Reviewer's report

Title: ESR1 Gene Promoter Region Methylation in free circulating DNA and its Correlation with Estrogen Receptor Protein Expression in Tumor Tissue in Breast Cancer Patients

Version: 3
Date: 18 October 2013
Reviewer: Luca Magnani

Reviewer's report:

This reviewer is unable to make a decision considering that the author did not address most of the issues raised during the initial submission.

Major compulsory revision

1- Reviewing manuscripts without a proper rebuttal letter really complicate the life of reviewers, at least in my opinion. It was very hard to see which kind of changes were done to the manuscript.

2- What is the status of ESR1 promoter methylation in the primary? Can you use the same PCR method used in the fcDNA? Correlation with ERa status is not sufficient. Interest would be elevated if the authors demonstrated correlation between DNA methylation status between primary and fcDNA.

3- What about tumour heterogeneity? What was the % of ERa positive cells in the primary? Could it be that fcDNA comes from the ER- compartment of a ER+ tumour?

4- The final conclusion “The results are promising in terms of early diagnosis, monitoring of response to treatment as well as a prognostic factor predictive of response” Page 14 is a gross overstatement not supported by any data. The
author now has changed it to” The results are promising in terms of breast cancer prognosis as well as a factor predictive of response to hormonal treatment”. This reviewer fail to see the difference.

5-Although the manuscript has been improved overall, there are still some paragraph where the English level is is not acceptable.

**Level of interest:** An article of limited interest

**Quality of written English:** Not suitable for publication unless extensively edited

**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