Reviewer’s report

Title: Estrogen independent gene expression defines clinically relevant subgroups of estrogen receptor positive breast cancer

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Reviewer: Ingrid Hedenfalk

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In an attempt to identify estrogen independent transcriptional differences among ER positive breast cancers, the authors used publicly available gene expression profiling data from post-menopausal women after treatment with letrozole, and identified six subgroups based on the expression of genes not affected by the treatment. Findings were validated using two additional datasets. The manuscript is well-written and uses an interesting approach to address the heterogeneity among ER positive breast cancers. A few minor points need to be addressed for the sake of clarity.

Minor Essential Revisions

1. How was ER status determined in the three cohorts? Cut-offs used?
2. Were these differences in extent or choice of endocrine treatment among the cohorts?

Discretionary Revisions

3. It would be interesting to know which functional categories the ER independent genes fall into. A gene ontology analysis could be performed to shed more light on the biological differences between the subgroups, especially given that they appear to be independent of the intrinsic subtypes.
4. While the growth reduction specifically in subgroup #1 upon etoposide treatment is interesting (Fig 4), the broad statement regarding the clinical significance of the identified subgroups remains to be confirmed. The authors should consider rephrasing this section.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests.