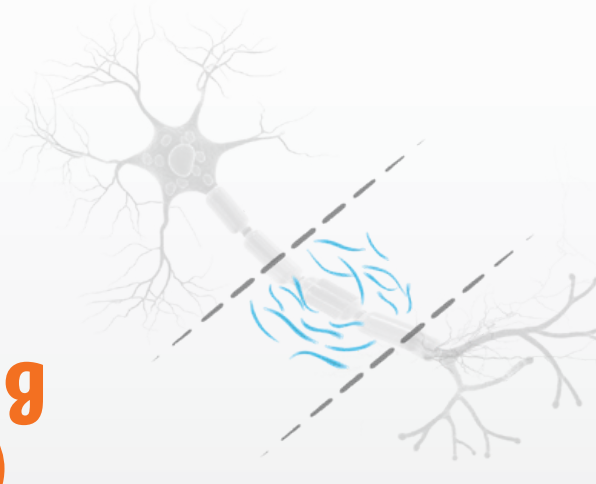


Neurofilament light chain (NfL)

A first-of-its-kind blood test aiding patient risk management in relapsing multiple sclerosis (RMS)

Now available for clinical use*

Introduction

Laboratory testing provides essential information supporting clinical decisions. Most testing is used to inform a diagnosis, such as the presence or absence of disease. However, a small, but growing, number of tests, including blood-based biomarkers, are increasingly being used for prognosis or establishing the risk of future events, such as disease progression or subclinical disease activity.[1]

Now, in a first-of-its-kind application, a fully automated blood-based (serum and plasma) assay for the quantitative detection of neurofilament light chain has achieved CE-marking† for use as a prognostic aid in patients with relapsing multiple sclerosis (RMS).

The Atellica IM Neurofilament Light Chain (NfL) assay is intended for use as an aid in identifying adult patients between 18–55 years of age with RMS who are at a **higher-versus-lower risk of multiple sclerosis (MS) disease activity** as defined by new or enlarging T2 (neT2) magnetic resonance imaging (MRI) lesions within a two-year period.[2]

**NfL is not for sale in the U.S. May not yet be commercially available in all countries. Future availability cannot be guaranteed and subject to local requirements.*

SIEMENS Healthineers

Types of MS

Multiple sclerosis is associated with the autoimmune-mediated destruction of the myelin sheaths protecting nerve fibers in the central nervous system (CNS) that can lead to progressive damage of the brain or spinal cord.[3,4] MS is currently categorized by four types (Figure 1), with ~85 percent of cases occurring as relapsing remitting MS (RRMS).[3] Females are twice as (or more than) likely to develop MS compared to males.[5]

