unclear”. Applicability of studies to the review question for each domain was also evaluated and judged in a “yes”, “no”, or “unclear” format, indicating low, high, and unclear risk of bias, respectively. Any disagreement was solved via consensus or by consulting a third author (FD).

Results

Identification and selection of the studies. A total of 1885 records were identified by literature search. After duplicate removal, 1709 papers were screened through title and abstract and 33 papers were obtained for full-text screening. No additional papers were retrieved from grey literature. Two authors (EM, CT) independently evaluated the papers (n = 33) selected for in-depth examination. Disagreement concerned two papers (inter-rater agreement: 94%) and was solved by consulting two other authors (FD, ST). Sixteen articles fulfilled the inclusion criteria and were therefore included in the systematic review (Figure 1). The included studies were heterogeneous in terms of cancer type, chemotherapy agents, CIPN severity and outcome measures. The retrieved studies were grouped according to the study design and aims. Six studies explored wearables, sensors and IoMT devices, of which five to detect or monitor CIPN [32-36], and one for other purposes, i.e., rehabilitation, in CIPN patients (Table 2) [37]. Ten studies assessed CIPN through devices that could be engineered into novel wearable/portable systems and integrated with IoT/IoMT architectures (Table 3) [38-47].

Studies assessing sensors and IoMT devices to detect or monitor CIPN. A pilot study compared PeriVib, a portable system for peripheral neuropathy detection with two other established devices (i.e., Biothesiometer, tuning fork) for sensation threshold estimation in 28 patients with CIPN and found better correlation between PeriVib and the Biothesiometer than with the tuning fork [32]. Balance, sway and gait metrics collected by PeriVib did not correlate with CIPN severity according to other devices, questioning the specificity of the metrics for CIPN grading.

A case-control study explored the relationship between postural sways, falls and neurotoxicity in 434 female cancer survivors with/without CIPN compared to 49 healthy controls through a principal component analysis of the data collected by an inertial sensor (Opal v1, APDM, Inc. Portland, OR USA) over the lumbar spine. The study found unique associations between specific components of sway, fall risk and CIPN, with jerkiness of resultant and anteroposterior postural sway being most associated with CIPN symptoms [33].

An observational cohort study explored whether two validated wearable technologies for gait and balance assessment, namely LEGSys™ and BalanSens™ (Biosensics LLC, Watertown, MA, USA), both based on the same hardware configuration of five wearable inertial sensors over shins, thighs, and lower back, could measure the magnitude of deterioration in motor performance in 84 cancer patients with different CIPN severity [34]. Despite reporting gait and balance measures to deteriorate over time irrespective of CIPN presence, the Authors confirmed the negative impact of CIPN on motor performance by showing an additional increase of vision dependency during balance testing when comparing patients with vs. without CIPN.

A cross-sectional pilot study explored the feasibility of remote functional CIPN assessment by means of

NeuroDetect, a smartphone application that collects both subjective (i.e., patient-reported outcome) and objective (i.e., gait and manual dexterity assessment) data on 26 cancer survivors, who were classified as having/not having CIPN according to a validated questionnaire and performed the functional assessment at a single timepoint after the completion of chemotherapy, with the device placed in a pocket [35]. The study confirmed the feasibility of remote CIPN assessment and showed that specific gait, balance, and hand dexterity features identified by smartphone sensors were significantly associated with CIPN symptoms.

A secondary case-control analysis nested within a previously conducted clinical trial examined the effect of cancer-related fatigue on mobility performance of 28 cancer survivors with CIPN of various severities [36]. Daily physical activity over a 48-hour period was recorded by PAMSys™ (BioSensics LLC, MA, USA), a tri-axial accelerometer that was worn by patients as a pendant. PAMSys™ detected a significant deterioration in mobility performance in terms of increased sedentary activities and cumulative sedentary postures, and decreased locomotion activities, in patients with vs. without cancer-related fatigue, thoroughly suggesting that this system may be considered to assess CIPN severity.

A pilot, single-blind, randomized controlled trial, tested the efficacy of a 4-week interactive motor adaptation balance training program based on wearable inertial sensors (LEGSys™ and BalanSens™, Biosensics LLC, Watertown, MA, USA) over shanks, thighs, and lower back, for improving balance in older cancer survivors with moderate-to-severe CIPN [37]. Wearable sensors were used both for providing real-time feedback during balance training and for assessing balance and gait as outcome measures to explore the effects of the proposed intervention and a significantly greater improvement of postural control was reported for active intervention than standard care.

Studies exploring devices that may be engineered and integrated with IoT/IoMT architectures. The included studies explored devices to assess NCS [38,39], autonomic system [40-42], pain pathways [43-46], and for the combined assessment of vibratory threshold and autonomic system [47] (Table 3).

A prospective observational study tested DPNCheck (NeuroMetrix Inc., Waltham, MA, USA), a point-of-care nerve conduction device originally developed for diabetic peripheral neuropathy, in 50 cancer survivors with a clinical diagnosis of CIPN [38]. The Authors found that CIPN severity according to the National Cancer Institute-Common Terminology Criteria for Adverse Events Version 4.0 (NCI-CTCAE 4.0) grade was associated with sural nerve conduction measured by the DPNCheck. A point-of-care nerve conduction device (Mediracer® NCS), previously tested on carpal tunnel syndrome and diabetic neuropathy, was evaluated for early detection of CIPN in a pilot prospective study on 12 patients receiving chemotherapy. The device could

detect peripheral nerve damage in patients undergoing oxaliplatin, by identifying longitudinal NCS changes, but measurements frequently failed especially in patients with pre-existing high-risk for neuropathy [39].

A proof-of-concept study on 24 cancer patients with CIPN diagnosis found laser Doppler imager $(LDI)_{FLARE}$, a noninvasive method for assessing small nerve fiber function, previously used in diabetic neuropathy, to significantly correlate with scores from subjective CIPN symptoms questionnaires [40].

A prospective observational study explored Sudoscan (Impeto Medical, Paris, France), a device designed to objectively measure sudomotor function, as an indirect measure of small nerve fiber impairment, in 88 cancer patients under neurotoxic treatment [41]. Patients were evaluated at each chemotherapy infusion with the Total Neuropathy Score clinical version (TNSc) and Sudoscan and worsening of electrochemical skin conductance was found to occur earlier than TNSc deterioration. A non-inferiority prospective study compared the sensitivity and specificity of the Sudoscan device (Impeto Medical, Paris, France) to NCS for early detection of bortezomib-induced peripheral neuropathy at baseline and at 6-month follow-up in 18 patients with multiple myeloma. Sudoscan was not inferior to NCS and showed better agreement with neuropathy scales than NCS [42].

In a secondary analysis of a prospective observational study on 29 cancer patients at CIPN risk, Neurometer (Neurotron, Baltimore, MD, USA), a device designed to measure current perception threshold by painless electrical stimulus, was found to be significantly associated with subjective and objective measures of CIPN [43].

Pain Vision® PS-2100 (Nipro Co., Ltd.), a device marketed for the assessment of electrical perceptual threshold in diabetic peripheral neuropathy, was tested in three prospective observational studies assessing neurotoxic symptoms in cancer patients. While all studies found a significant correlation between the decrease in pain perception/somatosensory threshold and subjective/clinician ratings-based measures of CIPN (e.g., NCI-CTCAE 4.0, Peripheral Neuropathic Questionnaire) [44-46], no significant results were found when comparing Pain Vision to objective measures of neurotoxicity [45].

In a cross-sectional, pilot study to explore the relationship between self-reported CIPN symptoms and sensory (i.e., vibration perception threshold, VPT) and autonomic (i.e., heart rate variability, HRV) objective measures, elevated VPTs and decreased HRV were found in cancer patients who developed neurotoxicity symptoms [47].

Risk of bias. Only studies aimed at CIPN detection and monitoring [39,41-46] were assessed with the QUADAS-2 tool. The patient selection domain was judged at low risk of bias for nearly all studies, in that most of them recruited consecutive patients and avoided case-control designs, or inappropriate exclusion criteria.

In contrast, the risk of bias for the remaining domains (i.e., index test, reference standard, flow and timing) was rated as being unclear, since information reported was insufficient to permit judgment. Nevertheless, applicability was considered of low concern for nearly all studies in all the considered domains (Figure 2).

Discussion

This systematic review on wearables, sensors, and other smart devices and related applications to detect and/or monitor CIPN signs and symptoms in cancer patients undergoing neurotoxic chemotherapy retrieved sixteen studies, of which five were on body worn wearables, sensors, and devices to detect or monitor CIPN [32-36], ten used devices that may be engineered and integrated in IoT/IoMT architectures [38-47] and one was an IoMT solution for CIPN treatment or prevention but was included as proof-of-concept study to assess CIPN lower-limb signs [37]. The included studies were quite heterogeneous in terms of patient populations (i.e., cancer patients at risk of developing CIPN vs. patients with already established CIPN), design (i.e., mainly pilot/feasibility trials), outcome measures, devices/wearables/sensors applied, all factors that precluded a meta-analytical approach. The risk of bias was unclear for many of the assessed domains, but the lack of a specific risk of bias tool for studies on wearables, sensors and IoMT solutions impede robust conclusions on this issue.

