artifactual conclusions, as cautioned by Sormani et al. (28,29). In fact, Fraser et al. (30) warned "that the new McDonald criteria lead to more than double the number of patients with a diagnosis of MS at 1 year compared with the use of the Poser criteria." Some studies on multiple sclerosis have used both sets of criteria (31,32).

A question that arises, not just for multiple sclerosis, but for any disease, is what to do when a standard of criteria is changed after the study has been set in motion. In an appropriate response to a change in standards, Grasso et al. (33) reported, "[w]e enrolled 270 MS patients admitted … with definite MS, as diagnosed according to the Poser criteria. We revised all the diagnoses of the MS patients according to the new criteria recently formulated by McDonald."

b. Biomarkers and Surrogates for Diagnosing Multiple Sclerosis

This provides an account of exploratory biomarkers and of an objective measure of multiple sclerosis, prior to reviewing disability scales, such as the Kurtzke Expanded Disability Status Scale (EDSS) score, and prior to reviewing magnetic resonance imaging (MRI). MRI is a gross measure of pathology and MRI data are somewhat remote from the mechanism of action of the disease.

Neurofilament light chains (NFL) and neurofilament heavy chains (NFH), or peptide fragments thereof, are biomarkers that can be acquired from samples of cerebrospinal fluid (CSF) (34,35). CSF can be safely obtained by lumbar puncture, though this procedure is invasive (more so than blood samples, less than liver biopsy). Neurofilament is a cytoskeletal protein of axons, and its presence in CSF results from damage to axons. NFL levels may reflect acute damage to axons, and can be useful for diagnosing patients recently converting from CIS to multiple sclerosis, while NFH levels may reflect chronic irreversible damage (36). Kuhle et al. (37) determined that NFL levels in CSF correlate with EDSS score, and

[28]Sormani MP, Tintorè M, Rovaris M, et al. Will Rogers phenomenon in multiple sclerosis. Ann. Neurol. 2008;64:428–33.

[29]Sormani MP. The Will Rogers phenomenon: the effect of different diagnostic criteria. J. Neurol. Sci. 2009;287 (Suppl. 1):S46–9.

[30]Fraser C, Klistorner A, Graham S, Garrick R, Billson F, Grigg J. Multifocal visual evoked potential latency analysis: predicting progression to multiple sclerosis. Arch. Neurol. 2006;63:847–50.

[31]Korporal M, Haas J, Balint B, et al. Interferon beta-induced restoration of regulatory T-cell function in multiple sclerosis is prompted by an increase in newly generated naive regulatory T cells. Arch. Neurol. 2008;65:1434–9.

[32]Kuhle J, Pohl C, Mehling M, et al. Lack of association between antimyelin antibodies and progression to multiple sclerosis. New Engl. J. Med. 2007;356:371–8.

[33]Grasso MG, Pace L, Troisi E, Tonini A, Paolucci S. Prognostic factors in multiple sclerosis rehabilitation. Eur. J. Phys. Rehabil. Med. 2009;45:47–51.

[34]Gnanapavan S, et al. Guidelines for uniform reporting of body fluid biomarker studies in neurological disorders. Neurology 2014;83:1210–6.

[35]Friese MA, et al. Mechanisms of neurodegeneration and axonal dysfunction in multiple sclerosis. Nat. Rev. Neurol. 2014;10:225–38.

[36]Teunissen CE, Khalil M. Neurofilaments as biomarkers in multiple sclerosis. Mult. Scler. 2012;18:552–6.

[37]Kuhle J, Plattner K, Bestnick JP, et al. A comparative study of CSF neurofilament light and heavy chain protein in MS. Mult. Scler. 2013;19:1597–603.