UTILIZING DIGITAL BIOMARKERS FOR THE MONITORING AND MANAGEMENT OF PARKINSON DISEASE

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Abstract
Technological advancement has led to a notable surge of interest in the integration of digital technologies into medical care, particularly within the realm of chronic diseases. Quantitative metrics derived from digital health technology (DHT) have the potential to serve as Digital Biomarkers (DBs), facilitating the continuous and quantitative monitoring of disease symptoms, even outside clinical settings. This capacity extends to the ongoing and precise assessment of treatment responses, presenting an opportunity for swift adaptations in medication pathways. Moreover, the integration of DBs generated by wearable devices into innovative decision support systems holds promise for enhancing longitudinal disease management, complementing existing standard practices. Furthermore, these novel biomarkers not only advance diagnostic capabilities but also contribute to predicting clinical outcomes. As a result, the emergence of DBs holds considerable promise, representing a transformative force in precision neurology.

Keywords: Digital Biomarkers, Parkinson's Disease, Wearable Devices

Η ΧΡΗΣΗ ΨΗΦΙΑΚΩΝ ΒΙΟΔΕΙΚΤΩΝ ΓΙΑ ΤΗΝ ΠΑΡΑΚΟΛΟΥΘΗΣΗ ΚΑΙ ΤΗΝ ΔΙΑΧΕΙΡΗΣΗ ΤΗΣ ΝΟΣΟΥ ΠΑΡΚΙΝΣΟΝ

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Περίληψη
Η αλματώδης εξέλιξη της τεχνολογίας έχει οδηγήσει σε μια αξιοσημείωτη αύξηση του ενδιαφέροντος για την ενσωμάτωση των ψηφιακών τεχνολογιών στην ιατρική, ιδίως στον τομέα των χρόνιων παθήσεων. Οι ποσοτικές μετρήσεις που προέρχονται από την χρήση ψηφιακών τεχνολογιών και χρησιμεύσουν ως ψηφιακοί βιοδείκτες (ΨΒ), διευκολύνουν τη συνεχή και ποσοτική παρακολούθηση των συμπτωμάτων της νόσου, ακόμη και εκτός κλινικών πλαισίων. Η ικανότητα αυτή επεκτείνεται στη συνεχή και ακριβή αξιολόγηση των αποκρίσεων στη θεραπεία, παρουσιάζοντας μια ευκαιρία για ταχείες προσαρμογές στο φαρμακευτικό σχήμα. Επιπλέον, η ενσωμάτωση των ΨΒ που παράγονται από φορέσιμες συσκευές σε καινοτόμα συστήματα υποστήριξης αποφάσεων, υπόσχεται την ενίσχυση της διαχρονικής διαχείρισης της νόσου, συμπληρώνοντας τις υπάρχουσες πρακτικές. Επιπλέον, αυτοί οι νέοι βιοδείκτες όχι μόνο προάγουν τις διαγνωστικές δυνατότητες αλλά συμβάλλουν και στην πρόβλεψη των κλινικών αποτελεσμάτων. Κατά συνέπεια, η εμφάνιση των ΨΒ υπόσχεται πολλά, αποτελώντας μια δύναμη μετασχηματισμού στη νευρολογία της ακριβείας.

Λέξεις κλειδιά: Ψηφιακοί Βιοδείκτες, Νόσος Πάρκινσον, Φορέσιμες Συσκευές

Introduction

Parkinson's disease (PD) currently stands as the second most prevalent neurodegenerative disorder following Alzheimer's disease. Global evidence underscores the escalating prevalence of PD, notably beyond the sixth decade, exhibiting an approximately tenfold surge in disease incidence between the sixth and ninth decades of life[1,2]. Anticipating a substantial rise in PD cases by 2030, the imperative to enhance healthcare systems and the escalating burden on healthcare providers globally may precipitate system overload and compromise patient care[3]. A crucial aspect of the pathological progression involves the degeneration of dopaminergic neurons within the pars compacta of the substantia nigra, leading to a significant reduction in dopamine levels within the striatum. Replacement therapy utilizing the dopamine precursor levodopa typically yields a remarkable amelioration of fundamental motor symptoms, encompassing bradykinesia, rigidity, and resting tremor[4]. Regrettably, as the disease advances and treatment persists, the initially seamless and continuous therapeutic response tends to exhibit erratic behavior. This is marked by the gradual emergence of fluctuations, gait freezing, postural instability, and additional abnormal involuntary movements, often manifesting at the zenith of the therapeutic effect. Once these motor response complications manifest, they persist, intensifying in severity and unpredictability, thereby significantly diminishing the overall quality of life for both the patient and the carer[5,6].