Nine studies were performed on cancer patients with established CIPN [32-36,38,40,42,47], and seven studies focused on cancer patients at risk of developing CIPN, i.e., receiving neurotoxic chemotherapeutic regimens, [37,39,41,43-46]. Five studies aimed to monitor CIPN evolution over time [39,41,43-45]. Taken together these reports suggest an increasing interest for wearables and other devices in CIPN objective assessment, but a still very limited contribution to CIPN detection and monitoring in the clinical setting.

Studies differed in the assessment of upper- and lower-limb outcomes and of motor, sensory and autonomic measures. Six papers focused on quantifying postural and walking impairment, with balance and gait being the most frequently assessed parameters [32-37]. Lower-limb sensory measures were reported in three studies [32,38,43]. Upper-limb sensorimotor function was assessed in one study evaluating manual dexterity with 9-Hole Peg Test [35], and five studies that explored upper-limb sensory parameters [39,44-47]. Four studies explored autonomic measures [40-42,47]. Sensory CIPN symptoms (e.g., numbness, tingling, altered touch sensation, impaired vibration) are known to develop first in CIPN, whereas motor and autonomic signs occur less frequently and to a varying degree according to chemotherapeutic agents [48]. Counterintuitively, only half of the studies assessed CIPN sensory symptoms [32,41,43-47] and NCS [38,39], while the other ones focused on motor [33-37] and autonomic measures [40-42,47]. This finding may be related to the more

advanced stage and larger clinical applications in other neurological conditions, e.g., Parkinson's disease [21] and diabetic peripheral neuropathy (DPN) [26], of wearable/sensor technologies to assess human movement features than those measuring sensory function. Lower-limb sensorimotor dysfunction is a relevant outcome in CIPN, as it increases the risk of falling. Hand sensorimotor function is frequently affected by neurotoxic effects of chemotherapy [49], being reduced manual strength, dexterity, and skilled hand functions (e.g., typing, writing, buttoning a shirt, picking up small objects) frequently impaired in CIPN patients [50]. Gait, balance, and hand motor function might be a promising target for wearables and IoMT devices in CIPN, but their impairment is due to sensory neuropathy, which is an indirect assay of sensory dysfunction rather than being solely focused on motor function. Thus, devices already applied to neurological conditions where motor symptoms/signs are prevalent (e.g., Parkinson's disease), might require a tailoring for optimal assessment of CIPN patients. Moreover, some studies explored pain-related outcomes [43-46], whose pathophysiology differs from that of other CIPN sensory symptoms (e.g., numbness, tingling, impaired stocking-and-glove sensation), and of proprioception changes that cause gait and balance deficits.

In light of the shared axonal degeneration mechanisms underlying both DPN and CIPN [4], some studies applied marketed medical devices already used for DPN in CIPN patients and reported interesting preliminary results [38,39,41-46]. The development of wearable systems to offer objective measures of peripheral nerve damage (e.g., nerve conduction measures) [18,38,39] may broaden their application in less specialized clinical centers and in home-based contexts, but data are very preliminary.

The included studies show an increasing interest on the use wearable/portable technologies in CIPN, though their development is less advanced than in other diseases such as Parkinson's disease [21,23], cardiovascular diseases [24,25], and diabetes [26], and the available studies had some critical limitations. First, many studies did not report or only partially reported clinical and chemotherapy information [32-34,36,37,39,40,43]. Data on chemotherapeutic agents/protocols and dose regimens are essential for the design of IoMT devices, because of the great variety of peripheral nerve (e.g., large vs. small fiber, sensory vs. motor, demyelinating vs. axonal, somatic vs. autonomic) damage that depends on the chemotherapy compound and cumulative dosage [51]. Second, most studies were performed in a laboratory or clinical setting [32-34,38-47], thus offering limited evidence on the possible real-world usefulness of these tools. Monitoring patients in a daily-living environment and over continuous periods of time can make CIPN assessment more feasible and ecological. Some of the included devices, e.g., NeuroDetect [35], Perivib [32], and inertial sensor [33], have been developed for convenient home-based remote monitoring. Other technologies, such as PainVision [44-46], Sudoscan [41,42], DPNCheck [38] and Mediracer® NCS [39] require specialized equipment that is not available for home

use and may be less convenient for daily monitoring, but they may be engineered and integrated with IoT/IoMT architectures. Some devices to measure autonomic function are available and marketed [52], while NCS and pain pathways testing will require the development of specific devices (Table 4). Third, most studies assessed a single population, often patients with established CIPN, without providing further data on their applicability or reproducibility for discriminating patients who are and are not developing CIPN. This is a necessary first step, but future studies will need to conduct repeated, longitudinal assessments to determine whether these tools detect CIPN accurately and perhaps earlier than current methods that are largely based on patient-reported outcomes. Also, the great variety of hardware used in the included studies, as well as the different methodologies, where reported, for the analysis of the acquired data make the comparison between studies difficult. Finally, several other critical technical features concerning IoMT devices such as portability, usability, cost, data accuracy and security, privacy issues, storage, and battery life/energy consumption parameters were not considered in the included studies.

Potential wearables and IoMT solutions that are commercially available and can be used for the assessment of CIPN outcome measures in a home-based setting are reported in Table 4. Patient reported outcomes, i.e., CIPN sensory symptoms and pain severity, disability, quality of life, and other symptoms and subjective complains, might be measured with speech interaction by environmental sensors, questionnaire administration, speech recognition systems and commercially available mobile phones. Somatosensory thresholds and function might be evaluated by wearable and portable devices, with some sensors already available. Assessment of sensorimotor function, gait and balance is based on wearable devices, smartwatches and wrist bands that integrate inertial and physiological sensors to recognize specific motor tasks, and smartphones with mobile apps and human activity recognition algorithms. A range of commercially available accelerometers, gyroscopes, compasses, GPS devices, mobile phones and smartwatches/wristbands may be used to assess sensorimotor function. Other instrumental measures, e.g., NCS, autonomic testing and pain pathways testing should be considered very preliminary in this context, as there are few available devices, mainly for autonomic testing (e.g., E4 Wristband, NeXus Skin Conductance Sensor, Emotion Pharos 180) and they have not been explored in CIPN, yet. The instrumental assessment of CIPN measures via devices and IoT/IoMT solutions might represent an important field of development that might be applied to other peripheral neuropathies.

Despite the limited number of retrieved studies and their heterogeneity, the results of this systematic review provide preliminary data on the potential application of wearables, sensors and IoMT solutions for CIPN

detection and monitoring. Whether these solutions are more sensitive than patient-related outcomes and more effective, less expensive, and more acceptable than other instrumental techniques are unanswered questions. However, there are still several issues and knowledge gaps that should be addressed to improve their implementation in clinical contexts. Based on these lines of reasoning, we propose a framework to enable the design of future studies on IoMT solutions for CIPN early detection and monitoring.

Future clinical studies are needed to continue moving this field forward. There are at least three separate study objectives, each with different designs. Most of the studies that have been conducted are pilot studies to test whether the sensors detect CIPN. This can be done in cross-sectional or case-control studies. The next step is to conduct prospective observational studies to determine whether the sensors, wearables and devices detect CIPN, and whether this occurs earlier than current methods. Clinical translation will likely require randomized prospective clinical trials to demonstrate that using the sensor improves a meaningful clinical outcome, such as occurrence of severe and/or irreversible CIPN, or chemotherapy treatment disruption due to CIPN. Finally, in analogy with other clinical conditions, the development of wearable biosensors to measure chemotherapy compound levels in patients' interstitial fluid to predict the dose threshold for developing severe grade 3 neurotoxicity, might be of a particular interest for future research to pursue [53].

Although details of these methods will depend on the objective, in general we recommend that trials take into considerations the following clinical and technical/engineering issues.

Clinical issues considering patient and CIPN characteristics are: a) always include clinical information on cancer participants (e.g., cancer type, stage, chemotherapy compound and cumulative dosage, CIPN staging and severity, comorbidities accounting for peripheral nerve damage); b) provide control groups allowing both the validation and comparison of novel solutions to established assessment methods, which should likely include a patient-reported outcome tool; c) design devices that combine CIPN related outcomes (i.e., patients reported outcomes, upper/lower-limb objective measures); d) focus on developing sensors/devices/wearables that could be applied remotely to assess real-world usefulness; e) include pre-treatment collection and repeated assessment during chemotherapy treatment, to enable determination of the sensitivity for CIPN detection in comparison to patient reported outcomes, clinical assessment or instrumental tools and its timing (i.e., earlier than traditional assessment); f) provide adequate analysis of the data (e.g., intention to treat, last observation carried forward); g) select appropriate devices by taking into consideration specific CIPN features to be explored (Table 5).

