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Organisational impact and patient management models for biomarker integration in multiple sclerosis care in Italy: the 0Tolerance project

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ABSTRACT

Background Despite advances in multiple sclerosis (MS) management, the need for more accurate biomarkers remains critical. Conventional MRI, while essential for diagnosis, prognosis and disease monitoring, has limitations in capturing the full complexity of disease progression. This paper aims to identify biomarkers likely to be available in clinical practice by 2028, define a prospective organisational follow-up model for patients with MS, explore organisational requirements and propose solutions to facilitate their implementation. These insights aim to inform and anticipate future discussions among policymakers regarding the adoption of prospective biomarkers into clinical practice.

Methods A multimethod qualitative design was employed, including a systematic literature review of 82 studies, two modified Delphi consensus processes and semistructured interviews with nine neurologists and three healthcare programming experts, applying the Structural, Technological, Organisational and Professional (STOP) framework. The STOP framework was used to assess structural, technological, organisational and professional requirements and to explore solutions.

Results The research identified a prospective organisational follow-up model that integrates the most probable prospective biomarkers into clinical practice. The prospective organisational follow-up model defined an optimal testing frequency of Serum Neurofilament Light Chain and Glial Fibrillar Acidic Protein every 6 months, as well as Cognitive Tests and Optical Coherence Tomography every 12 months. Combining biomarkers and aligning them with MRI was seen as beneficial. Despite the validation of the model through a modified Delphi consensus process based on organisational feasibility and economic sustainability, structural and organisational challenges need to be addressed to ensure smoother integration into clinical practice.

Conclusions This article aims to define an organisational model for the integration of prospective biomarkers into clinical follow-up in MS. It also explores potential strategies to facilitate their transition from research settings to routine clinical practice. The proposed approach provides a framework with potential for replication across various care pathways.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ MRI remains the gold standard for diagnosing and monitoring multiple sclerosis (MS). However, MRI has notable limitations in predicting clinical outcomes. To address these gaps, various biomarkers have been investigated; however, the organisational impact of their integration in clinical practice has not been explored yet.

WHAT DOES THIS STUDY ADD

⇒ This study identifies a prospective organisational follow-up model for patients with MS that integrates the biomarkers that are most likely to be available in clinical practice by 2028: Serum Neurofilament Light Chain, Cognitive Tests, Optical Coherence Tomography and Glial Fibrillar Acidic Protein. Additionally, it assesses their organisational requirements and explores potential solutions to lay the groundwork for their large-scale integration.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This research provides a foundation for policymakers to anticipate discussions on organisational requirements and potential solutions for integrating prospective biomarkers into clinical practice once available. By addressing key challenges in advance, it aims to facilitate decision-making, streamline implementation and accelerate their adoption.

INTRODUCTION

Multiple sclerosis (MS) is a chronic autoimmune inflammatory disease affecting the central nervous system, ultimately leading to disability.[1–4] As of 2024, Italy reported 140 000 people with MS (PwMS), representing one of the most prevalent chronic neurological diseases, especially in young adults, with a prevalence of 0.23%.[5] In addition, MS is a highly heterogeneous disease,[6] and its course varies significantly among individuals, particularly in terms of disability progression risk.[7]

Currently, MRI remains the primary tool for the diagnosing, prognosing and monitoring MS.[2 3 8 9] However, its role beyond diagnosis is still debated due to its limited ability to capture the full spectrum of underlying disease progression.[8–10] Hence, additional measures are needed for the detection of subclinical disease activity.[11] Moreover, high demand and sometimes limited availability often cause prolonged waiting times,[12] introducing organisational challenges related to the sustainability of disease monitoring based on MRI only. These limitations underscore the urgent need to incorporate non-invasive, cost-effective and easily repeatable complementary tools into the patient pathway, alongside MRI, for disease monitoring. This would provide more sensitive measures of disease activity, enhance efficiency and accessibility and ultimately enable tailored treatments to prevent relapses and slow disability progression.[2 5 7] Thus, in recent years, considerable efforts have been made to identify accurate biomarkers that can complement MRI in understanding disease processes and progression. While the body of knowledge on the clinical relevance of biomarkers for MS is extensive and still debated, their application remains largely confined to research settings and no similar research has assessed the organisational aspects related to their integration into clinical practice.

Given the focus of clinical research on identifying biomarkers to complement MRI, it is crucial to evaluate their potential organisational impact if implemented in clinical practice. Such an assessment would provide valuable insights to guide future organisational decisions and to facilitate their integration into the patient care pathway and overcome potential barriers to widespread adoption.

