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From Play to Precision Care: Clinical Telegaming Biomarkers to Evaluate Medication Efficacy for Improving Multiple Sclerosis Patients' Quality of Life*

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Abstract

Multiple sclerosis (MS) is a chronic autoimmune disease that affects motor, sensory, cognitive, and social functioning, often diminishing patients' independence and quality of life. Disease-modifying therapies (DMTs) aim to slow progression and support functional recovery. However, the heterogeneity of MS symptoms makes it difficult to determine which medications are most effective for individual patients. Current assessments rely on brief, clinic-based evaluations that, while informative for motor performance, rarely capture the social, affective, and cognitive dimensions that shape daily functioning and quality of life. The infrequent snapshots provided by clinic visits thus leave a critical gap in understanding how treatment affects patients' physical, cognitive, and social functioning in their everyday environments. To address this gap, we propose applying the framework of clinical telegaming as a complementary assessment platform that bridges home-based and in-clinic evaluation for individuals living with MS. By delivering structured, interactive games via augmented or mixed-reality displays in everyday environments, the system captures fine-grained motor-sensory and social-behavioral interaction data to generate digital biomarkers. These biomarkers aim to complement existing clinical assessments, enabling timely and comprehensively evaluation of medication efficacy and quality-of-life outcomes in support of precision care. We expect this approach to yield clinically meaningful digital biomarkers that continuously and individually capture how MS affects patients' daily functioning, providing a richer and more fine-grained record of treatment response than clinic visits alone can offer. By bridging the gap between in-clinic assessments and everyday functioning, the proposed system would have the potential to support more informed, timely, and cost-efficient treatment decisions, ultimately contributing to more precise and patient-centered MS care.

Keyphrases

Multiple sclerosis, clinical telegaming, digital biomarkers, precision care, quality of life.

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Contents

Introduction

Multiple sclerosis (MS) is a chronic autoimmune disease affecting motor, sensory, social, and cognitive functioning (Friedrich 2023), often diminishing independence and quality of life (Gómez-Melero et al. 2024). Disease-modifying therapies (DMTs) are pharmacologic treatments that aim to slow progression and support functional recovery of MS (Goodin et al. 2002). However, determining which medications work best for individual patients and monitoring their effects over time remains challenging (Pathak 2023). Moreover, current assessments for DMTs, which are typically brief, clinic-based evaluations, provide valuable insights into motor performance but rarely capture the social, affective, and cognitive dimensions that critically shape quality of life, underscoring the importance of evaluating daily functioning holistically. The World Health Organization defines quality of life as "an individual's perception of their position in life in the context of the culture and value systems in which they live, and in relation to their goals, expectations, standards, and concerns" (WHOQOL Group 1994).

DMTs for MS are among the most expensive chronic therapies in medicine, with annual costs often exceeding USD $70,000–$90,000

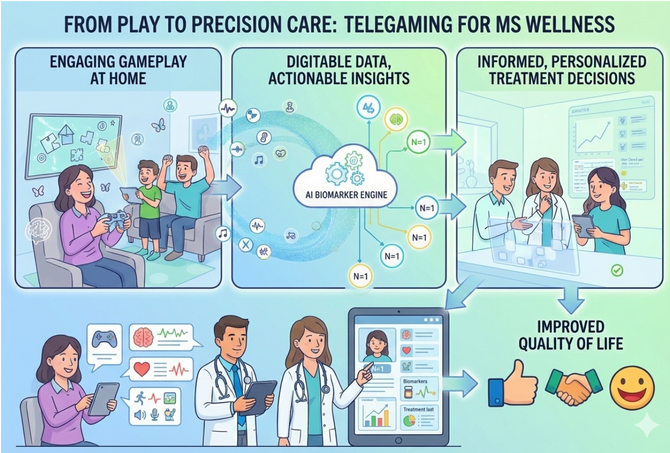

Figure 1: Overview of the proposed clinical telegaming framework for precision care in multiple sclerosis. Home-based gameplay captures motor, sensory, and social interaction data, which are transformed into digital biomarkers to support individualized (N-of-1) treatment decisions and improve quality of life.