Technical/engineering issues are: h) devices, sensors and data acquisition features should be tailored to the specific CIPN clinical features to be explored; i) device battery, computational resources, storage, wireless

communication protocols should be considered; j) usability, wearability, accessibility measures, compliance and persistence should be among the assessed outcomes; k) consider appropriate design, reliability, safety, security, affordability and privacy of IoMT infrastructures and related devices; l) define and tailor the procedures for the development of smart apps (Table 5).

An appropriate technological framework, pragmatic regulatory policies, and a standardized protocol for data acquisition and analysis are needed to develop easily accessible devices and increase results validity by recruiting larger number of patients in multicenter clinical trials. Addressing these points could broaden the application of IoMT solutions for CIPN detection and monitoring to real-world clinical contexts, to help the treating oncologists to better manage and hopefully prevent irreversible CIPN symptoms in patients with cancer. Future studies should assess digital biomarkers as potential new CIPN predictors and the role of IoMT solutions and digital biomarkers in neuroprotection clinical trial (Table 5).

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References

1. Cavaletti G, Alberti P, Argyriou AA, et al. Chemotherapy-induced peripheral neurotoxicity: A multifaceted, still unsolved issue. J Peripher Nerv Syst. 2019;24 Suppl 2:S6-S12. doi:10.1111/jns.12337
2. Tamburin S, Park SB, Alberti P, Demichelis C, Schenone A, Argyriou AA. Taxane and epothilone-induced peripheral neurotoxicity: From pathogenesis to treatment. J Peripher Nerv Syst. 2019;24 Suppl 2:S40-S51. doi:10.1111/jns.12336
3. Staff NP, Cavaletti G, Islam B, Lustberg M, Psimaras D, Tamburin S. Platinum-induced peripheral neurotoxicity: From pathogenesis to treatment. J Peripher Nerv Syst. 2019;24 Suppl 2(Suppl 2):S26-S39. doi:10.1111/jns.12335
4. Park SB, Goldstein D, Krishnan AV, et al. Chemotherapy-induced peripheral neurotoxicity: a critical analysis. CA Cancer J Clin. 2013;63(6):419-437. doi:10.3322/caac.21204
5. Seretny M, Currie GL, Sena ES, et al. Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy: A systematic review and meta-analysis. Pain. 2014;155(12):2461-2470. doi:10.1016/j.pain.2014.09.020
6. Mols F, Beijers T, Lemmens V, van den Hurk CJ, Vreugdenhil G, van de Poll-Franse LV. Chemotherapy-induced neuropathy and its association with quality of life among 2- to 11-year colorectal cancer survivors: results from the population-based PROFILES registry. J Clin Oncol. 2013;31(21):2699-2707. doi:10.1200/JCO.2013.49.1514
7. Hertz DL, Childs DS, Park SB, et al. Patient-centric decision framework for treatment alterations in patients with Chemotherapy-induced Peripheral Neuropathy (CIPN). Cancer Treat Rev. 2021;99:102241. doi:10.1016/j.ctrv.2021.102241
8. Gewandter JS, Kleckner AS, Marshall JH, et al. Chemotherapy-induced peripheral neuropathy (CIPN) and its treatment: an NIH Collaboratory study of claims data. Support Care Cancer. 2020;28(6):2553-2562. doi:10.1007/s00520-019-05063-x
9. Winters-Stone KM, Horak F, Jacobs PG, et al. Falls, Functioning, and Disability Among Women With Persistent Symptoms of Chemotherapy-Induced Peripheral Neuropathy. J Clin Oncol. 2017;35(23):2604-2612. doi:10.1200/JCO.2016.71.3552
10. Argyriou AA, Bruna J, Anastopoulou GG, Velasco R, Litsardopoulos P, Kalofonos HP. Assessing risk factors of falls in cancer patients with chemotherapy-induced peripheral neurotoxicity. Support Care Cancer. 2020;28(4):1991-1995. doi:10.1007/s00520-019-05023-5
11. Argyriou AA, Bruna J, Park SB, Cavaletti G. Emerging pharmacological strategies for the management of chemotherapy-induced peripheral neurotoxicity (CIPN), based on novel CIPN mechanisms. Expert Rev Neurother. 2020;20(10):1005-1016. doi:10.1080/14737175.2020.1796639
12. Loprinzi CL, Lacchetti C, Bleeker J, et al. Prevention and Management of Chemotherapy-Induced Peripheral Neuropathy in Survivors of Adult Cancers: ASCO Guideline Update. J Clin Oncol. 2020;38(28):3325-3348. doi:10.1200/JCO.20.01399
13. Kanzawa-Lee GA, Larson JL, Resnicow K, Smith EML. Exercise Effects on Chemotherapy-Induced Peripheral Neuropathy: A Comprehensive Integrative Review. Cancer Nurs. 2020;43(3):E172-E185. doi:10.1097/NCC.0000000000000801
14. Park SB, Tamburin S, Schenone A, et al. Optimal outcome measures for assessing exercise and

rehabilitation approaches in chemotherapy-induced peripheral-neurotoxicity: Systematic review and consensus expert opinion. Expert Rev Neurother. 2022;22(1):65-76. doi:10.1080/14737175.2022.2018300

15. Tamburin S, Park SB, Schenone A, et al. Rehabilitation, exercise, and related non-pharmacological interventions for chemotherapy-induced peripheral neurotoxicity: Systematic review and evidence-based recommendations. Crit Rev Oncol Hematol. 2022;171:103575. doi:10.1016/j.critrevonc.2021.103575
16. Eckhoff L, Knoop A, Jensen MB, Ewertz M. Persistence of docetaxel-induced neuropathy and impact on quality of life among breast cancer survivors. Eur J Cancer. 2015;51(3):292-300. doi:10.1016/j.ejca.2014.11.024
17. Pabst L, Velten M, Fischbach C, et al. Persistent taxane-induced neuropathy in elderly patients treated for localized breast cancer. Breast J. 2020;26(12):2376-2382. doi:10.1111/tbj.14123
18. Argyriou AA, Park SB, Islam B, et al. Neurophysiological, nerve imaging and other techniques to assess chemotherapy-induced peripheral neurotoxicity in the clinical and research settings. J Neurol Neurosurg Psychiatry. 2019;90(12):1361-1369. doi:10.1136/jnnp-2019-320969
19. Salgado TM, Quinn CS, Krumbach EK, et al. Reporting of paclitaxel-induced peripheral neuropathy symptoms to clinicians among women with breast cancer: a qualitative study. Support Care Cancer. 2020;28(9):4163-4172. doi:10.1007/s00520-019-05254-6
20. Mantovani E, Zucchella C, Bottiroli S, et al. Telemedicine and Virtual Reality for Cognitive Rehabilitation: A Roadmap for the COVID-19 Pandemic. Front Neurol. 2020;11:926. Published 2020 Sep 15. doi:10.3389/fneur.2020.00926
21. Corrà MF, Warmerdam E, Vila-Chã N, Maetzler W, Maia L. Wearable Health Technology to Quantify the Functional Impact of Peripheral Neuropathy on Mobility in Parkinson's Disease: A Systematic Review. Sensors (Basel). 2020;20(22):6627. Published 2020 Nov 19. doi:10.3390/s20226627
22. Demrozi F, Bacchin R, Tamburin S, Cristani M, Pravadelli G. Toward a Wearable System for Predicting Freezing of Gait in People Affected by Parkinson's Disease. IEEE J Biomed Health Inform. 2020;24(9):2444-2451. doi:10.1109/JBHI.2019.2952618
23. Omberg L, Chaibub Neto E, Perumal TM, et al. Remote smartphone monitoring of Parkinson's disease and individual response to therapy. Nat Biotechnol. 2022;40(4):480-487. doi:10.1038/s41587-021-00974-9
24. Steinhubl SR, Waalen J, Edwards AM, et al. Effect of a Home-Based Wearable Continuous ECG Monitoring Patch on Detection of Undiagnosed Atrial Fibrillation: The mSToPS Randomized Clinical Trial. JAMA. 2018;320(2):146-155. doi:10.1001/jama.2018.8102
25. Bayoumy K, Gaber M, Elshafeey A, et al. Smart wearable devices in cardiovascular care: where we are and how to move forward. Nat Rev Cardiol. 2021;18(8):581-599. doi:10.1038/s41569-021-00522-7
26. Golledge J, Fernando M, Lazzarini P, Najafi B, G Armstrong D. The Potential Role of Sensors, Wearables and Telehealth in the Remote Management of Diabetes-Related Foot Disease. Sensors (Basel). 2020;20(16):4527. Published 2020 Aug 13. doi:10.3390/s20164527
27. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1. Published 2015 Jan 1. doi:10.1186/2046-4053-4-1
28. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for

reporting systematic reviews. BMJ. 2021;372:n71. Published 2021 Mar 29. doi:10.1136/bmj.n71

