




Review

# Current Trends of Computational Tools in Geriatric Medicine and Frailty Management

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## Abstract

While frailty corresponds to a multisystem failure, geriatric assessment can recognize multiple pathophysiological lesions and age changes. Up to now, a few frailty indexes have been introduced, presenting definitions of psychological problems, dysregulations in nutritional intake, behavioral abnormalities, and daily functions, genetic, environmental, and cardiovascular comorbidities. The geriatric evaluation includes a vast range of health professionals; therefore, we describe a broad range of applications and frailty scales-biomarkers to investigate and formulate the relationship between frailty lesions, diagnosis, monitoring, and treatment. Additionally, artificial intelligence applications and computational tools are presented, targeting a more efficacy individualized geriatric management of healthy aging.

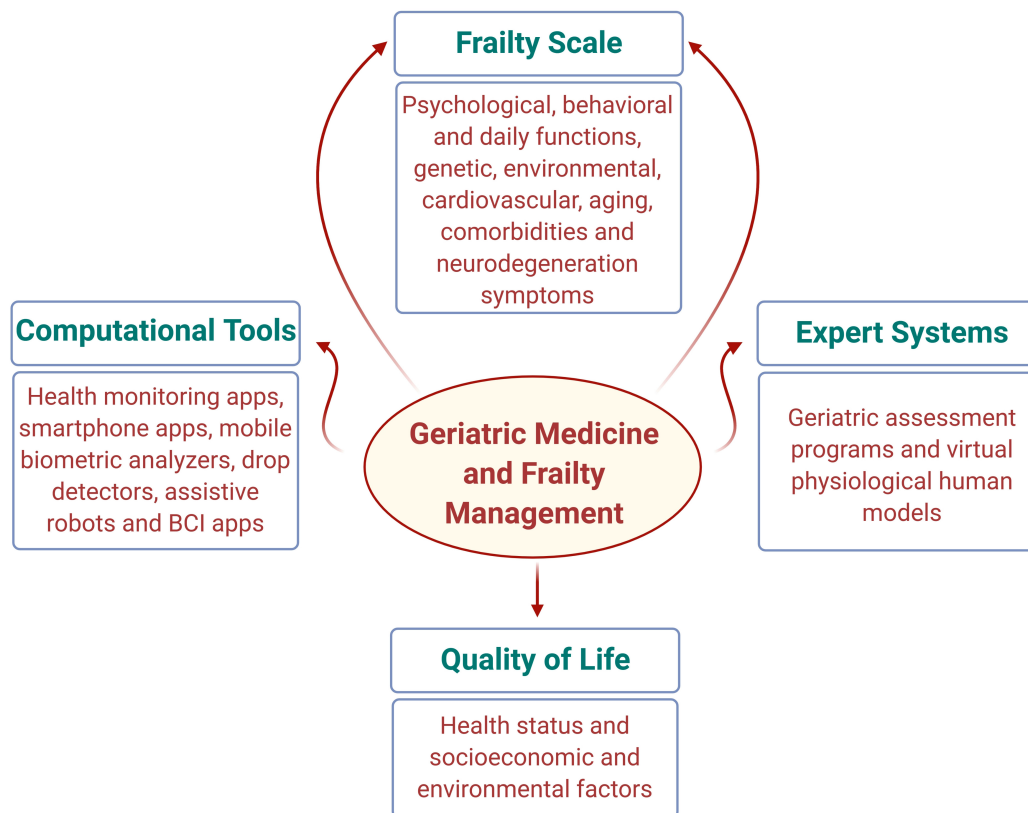
**Keywords:** aging; artificial intelligence; bioinformatics; brain-computer interface; dementia; expert systems; frailty; geriatrics

## 1. Introduction

Fundamentally, Geriatrics has been developed to understand better and manage aging, paving the way to healthy aging. While aging is progressive and determined as unavoidable for all humans, quality of life among elderly individuals is disrupted by many diseases occurring in aging but not caused by aging per se. A condition such as dementia and other neurodegenerative disorders and metabolic syndrome, cardiovascular and musculoskeletal

conditions affect most of the elderly population worldwide [1,2]. Their implications have been conceptualized under frailty, an umbrella term encompassing the multitude of dysfunctions in human biological mechanisms that influence several organ systems and quality of life and mainly refers to genetic, physiological, behavioral alterations, neurodegeneration, and other comorbidities coexistence. Comprehensive modeling of frailty is a prerequisite to conducting frailty-oriented research [3]. Currently, two models





**Fig. 1. Interim relationship of geriatric medicine and frailty management with quality of life, computational tools and expert systems.** The proposed multidisciplinary approach in this article will be significant for researchers from different fields, including frailty indexes and scores, artificial intelligence applications, and computational tools targeting frailty diagnosis and treatment.

of frailty have been reported, the phenotypic and the multi-dimensional model of frailty. The Cardiovascular Health Study has validated the phenotypic model and based on a pre-defined set of clinical features associated with aging and the severity of concomitant conditions. The Canadian Aging and Health study have validated the multidimensional model to predict all-causes mortality. Although both perceptions have contributed to geriatrics research, the frailty index is considered broader and more suitable for the study of populations with or tools related to dementia. Hence, the authors have focused on the multidimensional aging model in this study given numerous dementia and neurodegeneration—oriented computational tools [4]. In this context, it is established that individuals accumulate age-related disorders and conditions, subjecting them to potentially lethal internal and external stress factors. To evaluate the vulnerability of an old patient, the frailty index is commonly used. Increased frailty is linearly associated with adverse health outcomes and mortality [5,6]. The rapid development and success of computational tools have transformed healthcare and medical practice during the past decade, with their multidisciplinary applications extending from diagnostic algorithms, risk stratification to establishing treatment strategies, aiding physicians' and healthcare workers' decision making, as well as providing patients per-