per patient (Hartung 2021). When a medication proves ineffective or must be discontinued due to adverse effects, continued treatment wastes significant financial resources that can accumulate to tens of thousands of dollars within just a few months. Beyond economic burden, prolonged exposure to ineffective drugs increases risks of adverse effects, reduces adherence, and undermines patient trust. These challenges underscore the need for timely, objective, and ecologically valid indicators of treatment efficacy, enabling clinicians to make informed, cost-efficient decisions.

Clinical telegaming (Taswell 2010b; Lockery et al. 2011; Xu et al. 2015) offers a platform to provide such indicators by capturing real-world performance metrics that can support earlier and more accurate risk–benefit analysis. Additionally, it provides a non-stigmatizing, game-based environment that integrates naturally into everyday life, emphasizing quality of life rather than mental health labeling, which is an important consideration in MS care.

To this end, we propose applying the established framework of *clinical telegaming* to evaluate treatment efficacy and quality of life in MS. Clinical telegaming in our study will consist of structured, interactive games delivered at home via augmented displays, mixed-reality systems, or repurposed commercial video games. By capturing motor-sensory and social-interaction metrics during naturalistic, engaging tasks in clinical telegaming, we aim to generate and extract digital biomarkers that complement existing clinical assessments for DMTs. In doing so, we reposition clinical telegaming not merely as a therapeutic tool, but as a rigorous assessment modality grounded in ecological validity and patient-centered design. This approach does not replace clinician expertise, but it aims to provide richer, continuous evidence to support precision care.

Related Work

This section reviews prior work in two domains relevant to our system: (1) digital biomarkers, including their definition, clinical motivations, and methods of collection, and (2) clinical telegaming, a growing approach for remote assessment and rehabilitation. Together, these strands of research highlight opportunities for leveraging game-derived behavioral data as digital biomarkers for monitoring disease progression and treatment response in Multiple Sclerosis (MS).

Digital Biomarker

The and The US National Institutes of Health and the US Food and Drug Administration define a biomarker as "'a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or biological responses to an exposure or intervention, including therapeutic interventions'" (Group et al. 2016). In addition, a number of categories of biomarkers have been defined according to their purposes and applications with some overlaps: 1) diagnostic biomarker, 2) monitoring biomarker, 3) pharmacodynamic/response biomarker, 4) predictive biomarker, 5) prognostic biomarker, 6) safety biomarker and 7) susceptibility/risk biomarker (Califf 2018). These biomarkers serve critical functions across diagnosis, disease monitoring, treatment decision-making, and risk stratification, thereby forming the foundation for precision care. This is especially important for complex and multidimensional conditions such as MS.

However, collecting these biomarkers can be time-consuming when it requires the direct involvement of physicians or other healthcare professionals (Dillenseger et al. 2021). Moreover, a growing body of research has highlighted that clinic-based assessments overlook the lived experiences of patients and often do not reflect their real-world functioning (Shiffman et al. 2008). These limitations have motivated a shift toward digital biomarkers, which enable continuous and ecologically valid data collection in patients' everyday environments.

The term digital biomarker refers to "objective, quantifiable physiological and behavioral data that are measured and collected by digital devices" (Dillenseger et al. 2021). Digital biomarkers are typically collected through sensors embedded in smartphones, wearables, and other connected devices, capturing physiological signals (e.g., heart rate, gait characteristics) and behavioral patterns (e.g., mobility, interaction behaviors) in real-world environments (Coravos et al. 2019). These passive and active monitoring approaches will allow continuous, longitudinal assessment with low burden on patients and clinicians.

