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Biomarker Trajectories in Progressive Multiple Sclerosis: A Longitudinal Cohort Analysis

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Abstract

Progressive multiple sclerosis has traditionally been understood as a distinct clinical phase that follows relapsing disease, but longitudinal cohort and trial evidence over the past decade has reframed much of the disability patients accumulate, even during nominally relapsing disease, as progression independent of relapse activity (PIRA) -- a gradual process running beneath the clinically defined relapsing-progressive divide. This article synthesizes the literature on the biomarkers now used to track that process longitudinally. We review blood-based fluid markers, principally serum neurofilament light chain and glial fibrillary acidic protein, which index axonal injury and astrocytic reactivity respectively and show complementary, combinable prognostic value for relapse-independent worsening; MRI-based markers, including chronic active paramagnetic-rim lesions and brain-age-derived atrophy measures, which offer a spatially specific window onto smoldering, non-relapsing inflammation and diffuse neurodegeneration; optical coherence tomography, which detects subclinical retinal neuroaxonal thinning even in eyes without a history of optic neuritis; and the earlier-stage literature on digital and wearable monitoring, which addresses the sampling-frequency limitations of episodic clinical and imaging assessment. Read together, the evidence supports a coherent, multimodal biomarker strategy for tracking progressive MS, while leaving definitional standardization of PIRA, validation in real-world populations, and individual-patient reference ranges as open priorities for the field.

Keywords: progressive multiple sclerosis; neurofilament light chain; glial fibrillary acidic protein; progression independent of relapse activity; longitudinal biomarkers

1. Introduction

Progressive multiple sclerosis has always been the part of the disease that clinical trials, and clinical trial-derived thinking, have handled least well. For three decades the field's working model of MS divided cleanly into a relapsing phase, in which inflammatory attacks come and go against a background of otherwise stable function, and a progressive phase, in which disability accumulates gradually and relapses either stop altogether or become incidental. That two-phase picture, formalized in Lublin and colleagues' widely used 2013 phenotype revision, gave trialists a clean way to enroll homogeneous populations and regulators a clean way to label drugs, and it remains the vocabulary the field speaks [1]. It has also turned out to be a considerable simplification of what is actually happening inside an individual nervous system over time, and the last decade of biomarker research has been largely an exercise in taking that simplification apart.

The trouble starts with relapses themselves. Once cohorts with relapsing MS were followed carefully enough, and disability was measured often enough, it became clear that a great deal of the disability people accumulate over years is not explained by their relapses at all. Confirmed disability accumulation was occurring in patients with no recent clinical or radiological relapse activity to blame it on -- a phenomenon that acquired the label progression independent of relapse activity, or PIRA, and that a landmark 2019 analysis termed, more bluntly, "silent progression" [2]. A pooled analysis of two large randomized trials in typical relapsing MS subsequently showed that PIRA, not relapse-associated worsening, accounts for the greater share of confirmed disability accumulation events in this ostensibly "relapsing" population, a finding the authors argued directly challenges the clinical distinction between relapsing and progressive disease [3]. Tur and colleagues extended this into the earliest phase of the disease, showing that PIRA identified shortly after a first demyelinating event already predicts long-term disability outcomes [4]. By the time Müller and colleagues undertook a systematic review to try to harmonize how different groups were even defining PIRA, the concept had accumulated enough inconsistent operationalizations across studies that comparing results between cohorts had become a genuine methodological problem in its own right [5].

The randomized trials that established the first disease-modifying therapies with efficacy in progressive MS -- ocrelizumab in primary progressive disease and siponimod in secondary progressive disease -- were themselves instrumental in generating this reframing, because both trial programs collected the kind of dense, longitudinal clinical and imaging data against which a relapse-independent progression signal could first be reliably distinguished from relapse-driven worsening [6,7].

This article is a synthesis of the biomarker literature that has grown up around this reframing. If progressive disability accrual is not simply "what happens after relapses stop," but a process running underneath the relapsing phase from early on, then the central practical question for both clinicians and trialists becomes: what can be measured, longitudinally, in an individual patient, that tracks this underlying process closely enough to be useful -- for prognosis, for treatment selection, and eventually for trial endpoints that do not require years of clinical follow-up to read out. We organize the discussion around four broad classes of candidate biomarker that have matured substantially over the past decade: blood and cerebrospinal fluid markers of neuroaxonal and astroglial injury, chiefly neurofilament light chain and glial fibrillary acidic protein; MRI-based markers of tissue loss and of the chronic active lesions increasingly implicated in smoldering inflammation; retinal imaging via optical coherence tomography, which offers a uniquely accessible window onto neurodegeneration; and the earlier-stage but rapidly growing literature on digital and wearable measures of function collected outside the clinic. We close with an account of where the field's evidentiary base is genuinely strong and where it is still mostly promissory.