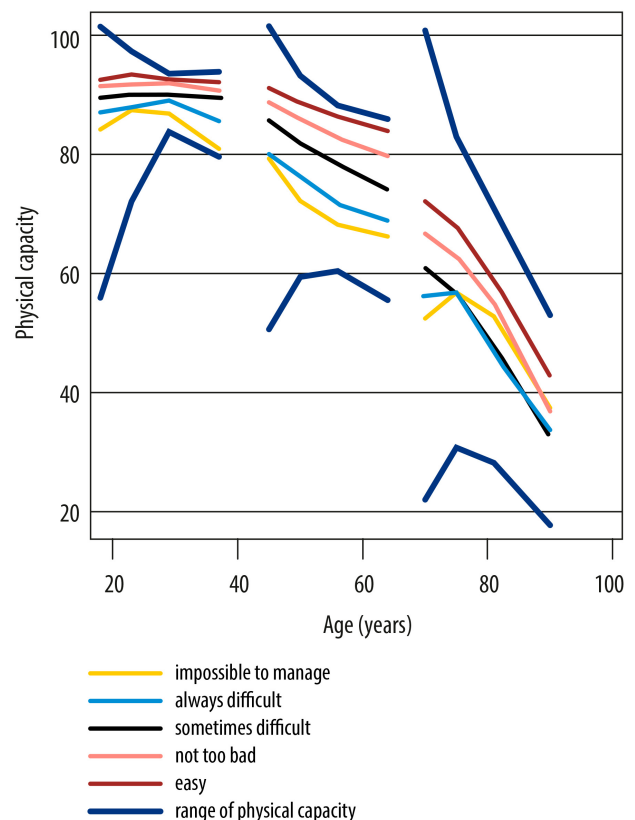
sonalized management and improved quality of life. In addition to refined Artificial Intelligence (AI) tools and applications, wearable devices and social assistive robotic systems have revolutionized the approach to senior services. Several recent publications in gerontology and geriatrics evaluating the use of modern technological approaches and AI in senior care indicate the need for their implication and proved efficacy in everyday clinical practice [6,7]. Frailty development and symptoms inflection points seem to vary among the elderly population. By taking into consideration some of the latest researches on geriatric medicine and frailty [8–12], a few lists for frailty scale and symptoms have already been presented concerning mainly psychological, behavioral and daily functions, genetic, environmental, cardiovascular, aging, comorbidities and neurodegeneration symptoms [13–17]. In the following sections, we describe the corresponding theory and highlight the core components of this review study, including the necessary framework to design a Geriatrics Clinical Decision Support System and well-known computational tools for the management of frailty and individualized diagnosis and treatment in geriatric patients (Fig. 1). Frailty scales enhanced with computational tools and expert systems have a positive outcome in frail populations' quality of life. At the same time, inherent characteristics and health determinants

of these populations can affect their access to this framework. While geriatric evaluation is based on a broad range of tests and frailty scales-biomarkers, several artificial intelligence applications and computational tools may provide holistic management of geriatric patients. This is a literature review study. We have searched biomedical (Pubmed) and tech-oriented (Intech) databases with keywords (frailty, geriatrics, classifications, computational system, and computational tool) to identify computational tools applied in geriatric medicine and frailty management. Original studies reporting or assessing the impact of such tools in the aforementioned fields were prioritized for inclusion. Technical reports, protocols published in peer-reviewed journals, and reviews and assessment reports of computational tools were also eligible for this study to fully assess the contemporary computational arsenal available in geriatrics and frailty management. We excluded reviewed studies published in languages other than English and non peer-reviewed material of commercial or promotional content.

## 2. Designing a Frailty Expert System

Fillit *et al.* [18] and Alexiou *et al.* [2] defined Geriatric Assessment Programs (GAPs) as multidimensional diagnostic processes to identify functional and pathophysiological problems in a frail person's life and design a long-term treatment. Within a rapidly increasing aging population and life expectancy worldwide, geriatric medicine focus on functional disabilities and other comorbidities that frail patients commonly present over 65 (Figs. 2,3, Ref. [19]). Several screening tests are already applied involving the evaluation of activities of daily living (ADL) and instrumental activities of daily living (IADL) efficacy, such as Mini-Mental State Examination (MMSE), Clinical Dementia Rating (CDR), Hachinski ischaemic Scale, Geriatric Depression Scale (GDS), Functional Assessment Questionnaire, Neuropsychiatric Inventory Questionnaire (NPI-Q), and Alzheimer's Disease Assessment Scale-Cognitive (ADAS-COG) [20–28] including physical, social and sexual function and cognitive health measure. The concepts of ADL/IADL have evolved in close proximity to dementia and cognition research. Hence, dementia-centered computational approaches consist of the bulk of related ADL/IADL evidence [29]. On top of the above, many disorders are not caused by aging itself and do not occur in every elderly patient like anemia, cardiovascular diseases, cancer, stroke, diabetes mellitus, hypothyroidism, osteoporosis, prostate disease, sexual dysfunction, vision loss, and free radicals, and this could be a crucial problem on the efficient recognition of frail patients. Many patients with Mild Cognitive Impairment (MCI) display the same morphological changes as Alzheimer's Disease (AD) patients and show no progression of symptoms. Others eventually develop other types of dementia [2,30]. Thus, patients with MCI are a mix of individuals that will and will not convert to AD. As far as imaging techniques are concerned,

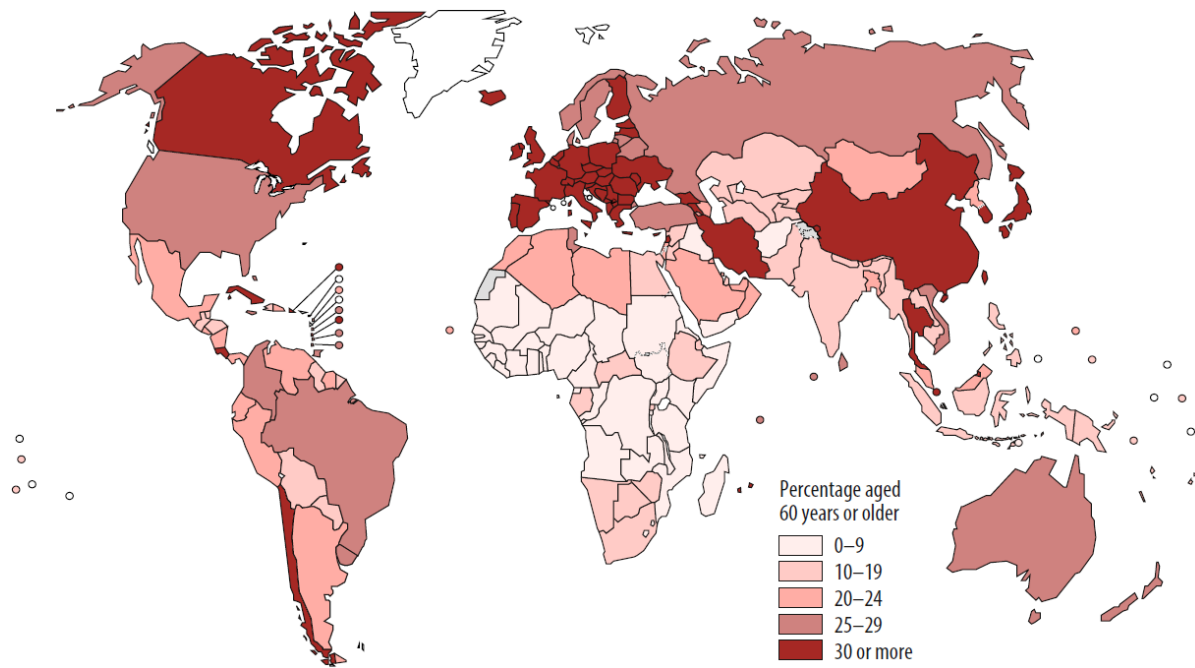
the hippocampal volume of medial temporal lobe atrophy as obtained by Magnetic Resonance Imaging (MRI) and the temporoparietal/precuneus hypometabolism hypoperfusion on or Single-Photon Emission Computed Tomography (SPECT) biomarkers of neurological injury is considered as biomarkers with high efficacy in frail patients [2,31]. Another biomarker of neuronal injury is tau/phosphorylated tau protein. When the two biomarkers, amyloid beta ( $A\beta$ ) and tau/phosphorylated tau proteins, are positively measured, the probability of AD development increases [31,32]. Both  $A\beta$  and phosphorylated tau are common biomarkers for many related disorders and can be detected *in vivo* or *in vitro* [33–36]. The biophysical formulation of frailty can be based on the well-known Excess Entropy Production (EEP) for Prigogine's human aging system, formulated regarding energy [37–41].