Expert neurologists endeavor to mitigate these issues through adjustments to the timing and intensity of individual levodopa doses, incorporation of supplementary medications, or transitioning to treatment modalities tailored for advanced Parkinson's disease[7]. Nevertheless, symptoms tend to progressively deteriorate over spans of months or years, displaying fluctuating patterns from one day to the next or even within the same day, rendering treatment adaptations arduous[8]. Consequently, there arises a compelling need for precise information regarding the clinical manifestations of the disease to be promptly conveyed to physicians. This facilitates informed decision-making regarding treatment interventions at optimal junctures. Presently, patients typically engage with their treating physicians once annually or every 3-6 months, with minimal communication in between. However, this standard practice fails to accommodate the diverse needs of all patients, as some experience a more accelerated disease progression necessitating evaluations every one or two months, while others maintain a comparatively stable condition.

Digital health technologies (DHTs), such as smart monitoring systems and wearable solutions, have emerged over the past two decades as supplementary tools to traditional face-to-face clinical assessments[9]. Notably, individuals affected by Parkinson's disease, along with their caregivers and healthcare professionals, have increasingly adopted these healthcare practices to address accessibility challenges related to healthcare facilities. Besides the imperative for objective symptom detection, which is crucial for informing treatment decisions, clinicians may exhibit hesitancy in embracing the paradigm shift toward the digitalization of their practice, often adhering to traditional methods[10]. Clinical evaluations are inherently subjective, reliant on the experience and expertise of clinicians, mostly relying on widely employed rating scales which may exhibit rating variability [11,12]. Advances in monitoring systems have facilitated precise recording of motor symptoms associated with parkinsonism using handheld devices, thereby supporting an objective assessment of patients[13].

Taking a significant stride toward "personalized care" in Parkinson's disease, wearable technology enables continuous monitoring with data collection within the home environment. This approach affords a detailed analysis of the patient's clinical status throughout the day, encompassing routine daily activities. Furthermore, it allows for a quantitative assessment of the patient's progression over extended periods spanning months and years. These technological advancements align with the established standard of care, enhancing it significantly and heralding a paradigm shift compared to prevailing practices.

Digital Health Technologies in PD and the Digital Biomarkers (DB's)

In the past decade, substantial financial resources have been directed towards the identification of biomarkers to elucidate the progression of Parkinson's disease (PD), primarily utilizing molecular, fluid, or imaging modalities. These endeavors have yielded valuable insights into PD, encompassing mechanistic targets, disease subtypes, and imaging biomarkers. While significant knowledge has been gained, the practical implementation of robust biomarkers for disease progression, serving as tools to quantify changes in disease status or severity, remains a challenging pursuit.

Biomarkers, as demonstrated in other fields such as oncology, have proven instrumental in improving health outcomes and expediting drug approvals, particularly in areas with critical unmet needs. However, in the context of PD, the development of progression markers is imperative across all stages of the disease. This not only acts as a catalyst for advancing drug development by enabling interventions aimed at halting or slowing disease progression but also facilitates the development of symptomatic treatments tailored to moderate stages of the disease.

The diffusion of wearable digital technologies in healthcare, yielding substantial volumes of big data, has given rise to a paradigm shift in medical information. DBs, derived from patient-generated data regarding their disease state or health management through digital health technologies, represent a pivotal development in the modern healthcare landscape. This evolution is particularly germane to Parkinson's disease (PD), where DBs play a pivotal role in enhancing diagnostic and therapeutic precision[14]. DBs, within the context of PD, encompass meticulous quantification of motor symptoms (bradykinesia, rest tremor, rigidity, postural instability and gait disturbances) and the concurrent treatment related complications, activities of daily living, and nuanced information on non-motor symptoms and treatment elements. This comprehensive dataset facilitates remote and continuous monitoring, providing actionable insights into the nuanced biological state of individuals[15].

The integration of these technologies into routine medical practice signifies a transformative approach. It heralds a multi-level strategy aimed at not only refining patient management and enhancing quality of life but also reshaping the structural dynamics and resource allocation within health systems. Furthermore, the establishment of a unified framework for research application fosters a new landscape for investigating innovative treatments and meticulously evaluating existing therapeutic modalities. This augurs well for advancing medical science and improving patient outcomes in the field of neurodegenerative diseases[16].

Remote symptom monitoring: Is it trustworthy and feasible at the same time?