It is worth being explicit about what kind of claim this article is and is not making. We are not reporting a new cohort or a new analysis; every quantitative figure below is drawn from a published, cited source, and where we describe a specific effect size -- a hazard ratio, a micrometer difference in retinal thickness -- it is because the underlying paper reported that number, not because it is a plausible-sounding estimate. Longitudinal biomarker trajectories in progressive MS are, more than most areas of neurology, an area where overclaiming is easy and has real consequences: a

biomarker that looks compelling in a well-characterized academic cohort can behave quite differently once it needs to inform decisions about de-escalating or escalating treatment for an individual patient. We have tried to be correspondingly careful about which claims in the literature are settled and which remain provisional.

2. Clinical Phenotypes and the Rise of Progression Independent of Relapse Activity

Any discussion of biomarkers in progressive MS has to start from the fact that "progressive MS" is no longer a clean clinical category, if it ever was. The 2013 phenotype revisions distinguished primary progressive MS, in which disability accumulates from onset without a preceding relapsing course, from secondary progressive MS, in which a period of clearly relapsing disease gradually gives way to gradual worsening, and further asked clinicians to characterize each as "active" or "not active" and as "with progression" or "without progression" based on recent clinical and imaging findings [1]. This was a genuine improvement on what preceded it, but it was built to be assessed at a single clinic visit using measures -- relapse counts, gadolinium-enhancing lesions, a documented step-change in Expanded Disability Status Scale score -- that are relatively insensitive to the kind of gradual, sub-relapse change that PIRA represents.

The silent progression literature that followed complicated this picture directly. Cree and colleagues, studying a relapsing MS cohort with no evidence of recent disease activity by conventional clinical and MRI criteria, found that a substantial fraction of the cohort nonetheless accumulated disability over the observation period, disability that by definition could not be attributed to relapses or new lesion formation as conventionally assessed [2]. Kappos and colleagues' pooled analysis of two phase 3 ocrelizumab trials in relapsing MS then quantified this at trial scale, applying a composite disability outcome to distinguish PIRA events from relapse-associated worsening events, and reporting that the majority of confirmed disability accumulation in this "relapsing" trial population occurred independently of relapse activity, with distinct baseline prognostic factors associated with PIRA versus RAW, and with ocrelizumab conferring benefit against both processes [3]. That last detail matters for how the field now interprets progressive MS clinical trials: a drug's effect on PIRA and its effect on relapse-associated worsening are not the same measurement and do not necessarily move together, which is exactly the kind of distinction a purely relapse-count-based trial design would have obscured.

Tur and colleagues pushed the PIRA concept to the earliest possible point in the disease course, examining patients within months of a first demyelinating event and showing that early PIRA -- disability accrual in this window that could not be attributed to relapse -- predicted long-term disability years later, essentially as strongly as more conventional early prognostic markers [4]. The implication, echoed across this literature, is that the biological process producing progressive disability is not a later "stage" that relapsing MS eventually transitions into, but is present, and in principle measurable, from very early in the disease.

The practical difficulty is that PIRA, as a construct, is defined by ruling things out -- disability accumulation not explained by a relapse, not explained by a confounding illness, confirmed at a subsequent visit -- rather than by a positive, mechanistically grounded signal. Müller and colleagues' systematic review of how PIRA has actually been operationalized across the published literature found meaningful heterogeneity in the specific definitions used: the required confirmation interval, the relapse-exclusion window, and the disability scale and threshold applied all varied enough between studies that the reported incidence and prognostic value of PIRA are not straightforwardly comparable across the field [5]. This is precisely the gap that biological biomarkers are positioned to fill: a fluid or imaging measure that rises before, or independently of, a clinically confirmed PIRA event would let PIRA be operationalized around a measurable underlying process rather than around what did not happen clinically. The next three sections take up that candidate biomarker literature in turn.

