# What Fluid Biomarkers Tell Us at Different Stages of Multiple Sclerosis

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Multiple sclerosis presents various challenges, leading to an exploration of fluid biomarkers that could provide insights into disease diagnosis, prognosis and treatment response. This editorial focuses on a few biomarkers that may be useful at different stages of multiple sclerosis, reviewing the evidence, potential uses and challenges to overcome for their clinical application. Fluid biomarkers, ranging from kappa free light chains for diagnosing multiple sclerosis to neurofilament light and glial fibrillary acidic protein for monitoring disease evolution or treatment response, could offer a more nuanced understanding of the disease and potential for targeted treatments.

**Keywords**

Diagnosis, fluid biomarkers, glial fibrillary acidic protein, kappa free light chains, multiple sclerosis, neurofilament light, prognosis, treatment response

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Multiple sclerosis (MS) is a complex disease that can pose significant challenges in diagnosis, monitoring and treatment. Over the years, the quest for more precise and accessible diagnostic tools has led to the exploration of different fluid biomarkers in cerebrospinal fluid (CSF) or serum. Fluid biomarkers can offer insights into the diagnosis, prognosis and treatment response of MS, from the initial diagnostic stages to long-term follow-up. This editorial reviews the use of several fluid biomarkers in MS, examining their utility and potential to transform the current paradigm.

## Early diagnosis of multiple sclerosis

Diagnosing MS requires a combination of clinical assessment with magnetic resonance imaging (MRI) and laboratory investigations.[1] The demonstration of CSF-restricted immunoglobulin G oligoclonal bands (OBs) has long been part of the diagnostic process.[2] Although their role has been modified across different iterations of the McDonald criteria,[1,3] their main contribution to MS diagnosis is the demonstration of the inflammatory nature of the symptoms and lesions observed on MRI.[4] A limitation of OBs involves comparing the number of CSF and serum bands using immunoblotting, a process that is rater-dependent. Conversely, kappa free light chains (KFLCs) have emerged as rater-independent biomarkers due to their automated quantification.[5] Of the different methods used to assess their intrathecal production, the KFLC index has the strongest evidence for differentiating MS from other diseases.[6] It has also shown predictive value for a second attack or the fulfilment of the McDonald criteria in typical clinically isolated syndromes (CIS), yielding similar results to those obtained with OBs.[7,8] No specific KFLC index cut-off has been established to date; however, recent studies have suggested that values above 6 could point towards an MS diagnosis if applied in the right clinical setting, demonstrating similar diagnostic properties to OB.[5–8] Does this mean that the KFLC index could replace OBs in the diagnosis of MS? Both methods have strengths and limitations, and neither is specific to MS. One potential approach could involve using the KFLC index as a screening test.[9] OB detection could be reserved for cases falling in a grey zone between clear negatives and positives or in negative cases, where the suspicion index of MS is high.

Neurofilament light chain (NfL) levels have also been studied in early MS. In radiologically isolated syndromes, increased CSF or serum NfL (sNfL) indicates a higher risk of future clinical activity.[10,11] In typical CIS, sNfL z-scores with values above 1.5 were found to increase the risk of future clinical activity and the fulfilment of the 2017 McDonald criteria.[12,13] Perhaps the use of NfL as a biomarker of MS diagnosis has not been fully explored due to its lack of specificity. However, it could be argued that OBs and KFLCs are useful in the right context, even though they are not specific to MS. Moreover, if increased NfL levels are associated with contrast-enhancing lesions, could they be used as a surrogate for dissemination in time? These are topics that our research group considers worth exploring, bearing in mind that the diagnosis of MS is a construct in which combinations of different findings may help increase diagnostic specificity, sensitivity or accuracy.