Source: G Peeters, J Beard, D Deeg, L Tooth, WJ Brown, A Dobson; unpublished analysis from the Australian Longitudinal Study on Women's Health.

**Fig. 2. Changes in life expectancy from 1950, with projections until 2050, by WHO Region and worldwide [19].**

A holistic approach to examining the geriatric population remains the wisest strategy to timely diagnose, provide adequate treatment, improve quality of life, and reduce morbidity and mortality rates associated with comorbidities. Additional to all these multiple pathologies, several cellular changes and molecular mutants can disrupt genetic



**Fig. 3. Proportion of the population aged 60 years or older, by country, 2050 projections [19].**

integrity, leading to cancer [23,42]. While several clinical trials for elderly medication therapies led novel therapeutic products like cholinesterase inhibitors for AD,  $\alpha$ -blockers for prostatic hyperplasia, bisphosphonates for osteoporosis [43], and many other entities, a medication error is a common problem that may be present in many different phases of the medication process. Therapeutic failure in frail persons is a common problem due to wrong prescribing, polypharmacy, difficulties in communication with the patient, non-adherence to medication, treatment dispensing, and administration [2]. The corresponding data for a Frailty Expert system will mainly consist of biomarkers and other related risk factors as well as social and social demographic data, classified into specific categories, to assist further geriatric evaluation and monitoring:

- Personal demographic data
- Current living conditions
- Information related to elderly health insurance
- Physicians, medical doctors-geriatricians or/and other medical professionals involved
- Personal and family health record
- Hereditary diseases involving the family history
- Information related to physical activity, exercise program, dietary restrictions, and medication records does not require a prescription
- Current medication
- Adverse drug reactions like allergies, intolerabilities, or other side effects
- Physical examination
- Functional inquiry including ADL, IADL, or other support in daily living
- Cognitive testing & behavior

- Results of recent medical examinations-diagnostics, critical medical tests, dental history as well as vaccination history, imaging tests.

Additionally, a frailty system's differential diagnosis must occur to the 2nd level of disease classification, regarding international standards. More details for implementing the above can be found in the Appendices (**Supplementary Material**). Considering the above, many studies aim at designing an integrative multiscale Virtual Physiological Human (VPH) model for the accurate evaluation of human frailty and the proposed diagnostic protocols in elderly populations. The clinical data for a VPH model should include neuropsychological test scores, molecular data, imaging, electrophysiological data, biomarkers detected from blood, patient history, and demographic data. While many tools have already been designed and developed to organize and analyze biological data [44,45], specialized Information and Communication Technologies (ICT) components should be used for the implementation of a VPH model, such as the Web Ontology Language (WOL), the Field Modeling Language (FieldML), and the OSIRIX Open-Source software (OsiriX MD 12.x (PIXMEO SARL, Geneva, Switzerland)) for the imaging data manipulation and storage [46–55].

### 3. Computational Applications in Advanced Geriatric Medicine

As humanity seeks ways to extend life expectancy [56], the need for advanced biological engineering tools is dire. Over the last decades, mounting experience of methodological scientific documentation and experimentation, resulted in the development of interdisciplinary ap-



proaches involving genetic engineering, nanotechnology, quantum mechanics, and computer science. While biomedical evolution and synthetic biology are formulating the so-called 4th industrial revolution, it is essential to highlight the available geriatric medicine tools. Considering the exponential growth of AI funding during the last years, healthcare AI has become an essential component of the majority of these tools. These applications aim to improve treatments' effectiveness, reduce costs, and leverage healthcare services by means of home health monitoring apps, mobile biometric analyzers, drop detectors, virtual companions, and anti-aging open data research [7,10–12,57]. 2019 marked a tremendous increase in healthcare AI funding. Despite the fact that a considerable decrease was noted during the last months of 2019, a positive trend towards higher funding has been observed from the beginning of 2020 onwards [58].

Several innovative tools focus on individualized monitoring and diagnosis in the elderly population based on mobile monitoring applications and wearables (Table 1, Ref. [29,59–89]). Apple offers the triplet of HealthKit (Apple Inc., California, USA), ResearchKit 2.0 (Apple Inc., California, USA), and CareKit (Apple Inc., California, USA) for multitasking data processing, targeting researchers, health professionals, and patients [59]. HealthKit is the core platform for safe data storage and manipulation, and interconnection between health apps. ResearchKit offers a reliable framework for the creation surveys and gather clinical data from end-users. Finally, CareKit provides the necessary framework for personalized healthcare and continuous communication between patients and doctors. One of the well-known and widely applied applications of Apple's ResearchKit library is the mPower 2.0 (Sage Bionetworks, Seattle, USA) [60], which is an evidence Smartphone-based study for the identification of Parkinson's Disease (PD) severity by measuring dexterity, balance, gait, and memory, providing with very low-cost clinical data from thousands of patients in a short time [61]. Similarly, the EpiWatch (Johns Hopkins Medicine Technology Innovation Center, Baltimore, USA) is a powerful application of Apple's ResearchKit library from the Johns Hopkins University, predicting seizure incidents using the Apple Watch [62,63]. This app could help manage epilepsy, creating a correlation between episode history and medication, based on the heart rate accelerometer and gyroscope sensors of the Apple Watch, simultaneously informing caregivers or family members of any produced alert situation. Another very useful for frailty management Apple's ResearchKit application is SleepHealth [64,65] (University of California, San Diego, USA). A mHealth study based on the iPhone, iPod Touch, and Apple Watch, offers a personalized wellness tool for the evaluation of sleep habits and their potential correlation with the comorbidities of the nowadays status quo, like diabetes, heart disease, obesity, and depression.

