

New Laboratory Criteria for Diagnosing Multiple Sclerosis

Background: Multiple sclerosis (MS) is the most common of the demyelinating diseases and occurs in approximately 1 in 700 U.S. citizens. The disease is more prevalent in women and young adults, particularly those who live in northern latitudes. The rationale behind MS treatment is to minimize disease activity and progression of disability. As a result, an early and accurate diagnosis is most important. In 2001, an international panel was convened to standardize criteria for diagnosis of MS (1). These recommendations, known as the McDonald criteria, combine the patient’s clinical presentation, laboratory testing, and radiological findings.

Although the diagnosis of MS still requires the objective demonstration of dissemination of lesions in both time and space, the McDonald criteria incorporate magnetic resonance imaging (MRI) to facilitate the diagnosis of MS. Since its introduction, however, there has been only moderate improvement in the sensitivity and specificity of predicting the conversion of suspected cases to MS. One explanation for these shortcomings is the lack of adequate guidelines for the performance and interpretation of CSF analysis. To address this issue, the Consortium of MS Clinics commissioned a study in 2005 that defines the “minimum standard” for neurologists and medical laboratory specialists in the evaluation of CSF (2).

NEW Interpretive Criteria for CSF Analysis:

The panel’s recommendations emphasize isoelectric focusing (IEF) on agarose gels with immunoblotting using specific antiserum to human IgG as the “gold standard” for detection of oligoclonal bands. This qualitative approach is emphasized over the IgG index or any other quantitative IgG analysis. The advantage of this approach is that there is improved sensitivity and specificity since it

compares the patient’s own IgG in serum in parallel with their CSF rather than a quantitative analysis in which the patient’s results are compared to a population, and thus, a broad reference range of blood-derived proteins in the CSF. A review by the panel of the published sensitivities and specificities using IEF/immunoblotting is summarized in Table 1.

Table 1. Published sensitivities and specificities of IEF with immunoblotting for MS (from Reference 2)

No. of patients	No. of patients with MS	Sensitivity, %
1114	58	100
1007	82	95
558	112	96
		Specificity, %
189	98	87
44	26	86

Additional Enhancements Further Improve the Specificity of Prediction of MS:

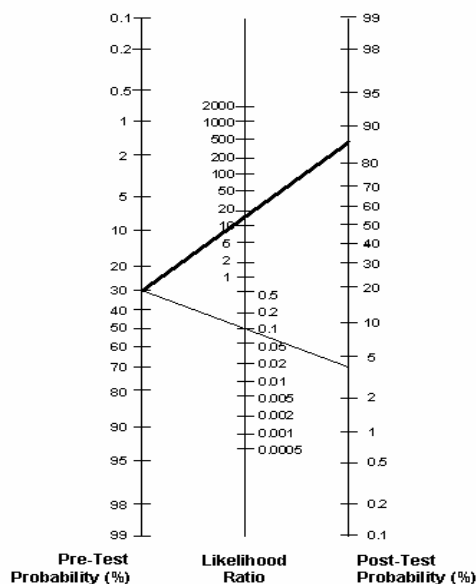
In a recent publication, a group of 55 patients presenting with a clinically isolated demyelinating syndrome were studied with brain MRI and IEF/immunoblotting over 6 years (3). The immunoblotting technique was based on an alkaline phosphatase labeled anti-IgG conjugate that significantly improved the detection and resolution of oligoclonal IgG bands over prior approaches. With this technique the authors detected conversion to MS with a sensitivity of 91%, and a specificity of 94% and a likelihood ratio (LR) of 15 suggesting that this is an excellent test.

“Approximately, 1 in 400 Maine citizens have been diagnosed with MS, a prevalence rate that is nearly 70% higher than the national average.”
 Source: National MS Society

