Reviewer’s report

Title: GENESIS: a French national resource to study the missing heritability of breast cancer

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Reviewer: Tomas Kirchhoff

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The manuscript describes an important familial breast cancer ascertainment resource, GENESIS, generated for the purpose of mapping the “missing” hereditability to breast cancer. This is a thoughtful effort that collects biological specimens as well as genetic, environmental and histological data in order to investigate additional genetic and environmental risk to breast cancer. Despite the solid description of this important resource, there are several potential concerns that should be addressed in the manuscript.

1. The study seems to be less powered on "classically high-risk families" (3 or more affecteds), which currently represent only about 30% of GENESIS. Therefore, assumption of a relative risk of 3 in power calculations on p.10 is overestimated, as such effect would likely only be relevant to “3 or more” type of families. While, as authors conclude, with longer follow-up this fraction may slightly increase, the power estimation should be re-written to reflect on this.

2. Limiting the selection criteria to BRCA1/2 mutation screening undermines another important “high-to-moderate” susceptibility genes that became clinically actionable since the study has launched, such as RAD51, PALB2, ATM, etc, some cumulatively explaining additional meaningful fraction of breast cancer risk. Some of these genes are already included in clinical panels for routine testing of high-risk breast cancer patients. It would be beneficial if the manuscript could provide some plan on how these other genes would be incorporated in testing of already ascertained patients (and going forward for new patients) and how will this modify exclusion criteria.

3. The strength of GENESIS is the incorporation of tumor histologies, as the expected breast cancer heterogeneity in this context is a key issue. However, it is not clear which data were (or will be) collected and what tests were (or will be) performed on the biopsies. If some tumor data were already analyzed, it would be useful to provide a summary table on the histological subtypes of collected specimens to-date with details on the methods used in these analyses. In addition, it is not clear if the study considers a plan on systematic collection of tumor specimens for other complementing molecular analysis in the future (e.g. mutations profiling, RNA-seq, etc).

4. Collection of blood specimens only from siblings raises a concern whether the study will be sensitive enough for potential co-segregation analysis on specimens
of additional affected and unaffected first-degree relatives (parents, offspring), which do not seem to be banked as part of this study. This seems to be a limitation as the absence of extended families had hampered similar discovery efforts in the past. This should be commented.

5. Does the study plan for collecting prospective follow-up information of ascertained index cases (and their affected relatives)? This would be a great opportunity to investigate, in a familial setting, other risk factors of breast cancer outcomes (e.g. genetic risk for metastatic progression, recurrence, etc.).

6. It would be beneficial, if the authors could comment and provide some plan on whether this resource would be available, in a collaborative setting, for utilization by other investigators, outside of France.

7. The manuscript should be extensively checked for the typo-errors.

**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