Reviewer's report

Title: Cost-effectiveness of a 21-gene recurrence score assay versus Canadian clinical practice in women with early-stage estrogen- or progesterone-receptor-positive, axillary lymph-node negative breast cancer.

Version: 1 Date: 10 January 2012

Reviewer: Doug Coyle

Reviewer's report:

1. Is the question posed by the authors well defined? Yes
2. Are the methods appropriate and well described? No. There are limitations as described below and some of the methodology is not transparent.
3. Are the data sound? No, the limitations to the clinical modeling requires reanalysis.
4. Does the manuscript adhere to the relevant standards for reporting and data deposition? Yes
5. Are the discussion and conclusions well balanced and adequately supported by the data? Yes
6. Are limitations of the work clearly stated? No – given the limitations described below
7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished? Yes
8. Do the title and abstract accurately convey what has been found? Yes
9. Is the writing acceptable? Yes

Specific Comments
This is a highly pertinent study which when published would be of high relevance. There are specific features of the study which are of excellent quality. However, current limitations relating to the clinical modelling requires a major revision. Major compulsory revisions
1. When evaluating a test the usual focus is on the sensitivity and specificity of the test. Thus, in this context the test (or CCP classification) is evaluated based on the ability to assign chemotherapy to the correct patients. The proportion of patients who are high, intermediate and low risk will be the same in both tests – the issue is that there will be differential rates of misclassification between these tests and therefore different degrees of “inappropriate” use of chemotherapy. The current standard does not take this approach. Rather it takes two separate cohorts of patients, one using the risk classification and the other using the assay and determines the patients risk and use of chemotherapy specific to these cohorts. The major concern is, are the cohorts truly comparable as any difference between these will lead to bias in the estimates of cost effectiveness.

An alternate approach would be to take the data from B-14 and B-20 and compare the risk stratification if we had applied the CCP classification as well as the RS assay. The analysis could then focus on the use of chemotherapy within these cohorts as defined by the RS assay. Survival curves could then be applied stratified by risk and chemotherapy use from the B-14 and B-20 trials. This would allow the two strategies to be compared using the same dataset.

2. In table 1, the proportion of patients at high, intermediate and low risk should be parameterized with a Dirichlet distribution.

3. The scenarios in Table 3 of the appendix are hard to follow and need to be explained better.

Other comments
Costs and utilities are appropriate.

**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:**

No conflicts