3. Neurofilament Light Chain: The Leading Fluid Biomarker

Neurofilament light chain (NfL) is a structural protein of the axonal cytoskeleton that is released into the extracellular space, and from there into the cerebrospinal fluid and blood, when axons are damaged, essentially regardless of the cause of that damage. Disanto and colleagues' 2017 study, examining a large Swiss MS cohort, established the modern case for serum

NfL as a clinically usable marker of neuronal damage in MS, showing that serum concentrations correlated with CSF concentrations closely enough that a blood draw could substitute for a lumbar puncture for this purpose, and that serum NfL tracked disease activity and, to a lesser extent, disability [8]. That correlation between an accessible blood test and an invasive CSF measurement is arguably the single development that made NfL a plausible biomarker for routine, repeated, longitudinal use rather than a research-cohort curiosity requiring serial lumbar punctures.

Kuhle and colleagues extended this into a direct test of NfL's value as a treatment-response biomarker, using blood samples from the fingolimod phase 3 trial program to show that elevated baseline serum NfL was associated with subsequent disease activity and future brain volume loss, and that treatment reduced serum NfL levels in parallel with its effect on relapses and MRI lesions -- establishing NfL not just as a static risk marker but as something that moves, longitudinally, in response to effective treatment [9]. Jakimovski and colleagues then took the question of longitudinal tracking further, following a relapsing and progressive MS cohort over five years and showing that serum NfL levels were associated with both concurrent and future clinical and cognitive performance, an important extension because cognitive decline is one of the harder-to-measure dimensions of MS progression that a blood biomarker would ideally help capture [10]. Thebault and colleagues, working with a similarly long observation window, reported that serum NfL measured early in the disease course predicted long-term clinical outcomes measured years later, reinforcing the idea that NfL is not merely a marker of concurrent injury but carries meaningful prognostic information about where a given patient's disease is heading [11].

The progressive-MS-specific evidence is, appropriately, the most directly relevant to this article's scope. Bar-Or and colleagues analyzed blood NfL data from the ocrelizumab phase 3 trial program spanning both relapsing MS and primary progressive MS, and found that NfL levels predicted non-relapsing disease progression -- essentially, PIRA-type worsening -- in both populations, with ocrelizumab's anti-CD20 mechanism associated with reductions in NfL that tracked its clinical benefit [12]. This is a genuinely useful result for the biomarker-trajectories framing of this article: it connects a fluid biomarker directly to the specific, relapse-independent progression phenotype that the preceding section argued is the dominant driver of long-term disability in MS, across both a relapsing and a primary progressive trial population within the same analysis.

What NfL is good at, and what it is not, is now reasonably well characterized across this literature. It is sensitive to acute axonal injury from any cause, which is a strength for detecting relapses and new lesion formation and a limitation for isolating the specific, slower, non-relapsing degenerative process that defines progressive MS -- a patient's serum NfL trajectory reflects the sum of all axonal injury occurring in their nervous system, inflammatory and degenerative alike, and disentangling the two components from a single blood value is not straightforward. It is also influenced by factors unrelated to MS disease activity, notably age and body mass index, which more recent work in this space has begun to correct for explicitly rather than relying on fixed population cutoffs, though the foundational cohort studies synthesized here largely predate that refinement and should be read with that caveat.

4. Glial Fibrillary Acidic Protein and Complementary Fluid Markers

Glial fibrillary acidic protein (GFAP) is the principal intermediate filament protein of astrocytes, and its release into blood and CSF reflects astrocytic activation and reactive astrogliosis rather than axonal injury per se. Because reactive astrogliosis is a prominent feature of the smoldering, non-relapsing inflammation increasingly implicated in progressive MS, GFAP has emerged as a natural complement to NfL rather than a competitor to it, and the most informative recent work in this space has explicitly tested the two markers side by side rather than in isolation.

Abdelhak and colleagues' broader review of blood GFAP across neurological disease establishes the physiological basis for this distinction, describing GFAP as indexing astrocytic reactivity and positioning it as informative in conditions -- progressive neurodegenerative disease chief among them -- where astrocyte-driven pathology runs somewhat independently of the acute axonal damage NfL is most sensitive to [13]. Meier and colleagues then tested this directly in an MS cohort, comparing serum GFAP and serum NfL as predictors of

disease progression, and reported that serum GFAP rose with age in a way that needed to be accounted for statistically, that patients with worsening progressive disease had significantly higher serum GFAP than those with stable disease, and that higher baseline serum GFAP was associated with subsequently faster gray matter brain volume loss [14]. The result that most directly bears on this article's synthesis, however, is what happened when the two markers were combined: patients with elevation of both serum GFAP and serum NfL had a substantially higher risk of subsequent disability worsening (hazard ratio 4.09, 95% CI 2.04-8.18) and of PIRA specifically (hazard ratio 4.71, 95% CI 2.05-9.77) than patients without dual elevation [14]. Figure 1 summarizes this combined-marker result, which is among the more striking single findings in the fluid-biomarker literature reviewed here precisely because it targets PIRA as an outcome directly, rather than relapse activity or a composite disability measure that mixes the two progression mechanisms together.

