Reviewer's report

Title: Do serum biomarkers really measure breast cancer?

Version: 1 Date: 15 November 2008

Reviewer: Richard R Drake

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This study by Jesneck et al. is a comprehensive examination by ELISA (Luminex platform) of 98 serum proteins associated with inflammation and cancer in a control, benign and breast cancer serum cohort. Emphasis on comparing feature selection approaches for discriminating differences in expression levels of these proteins across each cohort is the core focus of the study. The comprehensive nature of the study is timely and long overdue for the serum protein biomarker field. The study population is appropriate overall, emphasizing benign and malignant pre-menopausal subjects from the same clinic prior to a biopsy procedure, balanced with normal samples from a screening population. Inclusion of a relatively large proportion of African American subjects is an additional strength. The careful assessment and comparisons of data feature selection methods is particularly relevant to this study and to follow up approaches by this group and others in the serum protein biomarker field. No major revisions are suggested, just the minor revisions indicated below.

Major Compulsory Revisions: None recommended

Minor Essential Revisions:

1. Because of the emphasis on the likelihood of detecting markers indicative of inflammation, a bit more clinical detail could be included in the subject demographic table or methods text for the malignant and benign groups, like whether DCIS subjects were included, what was the cancer stage representation in the malignant group, and what major classes of benign lesion types were represented?

2. A reference or additional descriptive sentences to the specific Luminex protocol used should be included in the methods section.

3. Regarding the panel of 98 serum proteins, a list in the supplemental material of what the abbreviations for each protein name listed in Table 2 and indicate the commercial or laboratory source of the antibodies used for the assays. For some proteins like haptoglobin and S100, there are many isoforms and therefore different antibody reagents available towards them.

4. In the Results, in the first section Classifier Performance, it could be stated more clearly that the data described is for all 98 serum proteins assayed, or a subset? This is not particularly clear in the description. In subsequent sections, it is clearer that subsets of selected proteins are being used.
5. The Figure 5 legend refers to “cooler dark red colors”; is this supposed to be dark blue? In the text for this figure, it states that the same protein features were selected as the best classifiers. What proteins correspond to the brighter color bands in this figure?

6. Was the same type of feature selection comparisons done for benign vs. cancer and normal vs. benign groups, as per Figures 5 and 6? Was anything informative learned from this? How did this compare to the normal vs cancer comparison described in the text?

Discretionary Revisions:

1. The authors may want to comment on what is the next step in assessing the utility (or lack thereof) of these types of serum markers for breast cancer diagnostics. These markers may not find any utility for early detection screening strategies, as could be one conclusion, but could the approach be applied for therapeutic monitoring and prognostic applications once a breast cancer diagnosis is made? Will continued optimization and comparison of feature selection approaches on this data set improve discrimination of benign vs. cancer, for example, or do other samples and/or different protein serum markers need to be assessed?

Level of interest: An article of outstanding merit and interest in its field

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