Clinical Telegaming

An emerging approach to collecting digital biomarkers is the use of clinical telegaming, defined as "a medical subspecialty focused on delivery of telecare involving diagnostic and therapeutic telegaming" (Taswell 2010b). Prior to the formalization of clinical telegaming, game-based and remote rehabilitation approaches had been explored for conditions such as post-stroke recovery and upper-limb dysfunction, including haptic home-based telerehabilitation (Jadhav et al. 2006) and virtual environment-based remote therapy for stroke patients (Holden et al. 2007). Game-derived measures offer a promising pathway for developing digital biomarkers that capture fine-grained motor, cognitive, and behavioral signals in home settings. Compared to traditional clinical assessments, these measures are potentially useful to provide ecologically valid insights, as they are collected during activities that more closely resemble activities of daily living (ADLs).

Early work on clinical telegaming focused on infrastructure and resource management. Taswell (2010b) integrated telegaming registries into the broader Nexus-PORTAL-DOORS-Scribe (NPDS) framework (Taswell 2007; Taswell 2010a; Dutta et al. 2020), enabling metadata management for telecare and therapeutic interventions. Lockery et al. (2011) extended this effort through the Clinical Telegaming System (CTGS), supporting both clinic-based and home-based telerehabilitation. These systems provide crucial infrastructure but do not address patient-centered outcome evaluation.

Subsequent research demonstrated telegaming's therapeutic potential for neurological disorders. Xu et al. (2015) developed a web-enabled platform to evaluate multisensory integration and responses to auditory and visual stimuli in Parkinson's disease. Broadly, telerehabilitation studies report improvements in motor and cognitive outcomes (Maggio et al. 2024), enhanced adherence and quality of life (Dhamija et al. 2025; Sharma et al. 2024), and safe long-term use across neurological populations (Peretti et al. 2017).

The term Exergame is defined as "a video game that promotes (either via using or requiring) players' physical movements (exertion) that is generally more than sedentary and includes strength, balance, and flexibility activities" (Oh and Yang 2010). Adiwangsa et al. (Adiwangsa et al. 2025) explored its potential use in MS care through workshops involving researchers across disciplines and MS experts, and identified two key design themes: 1) the need for accessibility and equipment considerations, e.g., button placement and vertigo sensitivity, and 2) the importance of social interaction given the reduced physical accessibility experienced by people with MS. Building on these themes, Adiwangsa et al. (Adiwangsa et al. 2025) proposed design recommendations: leveraging AR HMD exergames to bridge home and clinic-based interventions, incorporating tangible objects in the home environment to enhance engagement, and enabling asynchronous interactions or virtual environments to simulate social scenarios.

Collectively, prior studies highlight the feasibility of clinical telegaming and offer design implications for rehabilitation through game-based interventions, directly informing and inspiring our proposed system. While prior work has explored games for cognitive monitoring (Pless, Woelfle, Naegelin, et al. 2023; Pless, Woelfle, Lorscheider, et al. 2025; Gromisch et al. 2025) and as rehabilitative interventions (Ortiz Gutierrez et al. 2013; Prosperini et al. 2014; Jonsdottir et al. 2018; Dalmazane et al. 2021), no existing work has leveraged telegaming-derived biomarkers specifically to evaluate medication efficacy or to systematically assess quality-of-life dimensions spanning motor, cognitive, emotional, and social domains in an integrated framework. Furthermore, the integration of telegaming biomarkers into precision-care frameworks for MS remains largely unexplored, representing a critical gap this work aims to address.

Research Plan

This project aims to develop a clinically validated, home-based telegaming system capable, in collaboration with neurologists and MS specialists, of generating digital biomarkers that support precision care for individuals living with MS. The planned research will characterize motor, sensory, cognitive, and social–behavioral functioning through structured gameplay. Sensory, cognitive, and motor assessments will examine limb coordination, balance, movement smoothness, and reaction speed, while social–behavioral assessments will focus on cooperative play, turn-taking, and caregiver–patient coordination. These domains are central to daily functioning yet remain difficult to measure in routine clinical visits. The following indicators were preliminarily selected based on their established relevance to MS-related functional impairments (Table 1).