As a result, this research seeks to explore the prospective biomarkers—those closest to being available in clinical practice by 2028—and their integration into routine care from an organisation perspective. In this paper, 'availability in clinical practice in Italy' refers to the integration of a biomarker into standard care pathways, including its accessibility for prescribing clinicians, its inclusion in diagnostic-therapeutic protocols and the availability of reimbursement through the Italian National Health Service.[13]

Furthermore, in Italy, MS care is centralised in hospitals and more specifically in specialised MS Centres (MSCs) located in major cities. As a result, patients are followed mostly by neurologists specialised in MS rather than by general neurologists.[5 14 15] The high specialisation of MSCs and their potential integration with other hospital departments for biomarker testing positions Italy as a valuable setting to investigate the prospective integration of biomarkers into MS care pathways.

Specifically, this paper seeks to identify a prospective organisational follow-up model for PwMS, integrating prospective biomarkers and addressing the structural, technological, organisational and professional requirements associated with these biomarkers, as well as potential logistical challenges and their possible solutions.

METHODS

Study design and participants

The 0Tolerance Project employed a multimethod qualitative approach, using systematic reviews, modified Delphi consensus processes and semistructured qualitative interviews (table 1). The project was conducted in Italy, in collaboration with Novartis, and involved an expert panel of nine neurologists, who participated in two modified Delphi consensus processes and individual semistructured interviews. The decision to compose the expert panel of neurologists was driven by their ability to provide insights into the advancement of innovative biomarkers in Italian hospitals, their hospital experience and availability in using biomarkers, to assess patient needs and to offer a perspective on practical organisational requirements. To identify participants of the expert panel, a survey table (online supplemental material 1) was sent to 17 Italian hospitals hosting MSC regional hubs, to gather information on neurologists' expertise on the use of the most

Table 1 Methodological steps of the 0Tolerance project

Stage	Method	Experts involved	Evidence generation
Stage 1	Systematic literature review	Researchers	Identification of the most extensively studied biomarkers
Stage 2	Modified Delphi consensus	Researchers and expert panel (nine neurologists) in a virtual workshop	Identification of the prospective biomarkers
Stage 3	Individual semistructured qualitative interviews	Researchers and expert panel (nine neurologists) individually	Identification of a preliminary prospective organisational follow-up model integrating prospective biomarkers and identification of organisational requirements for each prospective biomarker according to the STOP framework
Stage 4	Modified Delphi consensus	Researchers, expert panel (nine neurologists) in a virtual workshop	Validation of the prospective organisational follow-up model
Stage 5	Semistructured qualitative interviews	Researchers and three healthcare programming experts individually	Hypothesis of potential organisational solutions to overcome potential challenges in the integration of prospective biomarkers

STOP, Structural, Technological, Organisational and Professional.