29. Paez A. Grey literature: An important resource in systematic reviews [published online ahead of print, 2017 Dec 21]. J Evid Based Med. 2017;10.1111/jebm.12265. doi:10.1111/jebm.12265
30. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev. 2016;5(1):210. Published 2016 Dec 5. doi:10.1186/s13643-016-0384-4
31. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011;155(8):529-536. doi:10.7326/0003-4819-155-8-201110180-00009
32. Jacobs PG, Hanaway P, Leitschuh J, et al. Design and evaluation of a portable smart-phone based peripheral neuropathy test platform. Annu Int Conf IEEE Eng Med Biol Soc. 2018;2018:1-4. doi:10.1109/EMBC.2018.8513100
33. Fino PC, Horak FB, El-Gohary M, et al. Postural sway, falls, and self-reported neuropathy in aging female cancer survivors. Gait Posture. 2019;69:136-142. doi:10.1016/j.gaitpost.2019.01.025
34. Zahiri M, Chen KM, Zhou H, et al. Using wearables to screen motor performance deterioration because of cancer and chemotherapy-induced peripheral neuropathy (CIPN) in adults - Toward an early diagnosis of CIPN. J Geriatr Oncol. 2019;10(6):960-967. doi:10.1016/j.jgo.2019.01.010
35. Chen CS, Kim J, Garg N, et al. Chemotherapy-Induced Peripheral Neuropathy Detection via a Smartphone App: Cross-sectional Pilot Study. JMIR Mhealth Uhealth. 2021;9(7):e27502. Published 2021 Jul 5. doi:10.2196/27502
36. Sada YH, Poursina O, Zhou H, Workeneh BT, Maddali SV, Najafi B. Harnessing digital health to objectively assess cancer-related fatigue: The impact of fatigue on mobility performance. PLoS One. 2021;16(2):e0246101. Published 2021 Feb 26. doi:10.1371/journal.pone.0246101
37. Schwenk M, Grewal GS, Holloway D, Muchna A, Garland L, Najafi B. Interactive Sensor-Based Balance Training in Older Cancer Patients with Chemotherapy-Induced Peripheral Neuropathy: A Randomized Controlled Trial. Gerontology. 2016;62(5):553-563. doi:10.1159/000442253
38. Matsuoka A, Mitsuma A, Maeda O, et al. Quantitative assessment of chemotherapy-induced peripheral neurotoxicity using a point-of-care nerve conduction device. Cancer Sci. 2016;107(10):1453-1457. doi:10.1111/cas.13010
39. Jokimäki A, Iivanainen S, Mikkonen R, Mika K, Koivunen J. Assessment of chemotherapy-induced neurotoxicity using a point-of-care nerve conduction study device [published online ahead of print, 2022 Jul 11]. Cancer Rep (Hoboken). 2022;e1677. doi:10.1002/cnr2.1677
40. Sharma S, Venkitaraman R, Vas PR, Rayman G. Assessment of chemotherapy-induced peripheral neuropathy using the LDIFLARE technique: a novel technique to detect neural small fiber dysfunction. Brain Behav. 2015;5(7):e00354. doi: 10.1002/brb3.354
41. Saad M, Psimaras D, Tafani C, et al. Quick, non-invasive and quantitative assessment of small fiber neuropathy in patients receiving chemotherapy. J Neurooncol. 2016;127(2):373-380. doi:10.1007/s11060-015-2049-x
42. Allegra A, Rizzo V, Innao V, et al. Diagnostic utility of Sudoscan for detecting bortezomib-induced painful neuropathy: a study on 18 patients with multiple myeloma. Arch Med Sci. 2021;18(3):696-703. Published 2021 Jan 11. doi:10.5114/aoms/114269
43. Griffith KA, Couture DJ, Zhu S, et al. Evaluation of chemotherapy-induced peripheral neuropathy using

current perception threshold and clinical evaluations. Support Care Cancer. 2014;22(5):1161-9. doi: 10.1007/s00520-013-2068-0

44. Sato J, Mori M, Nihei S, Takeuchi S, Kashiwaba M, Kudo K. Objective evaluation of chemotherapy-induced peripheral neuropathy using quantitative pain measurement system (Pain Vision®), a pilot study. J Pharm Health Care Sci. 2017;3:21. doi: 10.1186/s40780-017-0089-4
45. Yoshida Y, Satoh A, Yamada T, et al. The Relationship Between Evaluation Methods for Chemotherapy-Induced Peripheral Neuropathy. Sci Rep. 2019;9(1):20361. doi: 10.1038/s41598-019-56969-9
46. Saito M, Odajima S, Yokomizo R, et al. A simple method of quantifying chemotherapy-induced peripheral neuropathy using PainVision PS-2100®. Asia Pac J Clin Oncol. 2020;16(1):80-85. doi:10.1111/ajco.13293
47. Marstrand SD, Buch-Larsen K, Andersson M, Jensen LT, Schwarz P. Vibration Perception Threshold and Heart Rate Variability as methods to assess chemotherapy-induced neuropathy in women with breast cancer - a pilot study. Cancer Treat Res Commun. 2021;28:100426. doi: 10.1016/j.ctarc.2021.100426.
48. Zajączkowska R, Kocot-Kępska M, Leppert W, Wrzosek A, Mika J, Wordliczek J. Mechanisms of Chemotherapy-Induced Peripheral Neuropathy. Int J Mol Sci. 2019;20(6):1451. Published 2019 Mar 22. doi:10.3390/ijms20061451
49. Wang AB, Housley SN, Flores AM, Kircher SM, Perreault EJ, Cope TC. A review of movement disorders in chemotherapy-induced neurotoxicity. J Neuroeng Rehabil. 2021;18(1):16. Published 2021 Jan 25. doi:10.1186/s12984-021-00818-2
50. Driessen CM, de Kleine-Bolt KM, Vingerhoets AJ, Mols F, Vreugdenhil G. Assessing the impact of chemotherapy-induced peripheral neurotoxicity on the quality of life of cancer patients: the introduction of a new measure. Support Care Cancer. 2012;20(4):877-881. doi:10.1007/s00520-011-1336-0
51. Cioroiu C, Weimer LH. Update on Chemotherapy-Induced Peripheral Neuropathy. Curr Neurol Neurosci Rep. 2017;17(6):47. doi:10.1007/s11910-017-0757-7
52. Beauchamp UL, Pappot H, Hollander-Mieritz C. The Use of Wearables in Clinical Trials During Cancer Treatment: Systematic Review. JMIR Mhealth Uhealth. 2020;8(11):e22006. Published 2020 Nov 11. doi:10.2196/22006
53. Rawson TM, Gowers SAN, Freeman DME, et al. Microneedle biosensors for real-time, minimally invasive drug monitoring of phenoxymethylpenicillin: a first-in-human evaluation in healthy volunteers. Lancet Digit Health. 2019;1(7):e335-e343. doi:10.1016/S2589-7500(19)30131-1

Table 1. Definitions of Internet of Things (IoT), Internet of Medical Things (IoMT) paradigms and related devices

Term	**Definition**
Paradigms	
IoT	A network of physical objects – "things" – that are embedded with sensors, software, and other advanced technologies to elaborate and exchange data with other devices and systems through the Internet and to control different appliances, autonomously, in the target scenario
IoMT	The application of a IoT network to healthcare and medical scenarios. IoMT architecture and devices must adhere to security and privacy rules concerning
Devices	
Sensor	A device that senses a physical phenomenon and produces an output signal. It has no computational capabilities and represents the lowest and simplest unit of the system. Examples are inertial (i.e., accelerometer, gyroscope, magnetometer, compass), or physiological sensors (i.e., body temperature, pulse, heart rate, blood pressure, pulse oximetry, photoplethysmography, electrocardiography, electroencephalography, electromyography, motion tracker)
Smart device	Any electronic equipment integrating computing, control and communication capabilities with sensors/actuators that can autonomously interact with the external environment, including humans. Wearables are a specific type of smart devices
Wearable device	Wearable is a specific type of smart device that is intended to be worn on the user's body composed of a computing unit integrated with sensors/actuators. It may have communication capabilities with other devices

Table 2. Details of the included studies exploring wearables, sensors, and IoMT devices to detect or monitor CIPN