Within the Smartphone-based applications and point-

of-care diagnostics [66,90–93], the latest nanoparticle-enabled Smartphone system (Harvard Medical School, Boston, USA) from the Harvard Medical School offers rapid and sensitive virus detection on a microchip labeled with specifically designed platinum nanoprobe using a convolutional neural network, such as HBV, HCV, and Zika virus [66]. Although these advances seem loosely connected to geriatrics, they have become relevant during the COVID-19 pandemic. Offering point-of-care diagnostics to vulnerable geriatric populations can mitigate the spread of viral infections such as COVID-19 and the seasonal flu. Repurposing such modalities for COVID-19 has been in the spotlight of ongoing research [94].

On top of these, it is worth to mention the beneficial At-Home Kidney Testing from Healthy.io (Boston, USA) [67,68], which turns the Smartphone camera into a medical device for urine analysis at home. The application aims to streamline the diagnosis and monitoring of Chronic Kidney Disease (CKD) in few simple steps: the Albumin to Creatinine ratio (ACR) test kit is sent to patients with their consent, the patients performs the urine test and use their smartphone to analyze the results, and eventually the exported ACR diagram is sent to physicians. Additionally, platforms with strong sensitivity and high diagnostic accuracy for Diabetic Retinopathy (DR), age-related macular degeneration, cataract, retinopathy of prematurity, retinal vein occlusion, and glaucoma gradually become available. The Google DeepMind convolutional neural network-based DR-detection algorithm (AlphaBet Inc, London, UK) [69], the IDx-DR AI diabetic screening system (Digital Diagnostics, Coralville, USA) is already being used to more effectively diagnose eye diseases [70] and the Eye-Art DL-based deep-neural networks system (Eyenuk Inc., Woodland Hills, USA) for imaging classification [71] are well known and highly applied in the market AI platforms for geriatric medicine (not limited). A different approach uses Brain-Computer Interaction (BCI) tools in patients with neurodegeneration combined with enriched sensorimotor stimulations offering cognitive-behavioral therapy and art therapy [72,73]. These neuroinformatics tools provide Electroencephalography (EEG)-based self-navigation through virtual worlds [74,75], reduce depression and apathy through enhanced environmental stimulation improving dendritic branching and synaptic density resulting in neurogenesis [76–78] or apply low-pressure ultrasounds for the activation of neurons in an effort to reduce or even reverse neurodegeneration [79–82].

It is crucial to include in this review, personal care robots, which are nowadays widely used increasing the quality of life of elderly population. Such social assistive robots are usually used on a non-medical basis offering assistance autonomously on patients with reduced decision-making ability also supporting the services of professional caregivers and geriatricians [83,84]. Even though several types of assistive robots are already launched in the market

**Table 1. The old and new computational tools/programs used in the geriatric health care system.**

Release date	Tool	Functionality	Target group
2014	Apple HealthKit API (Health App) [59]	Core platform for safe data storage and manipulation, interconnection between health apps	Researchers, Healthcare professionals, Patients
2015	Apple ResearchKit API (Health App) [61–63]	Creating surveys and gathering clinical data from end-users	Researchers, Healthcare professionals, Patients
2016	Apple CareKit API (Health App) [59]	Framework for personalized healthcare and continuous communication between patients and healthcare professionals	Researchers, Healthcare professionals, Patients
2015	mPower [60,61]	Smartphone-based study for the identification of Parkinson's Disease (PD) severity by measuring dexterity, balance, gait, and memory	Patients with PD and specialized healthcare professionals
2019	EpiWatch (combined with the Apple Watch) [62,63]	Prediction of seizures and management of epilepsy, Correlation between episode history, medication, vital signs, accelerometer and gyroscope sensors of the Apple Watch, Instant notification to caregivers	Patients with seizures/epilepsy, caregivers and specialized healthcare professionals
2016	SleepHealth [64,65]	Personalized wellness wearable for the evaluation of sleep habits and their correlation with comorbidities such as diabetes, heart disease, obesity, and depression	Patients and (seemingly) healthy individuals
2019	Harvard nanoparticle-enabled smartphone system [66]	Rapid and sensitive virus detection by means of a microchip labeled with specifically designed platinum nanoproboscopes using a convolutional neural network. Designed for HBV, HCV and Zika virus but can be adapted to SARS-CoV-2	Elderly, vulnerable populations, frontline workers (particularly those of advanced age)
2019	At-Home Kidney Testing from Healthy.io [67,68]	Urine analysis at home by means of smartphone camera, referral for the Albumin to Creatinine ratio (ACR) at-home test kit, results available for doctor's review	Patients with kidney disease and patients at risk of developing kidney disease (Diabetes mellitus, hypertension etc.)
2018	The Google IDx-Diabetic Retinopathy (DR) AI diabetic screening system [69,70]	DeepMind convolutional neural network-based Diabetic Retinopathy detection algorithm	Patients with diabetes mellitus and known or suspected Diabetic Retinopathy
2018	EyeArt® by EYENUK [71]	Deep Learning-based deep-neural networks system for imaging classification	Patients with diabetes mellitus and known or suspected Diabetic Retinopathy, patients with age-related macular degeneration, cataract, retinopathy of prematurity, retinal vein occlusion, and glaucoma
2006–2019	Brain-Computer Interaction (BCI) neuroinformatic tools [72–82]	Electroencephalography (EEG)-based self-navigation through virtual worlds, management of depression and apathy through enhanced environmental stimulation, or application of low-pressure ultrasounds for the activation of neurons in neurodegeneration. Mechanistically, these might improve dendritic branching and synaptic density resulting in neurogenesis	Patients with neurodegeneration combined with enriched sensorimotor stimulations who can benefit from cognitive-behavioral therapy and art therapy

**Table 1. Continued.**

Release date	Tool	Functionality	Target group
2015	Personal care robots (Care-O-bot®, Robot-Era®, the Zora®, the JustoCat®, PARO®) [83–88]	Social assistive robots mainly used on a non-medical basis offering assistance autonomously on patients with reduced decision-making ability and supporting the services of professional caregivers and geriatricians	Patients with a low level of functionality—autonomy, physicians, caregivers
2019	Clinattec and the University of Grenoble, France [89]	A mind-reading exoskeleton based on two brain implants that monitor the brain’s part responsible for movement	Tetraplegic patients
1950	(Instrumental) Activities of Daily Living (IADL–ADL), Barthel Index (BI), Katz Index of Independence in Activities of Daily Living, Functional Independence Measure (FIM), Activities of Daily Living (ADL) Profile, Activities of Daily Living Questionnaire (ADLQ) [29]	Indexes measuring and assessing personal demographic data, current living conditions, health insurance features, personal and family health record including hereditary diseases, available healthcare resources, physical activity, exercise program, dietary restrictions, medication (both on prescription and over the counter medication) records, adverse drug reactions, physical and laboratory examinations, imaging tests’ findings, functional inquiry, cognitive testing & behavior, dental history, vaccination history	Patients with limited functionality (Dementia, Motor deficits, Spinal Cord Injury, Dementia, Advanced Cancer etc.)

