Reviewer's report

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

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Reviewer: Philip L De Jager

Reviewer's report:

The authors explore an important question: namely, prognostication of disease course in multiple sclerosis (MS). The strategy of using RNA profiling in this setting is not novel, as the authors acknowledge by referring to several similar studies that have been published recently. Overall, the strategy and methodology are reasonable. The outcome assessed is of interest since a tool that predicted the likelihood of early relapse could influence clinical decisions such as treatment selection. The authors have also assembled a dataset of reasonable size in which to do their modeling. However, there are some concerns about the heterogeneity of this population (see below). In addition, while this report describes a good effort of modeling the occurrence of relapse in MS using RNA data from untreated subjects, there is no effort to validate these models. The various computational approaches at validation within the dataset are appropriate and meaningful. However, models are inevitably overfitted to their source data, and therefore replication in an independent set of data is essential for this type of analysis to be interpretable.

Overall, the study is of modest interest without a replication arm. There are several concerns about the composition of the subject cohort that need to be addressed by the authors.

Major Compulsory revisions:
1. requires a validation effort.

Minor essential revisions:
1. Subjects: There are several issues of concern with the subjects included in the study. First, the authors fail to reference which diagnostic criteria they are using for MS. Second, while the pooling of clinically isolated demyelinating syndrome (CIS) cases and MS cases is certainly defensible, I am concerned by the relatively long disease course of the MS subjects relative to the CIS. MS is a very dynamic disease, and the immunologic state of subjects with a demyelinating disease can be quite different at the end of their first decade of the disease. It would be helpful for the authors to assess whether there are significant differences between CIS and MS subjects in terms of their RNA profiles. Also, the authors should assess whether there is a differential distribution of subjects in these classes across the categories defined by the time to relapse.
2. Subjects: Another concern relating to the subjects is the small proportion of
them that initiate treatment after sampling (~50%) when standard of care suggests that all MS subjects (and probably CIS subjects) should be treated. Thus, do these subjects represent a unusual segment of the MS population? i.e. did they refuse treatment or have a benign course? The lack of information on prior treatment of the MS patients compounds these concerns as to the subset of subjects being profiled. Treatment with agents such as cyclophosphamide could have long-lasting effects and should be reported. Clearly, addressing these issues is key to interpret the generalizability of the authors’ findings.

3. Subjects: The lack of MRI data further weakens the authors’ modeling. It is well known that only a small fraction of inflammatory events are clinically apparent as attacks with neurologically discrete symptoms. While it is certainly understandable to rely on a clinical outcome for this type of study given the cost of repeated imaging, the lack of such data only increases the need for a robust replication effort.

4. RNA data: The authors should report how many samples failed QC and what fraction of probes met their final QC thresholds.

5. Parsing subjects into cohorts: No rationale is presented for selecting “500 days” as the cut-off for the first group, which becomes the focus of the analysis.

Level of interest: An article of limited interest

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

I declare that I have no competing interests