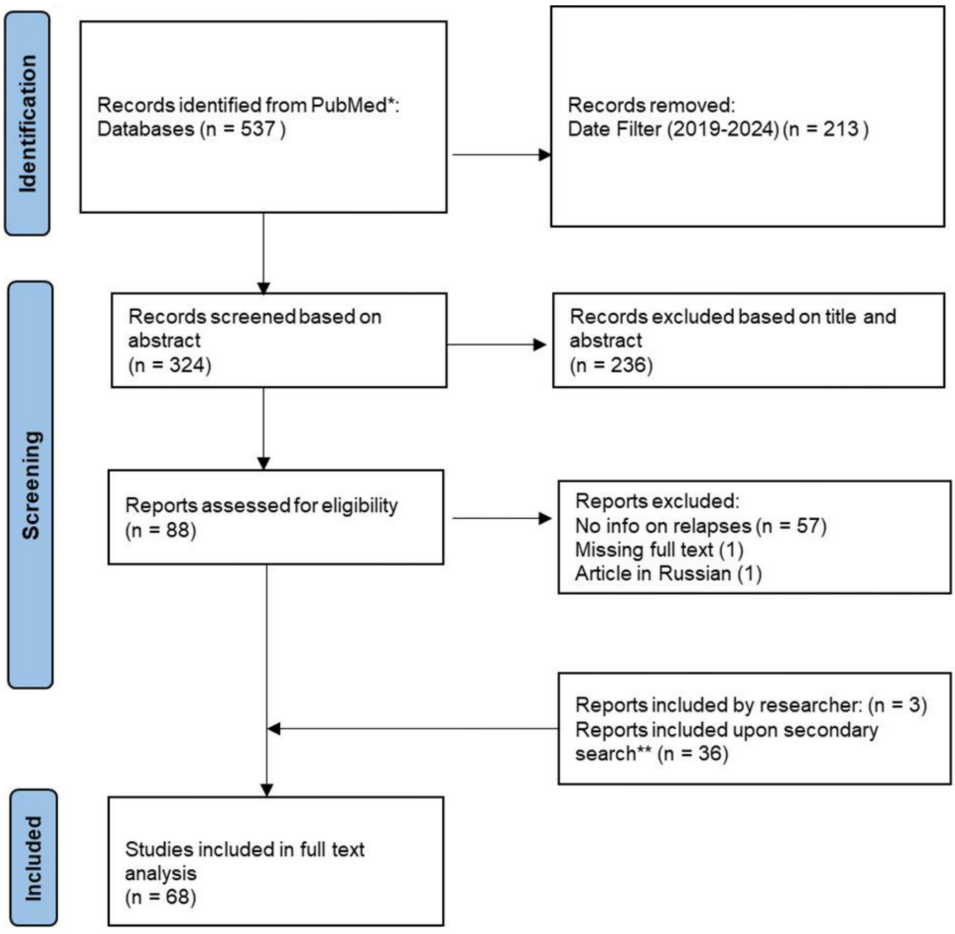

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram; systematic review focused on biomarkers for detecting subclinical disease activity in multiple sclerosis (MS). *Search: ((Multiple sclerosis [title]) AND ((biomarker [title/abstract]) OR (biomarkers [title/abstract])) AND (RRMS [title/abstract])). **Search: ((Multiple sclerosis [title]) AND ((biomarker [title/abstract]) OR (biomarkers [title/abstract])). In this secondary search, particular attention was given to keywords such as 'inflammation', 'inflammatory markers', 'disease severity', 'disease activity', 'subclinical activity', 'clinical/subclinical progression', 'prognostic value', 'cognitive tests' and 'patient reported outcome'.

extensively studied biomarkers. Based on their expertise, nine neurologists were selected on a voluntary basis. The selected neurologists were affiliated with renowned hospitals across six different Italian regions, including three university hospitals (AOU), three research hospitals (IRCCS) and one local health authority (ASL), providing diverse perspectives on organisational requirements. In the final phase, focused on addressing broader regional healthcare challenges, three healthcare programming experts from two Italian regions—one in the north and one in the centre—were involved.

Systematic review

A systematic review of the existing literature on biomarkers for detecting subclinical disease activity in MS was conducted. The review aimed to identify the most extensively studied biomarkers.

The systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA),[16 17] with PubMed as the primary database, covering studies published between 2019 and 2024. The resulting PRISMA flowcharts (figures 1 and 2) depict the stages involved in the selection process.

Additionally, posters and oral presentations from the 2024 European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) conference were also analysed to integrate the latest European research. The review of ECTRIMS materials focused on keywords such as 'biomarker', 'biomarkers', 'disease activity' and 'disease progression'.

Identified studies were categorised by biomarker type and study design to assess their relevance in current scientific discussions.

First modified Delphi consensus

A first modified Delphi consensus process (online supplemental material 2) was carried out with the expert panel to identify biomarkers expected to be available in clinical practice by 2028, thereby outlining potential prospective biomarkers.

A Delphi consensus process is a structured method for gathering expert opinions to build consensus and