like the Care-O-bot®, the Robot-Era®, the Zora®, the JustoCat, and the PARO, for monitoring daily activities, still the acceptance within the general population can be characterized as low, depending on the patients' age, gender, cognitive ability, education, culture and social status quo [83,85–88]. Closing this section, we present the latest presentation of an exoskeleton controlled by a brain-machine interface in tetraplegic patients. The French biomedical research center Clinec and the University of Grenoble, France, demonstrated a mind-reading exoskeleton based on two brain implants that monitor the brain's part responsible for movement [89].

#### 4. Discussion

Computational tools and particularly AI has multiple applications in medicine, specifically in acute clinical care and in the hospital setting, implementing various specialties and influencing healthcare delivery quality. Clinicians should be aware of the recent advances of AI in geriatrics. By endorsing programs and systems in their everyday clinical practice, decision-making will become more efficient and faster, providing different treatment options in individual patients. These systems will make extensive use of existing interoperability standards to address interoperability issues related to heterogeneous data sources, organize, analyze, and share vast quantities of biomedical research data, therefore clinicians will also be much more confident about their clinical decisions. While GAPS are already increasingly applied in nursing homes and individuals' health professionals for diagnostic accuracy, the proposed study enhances the scientific community with a new and efficient Aging Cure and Care tool. However, the implementation of such computational tools in clinical practice renders a variety of challenges. First and foremost, efficacy and proved patient safety can become quite disputable. For consideration, a diagnostic AI algorithm is deemed a high-risk tool since the consequences of an instant misdiagnosis could potentially prove problematic, even lethal to patients. Moreover, the liability in case of medical errors attributed to such tools can be quite intricate, varying among regions and legislative systems [95]. Without a doubt, computational tools whose human input remains minimal appear more troublesome comparing to AI advances with more human engagement. However, the deposition of confidential personal health-related data to this kind of software can also raise significant concerns.

What is more, a considerable number of individuals fulfilling the frailty criteria lack the digital skills necessary for the shift of their care towards computational diagnostics and management. During the COVID-19 pandemic, policymakers, healthcare providers and individuals have become more receptive and knowledgeable in terms of digital health. This familiarization in the context of COVID-19 or other communicable and non-communicable diseases has already paved the way of digital literacy among the el-

derly [96]. Cost-effectiveness and accessibility to AI programs consist of another two limitations that need further evaluation. For future direction, extensive clinical and non-clinical trials are necessary to evaluate these significant parameters for the AI systems to be approved and widely used by healthcare professionals [97–99]. The current study's limitations include the lack of a meta-analytic approach to assessing the reported tools' real-life effectiveness. This can be the scope of a future study. Overall, computational tools in contemporary geriatrics and frailty management aim to improve treatments' effectiveness, reduce costs, and increase healthcare validity, and capacitate home health monitoring apps, mobile biometric analyzers, drop detectors, virtual companions, and anti-aging open data research.

#### Informed Consent Statement

Not applicable.

#### Data Availability Statement

Frailty classification for differential diagnosis, according to the icd10data.com American system for medical coding rules and procedures in the Supplementary Material File.

#### Abbreviations

ADL, Activities Daily Living; ACR, Albumin to Creatinine Ratio; AD, Alzheimer's Disease; ADAS-COG, Alzheimer's Disease Assessment Scale-Cognitive;  $A\beta$ , Amyloid Beta; AI, Artificial Intelligence; ASD, Autism Spectrum Disorders; BCI, Brain-Computer Interaction; CKD, Chronic Kidney Disease; CDR, Clinical Dementia Rating; EEG, Electroencephalography; EEP, Excess Entropy Production; FieldML, Field Modeling Language; GAPS, Geriatric Assessment Programs; GDS, Geriatric Depression Scale; ICT, Information and Communication Technologies; IADL, Instrumental Activities of Daily Living; MRI, Magnetic Resonance Imaging; MCI, Mild Cognitive Impairment; MMSE, Mini-Mental State Examination; NPI-Q, Neuropsychiatric Inventory Questionnaire; PD, Parkinson's Disease; PET, Positron Emission Tomography; SPECT, Single-Photon Emission Computed Tomography; VPH, Virtual Physiological Human; WOL, Web Ontology Language.

#### Author Contributions

Conceptualization done by BS, MAK, GMA and AA; methodology design and implementation by AK, IH, IG, GZ, NKJ and MSU; data collection and analysis by AML, CT, PC, GZ, FA and PS; All authors contributed in writing manuscript, reviewing and editing, and final approval.

#### Ethics Approval and Consent to Participate

Not applicable.



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## Conflict of Interest

The authors declare no conflict of interest.

## Supplementary Material

Supplementary material associated with this article can be found, in the online version, at <https://doi.org/10.31083/j.fbl2708232>.