A demand for a more objective and continuous monitoring of Parkinson's disease (PD) features arises due to the challenges associated with accurately assessing the presence and severity of symptoms through solely subjective means and the lapses in care continuity due to infrequent in-person visits. Telemedicine services, including camera-based consultations, have emerged as viable solutions. However, in the context of Parkinson's disease, these modules do not always provide physicians with a complete assessment of patients. This limitation is attributed to the absence of a comprehensive view, coupled with time constraints reminiscent of traditional office visits. Quantitative parameters evaluating motor condition, derived from wearable technologies, are becoming increasingly recognized in the movement disorder community as the most credible option that has come to fill the void. Especially for advanced patents, who often do not easy to access to their treating physician, telemedicine empowered by wearable devices has turned out to be very helpful. Among the array of technologies, inertial measurement units (IMUs) emerge as the predominant choice. In the domain of PD remote monitoring, IMUs have been seamlessly integrated into patient-worn devices, encompassing wearable sensors and systems. Over time, wearable monitoring systems have consistently improved their efficacy in discerning Parkinsonian symptoms. Despite promising outcomes, the incorporation of wearables into routine clinical practice remains limited, and a dearth of "practical recommendations" persists, hindering the optimization of outcomes for PD patients, their caregivers, and healthcare professionals.

Most devices currently available on the market and approved for medical use, are considered reliable in detecting several cardinal motor symptoms, as well as treatment-related complications such as the OFF state and dyskinesias. Each monitoring system has undergone clinical validation to confirm that it provides relevant and correct information.

Familiarity with the existence of these devices does not represent a recent attainment. Their evolution has traversed multiple stages, spanning a duration of at least three decades. Tremor was one of the first symptoms recorded by wearable systems[17–19]. Moreover, ambulatory monitoring has proven effective in quantifying bradykinesia, dyskinesia, and overall activity in patients with Parkinson's disease[20–22]. Conversely, concerning gait analysis, although sensors were early applied to measure gait parameters and general activity, it took more time for their application in the detection of gait disturbance in PD[23,24]. Particularly for freezing of gait and postural instability —symptoms prevalent in the more advanced stages of the disease and crucial indicators for the risk of falling—machine learning techniques have advanced to discern and identify these symptoms[25–27].

However, while most systems exhibit good accuracy in measuring bradykinesia, tremor, gait, and detecting ON/OFF fluctuations and dyskinesias, only one has been identified as having the capability to simultaneously capture the entire spectrum[28–30].Whilst the first sensors and algorithms developed focused on detecting specific symptoms without being able to visualize the wide range of motor impairments and their variation over the course of each day, advanced systems possess the capability to continuously detect symptoms over time and subsequently present them to the physician, thereby generating a comprehensive digital file of disease history.

Although wearables have gained acceptance from both the medical community and patients, several factors may impede their widespread use. The complexity of operation and technological unfamiliarity among patients emerge as the primary barriers, contributing to low adherence despite reported high acceptance levels.

Longitudinal Management of PD patients using digital monitoring systems

Parkinson's disease, classified as a neurodegenerative disorder, unfolds along an extended and gradually advancing trajectory for the majority of afflicted individuals. Within this temporal progression, patients traverse successive stages marked by a gradual escalation of both motor and nonmotor symptoms over protracted intervals spanning months and years[31,32]. Noteworthy fluctuations in symptomatology also manifest within daily and hourly contexts, necessitating vigilant monitoring by medical practitioners. This diligence is imperative for fa-

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cilitating judicious interventions and the expeditious recalibration of pharmacotherapeutic regimens to align with dynamic patient requirements[33].

Clinical evaluations and Parkinson's disease (PD) scales have exhibited suboptimal reliability in capturing nuanced changes throughout the continuum of disease progression. In contrast, the application of machine learning algorithms to data derived from wearable sensors demonstrates a notable capacity to discriminate between discrete stages of PD. This technological approach proffers a robust and objective means for systematically monitoring the dynamic evolution of the disease[12,34].

Wearable systems, specifically designed for at-home utilization, facilitate continuous and precise monitoring. This enables proactive and preventive monitoring of diseases, as well as optimization of treatment protocols. This paradigm shift is poised to enhance medical care significantly, surpassing the efficacy of analogous devices functioning solely as Holter monitors. While Holter deployment remains a viable option, the unparalleled advantage of continuous usage provides a more comprehensive understanding of the patient's condition. This continuous, objective monitoring yields invaluable insights into the patient's status and symptom fluctuations over time, thus offering an enhanced foundation for the judicious adjustment of Parkinson's therapy[35]. The wealth of information obtained through this continuous monitoring approach is pivotal for optimizing treatment strategies.

The implementation of continuous, objective monitoring holds the potential for early detection of symptoms and fluctuations in patients who may not yet be cognizant of their presence or unable to articulate a precise understanding of their manifestations. The early identification and prompt treatment of motor fluctuations are anticipated to significantly enhance the prospects of leading a normal life or sustaining occupational effectiveness over extended periods. This bears a substantive impact on both the quality of life for patients and the health economics of the healthcare system[36,37].