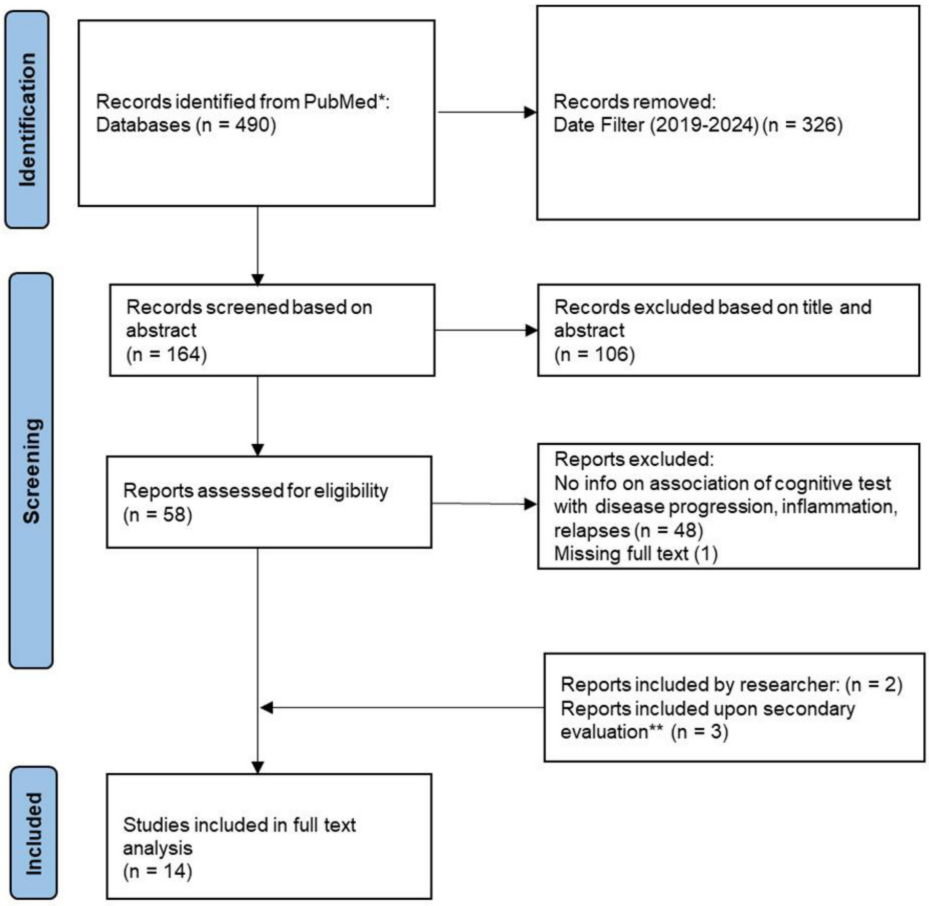

Figure 2 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram; systematic review focused on Cognitive Tests for detecting subclinical disease activity in multiple sclerosis (MS). *Search: ((Multiple sclerosis [title]) AND (cognitive test [title/abstract])); ((Multiple sclerosis [title]) AND (cognitive impairment [title])) performed on 15 November 2024. **Evaluation: three papers were included upon evaluation of a review citing material outside the time frame considered (2019–2024).

develop a shared understanding of a problem, as well as to identify potential solutions.[18] In this research, a modified Delphi approach was employed, consisting of a two-round Delphi conducted during an online expert panel workshop.

The findings from the systematic literature review were first shared with participants ahead of the expert panel workshop, and an initial set of biomarkers was proposed for inclusion in the modified Delphi process. This selection was based on biomarkers for which at least five supporting studies (n>5) were identified in the systematic review. Additionally, participants had the opportunity to suggest further biomarkers for consideration.

Ultimately, only the biomarkers that met the minimum threshold or were proposed by participants were included in the set to be submitted to the expert panel for evaluation in the modified Delphi consensus process.

In the first round, participants anonymously and independently rated biomarkers using a 5-point Likert scale, assessing their confidence in the availability of the biomarkers in clinical practice by 2028. Biomarkers rated ≥4 by at least 75% were included in the final set, while those rated ≤2 by 75% were excluded. Uncertain biomarkers proceeded to a second, requiring a two-thirds majority for final selection.

Individual semistructured interviews with the expert panel

Semistructured interviews were conducted individually with the expert panel (online supplemental material 3) to define a preliminary prospective organisational follow-up model and to determine the organisational requirements for prospective biomarkers. Addressing organisational requirements was guided by the Structural, Technological, Organisational and Professional (STOP) framework, a tool widely used in Italian healthcare settings, including Emilia-Romagna and Piedmont, to define institutional accreditation standards. The STOP framework evaluates structural, technological, organisational and professional aspects to assess implementation readiness based on regional standards.[19 20] This approach supports biomarker integration while ensuring healthcare system preparedness for high-quality care.

Second modified Delphi consensus

A second modified Delphi consensus process was conducted (online supplemental material 4) to validate

the prospective organisational follow-up model, which integrates prospective biomarkers. This process involved two rounds of electronic surveys conducted during an expert panel online workshop.

During the modified Delphi, the results of the semi-structured interviews with the expert panel, specifically regarding the prospective organisational follow-up model were presented to the participants. Participants were asked to rate their confidence in the model-related statements using a Likert scale from 1 to 5, based on organisational feasibility and economic sustainability.

The same validation thresholds applied in the previous Delphi phase were used. Only the information validated through the Delphi process was included in the prospective organisational follow-up model.

Semistructured interviews with healthcare programming experts

Semistructured interviews with healthcare programming experts were structured around the STOP framework requirements identified in previous interviews, exploring potential considerations and solutions for each requirement.

Analysis

The Modified Delphi results were analysed using descriptive statistics in Excel to present findings during the expert panel workshop, facilitating discussion after independent voting. Semistructured interviews were conducted and analysed by two researchers with expertise in healthcare organisation, neurology and qualitative research methods. Both researchers attended each interview simultaneously, independently taking notes. After completing all interviews, they reviewed and categorised the information and cross-validated findings to ensure consistency and minimise potential bias.