## References

- [1] Misiaszek BC. Geriatric Medicine Survival Handbook (Revised Version). Michael G. DeGroote School of Medicine, McMaster University: Hamilton, Canada. 2008.
- [2] Alexiou A, Chatzichronis S, Ashraf GM. Diagnosis and Management in Dementia. In Martin CR, Preedy VR (eds.) Prediction of Alzheimer's disease (pp. 365–378). Academic Press: USA. 2020.
- [3] Rohrmann S. Epidemiology of Frailty in Older People. *Advances in Experimental Medicine and Biology*. 2020; 1216: 21–27.
- [4] Cesari M, Gambassi G, Abellan van Kan G, Vellas B. The frailty phenotype and the frailty index: different instruments for different purposes. *Age and Ageing*. 2014; 43: 10–12.
- [5] Bowen ME. The Relationship between Body Weight, Frailty, and the Disablement Process. *Journals of Gerontology Series B: Psychological Sciences and Social Sciences*. 2012; 67: 618–626.
- [6] Simou P, Alexiou A, Tiligadis K. Artificial Humanoid for the Elderly People. *Advances in Experimental Medicine and Biology*. 2015; 821: 19–27.
- [7] Stafford IS, Kellermann M, Mossotto E, Beattie RM, MacArthur BD, Ennis S. A systematic review of the applications of artificial intelligence and machine learning in autoimmune diseases. *npj Digital Medicine*. 2020; 3: 30.
- [8] Espinoza S, Walston JD. Frailty in older adults: insights and interventions. *Cleveland Clinic Journal of Medicine*. 2005; 72: 1105–1112.
- [9] Rockwood K, Andrew M, Mitnitski A. A comparison of two approaches to measuring frailty in elderly people. *Journals of Gerontology: Series a, Biological Sciences and Medical Sciences*. 2007; 62: 738–743.
- [10] Bowers LJ. Clinical assessment of geriatric patients: unique challenges. In Mootz R, Bowers L (eds.) *Chiropractic Care of Special Populations* (pp. 168–170). 1st edn. Jones & Bartlett Learning: USA. 1999.
- [11] Choudhury A, Renjilian E, Asan O. Use of machine learning in geriatric clinical care for chronic diseases: a systematic literature review. *JAMIA Open*. 2020; 3: 459–471.
- [12] Hofer IS, Burns M, Kendale S, Wanderer JP. Realistically Integrating Machine Learning into Clinical Practice: A Road Map of Opportunities, Challenges, and a Potential Future. *Anesthesia & Analgesia*. 2020; 130: 1115–1118.
- [13] CSHA Working Group. Canadian Study of Health and Aging: study methods and prevalence of dementia. *CMAJ*. 1994; 150: 899–913.
- [14] CSHA Working Group. The incidence of dementia in Canada: the Canadian Study of Health and Aging Working Group. *Neurology*. 2000; 55: 66–73.
- [15] Rockwood K, Wolfson C, McDowell I. The Canadian Study of Health and Aging: organizational lessons from a national, multicenter, epidemiologic study. *International Psychogeriatrics*. 2001; 13: 233–237.
- [16] Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, *et al.* A global clinical measure of fitness and frailty in elderly people. *CMAJ*. 2005; 173: 489–495.
- [17] Vairaktarakis C, Tsiamis V, Soursou G, Lekkas F, Nikolopoulou M, Vasileiadou E, *et al.* A computer-aided diagnosis system for geriatrics assessment and frailty evaluation. *Advances in Experimental Medicine and Biology*. 2015; 820: 69–77.
- [18] Fillit HM, Rockwood K, Woodhouse K. *Brocklehurst's Textbook of Geriatric Medicine and Gerontology Book*. 7th edn. Elsevier: USA. 2010.
- [19] World Health Organization. World report on ageing and health. 2015. Available at: <https://apps.who.int/iris/handle/10665/186463/> (Accessed: 10 March 2021).
- [20] Buys CHCM. Telomeres, Telomerase, and Cancer. *New England Journal of Medicine*. 2000; 342: 1282–1283.
- [21] Mathuranath PS, Nestor PJ, Berrios GE, Rakowicz W, Hodges JR. A brief cognitive test battery to differentiate Alzheimer's disease and frontotemporal dementia. *Neurology*. 2000; 55: 1613–1620.
- [22] Wright WE, Shay JW. Telomere dynamics in cancer progression and prevention: fundamental differences in human and mouse telomere biology. *Nature Medicine*. 2000; 6: 849–851.
- [23] Cassel CK, Leipzig RM, Cohen HJ, Larson EB, Meier DE, Capello CF. *Geriatric Medicine, An Evidence-Based Approach*. 4th edn. Springer: New York. 2003.
- [24] Brodaty H, Low L, Gibson L, Burns K. What is the best dementia screening instrument for general practitioners to use? *American Journal of Geriatric Psychiatry*. 2006; 14: 391–400.
- [25] Moniz-Cook E, Vernooij-Dassen M, Woods R, Verhey F, Chattat R, De Vugt M, *et al.* A European consensus on outcome measures for psychosocial intervention research in dementia care. *Ageing and Mental Health*. 2008; 12: 14–29.
- [26] Zekry D, Herrmann FR, Grandjean R, Meynet M, Michel J, Gold G, *et al.* Demented versus non-demented very old inpatients: the same comorbidities but poorer functional and nutritional status. *Age and Ageing*. 2008; 37: 83–89.
- [27] Appels BA, Scherder E. The diagnostic accuracy of dementia-screening instruments with an administration time of 10 to 45 minutes for use in secondary care: a systematic review. *American Journal of Alzheimer's Disease and other Dementias*. 2010; 25: 301–316.
- [28] Hancock P, Larner AJ. Test your Memory test: diagnostic utility in a memory clinic population. *International Journal of Geriatric Psychiatry*. 2011; 26: 976–980.
- [29] Regal P, Carter A. Instrumental Activities of Daily Living Questionnaires for Dementia and Mild Cognitive Impairment. *Journal of Neurology Research*. 2015; 5: 153–159.
- [30] Mantzavinos V, Alexiou A. Biomarkers for Alzheimer's Disease Diagnosis. *Current Alzheimer Research*. 2017; 14: 1149–1154.
- [31] Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, *et al.* Mild Cognitive Impairment (MCI) due to Alzheimer's Disease Workgroup. *Current Medicinal Chemistry - Immunology, Endocrine & Metabolic Agents*. 2010; 3: 371–383.
- [32] Buée L, Bussièrè T, Buée-Scherrer V, Delacourte A, Hof PR. Tau protein isoforms, phosphorylation and role in neurodegenerative disorders. *Brain Research Reviews*. 2000; 33: 95–130.