Author, Year [Ref]	Study design	Population	Cancer type(s)	Chemotherapy agent(s)	Time since chemotherapy completion	Comparator	Data source (i.e., wearable/device/sensor type)	Assessment protocol	Extracted parameters	Results
Studies exploring wearables, sensors and IoMT devices to detect or monitor CIPN										
Jacobs, 2018 [32]	Pilot	N: 28	NR	NR	NR	PeriVib compared with two other established systems (i.e., Biothesiometer, tuning fork) on the same population	PeriVib (smartphone inertial tri-axial sensors ACC, GYR, voice-coil vibration motor device)	Biothesiometer: dorsal side of the right hallux, three trials up to 0.5 V each; tuning fork: dorsal side of the right hallux, three trials; PeriVib: PNST; balance test (30 sec standing); gait test (10 steps repeated five times)	Vibration threshold; balance metrics (sway distance, acceleration RMS, acceleration energy); gait metrics (gait speed, gait frequency, steps, gait stride time, stride time variance, stride imbalance)	Better correlation between PeriVib and Biothesiometer for sensation threshold estimation than with the tuning fork
Fino, 2019 [33]	Case-control study with cases identified within a previous clinical trial	N: 434 W (age: 62.5 ± 6.4)	Breast, colon, ovarian, lymphoma, uterine, lung, other	NR	Overall sample (N: 434): 61.0 ± 51.5 mos; CIPN+ (N: 216): 55.5 ± 46.5 mos; CIPN- (N: 218): 66.6 ± 55.5 mos	N: 49 healthy controls (age: 63.3 ± 6.9)	One inertial sensor (ACC, GYR, MAG; Opal v1, APDM, Inc. Portland, OR, USA) over the lumbar spine; sampling frequency: 128 Hz	Stance test (30 sec standing with eyes open and feet spaced apart 10 cm between heels and 15 cm between halluxes)	Postural sway measures (46, classified upon the direction of movement, i.e., AP, ML, resultant)	The frequency of ML sway was associated with falls across the entire cohort of cancer patients; CIPN+ showed higher resultant/AP sway frequencies than CIPN-; falls were significantly associated with ML sway in CIPN+ with more severe symptoms, and with resultant/AP sway frequency in CIPN+ with less severe symptoms
Zahiri, 2019 [34]	Observational, cohort	N: 84 (M: 36, W: 46; age: 71.1 ± 9.7), 58 CIPN+ (M: 33, W: 25; age: 68.0 ± 8.6), 24 CIPN- (M: 4, W: 20; age: 78.3 ± 8.5)	Lung, multiple myeloma, colorectal, breast, other	Platinum compounds, vinca alkaloid, taxane, proteasome inhibitor, interferon	NR	N: 57 healthy controls (M: 12, W: 45; age: 69.5 ± 9.8)	Five wearable inertial sensors (LEGSys™ and BalanSens™, Biosensics LLC, Watertown, MA, USA) over shins, thighs, lower back; Biothesiometer (Bio-Medical Instrument Co, Newbury, OH, USA) at the distal aspect of the great toe, 5th metatarsal head and heel	Gait assessment (15 m at a self-selected speed); balance assessment (30 sec standing still during eyes open/closed); VPT (CIPN severity estimation)	Gait metrics (stride velocity, stride length, stride time, double support); balance metrics (area of ankle sway, area of hip sway, area of CoM sway, CoM sway in the ML direction); plantar numbness	Cancer patients showed deterioration of all gait and balance parameters vs. controls; CIPN+ showed greater ankle sway during eyes-closed condition compared to CIPN-; CIPN severity measured with VPT significantly correlated with gait (i.e., stride time) and balance (i.e., CoM sway in the ML direction and hip sway during open-eyes condition) deterioration

Chen, 2021 [35]	Cross-sectional, case-control, pilot	N: 26 (age: 51.9 ± 9.8)	Breast, ovarian, lung, colorectal, liver, esophageal, prostate, cervical, pancreatic	Taxane, platinum compounds, vinca alkaloid	Overall sample: 3.72 ± 10.2 mos; CIPN+: 2.72 ± 2.94 mos; CIPN-: 5.32 ± 16.4 mos	N: 10 CIPN- (age: 49.5 ± 12.0)	NeuroDetect V1.0 app (smartphone inertial sensors ACC, pedometer)	Patient reported outcomes (EORTC QLQ-CIPN20, PRO-CTCAE); gait and balance assessment; 9 Hole Peg Test	Gait and balance metrics (87 features); hand dexterity metrics (60 features)	CIPN+ showed shorter step length, unique swaying acceleration patterns and shorter hand moving distance vs. CIPN- according to NeuroDetect
Sada, 2021 [36]	Case-control study with cases and controls collected from a previous clinical trial	N: 36; 28 completed the trial (M: 19, W: 9; age: 65.7 ± 9.8)	NR	Platinum compounds, vinca alkaloid, taxane, proteasome inhibitor, interferon	NR	The cohort was divided into patients with CRF (CRF+, N: 7) and those without CRF (CRF-, N: 21) that served as control	PAMSys™ (tri-axial ACC; BioSensics LLC, MA, USA) worn as a pendant (sampling frequency: 50 Hz); five wearable inertial sensors (LEGSys™ and BalanSens™, Biosensics LLC, Watertown, MA, USA) over shins, thighs, lower back (sampling frequency: 100 Hz)	Motor capacity (gait: habitual walking, dual-task walking, fast walking; balance: 30 s standing still with feet close together); mobility performance (48 hours daily physical activity)	Gait metrics (gait speed); balance metrics (CoM sway); daily physical activity metrics (lying + sitting %, standing %, walking + running %, daily activity level %, number of walking bouts and steps, stand-to-sit and sit-to-stand postural transitions, average duration of postural transitions)	PAMSys™ detected a significant deterioration in mobility performance (i.e., increased sedentary activities and cumulative sedentary postures, decreased locomotion activities) in CRF+ compared to CRF-
Studies exploring wearables and sensors for CIPN treatment										
Schwenk, 2016 [37]	Pilot, single-blind, randomized, controlled	N: 22 (M: 9, W: 13; age: 70.3 ± 8.7)	Lung, multiple myeloma, breast, colorectal, melanoma, bladder, prostate, pancreatic, chronic lymphoid leukemia	NR	NR	Standard care (N: 11)	Wearable inertial sensors (tri-axial ACC, GYR, MAG; LEGSys™ and BalanSens™, Biosensics LLC, Watertown, MA, USA) over shanks, thighs, lower back; sampling frequency: 100 Hz	Balance training: ankle point-to-point reaching task, virtual obstacle crossing task; balance assessment: 30 s standing with feet close together during eyes open/closed or with semi-tandem position during eyes open; gait assessment: 10 m at usual pace	Balance metrics (CoM sway in the AP and ML direction, ankle sway, hip sway); gait metrics (speed, stride velocity)	Interactive sensor-based balance training was well accepted by patients; inertial sensors detected a significant reduction of ankle and hip sway for patients undergoing the experimental training compared to the control group

Legend. ACC = accelerometer; AP = anteroposterior; CIPN = chemotherapy induced peripheral neuropathy; CIPN+ = patients with chemotherapy induced peripheral neuropathy; CIPN- = patients without chemotherapy induced peripheral neuropathy; CoM = center of mass; CRF = cancer related fatigue; DN4 = Douleur Neuropathique en 4 Questions; EORTC QLQ-CIPN20 = European Organization for Research and Treatment of Cancer Quality of Life - Chemotherapy-induced Peripheral Neuropathy Questionnaire; ESC = electrochemical skin conductance; GYR = gyroscope; Hz = Hertz; IoMT = Internet of Medical Things; M = men; MAG = magnetometer; ML = mediolateral; mos = months; N = number; NCI-CTCAE 4.0 = National Cancer Institute-Common Terminology Criteria for Adverse Events Version 4.0; NPSI = Neuropathic Pain Symptom Inventory; NR = not reported; PINRS = Pain Intensity Numerical Rating Scale; PNST = Peripheral Neuropathy Sensation Test; PRO-CTCAE = Patient Reported Outcomes – Common Terminology Criteria for Adverse Event; RMS = root mean square; VPT = vibration perception threshold; W = women.

Table 3. Details of the included studies exploring devices that may be engineered and integrated with IoT/IoMT architectures

