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: 8 March 2012

Reviewer: Sonal Gandhi

Reviewer's report:

Major Compulsory Revisions

1. page 4 - re: intermediate RS patients. the statement that it is unknown if patients will benefit from chemo is not entirely correct. From the original Paik 2006 publication, intermediate relapse score patients did not have a substantial chemotherapy benefit, from the wide CI range could not exclude a meaningful benefit. In addition, given the RS is a continuous variable, there is no specific RS at which chemotherapy benefit can be considered "none" example: "The magnitude of chemotherapy benefit appeared to increase continuously as the RS increased. A clear cutoff point for RS, below which there is no demonstrable benefit from chemotherapy, cannot be accurately defined."

2. Page 5-re: the use of “medium”…should be consistent and refer to intermediate score as intermediate

3. Page 5: re: the comment that the test is not publically funded in any Canadian province. THIS IS NOT TRUE!! It has been covered by the MOHLTC in Ontario since late 2010. In addition, other provinces are moving towards some types of coverage. Authors should read and include updated pub by J Ragaz (2010-2011 Report card):
The comment that the RS is not used by many oncologists in Ontario at least, is not true anymore.

4. Page 6: there should be more background on the actual findings of other such economic analysis, and why they are considered limited or inadequate (esp the Tsoi study, which was also done with Canadian perspective). The differences from that study should be highlighted. It would be useful to compare the ICERs (which were very similar, ie 63 000/Qaly in the Tsoi study). In addition, there has been in depth analysis pertaining to the Ontario setting (which helped fuel the coverage for the test), including another cost-utility analysis (although modeled was based on the Tsoi study.) See:

Medical Advisory Secretariat. Gene expression profiling for guiding adjuvant chemotherapy decisions in women with early breast cancer: an evidence-based and economic analysis. Ont Health Technol Assess Ser [Internet]. 2010 December [cited YYYY MM DD]; 10(23) 1-57. Available from:
5. Page 6: the concept of “CCP” needs to be better defined. Oncologists in Canada do not only use one set of guidelines to help direct practice. It should be mentioned that there are several models or methods of determining risk, including some guidelines (there are papers on the use of oncology guidelines in Canada), and the Adjuvant online program should be mentioned, especially as it is a specific modeling system (also based on patient data estimating benefits from chemo and endocrine therapy) and is the reference point for the Tsoi analysis (and there are ongoing studies on decision making with oncoype dx, vs AOL).

6. Page 6: it should be highlighted that these are also HER-2 negative patients.

7. Page 6: is this truly a Canadian perspective…all the data and costs are from Manitoba. I think more accurately this is a Manitoba perspective. If you can provide data showing treatment, outcomes, and costs are similar across provinces, then maybe can say it can be extrapolated to Canadian perspective. Costs and willingness to pay may be different across provinces, even if outcomes/treatments are similar.

8. Page 6: explain time spent in each disease state (it is shown in table as one month. Is that reasonable? Time spent in relapse more often is closer to 6 months).

9. Page 8: show data on chemotherapy use being the same in two time periods. The introduction of third generation regimens was during this time so reader should be convinced.

10. Page 10: comment should be made that these chemo regimes are older regimes still. What about FEC-D, ddAC-T, TC.. many oncologists use these (over TAC) in many provinces (at least in Ontario and BC). This is why provincial level data would be imperative if this is going to be called a “Canadian” perspective. Especially as data on specific chemo regimes was not found, you must clarify explicitly why these regimes were chosen (over others).


12. Page 15: describe more clearly what “limitations” were noted in Tsoi paper.

13. Page 16: limitations should include the types of chemo considered (does not take into account some other commonly used regimens.) also this data likely captures some high risk patients based on HER-2 unknown status that can impact on the data. Also more applicable to Manitoba setting given differences in provinces that can affect relevant data and apply to sensitivity analyses.

14. Figure 1: more accurately should state vs Canadian clinical practice (based on…what recommendations?)

15. Table 2: aromataZe inhibitors (spelling).
Minor Essential Revisions
1. Page 4 – need an extra “space” after most of the periods.
2. Pg 4. Consider changing “…adjuvant chemotherapy may be considered when
the benefits of treatment outweigh toxicities of therapy” (instead of “reduced
recurrence”).
3. Pg 4. Re: “…respond well from endocrine therapy” would be more accurate to
say “have good outcomes from endocrine therapy alone.” The concept of
“response” applies more so to metastatic disease where a response to therapy
can be actually measured (tumour shrinkage, etc). In adjuvant therapy, benefits
from therapy are more accurately “measured” as improvements in outcomes
(survival, DFS). On that vein, it may be useful to outline that the outcomes being
measured can be relapse or survival, but the focus on this analysis (given the
assay) is on relapse (particularly distant relapse).
4. Page 5: is the comment on the significance in the Asian population needed?
5. Page 5: response to adjuvant therapy should be, as above, benefit from
adjuvant therapy
6. Page 7: specific why pre vs post menopausal distinction was made (ie:
differences in outcomes/treatment modalities, cite some data.)
7. Extrapolate under “Costs” the modalities of treatment that were considered
(Chemo, radiation, etc.)
8. Page 12...highlight HER-2 negative or unknown given the time frame used
(2002)
9. Page 13: why was threshold of 100,000/QALY used as willingness to pay
threshold. Explain.

Discretionary Revisions

Level of interest: An article of importance in its field

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’