- [33] Chan DC. Mitochondrial dynamics in disease. *New England Journal of Medicine*. 2007; 356: 1707–1709.
- [34] Moncaster JA, Pineda R, Moir RD, Lu S, Burton MA, Ghosh JG, *et al.* Alzheimer's Disease Amyloid-beta Links Lens and Brain Pathology in Down Syndrome. *PLoS ONE*. 2010; 5: e10659.
- [35] Nazem A, Mansoori GA. Nanotechnology for Alzheimer's Disease Detection and treatment. *Insciences Journal*. 2011; 1: 169–193.
- [36] Uddin MS, Kabir MT, Jakaria M, Sobarzo-Sánchez E, Barreto GE, Perveen A, *et al.* Exploring the Potential of Neuroproteomics in Alzheimer's Disease. *Current Topics in Medicinal Chemistry*. 2020; 20: 2263–2278.
- [37] Prigogine I, Wiame JM. Biology and thermodynamics of irreversible phenomena. *Experientia*. 1946; 2: 451–453. (In French)
- [38] Prigogine I. Time, structure, and fluctuations. *Science*. 1978; 201: 777–785.
- [39] Hershey D, Lee WE. Entropy, aging and death. *Systems Research*. 1987; 4: 269–281.
- [40] Hershey D, Lee WE. Correspondence: Excess entropy (ee) and excess entropy production (eep) in aging, evolving systems. *Systems Research*. 1988; 5: 261–263.
- [41] Alexiou A, Rekkas J. The quantum human central neural system. *Advances in Experimental Medicine and Biology*. 2015; 821: 101–109.
- [42] Dipple A. DNA adducts of chemical carcinogens. *Carcinogenesis*. 1995; 16: 437–441.
- [43] Brown JP, Morin S, Leslie W, Papaioannou A, Cheung AM, Davison KS, *et al.* Bisphosphonates for the treatment of osteoporosis: expected benefits, potential harms, and drug holidays. *Canadian Family Physician Medecin de Famille Canadien*. 2014; 60: 324–333.
- [44] Huerta MF, Koslow SH, Leshner AI. The Human Brain Project: an international resource. *Trends in Neurosciences*. 1993; 16: 436–438.
- [45] Koslow SH, Huerta MF. *Neuroinformatics: an overview of the human brain project*. Lawrence Erlbaum Associates: Mahwah, New Jersey, USA. 1993.
- [46] Martone ME, Gupta A, Wong M, Qian X, Sosinsky G, Ludäscher B, *et al.* A cell-centered database for electron tomographic data. *Journal of Structural Biology*. 2002; 138: 145–155.
- [47] Martone ME, Zhang S, Gupta A, Qian X, He H, Price DL, *et al.* The cell-centered database: a database for multiscale structural and protein localization data from light and electron microscopy. *Neuroinformatics*. 2003; 1: 379–395.
- [48] Wang J, Williams RW, Manly KF. WebQTL: web-based complex trait analysis. *Neuroinformatics*. 2003; 1: 299–308.
- [49] Müller H, Kenny EE, Sternberg PW. Textpresso: an ontology-based information retrieval and extraction system for biological literature. *PLoS Biology*. 2004; 2: e309.
- [50] Bota M, Dong H, Swanson LW. Brain architecture management system. *Neuroinformatics*. 2005; 3: 15–48.
- [51] Ascoli GA, Donohue DE, Halavi M. NeuroMorpho.Org: a central resource for neuronal morphologies. *Journal of Neuroscience*. 2007; 27: 9247–9251.
- [52] Lein ES, Hawrylycz MJ, Ao N, Ayres M, Bensinger A, Bernard A, *et al.* Genome-wide atlas of gene expression in the adult mouse brain. *Nature*. 2007; 445: 168–176.
- [53] Martone ME, Sargis J, Tran J, Wong WW, Jiles H, Mangir C. Database resources for cellular electron microscopy. *Methods in Cell Biology*. 2007; 79: 799–822.
- [54] Martone ME, Zaslavsky I, Gupta A, Memon A, Tran J, Wong W, *et al.* The smart atlas: spatial and semantic strategies for multiscale integration of brain data. In Burger A, *et al.* (eds.) *Anatomy Ontologies for Bioinformatics: Principles and Practice*. Springer-Verlag: London, UK. 2007.
- [55] Fensel D. *Ontologies: Silver Bullet for Knowledge Management and Electronic Commerce*. Springer-Verlag: London, UK. 2000.
- [56] Alexiou A, Simou P, Alexiou F, Chatzichronis S, Ashraf GM. Social and Ethical Impact of Advanced Artificial and Biological Enhancements. *Open Public Health Journal*. 2020; 13: 62–68.
- [57] Battineni G, Sagaro GG, Chinatalapudi N, Amenta F. Applications of machine learning predictive models in the chronic disease diagnosis. *Journal of Personalized Medicine*. 2020; 10: 21.
- [58] De Nigris S, Craglia M, Nepelski D, Hradec J, Gomez-Gonzales E, Gutierrez EG, *et al.* AI Watch: AI Uptake in Health and Healthcare, 2020. Publications Office of the European Union: Luxembourg. 2020.
- [59] Apple. Research, Health and Care Kit. 2020. Available at: <https://www.researchandcare.org/> (Accessed: 3 March 2020).
- [60] Mangravite L, Larsson O. University of Rochester, Sage Bionetworks. 2015. Available at: <https://parkinsonmpower.org/> (Accessed: 10 March 2021).
- [61] Bot BM, Suver C, Neto EC, Kellen M, Klein A, Bare C, *et al.* The mPower study, Parkinson disease mobile data collected using ResearchKit. *Scientific Data*. 2016; 3: 160011.
- [62] Carmenate Y, Gonzalez E, Ge A, Collard M, Lee S, *et al.* Implementing a national study using ResearchKit and Apple Watch to collect biosensor and response data during seizures: preliminary results. American Epilepsy Society Annual Meeting. Houston, TX, USA. 2–6 December 2016.
- [63] Carmenate Y, Gonzalez E, Ge A, Collard M, Lee S, Crone NE, *et al.* Tracking heart rate changes during seizures: a national study using ResearchKit and Apple Watch to collect biosensor and response data during seizures. International Epilepsy Congress. Barcelona, Spain. 2–6 September 2017.
- [64] Deering S, Amdur A, Borelli J, Drobnich D, Headapohl W, Stepnowsky CJ, *et al.* SleepHealth Mobile App study: Bringing the sleep lab to you. *Sleep*. 2017; 40: A287–A288.
- [65] Deering S, Pratap A, Suver C, Borelli AJ, Amdur A, Headapohl W, *et al.* Real-world longitudinal data collected from the SleepHealth mobile app study. *Scientific Data*. 2020; 7: 418.
- [66] Draz MS, Lakshminarasimulu NK, Krishnakumar S, Battalappalli D, Vasan A, Kanakasabapathy MK, *et al.* Motion-Based Immunological Detection of Zika Virus Using Pt-Nanomotors and a Cellphone. *ACS Nano*. 2018; 12: 5709–5718.
- [67] Leddy J, Green JA, Yule C, Molecavage J, Coresh J, Chang AR. Improving proteinuria screening with mailed Smartphone urinalysis testing in previously unscreened patients with hypertension: a randomized controlled trial. *BMC Nephrology*. 2019; 20: 132.
- [68] Shore J, Green M, Hardy A, Livesey D. The compliance and cost-effectiveness of smartphone urinalysis albumin screening for people with diabetes in England. *Expert Review of Pharmacoeconomics & Outcomes Research*. 2020; 20: 387–395.
- [69] Gulshan V, Peng L, Coram M, Stumpe MC, Wu D, Narayanaswamy A, *et al.* Development and Validation of a Deep Learning Algorithm for Detection of Diabetic Retinopathy in Retinal Fundus Photographs. *Journal of the American Medical Association*. 2016; 316: 2402–2410.
- [70] Abramoff MD, Lavin PT, Birch M, Shah N, Folk JC. Pivotal trial of an autonomous AI-based diagnostic system for detection of diabetic retinopathy in primary care offices. *NPJ Digital Medicine*. 2018; 1: 39.
- [71] Rajalakshmi R, Subashini R, Anjana RM, Mohan V. Automated diabetic retinopathy detection in smartphone-based fundus photography using artificial intelligence. *Eye*. 2018; 32: 1138–1144.
- [72] Chatzichronis S, Alexiou A, Simou P, Mantzavinos V, Tsiamis V. Neurocognitive Assessment Software for Enrichment Sensory Environments. *Journal of Proteomics and Bioinformatics*. 2019; 12: 018–028.
- [73] Rubin JA. New York: Routledge. The Guilford Press: New