RESULTS

Identification of the most extensively studied biomarkers for detecting subclinical signs of activity in MS

In the first phase of the systematic review, 68 studies were included, while the second phase, focusing on Cognitive Tests, identified 14 studies, for a total of 82 studies. Additionally, the analysis of ECTRIMS 2024 materials identified 19 poster abstracts and three oral presentations.

After the categorisation of the studies based on the considered biomarkers, those that surpassed the threshold of n>5 studies were: Serum Neurofilament Light Chain (sNfL) (33 studies), Cognitive Tests (18 studies), Optical Coherence Tomography (OCT) (14 studies), Glial Fibrillar Acidic Protein (GFAP) (12 studies), Cerebrospinal Fluid Neurofilament Light Chain (CSF NfL) (12 studies) and Iron Rim Lesions (IRLs) detected via MRI (7 studies).

Identification of prospective biomarkers for detecting subclinical signs of activity in MS

Before the expert panel workshop, evidence from the systematic review was shared with participants, along with the proposed set of biomarkers surpassing the inclusion threshold. During this phase, participants suggested adding Cognitive Tests, prompting a focused review to ensure their relevance. As a result, the following biomarkers were included in the modified Delphi Consensus Process: sNfL, Cognitive Tests, OCT, GFAP, CSF NfL and IRLs.

Based on the consensus of the expert panel, the following biomarkers were identified as prospective biomarkers, that is, those most likely to become available and applicable in everyday clinical practice in Italy by 2028 (online supplemental material 5):

1. sNfL: included in the first Delphi round.
2. Cognitive Tests: included in the first Delphi round.
3. OCT: included in the first Delphi round.
4. GFAP: included in the second Delphi round.

Identification of organisational requirements of prospective biomarkers

The requirements of sNfL, Cognitive Tests, OCT and GFAP were investigated in the individual semistructured interviews with the expert panel using the STOP framework. Results are presented in table 2.

The integration of sNfL, GFAP, OCT and Cognitive Tests into routine MS management requires specific structural, technological, organisational and professional adaptations to ensure feasibility and applicability.

sNfL and GFAP: as both are blood-based biomarkers, sNfL and GFAP share similar requirements. Their integration into MS clinical practice necessitates laboratory infrastructure with dedicated platforms for biomarker analysis and refrigeration for sample storage prior to processing. From an organisational perspective, the use of a consistent analytical platform is recommended to enhance comparability. Given the lack of a defined threshold,[6 21 22] ensuring standardised execution using the same analytical platform and methodologies for each patient is essential for accurate result interpretation until a certified methodology is established.

OCT: as a non-invasive imaging tool, it necessitates the availability of dedicated space within ophthalmology or neurology departments to ensure appropriate equipment setup and patient accessibility. Beyond the required infrastructure, the involvement of trained personnel, such as ophthalmologists, neurologists or OCT technicians, is critical for accurate image acquisition and interpretation. To maintain consistency and ensure longitudinal comparability of measurements, follow-up assessments should ideally be conducted using the same OCT device. In MSCs lacking an on-site OCT unit, close coordination between neurology and ophthalmology departments is essential to secure dedicated appointment slots for patients with MS and to minimise variability in imaging procedures.

Table 2 Requirements for each biomarker identified through individual semistructured interviews with the expert panel applying the STOP framework

Biomarker	Structural	Technological	Organisational	Professional
sNfL	► Laboratory for the analysis of sNfL.	► Fridge for the conservation of the sample. ► Platform for the analysis of sNfL.	► For comparability of results, consistency in the execution on the same platform for analysis.	► Nurses for blood sampling.
GFAP	► Laboratory for the analysis of sNfL.	► Fridge for the conservation of the sample. ► Platform for the analysis of sNfL.	► For comparability of results, consistency in the execution on the same platform for analysis.	► Nurses for blood sampling.
OCT	► Space for the execution of the OCT (usually in ophthalmology).	► OCT equipment.	► Professional figure for the execution and reporting of the results (OCT technician, ophthalmologist or trained neurologist). ► To ensure comparability of results, tests should be conducted using the same machine. ► Time to execute the exam: around 15 min (variable depending on the health status of the patient). ► Coordination with other departments within the hospital for the execution of the OCT (department of ophthalmology), ensuring slots for PwMS. ► Possible mechanisms for consultation with an OCT expert in case of difficult results interpretation.	► Training of healthcare professionals (neurologists, ophthalmologists or technicians) for the execution of OCT images.
Cognitive Tests	► Dedicated room where the patient can be isolated in a quiet and silent environment, accompanied by the professional administering the test.	► Digital devices that support the execution of the test (eg, applications on the smartphones).	► Professional figure dedicated to the execution of the test, ideally a neuropsychologist, or otherwise a psychologist, neurologist or other trained healthcare professional. ► Time to execute the test: for complete batteries, like BICAMS, around 45 min, for single tests, like SDMT, around 5 min.	► Training healthcare professionals, other than neuropsychologists, to administer cognitive tests ► Continuous training and refresher courses, as testing is evolving, and doctors need to stay up to date.

