Reviewer's report

Title: Low expression of a few genes indicates good prognosis in estrogen receptor positive breast cancer

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Reviewer: Reinhold Schäfer

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Dr. Buechler describes a three-gene signature that distinguishes estrogen receptor-positive breast cancers likely to metastasize from less malignant tumors. The good prognosis group is characterized by low expression of the genes encoding MKI67, CDC6 and SPAG5. The data is based on array-based mRNA expression profiling. In contrast to the somewhat confusing statement that "gene expression is measured with Affymetrix GeneChip technology", this study does not provide novel data. Rather, it is based on the re-evaluation of several studies done before. The primary data including the clinical parameters can only be assessed by referring to Gene Expression Omnibus. No independent validation of the gene expression changes such as protein analysis, immunohistochemistry etc. is provided.

The mathematics underlying the identification of the prognostically relevant genes appears to be sound (although this reviewer is not a mathematician or statistician). The number of tumors in each cohort is sufficiently high.

Major points of criticism:

1) The relevance of the factors characterizing the good prognosis group ought to be tested in an independent tumor cohort by independent methods such as immunohistochemistry (as suggested by the author in the last sentence of the discussion) to warrant publication in BMC Cancer. This would also add sufficient novelty to the data set. It is very likely that this will reveal tumor heterogeneity as well. I believe that a retrospective study including tumors with well documented follow-up will suffice.

2) The author should comment on the biological contribution of SPAG5 (sperm associated antigen 5) to breast cancer malignancy. I wonder if this gene (or probe) can be replaced in the gene set by a factor that is better characterized functionally.

Minor questions:

3) The discussion about Ki-67 is lengthy. Ki-67 is a well characterized marker for proliferative cells, but does not indicate metastasis.

4) Chemoresistance is known to be caused by multiple factors. Therefore, it is not clear if the two factors discussed (GGI and TOP2A) will solely determine
chemoresistance or sensitivity.

5) What is the evidence for differential splicing of the MKI67 gene?

**Level of interest:** An article of importance 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.