Author, Year [Ref]	Study design	Population	Cancer type(s)	Chemotherapy agent(s)	Time since chemotherapy completion	Comparator	Data source (i.e., wearable/device/sensor type)	Assessment protocol	Extracted parameters	Results
Nerve conduction study										
Matsuoka, 2016 [38]	Prospective, observational	N: 52, 50 completed the trial (M: 22, W: 28; median age: 64, age range: 34-85)	Colon, breast, gastric, pancreas, hematology, gynecology, other	Platinum compounds, taxane, vincristine, bortezomib	Median interval: 21 days (interquartile range, 14-28 days; range, 3-1530 days)	None	POCD (biosensor and stimulating probes over the ankle lateral side; DPNCheck; NeuroMetrix Inc., Waltham, MA, USA)	SNAP and SNCV measurement procedure: automatic stimulation of the sural nerve 6–20 times within 15–20 s, sural nerve response recorded by a sensor on the lower calf	Nerve conduction measures of the sural nerve (SNAP, SNCV)	Progression of CIPN was associated with significant decrease in sural SNAP measures by the DPNCheck
Jokimäki, 2021 [39]	Prospective, pilot, observational	N: 11, 6 completed the trial (M: 3, W: 3; age: 65.5, age range: 51-70)	Prostate, metastatic colon, diffuse large B- cell lymphoma	Docetaxel, oxaliplatin, vincristine	NR	None	POCD (stimulating, recording and ground electrodes between the median and ulnar nerves; Mediracer® NCS)	NCS (median and ulnar SNCV and MNCV); neuropathy questionnaires (NPSI, EORTC QLQ-CIPN20); symptoms grading (NCI-CTCAE). Assessments performed at 6-week intervals up to 18 weeks or until chemotherapy end	Nerve and ulnar nerve conduction measures (velocity, amplitude, distal latency)	Mediracer® NCS detected decreased nerve conduction measures only in patients under oxaliplatin; measurements frequently failed especially in patients with pre-existing high-risk for neuropathy
Autonomic testing										
Sharma, 2015 [40]	Proof of concept	N: 24 (M: 14, W: 10; age: 65.42 ± 7.9) with CIPN (EORTC QLQ-CIPN20: 38.67 ± 9.27)	NR	Platinum compounds, taxane	13.1 ± 1.0 mos	Subjective CIPN measures (EORTC QLQ-CIPN20); objective CIPN measures (VPT, SNCV, SNAP)	LDI_{FLARE} technique	Heating of the dorsal foot skin to 47°C with a probe and measure of the resultant nerve-axon-related hyperemic response with a laser scanner	Size of the axon- reflex-mediated neurogenic flare (small nerve fiber function)	LDI_{FLARE} correlated with the EORTC QLQ-CIPN20 scores
Saad, 2016 [41]	Prospective, observational	N: 88 at risk for CIPN (M: 61, W: 27; age: 61.8 ± 1.3)	Bronchus, oropharynx, lung, colon, rectum, prostate, ovary, breast, other	Platinum compounds, taxane	At least 1 year after the last chemotherapy infusion	TNSc	Sudoscan (Impeto Medical, Paris, France)	CIPN assessment: TNSc (questionnaire, clinical evaluation); sweat gland function: 2 min stand still test, application of four combinations of 15 low (<4 V) direct current incremental voltages; assessments at each chemotherapy infusion	Sweat function measures (hands and feet ESC)	ESC showed a significant decrease in all the patients, while the TNSc scores were more stable during the study; ESC worsening occurred earlier than TNSc
Allegra, 2021 [42]	Prospective, non-inferiority study	N: 18 (M: 10, W: 8; median age: 70, age range: 39-87)	Multiple myeloma	Bortezomib, thalidomide	6 mos	NCS	Sudoscan (Impeto Medical, Paris, France)	NCS (sural and ulnar SNCV, peroneal, tibial and ulnar MNCV); ESC (2 min stand still test with application of four combinations of 15 <4 V direct current incremental voltages); pain and neuropathy scales (DN4, TNSc, PINRS)	Sweat function measures (hands and feet ESC)	Sudoscan not inferior to NCS; Sudoscan measures significantly correlated to pain and neuropathy scales at baseline and follow-up

Pain pathways testing										
Griffith, 2014 [43]	Secondary analysis of a prospective, observational, pilot	N: 35, 29 included in the analysis (M: 15, W: 14; age: 56.7 ± 10.4)	Breast, head/neck, lung, gastrointestinal, genitourinary, skin	Platinum, compounds, taxane	NR (N chemotherapy cycles: CIPN+ = 9.1 ± 3.3; CIPN- = 6.0 ± 2.8)	QST, motor function (right ankle deep tendon reflex, dominant hand grip strength), NPS, FACT GOG-Ntx	CPT (Neurometer©, Neurotron, Baltimore MD)	CIPN conventional assessment: QST, motor function, PROS questionnaires. CPT: mild electrical stimulation (5/250/2000 Hz, 0.01-9.99 mA) via distal finger electrodes	CPT	CPT (2000 Hz) was most often associated with objective and subjective measures of CIPN
Sato, 2017 [44]	Prospective, pilot, observational	N: 42 females at risk for CIPN (age: 55.8 ± 11.0)	Ovarian, cervical, endometrial	Platinum compounds, paclitaxel	NR (N cycles: 5.9 ± 0.4; CIPN+: 5.9 ± 0.3; CIPN-: 5.7 ± 0.7)	NCI-CTCAE 4.0, PNQ	Pain Vision PS-2100 (Nipro Co., Ltd.)	CIPN conventional assessment: NCI-CTCAE 4.0, PNQ; pain degree perception: voltage up to 200 V, current up to 256 μA, duration up to 30 sec	Pain degree perception: (pain perception current - lowest perceptible current) ÷ lowest perceptible current × 100	The decrease in pain degree perception with Pain Vision PS-2100 was associated with the onset of CIPN symptoms, as measured by NCI-CTCAE 4.0 and PNQ
Yoshida, 2019 [45]	Prospective, observational	N: 73 at risk for CIPN (M: 37, W: 36; age: 67.4 ± 9.9)	Metastatic colorectal adenocarcinoma	Oxaliplatin	NR	Perceived pain (VAS hand, foot)	Pain Vision PS-2100 (Nipro Co., Osaka, Japan)	CIPN conventional assessment: VAS, FACT GOG-Ntx (subjective measures), Disk-Criminator, monofilament test (objective measures); pain degree perception: electrical current (50 Hz; 0–150 μA RMS; pulse width: 0.3 ms), electrode mounted on the inside surface of the forearm	Pain degree perception: (pain perception current - lowest perceptible current) ÷ lowest perceptible current × 100	Pain Vision measures correlated with VAS (hand, foot) and FACT GOG-Ntx
Saito, 2020 [46]	Prospective, pilot, observational	N: 30 females at risk for CIPN (age: 51.6 ± 12.2)	Epithelial ovarian, fallopian tube, peritoneal	Carboplatin, paclitaxel	NR (median number of chemotherapy treatments/patient: 5; first quartile: 4; second quartile: 5; third quartile: 5)	NCI-CTCAE 4.0	Pain Vision PS-2100 (Nipro, Osachi Co., Ltd)	CIPN conventional assessment: NCI-CTCAE 4.0; CPT (0.3 ms-wide pulse, 50 Hz, 60 s total duration, 200 V maximum voltage); assessments done before and after chemotherapy	CPT	CPT (right forearm medial side) significantly correlated with numbness g measured with NCI-CTCAE 4.0
Combined testing										
Marstrand, 2021 [47]	Cross-sectional, pilot	N: 78 females (chemotherapy, N:30; no chemotherapy, N = 26; controls, N = 22; age range: 35-83)	Breast cancer	Taxane	51 mos (IQR: 27-84)	Subjective reporting of CIPN symptoms	VPT by VibroSense Meter (VibroSense Dynamics, Malmo¨, Sweden); HRV by eMotion Faros 180 (Mega Electronics Ltd, Kuopio, Finland)	VPT: probes placed at the second and fourth finger pulp (8, 16, 32, 64, 125, 250, 500 Hz); HRV: two electrodes below the collarbones, one below left breast (sampling, 1000 Hz, ECG recording, 7-15 min)	VPT, HRV	Elevated VPT and decreased HRV were found in patients reporting CIPN symptoms

Table 3 Legend. CIPN = chemotherapy induced peripheral neuropathy; CIPN+ = patients with chemotherapy induced peripheral neuropathy; CIPN- = patients without chemotherapy induced peripheral neuropathy; CPT = current perception threshold; ECG = electrocardiogram; EORTC QLQ-CIPN20 = European Organization for Research and Treatment of Cancer Quality of Life - Chemotherapy-induced Peripheral Neuropathy Questionnaire; ESC = electrochemical skin conductance FACT GOG-Ntx = Functional Assessment of Cancer Therapy/Gynecologic Oncology Group--Neuro-toxicity; HRV = heart rate variability; IQR = interquartile range; LDI = laser Doppler imager; M = men; MNCV = motor nerve conduction velocity; mos = months; N = number; NCI-CTCAE 4.0 = National Cancer Institute-Common Terminology Criteria for Adverse Events Version 4.0; NCS = nerve conduction study; NPS = Neuropathic Pain Scale; NR = not reported; PNQ = Patient Neurotoxicity Questionnaire; POCD = point-of-care nerve conduction device; PROs = patient reported outcomes; QST = quantitative sensory testing; RMS = root mean square; SNAP = sural nerve amplitude potential; SNCV = sural nerve conduction velocity; TNSc = Total Neuropathy Score Clinical version; V = volt; VAS) visual analogue scale; VPT = vibration perception threshold; W = women.