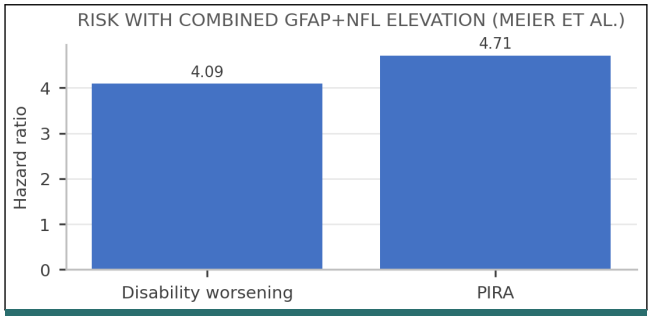

Figure 1: Risk of subsequent disability worsening and of progression independent of relapse activity (PIRA) in patients with combined elevation of serum GFAP and serum NfL, relative to patients without dual elevation, as reported by Meier et al. [14].

The practical reading of this combined result is that NfL and GFAP are picking up genuinely different, and apparently additive, components of the pathology driving progression -- axonal injury and astrocytic reactivity respectively -- and that a panel combining both is more informative about relapse-independent worsening than either marker alone. This is a meaningfully different claim than "GFAP is a better biomarker than NfL," which the data do not support; the two behave as complementary rather than substitutable, which is the more clinically useful finding of the two possibilities.

CSF markers beyond NfL and GFAP retain a role in this landscape as well, chiefly for their diagnostic and, to a lesser extent, prognostic value, even as the field's longitudinal-tracking interest has shifted toward blood-based measures for practical reasons of repeatability. Senel and colleagues' work on CSF kappa free light chains, a B-cell-derived intrathecal synthesis marker, found the measure to be a sensitive indicator of intrathecal immunoglobulin production in clinically isolated syndrome and early MS, broadly comparable to oligoclonal band status but more readily quantified [15]. Kappa free light chains have not accumulated the same longitudinal-trajectory evidence base in progressive MS specifically that NfL and GFAP now have, but they illustrate that the fluid-biomarker space extends beyond the two markers that have dominated recent progressive-MS-specific research, and that CSF-based approaches remain relevant particularly at the diagnostic end of the disease course.

5. Imaging Biomarkers: Brain Atrophy, Chronic Active Lesions, and Brain-Age

MRI has been central to MS diagnosis and monitoring since well before the current biomarker era, and Barkhof and colleagues' foundational criteria work, using lesion location and morphology at first presentation to predict conversion to clinically definite MS, is part of the reason MRI became load-bearing for MS diagnosis at all [16]. But the imaging features most relevant to progressive disease specifically -- diffuse tissue loss and chronic, non-relapsing lesion activity -- are a somewhat different set of measurements than the focal, gadolinium-enhancing lesions that dominate relapsing-MS monitoring, and it is these progression-relevant imaging markers that have matured substantially over the past decade.

Chronic active lesions, sometimes described as smoldering lesions, are MS plaques that retain a rim of iron-laden, activated microglia and macrophages at their edge long after the initial inflammatory episode that created them, visible on susceptibility-sensitive MRI sequences as a paramagnetic rim. Absinta and colleagues' original 7-tesla imaging work identified this phase-rim signature and showed that lesions displaying it were less likely to resolve and more likely to expand over follow-up than rim-negative lesions, establishing the paramagnetic rim as a marker of ongoing, low-grade inflammatory activity persisting well outside the acute relapse window [17]. A subsequent study by the same group linked the presence of chronic active, rim-positive lesions directly to clinical disability, reporting an association between the burden of these lesions and in

vivo disability measures that supported chronic active lesions as a plausible substrate for at least part of the PIRA phenomenon described earlier in this article [18]. The appeal of chronic active lesions as a biomarker candidate is that they offer a specific, visible, and mechanistically interpretable imaging correlate of "smoldering" pathology, rather than the more diffuse and less specific signal that whole-brain atrophy measures provide.