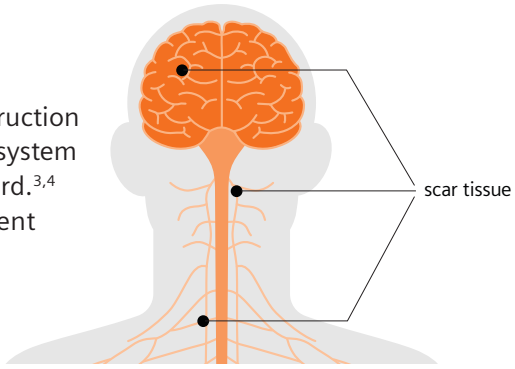
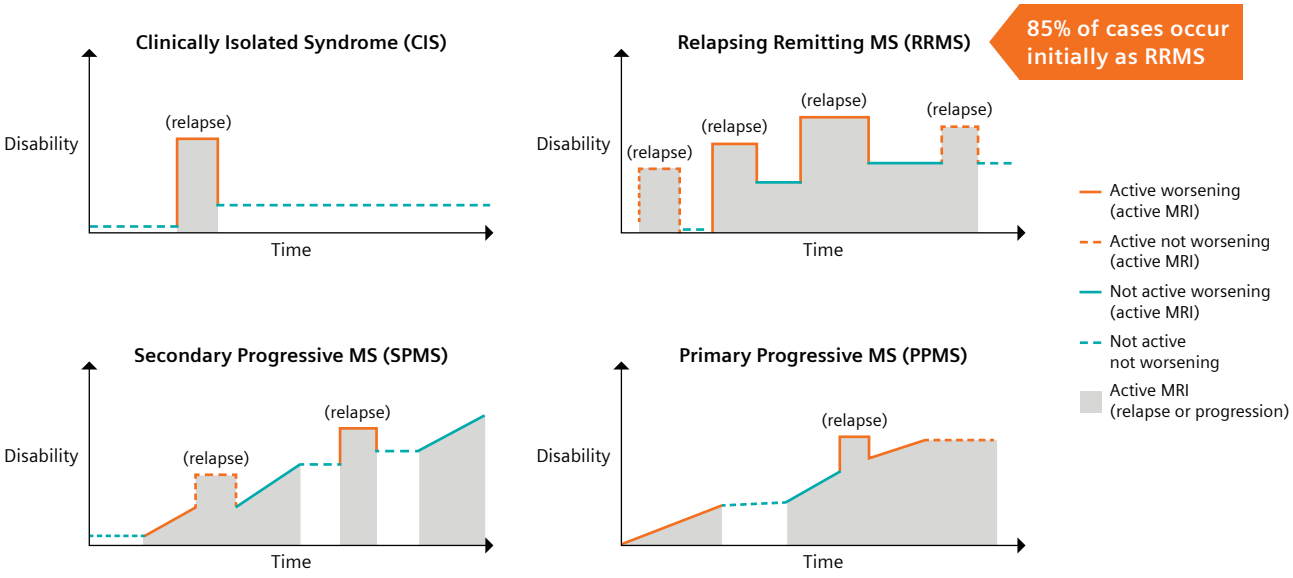


Figure 1. Four types of MS



While disease onset can appear at any age, MS is most commonly diagnosed between the ages of 20–40 years (~85 percent or more of cases).[6,7] Limited emerging data suggests a potential shift to a slightly higher age of onset in some individuals (above the ages of 40) although it remains unclear if this is a global trend.[6,7]

A significant subset of RRMS patients may progress to secondary progressive MS (SPMS), which is associated with poorer outcomes, including increased disability.[8] RMS may include patients with RRMS or SPMS. **Rates of MS are rising globally, with a ~30 percent increase observed from 2013 to 2020**, including a 32 percent increase in European nations.[5]

Prognosis in RMS patients: An unmet clinical need aiding patient-centric management

Early treatment initiation for patients diagnosed with RRMS is commonly recommended to help avert the accumulation of significant neurologic damage or conversion to SPMS.[9,10] Multiple treatment interventions (disease-modifying therapies or DMTs) can mitigate damage and slow or stall disease progression.

The choice of an efficacious therapy is challenged by the high variability of disease activity (including subclinical factors that can be difficult to assess) among patients and inconsistencies in DMT response rates.[9,10] It is also important to balance treatment risks (adverse side effects) vs. therapeutic benefit. Generally, two contrasting options exist: escalation vs. high-efficacy DMTs.[9,10]

Escalation attempts to balance efficacy vs. risk by starting with drugs known to have low-to-moderate effectiveness, but a lower risk of adverse effects. More aggressive treatment using higher efficacy DMTs can be used in patients perceived at higher risk or failing to display an adequate treatment response. While this approach may reduce the likelihood of therapy-related adverse events, progression—including irreversible damage—can occur prior to recognition of worsening disease.[10,11] Currently, this "silent progression" is incompletely assessed using existing tools, including MRI and other clinical parameters.[11]

High-efficacy therapy is more aggressive, starting with more effective treatments that may not be as well-tolerated and with higher risk of therapy-related adverse events.[9-11] While data supports more aggressive management (high-efficacy therapy) early in patients with an active/highly active disease course, current tools (including MRI and clinical assessment) may be insufficient to identify those at higher risk of disease activity prior to development of overt damage.[11-13]