Of particular significance is the identification of gait-related symptoms, including freezing of gait and postural instability, as pivotal components in the optimization of pharmacological and nonpharmacological interventions for Parkinson's disease[38]. These symptoms exert a profound influence on the overall quality of life. Consequently, wearable systems designed to monitor gait impairment, among other symptoms, address an unmet need in the comprehensive evaluation and treatment of Parkinson's disease patients. Furthermore, even in the advanced stages of Parkinson's disease, patients persist in experiencing both motor and nonmotor fluctuations, albeit potentially of reduced amplitude compared to earlier stages. A monitoring system remains highly pertinent even in this late disease stage, as ongoing treatment optimization continues to be imperative, representing the closest approximation to a sustainable cure for the disease[39].

Understanding how symptoms change throughout the day could help make treatments better, especially for managing levodopa-induced dyskinesia. Some patients aren't happy with even mild dyskinesia, while others can handle more severe symptoms. Most people get dyskinesia when their medication is at its highest level, but some get it when the medication is wearing off or in a different pattern. So, knowing how symptoms vary during the day is crucial for improving Parkinson's disease management[40]. This diversity in symptomatology unfolds across different temporal phases, characterized by varying intensity and duration. However, during conventional clinical encounters, physicians are afforded a mere snapshot of the patient's condition, thereby missing the comprehensive panorama. Consequently, the availability of data that methodically depicts, in a clinically meaningful manner, the dynamic conditions of the patient throughout the day—encompassing both symptom fluctuations and dyskinesias—becomes paramount. Such visual representations hold the promise of refining the current management paradigms for Parkinson's disease as they urge the physicians to decide based on objective outcomes and not on their inner ranking.

At present, there exists a pronounced underutilization of advanced therapies in the realm of Parkinson's disease, primarily attributed to the challenges encountered by physicians in accurately identifying suitable candidates. A number of Parkinson's disease centers have incorporated objective monitoring into the patient screening process for advanced therapy, a trend likely to gain prominence in the future[41,42]. This approach provides a more precise foundation for decisions regarding the necessity and type of invasive therapy, concurrently furnishing valuable support to decision-makers within both state and private insurance sectors.

Simultaneously, the management of patients undergoing advanced therapy stands to benefit significantly from objective monitoring, facilitating informed decisions pertaining to treatment adjustments to optimize efficacy. Conversely, should optimal results remain elusive, such monitoring aids in the deliberation to transition care delivery from secondary to primary levels. Additionally, extant ambiguities surrounding therapeutic choices are anticipated to prompt eventual regulatory or insurance imperatives, mandating healthcare providers to substantiate their decisions through objective validation concerning patient stratification for these invasive and resource-intensive interventions[43,44].

Despite the significant role played by DBs in the early detection of symptoms, the mitigation of motor fluctuations, and the objective referral for second-line therapies, reliance on single biomarker proves insufficient for the reliable prognosis of Parkinson's disease (PD). This inadequacy extends to predicting responses to specific drugs or identifying distinct patient subgroups. The complexity and heterogeneity inherent in PD, influencing a multitude of biological mechanisms, preclude the efficacy of isolated biomarkers. Consequently, the imperative arises for comprehensive, multifactorial biomarker signatures to enhance diagnostic precision and prognostic capabilities in the context of Parkinson's disease progression and therapeutic responses.

Digital Biomarkers' prognostic potential

The identification and validation of such marker signatures present formidable challenges demanding state-of-the-art methodologies. In recent significant developments in Parkinson's disease research, there have been instances of predicting an individual patient's risk of receiving a clinical diagnosis of PD. This prediction is made using routinely collected data from electronic health records, with a foresight of about 5 years in advance[45]. Another notable example involves using a machine learning approach to predict the progression of Parkinson's disease. This approach utilizes a signature composed of a mix of inflammatory cytokines measured in blood serum[46]. Additionally, there's a study where data from mobile phone gyroscopes and accelerometers, combined with demographic and clinical information, have been used to predict various measures of Parkinson's disease symptom severity[47].

Altogether, an escalating cognizance underscores the imperative to transition towards precision neurology, demanding a holistic conceptualization of the disease. This entails a synergistic integration of aging processes, genetic and epigenetic variants, environmental determinants, lifestyle factors, comorbidities, and clinical assessments. Within the existing paradigm, the emergence of technologies geared towards furnishing a comprehensive and easily interpretable portrait of patient status, bolstering physician decision-making through Clinical Decision Support Systems (CDSS), epitomizes the most innovative domain in the evolution of precision neurology [48].

However the extensive use of big data AI technologies to strengthen the prognostic, progression and the overall delivery of care in PD entail multiple ethical, legal and social implications[49]. In this context mechanisms are launched in order to determine the framework of use with respect to ensure ethical and legal data processing and AI engagement and human accountability[50,51].

Conclusion

Based on the findings of this narrative, we posit that in the forthcoming years, DB's will assume a heightened significance in this context. Consequently, we anticipate that DMs could be synergistically integrated with other data modalities, encompassing genetic variants, to enable earlier, more resilient, and precise diagnosis of the disease and prediction of its progression.

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