Brain atrophy measurement itself has taken a somewhat different methodological turn in recent years, moving from raw volumetric change toward composite, machine-learning-derived summary measures. Cole and colleagues' brain-age paradigm, applied longitudinally to an MS cohort, estimates an individual's apparent brain age from structural MRI and tracks how the gap between that estimate and chronological age evolves over time; in their MS cohort this brain-predicted age difference widened progressively and was associated with clinical disability and with future disability worsening, offering a single interpretable summary statistic -- "your brain looks N years older than it should" -- that folds together the diffuse, whole-brain component of neurodegeneration that lesion-focused measures do not capture [19]. Filippi and colleagues' broad review of MS as a disease entity situates both the chronic-active-lesion and brain-atrophy literatures within the wider mechanistic picture of the disease, describing the shift in the field's understanding of progressive MS toward a compartmentalized, smoldering neuroinflammatory process running behind an intact blood-brain barrier -- a mechanistic account that both the paramagnetic-rim-lesion and brain-age findings can be read as specific, measurable instances of [20].

Taken together, these imaging markers are complementary to the fluid biomarkers discussed above in a specific way: NfL and GFAP report a whole-body-accessible, cheap, and repeatable signal that is nonspecific about location, while chronic active lesions and brain-age measures report a spatially specific, mechanistically interpretable signal that requires MRI access and more elaborate post-processing. Neither is straightforwardly superior; a longitudinal monitoring strategy that combines an inexpensive blood draw with periodic MRI is, in the reading of the literature synthesized here, better positioned to capture the multiple, only partially overlapping pathological processes that PIRA appears to comprise than either modality alone.

6. Retinal Biomarkers via Optical Coherence Tomography

The retina offers something no other part of the central nervous system does: direct, non-invasive, high-resolution optical access to axons and neurons, via optical coherence tomography (OCT), without the cost, scan time, or claustrophobia concerns of MRI. Because the retinal nerve fiber layer and the ganglion cell layer are unmyelinated in the eye itself, OCT-measured thinning of these layers is thought to reflect neuroaxonal loss relatively directly, largely uncomplicated by the demyelination that affects interpretation of some other neurodegeneration measures in MS.

Petzold and colleagues' systematic review and meta-analysis, pooling OCT data across a large number of published MS cohorts, quantified this thinning with a level of precision that individual smaller studies could not achieve on their own. Comparing eyes with a history of optic neuritis (MSON) to healthy control eyes, they found the peripapillary retinal nerve fiber layer (pRNFL) was thinner by a mean of 20.10 μm (95% CI -22.76 to -17.44), and the macular ganglion cell-inner plexiform layer (GCIPL) was thinner by 16.42 μm (95% CI -19.23 to -13.60) [21]. Critically for the progressive-MS biomarker question, the effect was not confined to eyes with a clinical history of optic neuritis: MS eyes without any history of optic neuritis (MSNON) were still significantly thinner than healthy control eyes, by 7.41 μm for pRNFL (95% CI -8.98 to -5.83) and 6.31 μm for GCIPL (95% CI -7.75 to -4.87) [21]. Table 1 summarizes these four comparisons. This MSNON finding is the more biomarker-relevant of the two results, because it demonstrates that retinal thinning is detectable in MS eyes that have never had a clinically apparent optic nerve attack -- consistent with a subclinical, ongoing neurodegenerative process rather than simply scarring from a past relapse, and structurally analogous to the PIRA framing this article has organized around: a measurable process occurring independent of, rather than because of, a clinically recognized inflammatory event.

Table 1: Mean retinal layer thinning (OCT) in MS eyes with a history of optic neuritis (MSON) and MS eyes without such a history (MSNON), relative to healthy control eyes, pooled across cohorts by Petzold et al.'s systematic review and meta-analysis [21].

Retinal layer	Comparison	Mean difference (μm)	95% CI
Peripapillary RNFL	MSON vs healthy controls	-20.10	-22.76 to -17.44
Peripapillary RNFL	MSNON vs healthy controls	-7.41	-8.98 to -5.83
Macular GCIPL	MSON vs healthy controls	-16.42	-19.23 to -13.60
Macular GCIPL	MSNON vs healthy controls	-6.31	-7.75 to -4.87

The clinical utility case for OCT in progressive MS specifically rests on this subclinical signal being trackable over time in individual patients, not just detectable cross-sectionally in group comparisons, and on it predicting things clinicians actually want to predict -- future disability, and specifically future disability accrued outside of relapses. That said, OCT measurement is not without its own confounds: comorbid ophthalmological conditions, image segmentation artifacts, and the substantial between-device variability across OCT platforms all complicate its use as a fully standardized longitudinal tool across multi-site cohorts and clinical trials, a set of practical issues that has occupied a meaningful share of the more recent OCT-in-MS methodological literature and that any deployment of OCT as a formal trial or clinical monitoring endpoint has to reckon with directly.