Blood-based NfL testing supports individualized risk stratification

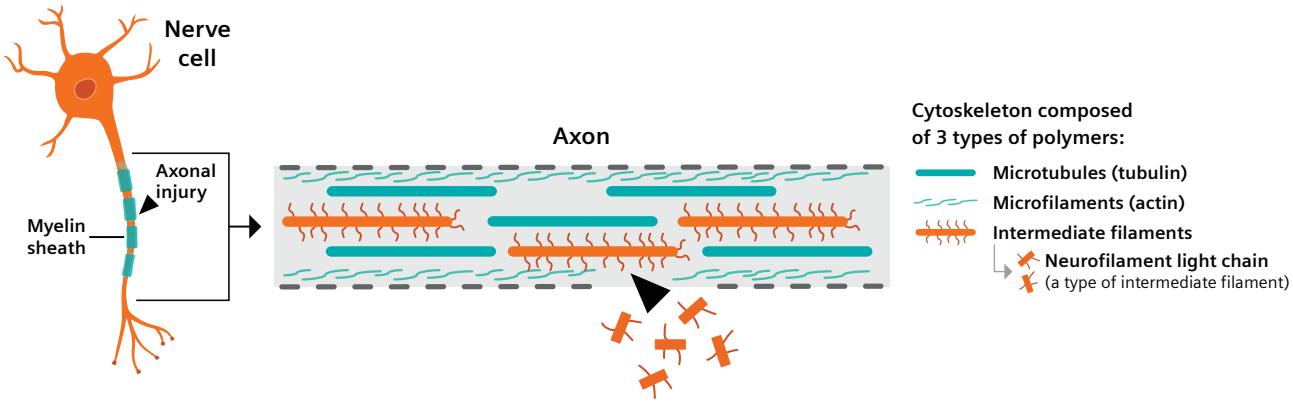
Tailored individualized management, including assessment of risk for disease activity or progression, is desirable when considering treatment selection and determining response. Until now, risk-assessment tools have been limited for RMS patients.[13] **Today, availability of a blood-based (serum or plasma) test that detects NfL and has been certified in the EU for prognostic use in patients with RMS offers a novel aid to help predict the risk of RMS-related disease activity.[2]**

Elevated levels of NfL are associated with inflammatory, demyelinating lesion activity with axonal damage occurring in RMS.[13-16] NfL is not intended to replace MRI, which provides important information related to spatial localization and lesion stage, but as an additional test supporting clinical management decisions.[13]

What is NfL?

NfL belongs to a group of cytoskeletal elements called intermediate filaments specific to neurons.[13-16] As intracellular components, these proteins are found at lower levels in the blood of healthy individuals but can increase following neuroaxonal damage.[13-16] Elevated levels in the blood (and CSF) can occur as a result of multiple causes of nerve injury, including the neuroinflammatory axonal damage associated with MS-mediated myelin sheath destruction.[13-16] These large-caliber, myelinated axons—commonly injured in MS—are a significant source of NfL.[15]

Figure 2. NfL is released with neuroaxonal damage



Risk assessment in RMS: Addressing an unmet need supporting individualized patient management

According to recent published guidance, blood-based NfL testing is poised to address a major unmet need in the management of MS.[13] The authors state that "Neurofilament light chain (NfL) is a long-awaited blood biomarker that can provide clinically useful information about prognosis..."[13] While many studies validating the value of quantitative NfL testing in RMS for disease progression exist,[13-25] access to NfL testing has been limited until now to investigative studies using research-use-only assays (principally, the SIMOA NfL assay offered by Quanterix).[13]

> *"Neurofilament light chain (NfL) is a long-awaited blood biomarker that can provide clinically useful information about prognosis..."*[13]

The Quanterix SIMOA NfL assay uses proprietary (Uman) monoclonal antibodies with high specificity for the NfL analyte[26] and is well validated.[13] However, access is currently limited to labs with the required specialized analytical platform. Like other NfL assays utilized in published studies, the Quanterix SIMOA NfL assay is currently available only for clinical and diagnostic research applications (research-use-only, as of November 2024),[27] although future availability for clinical use is probable.