BICAMS, Brief International Cognitive Assessment for MS; GFAP, Glial Fibrillar Acidic Protein; OCT, Optical Coherence Tomography; PwMS, people with multiple sclerosis; SDMT, Symbol Digit Modalities Test; sNfL, Serum Neurofilament Light Chain; STOP, Structural, Technological, Organisational and Professional.

Cognitive tests: a dedicated environment where patients can be evaluated in a quiet and controlled setting is required. From a technological standpoint, digital solutions, such as tablet-based or smartphone-based applications, could enhance test administration and data collection. From an organisational perspective, the presence of trained professionals, preferably neuropsychologists, with available time to administer a test or complete batteries of tests, is crucial, alongside continuous training programmes.

Definition of a preliminary prospective organisational follow-up model

Semistructured individual interviews with the expert panel were categorised to define a preliminary prospective organisational follow-up model for patients (table 3), integrating prospective biomarkers. The model considers testing frequency, biomarker combination strategies and alignment with MRI schedules.

In terms of frequency, sNfL and GFAP were suggested every 6 months, as they are blood tests, making them easier to administer and less resource-intensive. Cognitive tests and OCT were recommended annually, as more frequent testing could raise feasibility concerns due to the costs associated with biomarkers and the time required for their administration, along with potential learning effects or minimal clinical variations. Moreover, combining biomarkers was considered advantageous in reducing patient travel, providing a comprehensive clinical overview and minimising organisational obstacles. However, the expert panel emphasised the need to prevent patient fatigue during cognitive assessments to avoid impacting test performance. sNfL and GFAP were often suggested to

Table 3 Preliminary prospective organisational follow-up model integrating prospective biomarkers, hypothesised based on the individual semistructured interviews conducted with the expert panel

Biomarker	Frequency	Combination	Alignment with MRI
sNfL	Every 6 months	In combination with other biomarkers, specifically GFAP and Cognitive Tests	Within 2 months before or after an MRI or staggered 6 months apart from an MRI
GFAP	Every 6 months	In combination with other biomarkers, specifically sNfL	Within 2 months before or after an MRI or staggered 6 months apart from an MRI
OCT	Every 12 months	In combination with other biomarkers	Within 2 months before or after an MRI
Cognitive Tests	Every 12 months	In combination with other biomarkers, specifically sNfL	Within 2 months before or after an MRI

GFAP, Glial Fibrillar Acidic Protein; OCT, Optical Coherence Tomography; sNfL, Serum Neurofilament Light Chain.

be conducted together due to their similar organisational requirements for execution and analysis. Regarding MRI scheduling, it is preferable for OCT and Cognitive Tests to be conducted within 2 months before or after an MRI to ensure improved organisation and a thorough evaluation of disease activity. sNfL and GFAP could be performed in conjunction with MRI and staggered 6 months apart, facilitating a more continuous monitoring strategy.

Validation of a prospective organisational follow-up model

The hypothesised prospective organisational follow-up model, initially developed through semistructured interviews, was subsequently validated using a modified Delphi consensus process. All statements derived from the preliminary model achieved consensus during the first round of the Delphi process (table 4).

As a result, the validated model (table 5) defined an optimal testing frequency of sNfL and GFAP every 6 months and Cognitive Tests and OCT annually. Combining biomarker assessments with each other and with MRI was considered beneficial. Accordingly, the model recommends that at the first follow-up visit of the year, only sNfL and GFAP are repeated, maintaining the 6-month testing interval and ideally aligning with MRI scheduling when biannual imaging is required. At the second follow-up visit, scheduled 6 months later, all biomarkers are tested within 2 months before or after the MRI.