## Monitoring disease activity, progression and treatment response

It has long been established that sNfL levels correlate with concentrations in CSF and are associated with clinical and MRI inflammatory activity in MS.[14] Thus, they could be used regularly

in clinical practice to monitor disease activity. Baseline sNfL levels, along with clinical and MRI findings, could aid in tailoring the selection of disease-modifying treatments (DMTs) for patients with differing degrees of inflammatory activity. Furthermore, sNfL levels decrease after starting DMT, particularly with highly effective treatments.[14,15] These findings suggest that incorporating sNfL measurements into routine clinical assessments will help monitor treatment response; however, the methodology for doing so is yet to be clearly defined.

MRI is a very useful tool to assess treatment response, and it is currently difficult to envision a therapeutic landscape without it. What sNfL measurements could bring to the table is more frequent, real-time disease monitoring, enabling more timely interventions when necessary. However, sNfL levels are less clearly associated with disability progression. They are probably associated with inflammatory activity-related disability accrual, but they do not seem to predict progression independent of relapse activity or MRI inflammatory activity.[13,16] Another emerging biomarker, glial fibrillary acidic protein (GFAP), appears to be associated with the severity of MS worsening, especially in progressive forms.[17] Indeed, recent data suggest serum GFAP (sGFAP) to be a prognostic biomarker for future progression independent of relapse activity.[16] That this biomarker can also be reliably measured in serum makes it complementary to sNfL. Using both sGFAP and sNfL as biomarkers would, therefore, assist clinicians in obtaining a more comprehensive view of neuroinflammation and neurodegeneration in individual patients; this, in turn, would improve decision-making processes. One common clinical scenario in which measuring both biomarkers could prove useful is when it is difficult to determine, from a purely clinical perspective, whether a patient is experiencing a relapse, a pseudo-relapse or a more severe disability accrual. In this setting, blood biomarker measurements could be conducted faster than an MRI in some institutions, again expediting the decision-making process.

However, the utility of sGFAP measurements for monitoring treatment response is a subject of consideration. While we still need to fine-tune the integration of sNfL with MRI findings and clinical biomarkers such as relapses, questions on the use of sGFAP for this purpose remain: Could increasing sGFAP levels indicate that certain DMTs are no longer useful in a given patient? Can highly efficacious DMTs decrease or at least stabilize sGFAP levels? Finally, could the value of other fluid biomarkers be enhanced if they were used in combination with sNfL and sGFAP? For instance, the KFLC index returns a metric result. In this sense, indexes above 100 increase the risk of a second attack in the following year after a CIS, particularly in subjects who also have sNfL z-scores of >1.5 and especially >3.0.[7,12] However, evidence regarding the predictive value of the KFLC index for disability accrual remains limited.[7]

## Challenges and opportunities

While the potential of fluid biomarkers in MS management is undeniable, several challenges must be addressed to ensure their successful integration into clinical practice. Standardization of measurement techniques, establishment of reference ranges and validation across different patient populations are crucial steps towards reliable biomarker adoption. Guaranteeing accessible and affordable testing is key, especially since some biomarker determinations may remain centralized in the foreseeable future. Efficient logistics, including the management of sample storage and shipping, must be carefully planned, particularly in regions with limited access to biomarker evaluation. Furthermore, the clinical implementation of fluid biomarkers and their interplay with imaging and clinical findings during disease evolution must be better defined, especially in progressive MS. Although no fluid biomarker is specific for MS, as our understanding of its disease mechanisms deepens, it seems clear that using fluid biomarker panels may be required to capture the multifaceted nature of MS. In turn, such detailed phenotyping could lead to targeted drug developments and a better design of clinical trials in specific patient subgroups.

## Conclusions

Remarkable progress in our understanding of the trajectory of MS, from diagnosis to follow-up, and the assessment tools at our disposal. Fluid biomarkers, though not specific to MS, are proving valuable for its management. They contribute to the early diagnosis of MS and can be useful for optimizing treatment and monitoring disease evolution. Alongside existing clinical tools, such as MRI, these biomarkers have the potential to refine how we manage MS, ultimately improving outcomes and quality of life for those affected by this disease. ❑


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