Reviewer’s report

Title: Do serum biomarkers really measure breast cancer?

Version: 1 Date: 6 November 2008

Reviewer: Emanuel Petricoin

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Major Essential Revisions:

1. Is the Luminex platform assessed for precision and accuracy for all 98 protein analytes? Were each of these analytes assessed in the linear dynamic range of the assay? How many technical and analytical replicates were performed? What is the inter and intra CV for each analyte using this approach for these specific markers. In general: how accurate and precise is any data collected? How were the antibodies validated for specificity?

2. It appears that none of the models were applied to an independent test set for cancers, benign, or controls. To understand and appreciate the context of the authors’ findings, this type of analysis should be performed. How well does the cancer vs control model hold up in blinded independent testing, for example. This could affect their conclusion since degradation in model performance in this setting would call into question the conclusions of the analyte fingerprint itself.

3. Why were these 98 protein chosen, and what was the criteria for their selection?

Minor Essential Revisions:

1. Page 5: Don’t most solid tumors cause changes in the surrounding tissue? Thus, most cancers will and are plagued by specificity issues and benign disease: breast is not unique in this regard! So, I don’t understand the emphasis placed here

2. Page 5: Specificity and sensitivity are defined by the INTENDED USE of the marker. For general population screening where a low-cost secondary screen is available, sensitivity needs to be 100% but specificity could be sacrificed. Vice versa for other indications, such as recurrence monitoring. This should be discussed.

3. Page 5: The authors should discriminate their study from others: Belucco et al used MS serum profiling for a large set of cancers, benign and controls and they screened through dozens to hundreds of unknown analytes. What these authors mean here, I think, is that they are looking at a predefined collection of known candidate markers, whereas the aforementioned study, as an example, was using MS profiling techniques of unidentified makers.

Level of interest: An article of importance in its field
Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:
I declare that I have no competing interests