As of February 2025, only the NfL assay from Siemens Healthineers has achieved CE marking† for clinical use in patients, reflecting the extensive validation and verification required for approved assays. CE marking ensures that safety, compliance, and performance standards per EU regulations have been met, supporting confidence for clinical use.

NEW! Blood based NfL testing now CE-marked† for clinical use: Fully automated Atellica IM testing with serum or plasma

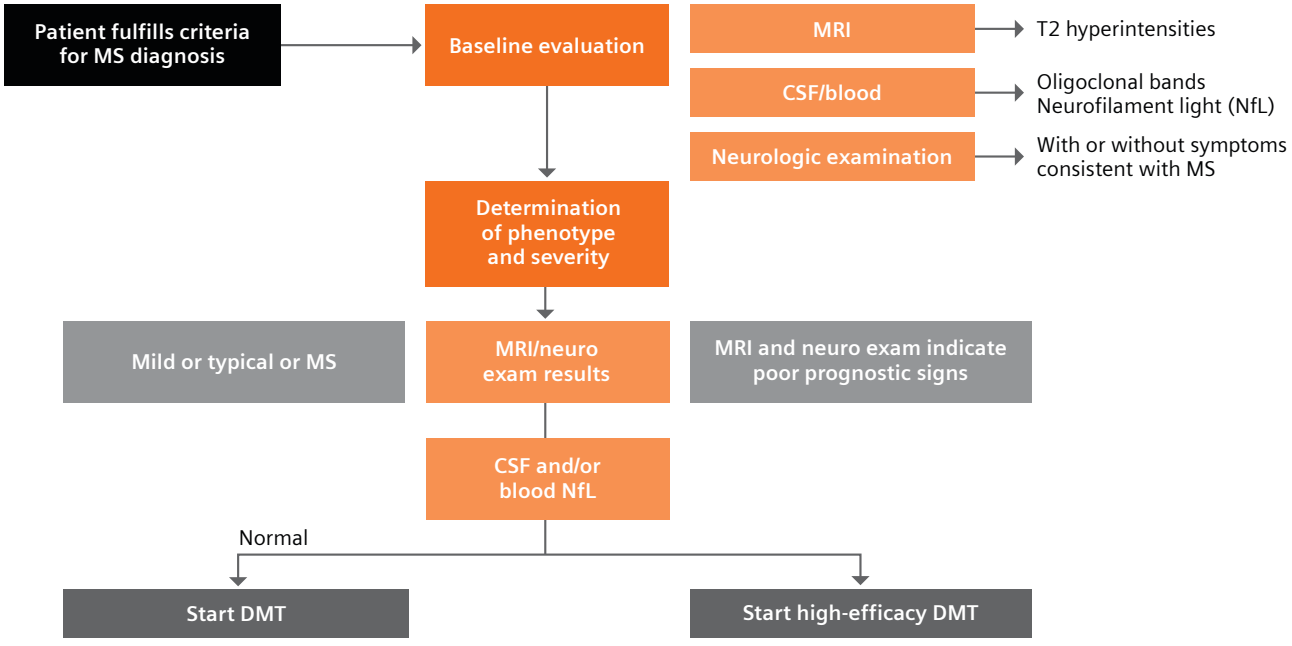
The NfL assay from Siemens Healthineers can now address access to clinical testing by offering a fully automated assay with a CE mark for use in RMS patients ages 18–55 years. It utilizes the same antibodies (Uman) from the highly investigated SIMOA NfL assay, but with an assay-specific architecture designed for sensitive and automated detection on the Siemens Healthineers Atellica IM and CI, as well as the ADVIA Centaur XP/XPT analyzers. Siemens Healthineers analyzers are widely used in labs globally, supporting broad access to NfL testing for clinicians managing MS patients. **Moreover, the NfL assay from Siemens Healthineers has a simple, validated, quantitative cut point for assessing a higher risk of future (within two years) disease activity (≥ 12.9 pg/mL).**[2] Having a defined cut point is essential, as NfL assays currently lack standardization, meaning any assays intended for clinical use must establish a value specific to that test.[13,28]