Table 4 Results emerged from the second modified Delphi, in which participants rated their agreement—based on organisational feasibility and economic sustainability—with the proposed statement. Ratings were assigned using a 5-point Likert scale, ranging from 1 (total disagreement) to 5 (total agreement)

Statement	Score 1–2 (%)	Score 3 (%)	Score 4–5 (%)	Result
For patients with MS in follow-up, it is recommended that the biomarkers be performed in combination, that is, within 2 months of the first one	0	11	89	Validated
For patients with MS in follow-up, it is recommended to perform sNfL testing every 6 months	11	0	89	Validated
For patients with MS in follow-up, it is recommended to perform sNfL testing within 2 months before or after the MRI, and staggered by 6 months from the MRI	0	22	78	Validated
For patients with MS in follow-up, it is recommended to perform GFAP testing every 6 months	11	0	89	Validated
For patients with MS in follow-up, it is recommended to perform GFAP testing within 2 months before or after the MRI, and staggered by 6 months from the MRI	0	22	78	Validated
For patients with MS in follow-up, it is recommended to perform OCT every 12 months	0	0	100	Validated
For patients with MS in follow-up, it is recommended to perform OCT within 2 months before or after the MRI	11	0	89	Validated
For patients with MS in follow-up, it is recommended to perform Cognitive Tests every 12 months	0	0	100	Validated
For patients with MS in follow-up, it is recommended to perform Cognitive Tests within 2 months before or after the MRI	**0**	11	89	Validated

GFAP, Glial Fibrillar Acidic Protein; MS, multiple sclerosis; OCT, Optical Coherence Tomography; sNfL, Serum Neurofilament Light Chain.

Table 5 Prospective organisational follow-up model for patients with MS, which integrates prospective biomarkers and has been validated by the expert panel through a modified Delphi consensus process

Biomarker	6-month follow-up visit	12-month follow-up visit
MRI	Optional/if needed	✓
sNfL	✓	✓
GFAP	✓	✓
OCT	–	✓
Cognitive Tests	–	✓

GFAP, Glial Fibrillar Acidic Protein; MS, multiple sclerosis; OCT, Optical Coherence Tomography; sNfL, Serum Neurofilament Light Chain.

DISCUSSION

Currently, MRI remains the primary tool for the diagnosing, prognosing and monitoring MS.[2 3 8 9] However, it has limitations in capturing the full complexity of disease progression,[8–22] and this reliance also poses organisational challenges.[12] As a result, additional biomarkers are needed for detecting disease activity.[11] Between 2019 and 2024, sNfL, Cognitive Tests, OCT, GFAP, CSF NfL and IRLs were the most extensively studied biomarkers for detecting the progression of MS, to be used alongside MRI. While all demonstrated potential, neurologists with research expertise and clinical experience expressed confidence in adopting sNfL, GFAP, OCT and Cognitive Tests in clinical practice by 2028, whereas CSF NfL and IRLs were considered less feasible due to practical and implementation barriers.

As a result, a prospective organisational follow-up model was developed to support future policy discussions and facilitate their integration into clinical practice. The model was designed by engaging a panel of experts to define optimal testing frequency, combination strategies and MRI alignment for each biomarker. The validated model proposes that only sNfL and GFAP should be assessed at the first follow-up visit, maintaining a 6-month testing interval and, where applicable, aligning with biannual MRI scans. At the second follow-up visit, scheduled 6 months later, all biomarkers are tested within 2 months before or after the MRI.

However, implementing prospective biomarkers entails significant organisational and structural adjustments. Workforce availability and interdepartmental coordination represent common challenges across all biomarkers. For sNfL and GFAP, key issues include laboratory capacity and the need for standardised sample processing protocols, underscoring the importance of establishing structured laboratory networks to ensure result consistency and improve accessibility. Although cognitive assessments offer valuable clinical insights, their routine use is limited by the scarcity of neuropsychologists in many MSCs. Similarly, the integration of OCT necessitates the availability of expert technicians or neurologists if the OCT is performed within the MSC, or the allocation of dedicated time slots within ophthalmology departments and the development of clear referral pathways to ensure continuity of testing.

To address these challenges, healthcare programming experts proposed potential solutions to support biomarker integration.