Research Goals and Rationale

A key goal of this research is to link these behavioral signals to individual treatment trajectories, enabling digital biomarkers to serve as indicators of medication effectiveness at the level of 'N-of-1' precision care.

International MS research communities have articulated several strategic priorities that guide collaborative efforts worldwide (see Appendix, Table 2 for a summary of key organizations and their research priorities). The International Progressive MS Alliance (IPMSA) identifies the lack of validated biomarkers capable of detecting disease progression and treatment response as a critical barrier to developing effective therapies for progressive MS (Kapoor et al. 2020). Similarly, the Multiple Sclerosis International Federation (MSIF) highlights persistent global disparities in access to MS diagnosis and care (Solomon et al. 2023), and has called for greater integration of patient-reported outcome measures that reflect real-world functioning (Morra et al. 2024).

In recent years, the Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS), the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), the National Multiple Sclerosis Society (NMSS), and other organizations have emphasized the importance of precision medicine, including the development of predictive and prognostic biomarkers to support individualized treatment selection, as a central priority in their research roadmaps (*e.g.*, Bebo et al. 2022). These international priorities collectively reflect a broader shift from episodic, clinic-centered evaluation toward continuous, data-driven, and ecologically valid monitoring of disease impact. Furthermore, the Japan Agency for Medical Research and Development (AMED) promotes precision medicine and data-driven healthcare innovation, while the International Society for Neuroimmunology (ISNI) advances research on neuroimmunological mechanisms and clinical optimization of MS and related disorders. These national and international initiatives all emphasize the importance of integrating innovative digital technologies with rigorous clinical research infrastructure.

Our proposed clinical telegaming framework directly aligns with these goals. By capturing structured performance metrics across sensory, motor, cognitive, and social domains during engaging, home-based tasks, the system aims to generate digital biomarkers sensitive to subtle functional changes. Such measures may enable earlier identification of suboptimal treatment response and support more timely adjustment of DMTs. In addition, by leveraging widely available consumer technologies and enabling remote deployment, this approach contributes to broader efforts to reduce disparities in MS care, facilitating scalable, patient-centered monitoring across diverse healthcare systems. Rather than replacing established clinical metrics, clinical telegaming is positioned as a complementary layer of continuous functional evidence, supporting precision care, outcome innovation, and quality-of-life-oriented MS management.

Participants and Sampling

Participants will include adults diagnosed with MS and their caregivers. MS participants must meet the following inclusion criteria: (1) confirmed diagnosis of MS according to the McDonald criteria (Montalban et al. 2025), (2) aged 18 years or older, (3) sufficient cognitive function to understand and follow game instructions, and (4) sufficient upper limb function to operate a VR device. Exclusion criteria include: (1) significant neurological or psychiatric conditions that may confound biomarker interpretation, (2) severe cognitive impairment, (3) contraindications to VR device use (e.g., epilepsy, severe vertigo), and (4) clinically unstable disease status or relapse within the preceding three months.

Caregivers of enrolled MS participants will also be invited to par-

Table 1: Tentative digital biomarker indicators, corresponding clinical constructs, relevance to MS, and established clinical measures.

Indicator	Clinical Construct	Relevance to MS
Limb coordination	Motor function	Upper limb dysfunction, MSFC (Fischer et al. 1999)
Balance	Postural stability	Increased fall risk, BBS, TUG (Berg 1992; Podsiadlo and Richardson 1991)
Movement smoothness	Cerebellar function, ataxia	SARA (Schmitz-Hubsch et al. 2006)
Reaction speed	Motor & cognitive processing speed	MS-related slowing, SDMT (Benedict et al. 2017)
Cooperative play	Social cognition	Social withdrawal
Turn-taking	Executive function	Real-world daily activities
Caregiver-patient coordination	Functional independence	Proxy for daily living performance

Table 2: International Research Priorities in Multiple Sclerosis (MS)