Testing pathways

An NfL testing pathway for RMS has been proposed in recent guidance issued on the incorporation of NfL testing in MS.[13] (Figure 3)

Use of this, or any pathway that may utilize NfL testing (including the Atellica IM NfL assay from Siemens Healthineers), is at the discretion of the ordering clinician or local guidance.

Figure 3. Proposed testing pathway for use of NfL testing in RMS[13]



Validation and performance of the Atellica IM NfL assay

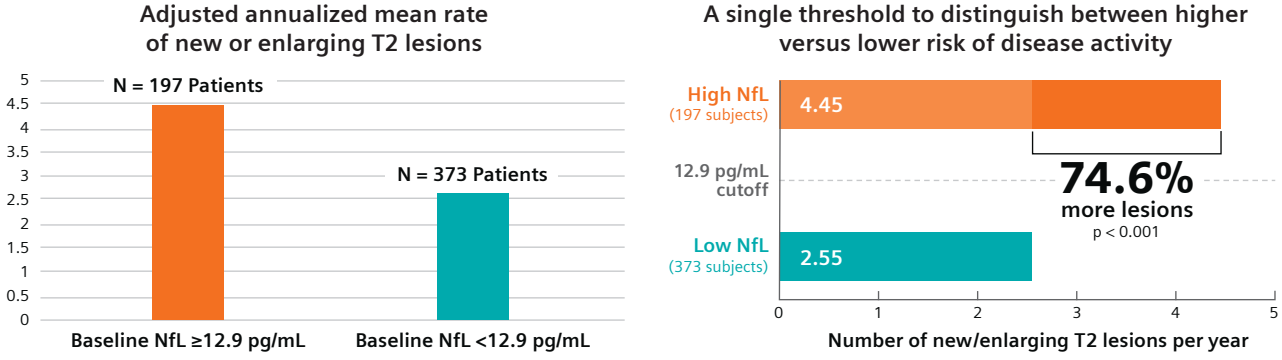
Study design

Prognostic performance of the Atellica IM NfL assay using the Atellica IM Analyzer was evaluated using 570 samples from adults with RMS aged 18–55, as part of a prospective, pharmaceutical clinical trial.[2] Baseline NfL samples were collected along with baseline MRIs. Patients were followed for up to two years. Outcomes associated with worsening disease were defined as the annualized rate of **new or enlarging T2 (neT2)** lesions observed between the baseline MRI and the last follow-up scan collected in the study, standardized to one year.

Study outcomes

RMS subjects with a higher baseline NfL concentration **(≥ 12.9 pg/mL)** vs. subjects with a lower baseline **(<12.9 pg/mL)** displayed a significantly greater risk of disease activity associated with neT2 lesions.[2] RMS patients with elevated levels of NfL experienced, on average, an almost 75 percent greater rate of neT2 lesions on an annualized basis when compared to subjects with baseline NfL <12.9 pg/mL.