Table 4. Overview of CIPN outcome measures, currently used scales/tools and potential solutions based on smart devices and applications for their assessment in home-based settings

Outcome Measure	Description	Examples of currently used scales/tools	Potential wearables and IoMT solutions	
			Description	Available Sensors and Devices
Patient Reported Outcomes				
CIPN symptoms	Sensory (e.g., tingling, numbness, hypasthesia) and motor symptoms reported by the patient	• EORTC QLQ-CIPN20 • FACT/GOG-Ntx • NRS • CIPNAT • PNQ • PRO-CTCAE	• Smart-home assistant-based system for CIPN related symptoms assessment through speech interaction • Smartphone mobile application for CIPN related symptoms assessment through questionnaires	• Environmental sensors (audio for speech recognition) • Commercially available mobile phones
Pain symptoms	Severity of (neuropathic) pain reported by the patient	• S-LANSS • PainDETECT • NRS • BPI	• Smart-home assistant-based system for pain assessment through speech interaction • Smartphone mobile application for pain assessment through questionnaires	• Environmental sensors (audio for speech recognition) • Commercially available mobile phones
CIPN related disability	Disability associated to CIPN	• CIPN R-ODS	• Smart-home assistant-based system for disability assessment through speech interaction • Smartphone mobile application for disability assessment through questionnaires	• Environmental sensors (audio for speech recognition) • Commercially available mobile phones
Quality of life	Quality of life reported by the patient, either generic or CIPN-specific measures	• EORTC QLQ-C30 • FACT-G • SF-36 • MQOL	• Smart-home assistant-based system for QoL assessment through speech interaction • Smartphone mobile application for QoL assessment questionnaires	• Environmental sensors (audio for speech recognition) • Commercially available mobile phones
Other CIPN related symptoms, signs, and outcome measures	Other symptoms associated to CIPN and reported by the patient (e.g., fatigue, sleep, psychological, mood, hand function)	• Fatigue (MFI20) • Sleep difficulties (PSQI) • Psychological distress (BSI) • Mood (HADS) • Hand function (DASH)	• Smart-home assistant-based system for the assessment of other symptoms associated to CIPN through speech interaction • Smartphone mobile application for the assessment of other symptoms associated to CIPN through questionnaires administration	• Environmental sensors (audio for speech recognition) • Commercially available mobile phones
Upper-and lower-limb objective measures				
Upper and lower-limb somatosensory function	Clinical and functional test to assess the sensory function of the upper and lower limbs	• VPT (tuning fork) • Quantitative sensory testing • Biothesiometer	• Wearable devices and portable tools to assess somatosensory thresholds and function in the upper and lower limbs	• Portable Biothesiometer device • Neuropen
Upper-limb sensorimotor function	Functional tests to assess the sensorimotor function of the upper limbs	• 6/9-hole buttoning test • Coin test • Heal-to-toe test	• Wearable devices that integrate inertial and physiological sensors to recognize specific hand exercises/activities • Smartwatches and wrist bands to recognize specific hand exercises/activities Smartphone mobile apps to measure the pressure/precision applied by the subject over the smartphone screen	• Accelerometers • Gyroscopes • Compasses • GPS devices • Commercially available mobile phones • Commercially available smartwatches/wristbands
Balance	Clinical and functional test to assess balance function	• Postural sway • Tandem stance • Limit of stability test • Berg balance scale • FAB • GGT-Reha balance scale • CTSIB-M • Stance and Romberg tests	• Wearable devices that integrate inertial and physiological sensors to recognize human activities • Smartwatches and wrist bands to assess balance function • Mobile apps to perform balance functional tests • Human activity recognition algorithms to detect balance abnormalities	• Accelerometers • Gyroscopes • Compasses • GPS devices • Commercially available mobile phones • Mobile applications (e.g., NeuroDetect) • Commercially available smartwatches/wristbands

Gait	Clinical and functional test to assess gait function	• Chair rise test • Sit to stand • Partial curl up • TUG • Sit and reach • Walking tests (50 step walk; stair walking; modified Borg scale; 6MWT, tandem walk)	• Wearable devices that integrate inertial and physiological sensors to recognize human activities • Smartwatches and wrist bands to assess gait • Mobile apps to perform gait functional tests • Human activity recognition algorithms to detect gait abnormalities	• Accelerometers • Gyroscopes • Compasses • GPS devices • Commercially available mobile phones • Mobile applications (e.g., NeuroDetect) • Commercially available smartwatches/wristbands
Other instrumental measures				
Nerve conduction study	Tests to assess the function of sensory and motor large nerve fiber; current gold standard to document peripheral nerve or dorsal root ganglion damage, especially for sensory fiber	• Sensory nerve action potential and conduction velocity • Motor nerve conduction study and F-wave • Needle electromyography • Assessment of the dorsal sural nerve	• Wearable or portable devices to periodically perform a nerve conduction study in a standardized fashion	• N/A
Autonomic testing	Tests to assess the function of autonomic small nerve fiber	• Quantitative sudomotor axon reflex test • Sympathetic skin response • HRV	• Wearable or portable devices to periodically assess autonomic nerve function in a standardized fashion	• E4 Wristband • NeXus Skin Conductance Sensor • Emotion Pharos 180
Pain pathways testing	Tests to assess the function of pain pathways (peripheral small nerve fiber, central pathways)	• Laser evoked potentials • Contact heat evoked potentials	• N/A (technically too demanding, requires an expert assessor)	• N/A
Other instrumental measures	Mixed measures (seldom-used, mainly experimental)	• Nerve excitability • Microneurography • Skin biopsy • Corneal confocal microscopy	• N/A (technically too demanding, requires an expert assessor)	• N/A

Legend. BPI = Brief Pain Index; BSI = Brief Symptom Inventory; CIPN = chemotherapy induced peripheral neuropathy; CIPNAT = CIPN Assessment Tool; CIPN R-ODS = Rasch - built Overall Disability Scale CIPN; CTSIB-M = modified clinical test for sensory interaction in balance; DASH = Disability of the Arm, Shoulder and Hand Scale; EORTC QLQ-CIPN20 = European Organization for Research and Treatment of Cancer Quality of Life - Chemotherapy Induced Peripheral Neuropathy Questionnaire; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; FAB = Fullerton Advanced Balance Scale; FACT-G = Functional Assessment of Cancer Therapy - General; FACT/GOG-Ntx: Functional Assessment of Cancer Therapy/Gynecologic Oncology Group - Neurotoxicity; GGT = Gleichgewichts wurden der Gleichgewichtstest; GPS = Global positioning system; HADS = Hospital Anxiety and Depression Scale; HAR = Human Activity Recognition; HRV = heart rate variability; IoMT = Internet of Medical Things; MFI20 = Multidimensional Fatigue Inventory; MQOL = McGill Quality of Life Questionnaire; NCI-CTCAE = National Cancer Institute Common Terminology for Adverse Events; N/A = not available; NRS = numerical rating scale; PNQ = Patient Neurotoxicity Questionnaire; PRO-CTCAE = Patient Reported Outcomes – Common Terminology Criteria for Adverse Event; PSQI = Pittsburgh Sleep Quality Index; QoL = Quality of Life; SF-36 = Short Form Health Survey; S-LANSS = Self- administered Leeds Assessment of Neuropathic Symptoms and Signs; 6MWT = Six minute walking test; TUG = Timed up and go; VPT = vibration perception threshold.

Table 5. Recommendations for the development of IoMT solutions for CIPN monitoring and early diagnosis and for studies assessing their efficacy

Patient and CIPN characteristics	
Patient selection	• Cancer type(s) should be reported in detail • Chemotherapy type(s) should be reported in detail (e.g., compound, dosage, number of treatments)
CIPN characteristics	• CIPN diagnostic criteria should be specified • CIPN clinical features (e.g., sensory and motor involvement, presence of pain, large vs. small fibre involvement, symptoms severity) should be reported
Outcome measures, comparators, and study design	
Outcome measures	• Outcome measures to be assessed by smart devices and applications should be defined and specifically tailored according to patient populations, chemotherapy type, and study objective • Attention should be paid to the site of assessment (i.e., upper, lower limb function), according to CIPN features • Devices assessing multiple outcome measures (e.g., sensory, motor, autonomic and/or patients reported outcomes and upper/lower-limb objective measures) might be more clinically relevant than those exploring a single outcome (e.g., sensory symptoms, motor function) and should be compared to multi-outcome clinical tools (e.g., TNS) • Acceptability, adherence, persistence, and drop-out rate should be included as outcome measures
Comparators	• Studies should include conventional patient-reported outcome and clinician assessment tools, as comparators when assessing validity • A comparator group (e.g., patients without CIPN and/or healthy subjects) should be used for studies assessing sensitivity and specificity of the device
Study design	• Appropriate study design a) to explore whether IoMT solutions can detect CIPN, b) then to determine whether IoMT solutions achieve CIPN detection earlier, cheaper, and more reliably than conventional patient-reported outcome, clinician assessment tools and instrumental techniques, c) then prospective clinical trials to demonstrate that using IoMT improves clinical outcomes • Primary and secondary outcome measures should be defined, and sample size calculated a priori • Intention to treat analysis and the last observation carried forward method should be applied
Technical and engineering issues	
Devices	• Device selection based on specific CIPN clinical features to be explored • Sensors integrated in the devices (e.g., accelerometer, gyroscope, magnetometer, heart rate sensors, PPG) should measure relevant information to derive the severity of dysfunction (e.g., gait, balance) and the occurrence of target events (e.g., falls) • The dataset collected by sensors must be accurately designed to allow an effective training of artificial intelligence algorithms • The frequency of data acquisition from sensors (i.e., number of samplings per time unit) should allow artificial intelligence algorithms to accurately elaborate the data • The capacity of the device's battery must be compliant with the required monitoring period • Onboard computational resources (i.e., CPU and RAM memory) should allow executing part of the data elaboration on the edge (i.e., inside the device) when real-time reaction is necessary (e.g., for prompt alerting), to decrease the computation latency due to transferring a large amount of data through the network, and when Internet connection is not available