Organization	Primary Research Goals	Strategic Keywords
National Multiple Sclerosis Society (USA)	Accelerate therapy development; precision medicine; improve quality of life; health equity	Precision medicine; biomarkers; patient-centered outcomes; access to care
Multiple Sclerosis International Federation (Global)	Reduce global inequities in MS care; early diagnosis; access to effective treatment; improve quality of life worldwide	Global equity; early intervention; data harmonization; patient advocacy
International Progressive MS Alliance (Global)	Accelerate development of treatments for progressive MS; identify mechanisms of progression; develop sensitive outcome measures	Progressive MS; neurodegeneration; innovative trial design; outcome measures
European Committee for Treatment and Research in Multiple Sclerosis (EU)	Advance understanding of disease mechanisms; optimize treatment strategies; develop predictive and prognostic biomarkers	Translational research; predictive markers; treatment optimization
National Institute of Neurological Disorders and Stroke (USA)	Fundamental and translational neuroscience research; biomarker discovery; neurotechnology innovation	Translational science; digital biomarkers; neurotechnology
Japan Agency for Medical Research and Development (Japan)	Promote precision medicine; integrate medical data platforms; advance innovative medical devices and digital health technologies	Data-driven medicine; digital health; translational innovation
Japanese Society for Neuroimmunology (Japan)	Advance research in neuroimmunological diseases including MS; foster interdisciplinary collaboration	Neuroimmunology; clinical optimization; biomarker research

ticipate, particularly to support the assessment of caregiver–patient coordination as a dimension of social functioning. The final sample size will be determined during the co-design phase in consultation with neurologists and MS specialists, informed by the specific biomarker domains and statistical requirements of the planned feasibility and validation studies.

Three-Phase Project Timeline

The development plan is structured across three years as illustrated in Figure 2. The first year will focus on the co-design of clinical telegaming and an initial prototype for game-based data collection, suitable for laboratory testing The second year will emphasize algorithmic refinement and home-based feasibility testing with MS patients, examining engagement, adherence, and data quality under real-world conditions. The third year will involve preliminary clinical validation, establishing the relationship between biomarker trajectories and treatment outcomes, and producing guidelines for integrating the system into clinical workflows. By the end of the project period, the goal is to deliver a scientifically grounded, clinically meaningful system that advances precision care and supports continuous monitoring in everyday environments.

Framework Design Phase 1: The first phase of the research will involve a collaborative co-design process with neurologists, MS specialists, patients, and caregivers. This phase will define the clinical requirements, safety considerations, and design constraints necessary for creating gameplay tasks that are both engaging and clinically meaningful. Co-design workshops will guide the creation of early prototypes and interaction concepts, ensuring that the system reflects the needs and lived experiences of its target users. Following design recommendations from prior work (Adiwangsa et al. 2025), the potential integration of tangible objects available in patients' home environments will also be explored during co-design, as object manipulation has been shown to support the transfer of rehabilitation gains to activities of daily living. Whether to incorporate specialized equipment will be determined in consultation with neurologists and MS specialists during this phase. Given the varying mobility levels among people with MS, we will design social interaction within the telegaming system to accommodate both synchronous and asynchronous modes of play. Synchronous multiplayer interactions may be suitable for patients with higher functional capacity,