Figure 4. Baseline levels of NfL associated with a ~75 percent higher rate of new or enlarging lesions/year (Siemens Healthineers NfL decision cut point of ≥12.9 pg/mL)[2]



Levels of NfL in healthy patients

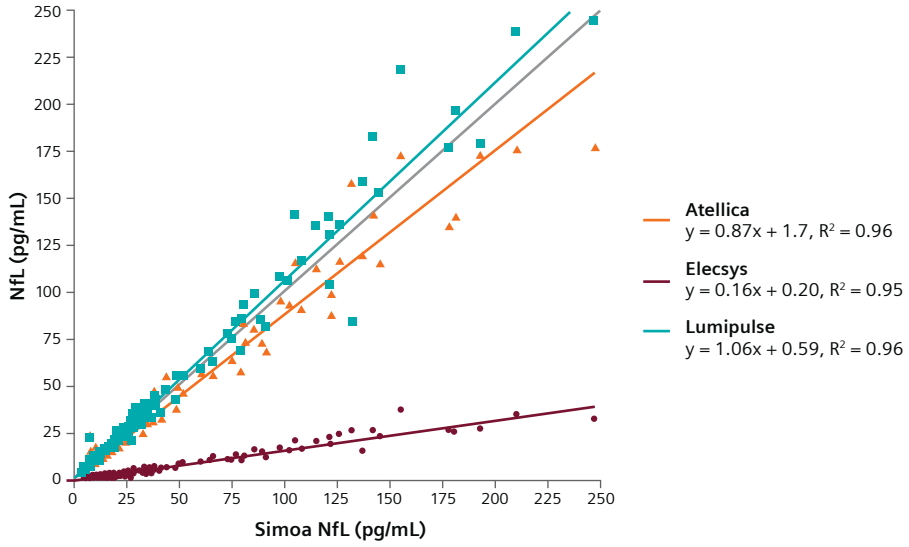
A total of 684 samples were collected from apparently healthy subjects (blood-donor population) and tested on the Atellica IM NfL assay.[2] The upper reference limit was determined by calculating the 95th percentile of the distribution of values and determined to be 13.9 pg/mL with a **mean of 7.7 pg/mL**.

Correlation of the Atellica IM NfL Assay to the Quanterix SIMOA NfL Assay

While the Atellica IM NfL assay utilizes the same antibodies as the Quanterix assay,[29] the assay designs and detection technologies differ, and results are not interchangeable between the assays.

In a study comparing four RUO blood-based NfL assays, including the Atellica IM assay from Siemens Healthineers and the SIMOA assays, along with two other assays in development for clinical use, the authors reported a good correlation, although some proportional bias was observed.[29] In particular, they noted the Roche assay results were significantly lower than the other three assays (Figure 5), reinforcing the need to utilize assay-specific values. Other data supports the current lack of standardization for quantitative values between blood-based NfL assays, including those in development for clinical use.[13,30]

Figure 5. Correlation between four blood-based NfL assays[29]



Factors potentially impacting NfL levels

While NfL is neuron specific, it is not disease specific as it can be released with multiple conditions associated with neuroaxonal damage.[24,25] Promising studies have explored the utility for NfL in a range of neurologic disease states (with MS being the most highly studied to date).[13,15,24,25] While multiple non-neurologic factors potentially impacting NfL levels have been investigated, increasing age (associated with increased NfL) and higher BMI (associated with decreased NfL levels) have been commonly observed.[13]

Age and NfL levels

Levels of NfL may increase with age, including in those with no known neurologic conditions.[13,31,32] This may reflect subclinical, comorbid pathologies, although definitive evidence is needed.

Most MS cases currently are diagnosed in younger individuals (<40 years)[33] where reported NfL levels in a healthy reference population are lower.[31,32] Some data suggest the influence of age may be most pronounced in individuals ≥60 years.[28,31,32] The Atellica IM NfL assay was validated in patients from ages 18–55 using a single, age-range-defined, prognostic quantitative cut point.[2]

A clinically meaningful impact on the prognostic performance of NfL testing in MS across age strata is less clear. In a large subgroup analysis (1,882 RMS patients) of the Phase 3 ASCLEPIOS I/II trials, the authors concluded that baseline levels of NfL remained prognostic for future lesion formation irrespective of baseline age or BMI.[34] Additional evidence on a clinically relevant influence of age on levels of NfL, including individuals with later-age onset of MS, will be informative as to value of age specific cut points or reference ranges.