7. Digital and Wearable Biomarkers

The biomarkers discussed so far -- blood draws, MRI scans, OCT imaging -- all share a structural limitation: they capture a single time point, separated from the next by months, in a disease whose defining feature, per the PIRA literature reviewed above, is gradual change that a sparse sampling schedule can miss or badly mistime. Digital and wearable measures, collected continuously or near-continuously as patients go about ordinary life, are a candidate answer to that sampling problem, and the underlying technology -- accelerometers, smartphone-based gait and typing tests, passive activity monitoring -- has matured enough over the past decade to make this a genuinely active area of MS research rather than a purely speculative one.

Block and colleagues' systematic review of remote physical activity monitoring across neurological disease, MS prominent among the conditions covered, surveyed the state of wearable-sensor-based monitoring as of the mid-2010s and found a rapidly growing but still heterogeneous literature: studies varied widely in device type, monitoring duration, and outcome measures, and the review's central methodological conclusion was that the field lacked the standardization needed to compare results across studies or to establish which specific digital metrics track clinically meaningful change most reliably [22]. That heterogeneity problem is broadly the same one the PIRA-definition literature ran into a few years later, and for a similar underlying reason: a genuinely promising measurement concept, adopted independently by many research groups before any consensus existed on how exactly to operationalize it, produces a body of positive but not directly comparable findings.

For progressive MS specifically, the appeal of continuous digital monitoring is fairly direct: PIRA is, by construction, a slow process that a twice-yearly EDSS assessment is not well suited to catch early, and a passively collected measure of gait speed, activity level, or fine motor function sampled daily or weekly could in principle detect an inflection in trajectory months before it would be confirmed by conventional clinical assessment. Realizing that potential requires exactly the kind of longitudinal validation against biological and clinical progression outcomes -- NfL and GFAP trajectories, OCT trajectories, confirmed PIRA events -- that the other three biomarker classes in this article are further along in accumulating; digital measures are, at the time of this synthesis, the least mature of the four candidate biomarker classes reviewed here, more a promising direction than an established one.

8. Open Challenges

Several gaps recur across this literature and are worth stating plainly rather than leaving implicit. First, the PIRA definitional heterogeneity documented by Müller and colleagues is not a narrow methodological footnote; it means that when different biomarker studies report an association with "PIRA" or with "disability progression," they may not be measuring quite the same clinical construct, which complicates any attempt to compare, say, the prognostic strength of NfL against that of chronic active lesion burden across studies that used different PIRA definitions in the first place [5]. A shared, prospectively applied PIRA definition, adopted before rather than after data collection, would materially

improve the comparability of the biomarker literature going forward.

Second, most of the strongest longitudinal biomarker evidence reviewed here comes from clinical trial populations or single-center academic cohorts with relatively intensive, protocol-driven follow-up -- the ocrelizumab and fingolimod trial programs that produced the NfL and PIRA findings discussed above, and OCT and imaging cohorts run at expert centers with standardized acquisition protocols. Real-world clinical populations, with irregular follow-up intervals, more comorbidity, and non-standardized imaging across sites and vendors, have not been anywhere near as thoroughly characterized, and the field cannot yet say with confidence how well the reported effect sizes -- the GFAP-NfL combined hazard ratios reported by Meier and colleagues, for instance -- will hold up outside the relatively controlled settings that produced them [14].

Third, and closely related, none of the individual biomarkers reviewed here has an established, validated, individual-patient decision threshold analogous to, say, a blood pressure or HbA1c cutoff in other areas of medicine. NfL and GFAP levels are influenced by age, body mass index, renal function, and other factors that vary between patients independent of MS disease activity, and the field's handling of this -- largely, at the time of the cohort studies synthesized here, through population-level statistical adjustment rather than fully individualized reference ranges -- remains a work in progress rather than a solved problem. A biomarker that predicts group-level risk reliably is not automatically a biomarker ready to guide an individual treatment decision, and that gap between population-level evidence and individual-patient actionability is, in our reading, the single largest barrier between the encouraging findings reviewed in this article and routine clinical deployment.

Fourth, the four biomarker classes discussed here -- fluid markers, chronic-active-lesion and atrophy imaging, OCT, and digital monitoring -- have mostly been validated in parallel rather than in combination, within their own separate literatures. The one notable exception in the papers reviewed here is the direct NfL-versus-GFAP, and combined NfL-and-GFAP, comparison by Meier and colleagues, which is exactly the kind of head-to-head, same-cohort analysis that lets a field determine whether two candidate biomarkers are redundant or complementary [14]. Comparable direct comparisons between, for instance, OCT trajectories and chronic active lesion burden, or between digital gait metrics and serum NfL, in the same patients over the same follow-up period, are much rarer, and are arguably the next methodological step the field needs in order to move from "many individually promising biomarkers" toward an efficient, minimal combined panel.

