Reviewer’s report

Title: Multiplex plasma protein profiling identifies novel markers to discriminate patients with adenocarcinoma of the lung

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Reviewer: Simon Spivack

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The manuscript reports considerable work on a set of well-known (plasma) analytes for cancer (CXCL17, CEACAM5, VEGR2, ERBB3, and others screened), using a highly sensitive Ab-DNA hybrid sensor to enhance technical sensitivity. The sample size is considerable n~343, including 144 mostly early stage adenocarcinoma's (LAC), 68 all "non-malignant/benign" disease, and additional colorectal mets and typical carcinoids as well. The training set analysis is well justified. Multivariate modelling is obligate, and performed after comparison of discriminant performance in several formalized comparisons, a virtue, before choosing the procedure called "TreeBagger". The authors do not over-reach the data presented, in thei conclusions.

My concerns in the main are:

a. The case-control comparison of interest is benign nodules vs. malignant nodules. The "benign" category however includes more than half inflammatory/non-nodule conditions (Table 2). But this is not the most important clinical discrimination to be made, so a subset analysis on early stage nodules versus benign nodules is warranted.

b. There is no separate validation set, as authors acknowledge, so overfit data, and lack of biological replication can be remedied by performing such a replication on a separate and independent set of subjects.

c. NSCLC as a whole, and Squamous cell carcinomas, should also be included for comparison...an LAC specific test would be less applicable in the clinical setting if it only compared adenocarcinomas, but not other malignant NSCLC tumors, which are considerable (minor).

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.
No

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I recommend additional statistical review

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