BMI and NfL levels

A negative association (lower values) associated with higher BMI on NfL levels has been reported.[31,35] Whether this might influence the clinical interpretation of NfL levels in patients with MS remains uncertain, with some data suggesting no significant clinical impact by baseline BMI.[34,36] Additional evidence supporting or refuting a clinically significant influence of BMI on the prognostic performance of serum/plasma NfL levels in patients with RMS will be instructive.

Z scores vs. a single quantitative cut point for NfL testing in RMS

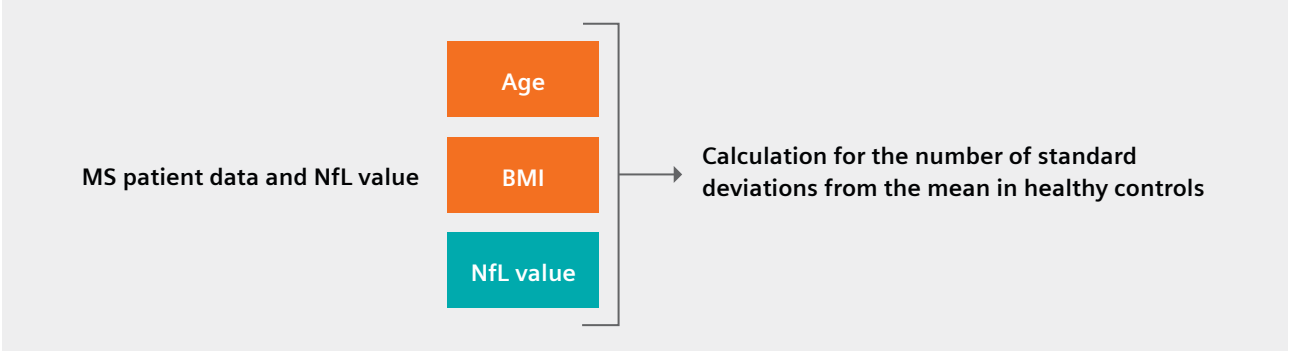
Z scores have been investigated as one approach to help address a potential influence of age or BMI on levels of NfL in MS patients.[37,38] One large study utilized a reference database with age and BMI-adjusted serum NfL concentrations derived from a population with no known CNS disease.[37] Deviation was assessed in the MS population by comparison to the serum NfL value (Quanterix NfL assay) relative to values observed in the control population in persons of the same age and BMI (using a Z score utilized for academic research).[39]

Unlike a single quantitative NfL value, the proposed Z score requires additional patient demographic data (age and BMI) be included in the calculation.[37,39] In addition, any impact of the assay-specific NfL value would require investigation, as assays are not currently standardized.[13,37]

More data on the benefit of using a Z score calculation vs. the quantitative value of NfL (with or without reference ranges) would be informative. One recent study reported a "marginal" impact when comparing the predictive performance of a of a Z score vs. the quantitative serum NfL value in an MS population.[38] Whether Z scores vs. absolute or reference range NfL values provide a clear clinical advantage requires further investigation.[13,28]

A possible drawback to the use of a Z score is ensuring easy access to the necessary demographic data for each patient calculation, and use of a well-validated reference database.[37] (Figure 6) Currently, the Atellica NfL assay provides a fully automated, clinically validated, reportable quantitative result in <60 minutes without need for additional information and a score calculation.

Figure 6 (adapted from references 37,39). **Z score calculation (example)**



Conclusion

A clinically accessible NfL assay validated for prognostic use in RMS patients has been highly anticipated,[13] supporting timely and confident clinical decisions via a routine blood draw. The NfL assay from Siemens Healthineers is fully automated and can be run on analyzers broadly available in labs worldwide and provides a simple-to-interpret, quantitative NfL value. Clinician awareness of this new test as a meaningful indicator of disease activity aiding risk assessment in RMS patients is expected to provide added utility supporting improved patient management.[13]

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