Reviewer's report

**Title:** Prognostic relevance of Wnt-inhibitory factor-1 (WIF1) and Dickkopf-3 (DKK3) promoter methylation in human breast cancer

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**Reviewer:** Mario Fraga

Reviewer's report:

Veeck and colleagues report the possible use of DKK3 promoter hypermethylation as a prognostic marker in breast cancer. The results could be interesting and they could have a direct clinical application. However, there are several points that the authors must address before they can publish this manuscript. As the authors admit, aberrant promoter hypermethylation of DKK-3 and WIF1 has been previously published and thus, the real contribution of this work is the finding that DKK3 promoter hypermethylation is a prognostic marker in breast cancer. A key issue is that the authors also found a positive correlation between DKK3 methylation and age and thus, it could be possible that the real association is between age of the patient and prognostic. An interesting aspect to explore here is why DKK3 is more prompt to be methylated in oldest breast cancer patients.

At the Discussion section, the authors state that Dickkopf-3 is an antagonist of the Wnt pathway that “more likely inhibits a non-canonical branch of the Wnt pathway by a so far unidentified mechanisms”. Actually this is still a hotly disputed issue. Up to now, Dickkopf-3 has been demonstrated to play a Wnt inhibitor role just in lung cancer (Yue et al., 2008. Carcinogenesis 29: 84-92). It has also been shown that Dkk-3 does not affect Wnt/β-catenin signaling in prostate cancer cells (Kawano et al., 2006. Oncogene 25: 6528–6537). Whether DKK-3 is or not a Wnt inhibitor in breast tumours is something that needs to be further investigated. Moreover, it has not been published yet that WIF1 exerts a Wnt pathway inhibitor role of in breast cancer. So, inactivation of both genes does not necessarily involve an aberrant activation of the Wnt pathway in breast cancer.

The authors show that DKK-3 and WIF1 promoter methylation in patients are strongly correlated and that, at the same time, DKK3 alone is a good marker of prognostic. Thus, it must be explained and discussed why WIF1 is not.

MSP results should be validated in some of the samples using bisulfite sequencing or pyrosequencing.

It would be interesting to provide expression data in order to assess the real biological role of DKK-3 and WIF1 hypermethylation in breast cancer.

**Level of interest:** An article whose findings are important to those with closely...
related research interests

**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