	• The size of the local storage must be considered when Internet connection is not available for long periods, while no-storage devices can be used when the connection is guaranteed, or any loss of data is acceptable • Wireless communication protocols for transferring data among devices and towards the cloud (e.g., Bluetooth Low Energy, Wi-Fi, ZigBee) should be accurately analyzed, as it impacts relevant technical features, like the frequency of data acquisition, the duration of the device's battery and the computational latency • Device usability, wearability, accessibility, compliance, and persistence should be assessed through ad-hoc standardized questionnaires • Safety and security issues, and device certifications (e.g., FDA, CE or dedicated medical grade certification) must be considered • Data collection and storage inside the devices must respect the regulations concerning privacy, also considering the role of human operators
IoMT Infrastructure	• The design of the IoMT infrastructure must consider, in an holistic way, users type, communication technologies, data representation, used devices and the overall data workflow • To guarantee an effective level of heterogeneity and interoperability, the design of the IoMT infrastructure must consider the communication protocols supported by the devices, their data representation formats, and the inclusion of algorithms for data integration • Study design must be conducted in terms of constrains over network performance (i.e., bandwidth, the maximal number of connected devices per subject, the maximal number of connected subjects and caregivers) • Issues concerning reliability, safety, security, affordability, and privacy must be considered at the infrastructure level
Smart apps	• Data collected by and exchanged among IoMT devices are elaborated by software applications through artificial intelligence either on the edge (i.e., inside the devices themselves) or on the cloud (i.e., in dedicated servers). This requires the definition of procedures for data collection, feature extraction and processing, including the selection and implementation of machine learning and/or deep learning algorithms for classification and automatic recognition of the target observations
Future developments	
Biomarkers	• Assessment of digital biomarkers as potential new predictors of CIPN development
Neuroprotection	• Assessment of the role of IoMT solutions and digital biomarkers to inform treatment decisions to reduce CIPN or to identify patients for enrolment onto clinical trials testing CIPN prevention or treatment strategies. The smart device either might represent the intervention itself to guide clinical treatment or be used to enroll patients in studies on neuroprotective agents

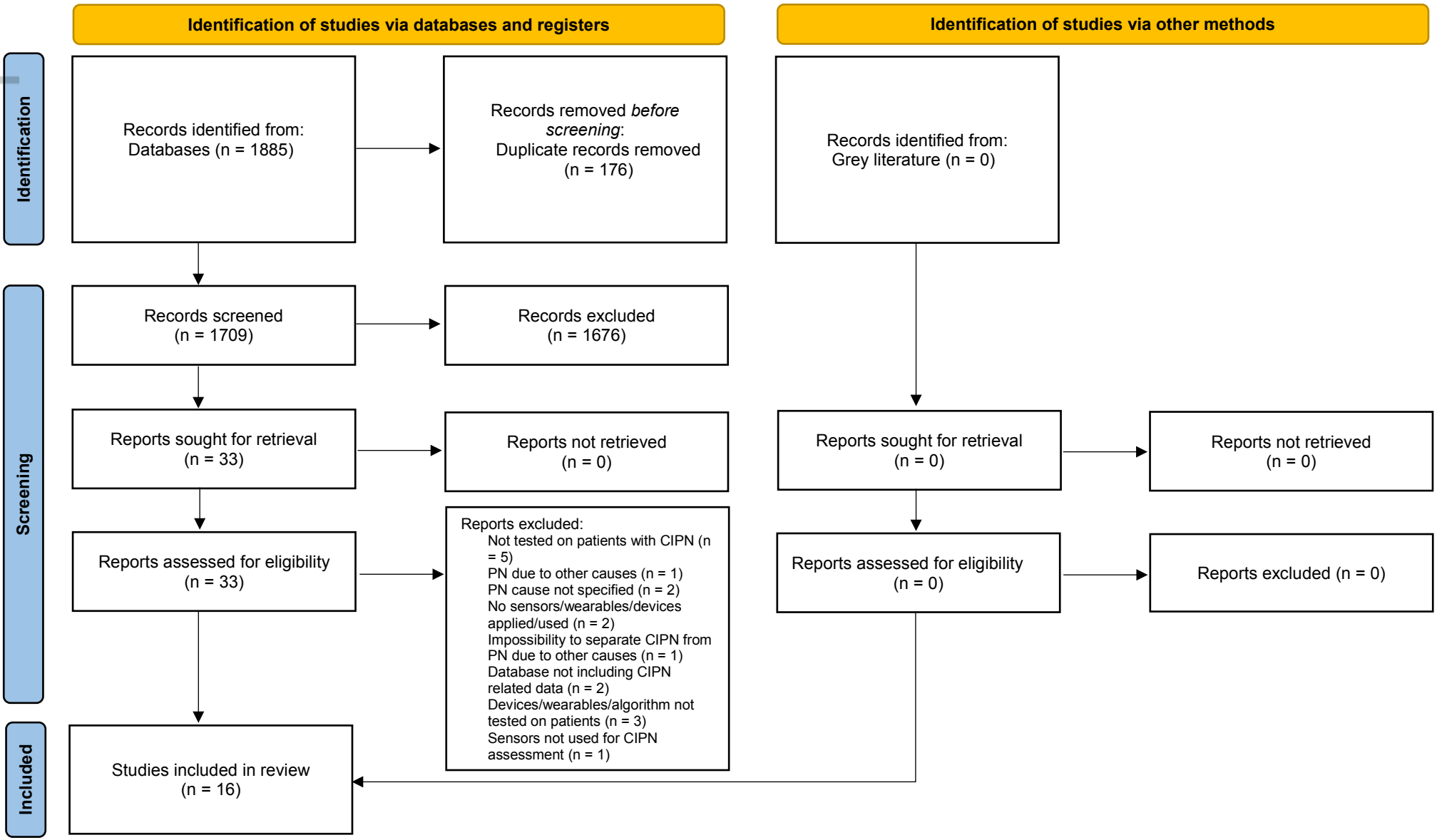
Legend. CE = European conformity; CIPN = chemotherapy induced peripheral neuropathy; CPU = central processing unit; FDA = Food and Drug Administration; IoMT = internet of medical things; PPG = photopletismography; RAM = random access memory; TNS = Total Neuropathy Score; WiFi = Wireless Fidelity.

Figure legends

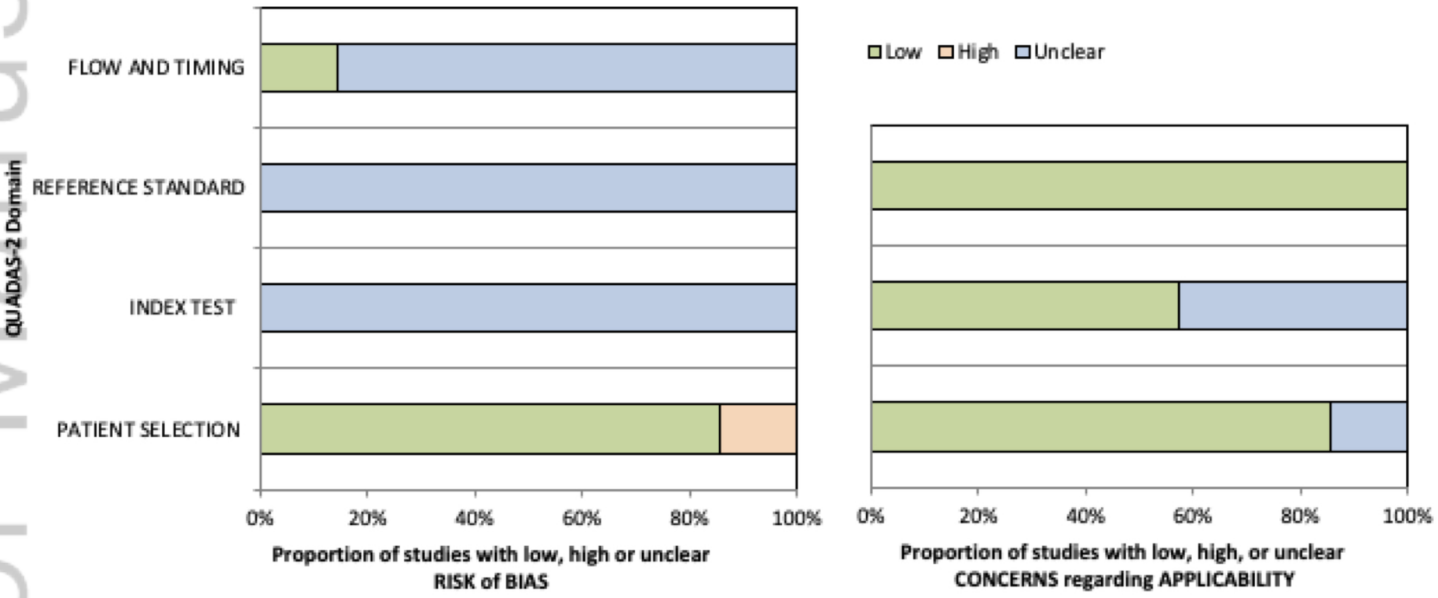
Figure 1. PRISMA diagram of the study (http://www.prisma-statement.org) [28]. CIPN: chemotherapy-induced peripheral neuropathy; PN: peripheral neuropathy.

Figure 2. Risk of bias and applicability concerns.

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/



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