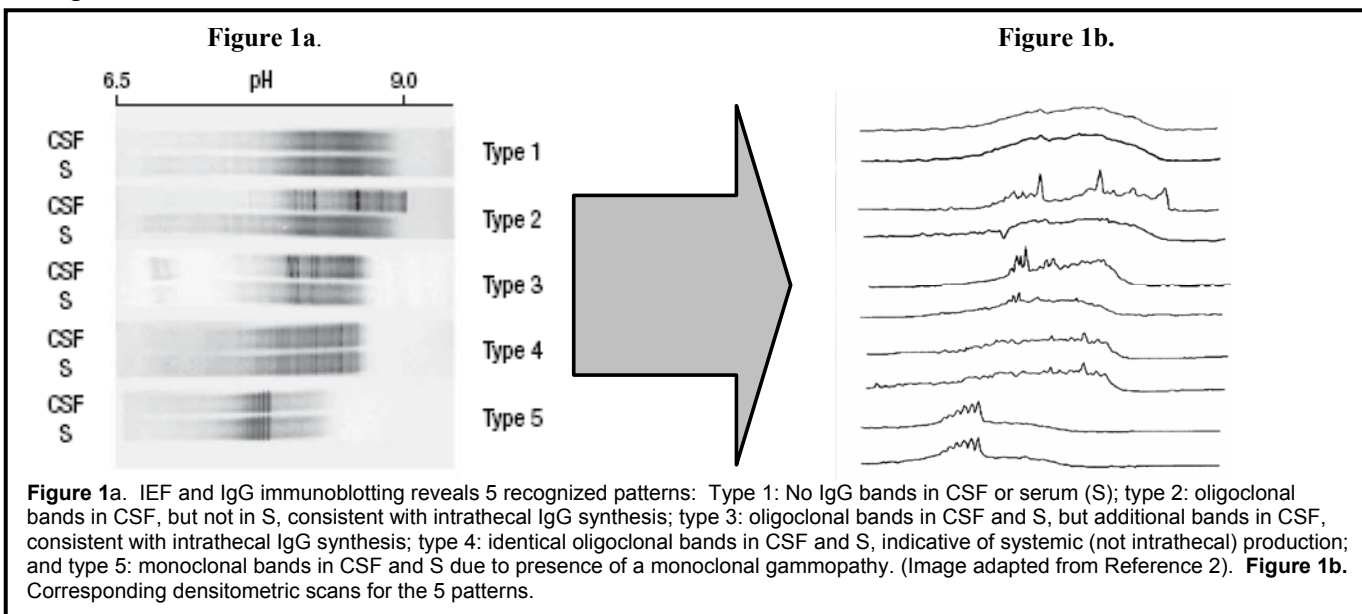
An LR of 15 has a Significant Impact on the Ability to Predict MS:

The nomogram on page 2 can be used to plot the post-test probability of MS given your clinical estimate of the patient’s

probability of MS prior to oligoclonal band determination. The lines plotted are for a patient you feel has a 30% probability of converting to MS. The thick line plots the post-test probability if oligoclonal bands are found and the thin line if they are not (the $LR_{negative}$ for absence of oligoclonal IgG bands is ~ 0.1).



Interpretation of IEF Patterns: There are five recognized patterns for CSF/Serum based on direct probing for IgG antibodies; these are shown in Figures 1a and 1b below.



Methodology

FBR uses isoelectric focusing and immunoblotting with an alkaline phosphatase labeled anti-human

IgG conjugate applied to serum and CSF (CPT codes 83916 x 2 and 84181 x 2). Quantitative analysis of IgG and Albumin in serum and CSF is performed using immunonephelometry (CPT codes 82784 x 2 and 83520 x 2, respectively) to calculate the IgG index.

Ordering Information

Check the Demyelinating Disease Profile Box (Block V) on the General Requisition form. Testing is performed daily.

Specimen: 2 mL of nonhemolyzed, nonlipemic serum and 2.0 mL of clear CSF.

Storage and Shipping: Room temperature (or 4°C if delayed more than 48 hours).

Price: Refer to FBR's Fee Schedule.

Further Information

For additional clinical information, please contact Walt Allan, M.D. or Robert F. Ritchie, M.D.; for technical information, contact Thomas B. Ledue, BA, or Wendy Y. Craig, Ph.D.

References

1. McDonald W, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. *Ann Neurol.* 2001 Jul;50(1):121-7.
2. Freedman MS, et al. Recommended standard of cerebrospinal fluid analysis in the diagnosis of multiple sclerosis: a consensus statement. *Arch Neurol.* 2005 Jun;62(6):865-70.

3. Masjuan J. et al. Clinically isolated syndromes: A new oligoclonal band test accurately predicts conversion to MS. *Neurology* 2006;66:576-78.