9. Conclusion

The literature reviewed here supports a reasonably specific set of claims about biomarker trajectories in progressive multiple sclerosis. The clinical picture that motivates this biomarker effort has shifted meaningfully: disability accumulation independent of relapse activity, rather than relapse-driven step-changes, now appears to be the dominant contributor to long-term disability even in ostensibly relapsing populations, and it is detectable from very early in the disease course [2,3,4]. Against that backdrop, blood-based fluid biomarkers have matured the furthest toward practical, repeatable, longitudinal use: serum neurofilament light chain tracks neuroaxonal injury and predicts both relapsing and non-relapsing progression, and serum GFAP, reflecting a mechanistically distinct astrocytic-reactivity process, adds meaningfully to that prediction when the two are combined rather than considered separately [8,9,12,14]. Imaging biomarkers -- chronic active, paramagnetic-rim-positive lesions and brain-age-derived atrophy measures -- offer a spatially and mechanistically specific complement to the fluid markers' whole-body accessibility [17,18,19]. Retinal imaging via OCT demonstrates that subclinical neurodegeneration, detectable in eyes with no history of a clinical optic nerve attack, is measurable with a few minutes of non-invasive scanning, echoing the PIRA framing at a tissue level [21]. Digital and wearable monitoring remains the least mature of the four classes but addresses a sampling-frequency limitation that all of the others share [22].

None of these four biomarker classes, on the evidence synthesized here, is positioned to fully replace the others; the more compelling reading of the literature is that they capture at least partially distinct components of a pathological process -- axonal injury, astrocytic reactivity, chronic focal inflammation, diffuse neurodegeneration, and functional decline -- that clinical PIRA criteria alone cannot cleanly separate.

Realizing the practical promise of biomarker-guided monitoring in progressive MS will depend on the field doing the comparative, same-cohort work needed to combine these measures efficiently, on validating the resulting panels in real-world rather than purely trial-derived populations, and on developing individual-patient reference ranges robust enough to inform treatment decisions rather than only group-level risk estimates. That is a substantial research agenda, but the consistency with which independent groups, using genuinely different measurement modalities, have converged on the same underlying picture of gradual, partly relapse-independent progression is, in our view, the strongest available evidence that this is a coherent biological process worth continuing to pursue with exactly this kind of longitudinal, multimodal biomarker strategy.

10. References

1. Lublin FD, Reingold SC, Cohen JA, et al. (2014) Defining the clinical course of multiple sclerosis: The 2013 revisions. Neurology, 83(3): 278-286. DOI: 10.1212/WNL.0000000000000560

2. Cree BAC, Hollenbach JA, Bove R, et al. (2019) Silent progression in disease activity-free relapsing multiple sclerosis. Annals of Neurology, 85(5): 653-666. DOI: 10.1002/ana.25463

3. Kappos L, Wolinsky JS, Giovannoni G, et al. (2020) Contribution of Relapse-Independent Progression vs Relapse-Associated Worsening to Overall Confirmed Disability Accumulation in Typical Relapsing Multiple Sclerosis in a Pooled Analysis of 2 Randomized Clinical Trials. JAMA Neurology, 77(9): 1132-1140. DOI: 10.1001/jamaneurol.2020.1568

4. Tur C, Carbonell-Mirabent P, Cobo-Calvo Á, et al. (2023) Association of Early Progression Independent of Relapse Activity With Long-term Disability After a First Demyelinating Event in Multiple Sclerosis. JAMA Neurology, 80(2): 151-160. DOI: 10.1001/jamaneurol.2022.4655

5. Müller J, Cagol A, Lorscheider J, et al. (2023) Harmonizing Definitions for Progression Independent of Relapse Activity in Multiple Sclerosis: A Systematic Review. JAMA Neurology, 80(11): 1232-1245. DOI: 10.1001/jamaneurol.2023.3331

6. Montalban X, Hauser SL, Kappos L, et al. (2017) Ocrelizumab versus Placebo in Primary Progressive Multiple Sclerosis. New England Journal of Medicine, 376(3): 209-220. DOI: 10.1056/NEJMoa1606468

