Reviewer’s report

Title: Prediction of acute multiple sclerosis relapses by transcription levels of peripheral blood cells

Version: 2 Date: 22 June 2009

Reviewer: Philip L De Jager

Reviewer’s report:

Overall, the authors have made good progress on addressing my comments. I appreciate their effort in this regard. However, a few minor comments remain, which are outlined below. The breakdown refers to the original organization of comments in the first review.

Major compulsory revisions:

• Validation effort: We appreciate the effort of the reviewers in assembling a dataset of 10 additional subjects. Its content is a little surprising given the over-abundance of men. Despite, reading the results section several times, I cannot see where the replication analysis is presented. I apologize if I am missing it, but this is a critical point for the manuscript and should be presented clearly. 10 subjects is a small number, but the difficulty in gathering such data is appreciated. So, a small number is acceptable if the results are consistent in this initial report of the method.

Minor essential revisions:

1. Subjects: the issues relating to diagnostic criteria and subject heterogeneity have been addressed adequately. However, the distribution of CIS and MS subjects across the three subject categories is quite different, so I would recommend removing the comment that they are similar. Presenting the details of the distribution of patients without comment adequately deals with this issue: there is heterogeneity in the subject population and this may affect the results. However, it does appear that the predictors, in this dataset, are not affected by this heterogeneity.

2. Subjects: previous comments have been addressed. However, the authors should more clearly state (A) how their subjects were selected (prospective collection vs retrospective use of existing data), was time to event a selection criterion (as may be interpreted from the methods section)? (B) was the blood sample collected for this analysis? Were PBMC frozen and profiled at a later time or profiled fresh for each subject?

3. Clinically silent lesions: the authors should strike the comment in the introduction that clinically silent lesions are controversial in the field. There is no controversy here: (1) these lesions are a major part of the McDonald criteria that the authors report using and (2) they are an important outcome of virtually all current MS clinical trials. The lack of using this MRI outcome clinically reflects the health care policies of each country and the decision of how to allocate resources
not the preference of neurologists. If available, routine MRIs are clearly used in routine MS clinical practice and helps to guide therapeutic decisions. Thus, the authors have not adequately addressed this important limitation of their study. In the end, they simply need to clearly state this important limitation in their manuscript.

4. RNA data: comment addressed
5. Cohort definition: comment addressed