- York. 2016.
- [74] Scherer R, Lee F, Schlogl A, Leeb R, Bischof H, Pfurtscheller G. Toward self-paced brain-computer communication: navigation through virtual worlds. *IEEE Transactions on Bio-Medical Engineering*. 2008; 55: 675–682.
- [75] Leeb R, Friedman D, Müller-Putz GR, Scherer R, Slater M, Pfurtscheller G. Self-Paced (Asynchronous) BCI Control of a Wheelchair in Virtual Environments: a Case Study with a Tetraplegic. *Computational Intelligence and Neuroscience*. 2007; 2007: 79642.
- [76] Park H, Pringle Specht JK. Effect of Individualized Music on Agitation in Individuals with Dementia who Live at Home. *Journal of Gerontological Nursing*. 2009; 35: 47–55.
- [77] Nithianantharajah J, Hannan AJ. Enriched environments, experience-dependent plasticity and disorders of the nervous system. *Nature Reviews Neuroscience*. 2006; 7: 697–709.
- [78] Belkofer CM, Konopka LM. Conducting Art Therapy Research Using Quantitative EEG Measures. *Art Therapy*. 2008; 25: 56–63.
- [79] Ibsen S, Tong A, Schutt C, Esener S, Chalasani SH. Sonogenetics is a non-invasive approach to activating neurons in *Caenorhabditis elegans*. *Nature Communications*. 2015; 6: 8264.
- [80] Deuel TA, Pampin J, Sundstrom J, Darvas F. The Encephalophone: a Novel Musical Biofeedback Device using Conscious Control of Electroencephalogram (EEG). *Frontiers in Human Neuroscience*. 2017; 11: 213.
- [81] Bergstrom I, Seinfeld S, Arroyo-Palacios J, Slater M, Sanchez-Vives MV. Using music as a signal for biofeedback. *International Journal of Psychophysiology*. 2014; 93: 140–149.
- [82] Simou P, Vakalos P, Alexiou A, Chatzichronis S, Ali MA, Haranas I, *et al.* Strengthen Alzheimer’s Awareness through Biomusic. In Ashraf G, Alexiou A (eds.) *Biological, Diagnostic and Therapeutic Advances in Alzheimer’s Disease* (pp. 117–128). Springer: Singapore. 2019.
- [83] Johansson-Pajala R, Thommes K, Hoppe JA, Tuisku O, Hennala L, Pekkarinen S, *et al.* Care Robot Orientation: what, who and how? Potential Users’ Perceptions. *International Journal of Social Robotics*. 2020; 12: 1103–1117.
- [84] Johansson-Pajala RM, Gustafsson C. Significant challenges when introducing care robots in Swedish elder care. *Disability and Rehabilitation: Assistive Technology*. 2020; 1–11.
- [85] Hudson J, Orviska M, Hunady J. People’s Attitudes to Robots in Caring for the Elderly. *International Journal of Social Robotics*. 2017; 9: 199–210.
- [86] Gustafsson C, Svanberg C, Müllersdorf M. A robotic cat in dementia care—a pilot study. ISG 2016. World Conference of Gerontechnology. Daegu, Korea, 18–21 October 2016; 15: 151.
- [87] Efrting H, Frennert S. Designing a social and assistive robot for seniors. *Zeitschrift Fur Gerontologie Und Geriatrie*. 2016; 49: 274–281.
- [88] Jenkins S, Draper H. Care, Monitoring, and Companionship: Views on Care Robots from Older People and their Carers. *International Journal of Social Robotics*. 2015; 7: 673–683.
- [89] Benabid AL, Costecalde T, Elisseyev A, Charvet G, Verney A, Karakas S, *et al.* An exoskeleton controlled by an epidural wireless brain-machine interface in a tetraplegic patient: a proof-of-concept demonstration. *Lancet Neurology*. 2019; 18: 1112–1122.
- [90] Johansson-Pajala RM, Gustafsson C. Significant challenges when introducing care robots in Swedish elder care. *Disability and Rehabilitation: Assistive Technology*. 2020; 1–11.
- [91] Perkel JM. Pocket laboratories. *Nature*. 2017; 545: 119–121.
- [92] Draz MS, Kochehyoki KM, Vasan A, Battalapalli D, Sreeram A, Kanakasabapathy MK, *et al.* DNA engineered micromotors powered by metal nanoparticles for motion based cellphone diagnostics. *Nature Communications*. 2018; 9: 4282.
- [93] Wood CS, Thomas MR, Budd J, Mashamba-Thompson TP, Herbst K, Pillay D, *et al.* Taking connected mobile-health diagnostics of infectious diseases to the field. *Nature*. 2019; 566: 467–474.
- [94] Shokr A, Pacheco LGC, Thirumalaraju P, Kanakasabapathy MK, Gandhi J, Kartik D, *et al.* Mobile Health (mHealth) Viral Diagnostics Enabled with Adaptive Adversarial Learning. *ACS Nano*. 2021; 15: 665–673.
- [95] Nebeker C, Torous J, Bartlett Ellis RJ. Building the case for actionable ethics in digital health research supported by artificial intelligence. *BMC Medicine*. 2019; 17: 137.
- [96] Moore RC, Hancock JT. Older Adults, Social Technologies, and the Coronavirus Pandemic: Challenges, Strengths, and Strategies for Support. *Social Media + Society*. 2020; 6: 2056305120948162.
- [97] Rosse C, Mejino JLV. A reference ontology for biomedical informatics: the Foundational Model of Anatomy. *Journal of Biomedical Informatics*. 2003; 36: 478–500.
- [98] Rubenstein LV, Calkins DR, Greenfield S, Jette AM, Meenan RF, Nevins MA, *et al.* Health status assessment for elderly patients: reports of the Society of General Internal Medicine task force on health assessment. *Journal of the American Geriatrics Society*. 1989; 37: 562–569.
- [99] Draz MS, Vasan A, Muthupandian A, Kanakasabapathy MK, Thirumalaraju P, Sreeram A, *et al.* Virus detection using nanoparticles and deep neural network-enabled smartphone system. *Science Advances*. 2020; 6: eabd5354.