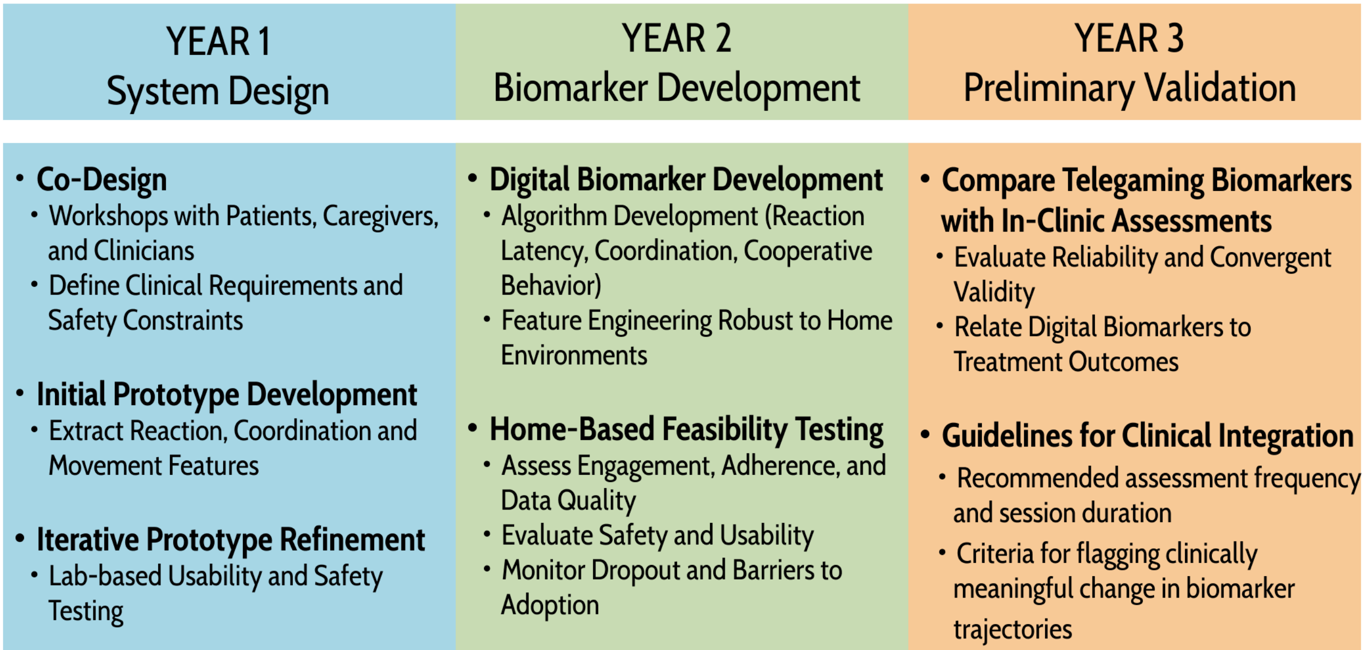

Figure 2: Three-phase development timeline for the clinical telegaming framework. Phase 1 focuses on co-design with neurologists, MS specialists, patients, and caregivers to establish clinical requirements and develop an initial prototype. Phase 2 emphasizes biomarker algorithm development and home-based feasibility testing. Phase 3 addresses clinical validation against established assessments and treatment outcomes.

while asynchronous modes — such as turn-based gameplay or shared virtual environments — will be explored to ensure inclusivity across a wider range of physical capabilities. We will determine the appropriate interaction modes for each game task during the co-design phase in consultation with patients, caregivers, and MS specialists. These workshops will also serve as an opportunity to define and refine the measurement models for each latent construct — such as motor function, cognitive processing speed, and social cognition — in collaboration with neurologists, MS specialists, and patients. Establishing these models early in the development process will ensure that the selected game tasks and biomarker indicators are grounded in clinically meaningful constructs and aligned with established assessment frameworks, as outlined in Table 1. The resulting prototypes will undergo iterative refinement to achieve a stable and usable system architecture suitable for further evaluation.

Biomarker Development Phase 2: Following the design phase, the project will focus on transforming gameplay telemetry into interpretable digital biomarkers. This work will include the development of algorithms to extract reaction latencies, coordination measures, temporal movement features, and indicators of cooperative behavior. Special attention will be given to creating features that are robust to variations in home environments and consumer-grade hardware. This technical component will produce the computational foundation required for examining how behavioral patterns relate to medication response and overall patient well-being.