7. Kappos L, Bar-Or A, Cree BAC, et al. (2018) Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study. The Lancet, 391(10127): 1263-1273. DOI: 10.1016/S0140-6736(18)30475-6

8. Disanto G, Barro C, Benkert P, et al. (2017) Serum Neurofilament Light: A Biomarker of Neuronal Damage in Multiple Sclerosis. Annals of Neurology, 81(6): 857-870. DOI: 10.1002/ana.24954

9. Kuhle J, Kropshofer H, Haering DA, et al. (2019) Blood neurofilament light chain as a biomarker of MS disease activity and treatment response. Neurology, 92(10): e1007-e1015. DOI: 10.1212/WNL.0000000000007032

10. Jakimovski D, Zivadinov R, Ramanthan M, et al. (2019) Serum neurofilament light chain level associations with clinical and cognitive performance in multiple sclerosis: A longitudinal retrospective 5-year study. Multiple Sclerosis Journal, 26(13): 1670-1681. DOI: 10.1177/1352458519881428

11. Thebault S, et al. (2020) Serum neurofilament light chain predicts long term clinical outcomes in multiple sclerosis. Scientific Reports, 10: 10381. DOI: 10.1038/s41598-020-67504-6

12. Bar-Or A, Thanei GA, Harp C, et al. (2023) Blood neurofilament light levels predict non-relapsing progression following anti-CD20 therapy in relapsing and primary progressive multiple sclerosis. eBioMedicine, 93: 104662. DOI: 10.1016/j.ebiom.2023.104662

13. Abdelhak A, Foschi M, Abu-Rumeileh S, et al. (2022) Blood GFAP as an emerging biomarker in brain and spinal cord disorders. Nature Reviews Neurology, 18(3): 158-172. DOI: 10.1038/s41582-021-00616-3

14. Meier S, Willemse EAJ, Schaedelin S, et al. (2023) Serum Glial Fibrillary Acidic Protein Compared With Neurofilament Light Chain as a Biomarker for Disease Progression in Multiple Sclerosis. JAMA Neurology, 80(3): 287-297. DOI: 10.1001/jamaneurol.2022.5250

15. Senel M, Tumani H, Lauda F, et al. (2014) Cerebrospinal Fluid Immunoglobulin Kappa Light Chain in Clinically Isolated Syndrome and Multiple Sclerosis. PLoS ONE, 9: e88680. DOI: 10.1371/journal.pone.0088680

16. Barkhof F, Filippi M, Miller DH, et al. (1997) Comparison of MRI criteria at first presentation to predict conversion to clinically definite multiple sclerosis. Brain, 120(11): 2059-2069. DOI: 10.1093/brain/120.11.2059

17. Absinta M, Sati P, Schindler M, et al. (2016) Persistent 7-tesla phase rim predicts poor outcome in new multiple sclerosis patient lesions. Journal of Clinical Investigation, 126(7): 2597-2609. DOI: 10.1172/JCI86198

18. Absinta M, Sati P, Masuzzo F, et al. (2019) Association of Chronic Active Multiple Sclerosis Lesions With Disability In Vivo. JAMA Neurology, 76(12): 1474-1483. DOI: 10.1001/jamaneurol.2019.2399

19. Cole JH, et al. (2020) Longitudinal Assessment of Multiple Sclerosis with the Brain-Age Paradigm. Annals of Neurology, 88(1): 93-105. DOI: 10.1002/ana.25746

20. Filippi M, Bar-Or A, Piehl F, et al. (2018) Multiple sclerosis. Nature Reviews Disease Primers, 4: 43. DOI: 10.1038/s41572-018-0041-4

21. Petzold A, Balcer LJ, Calabresi PA, et al. (2017) Retinal layer segmentation in multiple sclerosis: a systematic review and meta-analysis. Lancet Neurology, 16(10): 797-812. DOI: 10.1016/S1474-4422(17)30278-8

22. Block VAJ, Pitsch E, Tahir P, Cree BAC, Allen DD, Gelfand JM. (2016) Remote Physical Activity Monitoring in Neurological Disease: A Systematic Review. PLOS ONE, 11: e0154335. DOI: 10.1371/journal.pone.0154335

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Conflict of Interest

The authors declare that they have no competing interests relevant to this work.

Data Availability Statement

This is a literature synthesis and no new clinical, imaging, or laboratory data were generated. All findings discussed are drawn from the cited publications, and readers are directed to those sources for the underlying data.

Ethical Approval

Not applicable. This article synthesizes previously published literature and did not involve the recruitment of human participants, animal subjects, or the collection of primary clinical data.

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