For sNfL and GFAP, two organisational models were suggested: centralised laboratory hubs, where samples are processed at specialised centres, or decentralised testing platforms to expand local processing capacity. Centralised laboratories are not a new concept in the Italian context; they have already been implemented for oncology screening tests in Tuscany[23 24] and for the analysis of histological and biological samples in paediatric haematology.[25] This centralised testing model is frequently viewed as more cost-effective, as it leverages economies of scale[26] and ensures compliance with high-quality standards.[24 25] However, it is crucial to evaluate the capacity of these centralised laboratories and the logistics involved to avoid potential delays, which are often more characteristic of centralised systems compared with decentralised ones.[23 26] Additionally, mapping laboratory networks and establishing automated data-sharing mechanisms between laboratories and clinical records were also identified as key steps for optimising sample management. Indeed, mapping laboratories improves the logistics and helps to connect existing laboratories to establish standards and maintain best practices.[27]

For OCT, experts emphasised the need for standardisation and accessibility of OCT across different centres. Centres with an available OCT should have expert neurologists or technicians with dedicated time to perform the exam. Large hospitals with ophthalmology departments could allocate dedicated slots for patients with MS, ensuring consistent machine use to maintain result comparability. Smaller centres could establish referral pathways to ophthalmology services to ensure continuity in testing protocols. Additionally, training programmes for ophthalmologists and neurologists were recommended to ensure that OCT aligns with MS-specific needs. Moreover, AI-assisted automated reporting for OCT is a key area of contemporary research and it may reduce interpretation variability and streamline workflows.[28 29] In terms of structural requirements, experts noted that existing OCT machines could be operated for longer hours to maximise capacity and limit new purchases.

Cognitive test accessibility could be improved by implementing a tiered approach, where neurologists administer initial screenings (eg, the Symbol Digit Modalities Test) while neuropsychologists focus on more complex assessments (eg, the whole Brief International Cognitive Assessment for MS). This approach aims to ensure test accessibility while acknowledging the limited availability of human resources. A tiered approach has also been proposed in other research contexts related to cognitive evaluation[30] and in the diagnosis of Alzheimer's disease,

as this approach enables accurate diagnosis at a lower cost, with the flexibility to incorporate additional tests when clinically needed.[31] Additionally, large MS referral centres could serve as training hubs, supporting smaller centres in providing expertise and facilitating access to full cognitive assessments. Moreover, the digitalisation of cognitive testing may further enhance efficiency by streamlining data management, reducing reliance on paper-based documentation and expediting clinical reporting. In fact, current research supports the effectiveness of digital neuropsychology tools in clinical use.[32]

Overall, these findings underscore the need for proactive planning to anticipate the structural and organisational requirements of these biomarkers before their widespread adoption. Moreover, robust evidence on the cost-effectiveness of biomarker use in MS management is essential to support policy discussions on their integration into clinical practice, although current data remain limited. Future research should also consider the role of patient-reported outcomes (PROs) as low-cost, patient-centred biomarkers. PROs could offer valuable insights into the impact of treatment, yet challenges remain in achieving standardised, comprehensive and universally interpretable measures.[33]

Strengths and limitations

This research offers an innovative perspective by presenting a prospective organisational follow-up model, integrating prospective biomarkers in MS care and by anticipating related organisational challenges. By identifying this model and examining structural, technological, organisational and professional requirements, it provides a foundation for policymakers to facilitate early planning and resource allocation, potentially accelerating implementation and improving patient access in MS care.

However, some limitations should be acknowledged. The limited search terms used in the systematic review, excluding keywords such as 'monitoring', may have led to the omission of relevant studies; future research should adopt a broader search strategy to ensure more comprehensive coverage of the literature. Further, as a preliminary organisational analysis, the findings are not based on real-world implementation and lack observational validation, which may affect generalisability. The exclusive involvement of Italian experts may limit applicability to other healthcare systems, and even within Italy, regional variability in resources and practices could hinder its transferability. Although expert selection was based on documented expertise and geographic representation, selection bias cannot be excluded—particularly regarding perspectives from centres with limited access to advanced biomarker technologies. Additional limitations include the absence of economic modelling or cost analysis. Thus, findings remain subject to expert discretion, local practices and evolving guidelines. Future research should validate the model through real-world studies and reassess its feasibility, adaptability and impact on patient outcomes as biomarkers enter routine use.

CONCLUSIONS

This research—through a systematic review, two modified Delphi consensus processes and semistructured expert interviews—proposes a prospective organisational follow-up model for PwMS and anticipates the structural and organisational requirements for integrating prospective biomarkers (sNfL, Cognitive Tests, OCT and GFAP) into clinical practice. While the follow-up model has been validated through expert consensus, the successful integration of these biomarkers will require careful consideration of organisational requirements and proactive planning. These findings, together with more robust evidence on the cost-effectiveness of biomarkers, could offer a foundation for policymakers to guide resource allocation and support the adoption of prospective biomarkers in MS monitoring. However, as a preliminary study, the conclusions remain contingent on validation in real-world clinical settings. Future research will be essential to reassess and refine the proposed model as these biomarkers are incorporated into routine care, ensuring alignment with clinical feasibility and patient-centred outcomes.

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