Since the system collects data from each patient over an extended period, the analysis can track how an individual's biomarkers change over time, rather than simply comparing averages across patients. This within-individual longitudinal approach, using methods such as mixed-effects models (Bates et al. 2015), will enable the system to detect meaningful changes in a single patient's functioning in response to treatment, even when patients differ substantially from one another. This individualized approach remains especially important in MS, where the disease varies widely between individuals, making population-level statistics a poor guide for individual care. By focusing on change within each person, the framework directly supports the N-of-1 precision care goal described earlier.

Validation Studies Phase 3: Building on the game tasks and biomarker indicators established during the co-design phase, the system will undergo iterative development until it reaches functional stability, defined here as achieving a task completion rate of 90% or above across test sessions and consistent data recording fidelity with no missing or corrupted biomarker streams. We will conduct home-based feasibility studies only after the game tasks meet this threshold, ensuring that the system is sufficiently reliable to support meaningful data collection in real-world environments. We will conduct feasibility studies in real home environments to assess usability, safety, patient acceptance, and data fidelity. These studies will provide critical insights into the validity of the system and reveal potential barriers to long-term adoption. Building on feasibility results, the project will conduct preliminary validation by comparing telegaming-derived biomarkers with established in-clinic motor assessments and caregiver reports. This phase will evaluate reliability across multiple sessions within individuals, convergent validity against established clinical measures outlined in Table 1, and responsiveness to treatment-related changes, laying the groundwork for subsequent large-scale clinical evaluation. We will assess reliability through repeated measurement sessions within individuals, with specific metrics to be determined during the co-design phase in consultation with neurologists and MS specialists. Candidate metrics include intraclass correlation coefficients across sessions and raters, and test-retest reliability indices assessed over clinically meaningful intervals, e.g., days to weeks, aligned with known MS symptom fluctuation patterns. We will evaluate convergent validity by comparing telegaming-derived biomarkers against established in-clinic assessments, as outlined in Table 1, with the precise selection of reference measures finalized during co-design.

Conclusion

This paper outlines a research agenda and plan for developing a clinically validated, home-based telegaming system capable of generating digital biomarkers that support precision care for individuals living with MS. By shifting assessment beyond the constraints of brief clinical visits and into patients' daily environments, the proposed approach has the potential to reveal motor, sensory, and social–behavioral dimensions of functioning that are systematically underrepresented in conventional in-clinic evaluations. The integration of gameplay-derived digital biomarkers offers a pathway toward earlier identification of suboptimal treatment response, improved longitudinal monitoring of quality-of-life outcomes, and more informed decisions regarding the continuation or adjustment of costly disease-modifying therapies.

Importantly, this research aims to bridge clinical neuroscience, rehabilitation science, and human–computer interaction by repositioning telegaming not merely as a therapeutic tool, but as a rigorous assessment modality with ecological validity and patient-centered design at its core. The proposed three-phase development plan—encompassing co-design, biomarker algorithm development, and feasibility and validation studies—provides a structured and scientifically grounded pathway toward a system that is both clinically meaningful and deployable in real-world settings. The participation of neurologists, MS specialists, rehabilitation specialists, patients, and caregivers will position the system to reflect the lived experiences of its target users while meeting the rigorous standards required for clinical adoption.

Beyond its immediate contributions, this work addresses broader challenges in MS care. The ability to monitor patients continuously in their home environments may enable earlier detection of disease progression and treatment failure, reducing the period during which patients are exposed to ineffective and costly therapies.Furthermore, by leveraging accessible consumer technologies, the proposed framework supports international efforts to reduce disparities in MS care, offering a scalable and patient-centered monitoring solution across diverse healthcare systems.

This work will contribute to an emerging paradigm in which continuous, context-rich behavioral data complement traditional clinical measures, empowering clinicians with actionable insights and offering patients engaging, non-stigmatizing ways to actively participate in their own care. Ultimately, the proposed clinical telegaming system has the potential to enhance therapeutic decision-making, reduce unnecessary healthcare expenditure, and improve long-term quality of life for individuals living with MS, advancing the broader goal of precision, data-driven, and patient-centered neurological care.

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