Author's response to reviews

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.

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Author's response to reviews: see over
To the Reviewers,

We would like to thank the reviewers for reading and commenting on our submission to BMC Cancer entitled "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". We are pleased to resubmit a revised version of our manuscript after considering all reviewers’ comments. We have provided a point by point summary of the changes that we considered based on the reviewers comments:

Reviewer 1:

1. In the first comment the reviewer raises 3 main points. We address them separately.

i. “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 different rates of misclassification between these tests and therefore different degrees of “inappropriate” use of chemotherapy. The current standard does not take this approach.”

We agree with the reviewer that this would be the standard approach when comparing two diagnostic tests for a certain condition (e.g., two tests for HCV infection). A typical decision-analytic model would begin with a decision node about which test to use, followed by a chance node for “true state of nature” (HCV+ vs. HCV-), followed by a chance node for test result (“+” or “-”), followed by additional branches and Markov models, as required by the specific situation. (In the preceding description we employed the common modeling trick of putting the true state of nature before the test result.) The difference between this common setup and the problem that we are investigating is that in our problem the true state of nature, “being high-risk”, is not well defined. Furthermore, there is no gold standard for identifying people who are high risk The RS-assay provides a useful proxy for this construct. Thus, we treat the RS-assay as the gold standard, and assume that the RS-assay has 100% sensitivity and specificity for predicting itself.

ii. “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.”

We agree that it would be useful to have data on the proportion of the Canadian population falling into each of the 3 risk groups as defined by the RS-assay. However, this information is not available. In the absence of this information our best estimates are the proportions observed in the retrospective analyses of B-14 and B-20 trials. We varied these proportions in sensitivity analysis to account for possible differences between the Canadian and US populations but this did not substantially influence our results.

Note that we had enough patient, clinical and treatment data from the Manitoba Cancer Registry to make our study cohort comparable to the populations targeted in B-14 and B-20 (hormone...
receptor positive, lymph node negative, and early stage breast cancer (stage I and II)). In addition, we have provided all tumour and patient characteristics of our cohort in table 3 to allow readers to determine comparability of our cohort with B-14 and B-20 trials.

iii. “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.”

Applying the CCP classification on patients from B-14 and B-20 may not be possible. CCP classification requires us to have individual patient information on tumour size, grade differentiation, vascular invasion and age. We do not have access to full data from these trials, nor do we know if all of the variables that are relevant to CCP classification were even collected as part of the trials. In addition, if we were to proceed with this approach, chemotherapy assignment within each risk strata by the CCP would need to be based on assumptions (e.g. all high risk patients would receive chemotherapy in addition to chemotherapy and all low risk patients would receive hormone therapy alone). We are concerned that this may not reflect real world Canadian clinical practice since, within each CCP risk group, some women receive chemotherapy and some do not. In fact, we have highlighted in our analysis that in Manitoba not all high-risk patients by CCP have received chemotherapy and not all low risk patients by CCP would forgo chemotherapy.

To summarize: We do not use the suggested approach for evaluating diagnostic tests because the underlying true states of nature (high, medium and low risk of recurrence) are not well defined. Instead, we treat the scores from the RS-assay as the true state. We do not have data on the distribution across risk group in Canada for the RS-assay so we assume that the distributions observed in the B14 and B20 trials are the same as would be observed in Canada. We vary this distribution in sensitivity analysis. We are not able to re-analyze the B14 and B20 data as suggested.

2. Reviewer’s comment: “In table 1, the proportion of patients at high, intermediate and low risk should be parameterized with a Dirichlet distribution.”

Response to reviewer: We have made this change.

3. The reviewer’s comment: The scenarios in Table 3 of the appendix are hard to follow and need to be explained better.

Response to reviewer: We have more clearly named the tables and the columns, and we have provided a footnote to explain the interpretation.
Reviewer 2:

Major Compulsory Revisions:

1. Reviewer’s comment: 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."

Response to reviewer: We agree with the reviewer’s explanation that the recurrence score is a continuous variable and there is no specific recurrence score at which chemotherapy benefit can be considered "none". We have revised our statement as follows:

“Women with a score between 18 and 30 have an intermediate risk and do not appear to have a large benefit from chemotherapy but the uncertainty in the estimate cannot exclude a clinically important benefit”.

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

Response to reviewer: we have fixed this.

3. Reviewer’s comment: 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): http://www.canceradvocacy.ca/reportcard/2011/The%2021-Gene%20Assay%20Canadas%20Uneven%The comment that the RS is not used by many oncologists in Ontario at least, is not true anymore.

Response to reviewer: we are aware that the test is covered for patients in Ontario by the “Out-of Country Health Services” branch of the health ministry, if requested by an oncologist and approved in advance. In addition, we are also aware that other provinces are moving towards some types of coverage such as British Colombia which initiated a registration study for the 21-gene assay in Vancouver clinic and Quebec were Quebec’s RAMQ has started to fund the test for an increasing number of selectively chosen patients for testing by their oncologist. However, this type of coverage in Canada is limited for selective patients and may not represent a consistent funding program for the assay. The article by Ragaz, as mentioned by the reviewer, has highlighted the massive under-utilization of this predictive tool in Canada. For instance, Ragaz highlighted that out of 22,000 patients diagnosed with breast cancer each year in Canada, at least 10,000 women would be eligible for the 21 gene assay. However, in 2010, only 10 per cent of eligible women received the test. We think this underutilization of the assay in Canada is likely due to inconsistent reimbursement programs across Canadian provinces and thus clinical
practice regarding adjuvant chemotherapy treatment recommendations by most Canadian oncologists has not been influenced by the RS-assay. We revised our statement on page 5 as follows: “public coverage of the 21-gene assay is limited and inconsistent across Canada. It is available in Ontario through “out-of-country health services” which requires a request from an oncologist and pre-approval [1-2]. In 2010 the Ontario Health Technology Advisory Committee (OHTAC) recommended that the assay be made available “within the context of a field evaluation” [3]. It is also available in a limited fashion in British Columbia and Quebec [2]. The test is not widely used and in 2010 less than 1000 patients received the test across Canada [2]”.

4. Reviewer’s comment: 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: http://www.health.gov.on.ca/english/providers/program/mas/tech/reviews/pdf/ge_20101213.pdf and: OHTAC: http://www.health.gov.on.ca/english/providers/program/ohtac/tech/recommend/rec_gep_20101213.

Response to reviewer: we have elaborated on this in the discussion section on page 14-15. In addition, we have also highlighted the differences between our study and the Tsoi study which was done from the Canadian perspective.

5. Reviewer’s comment: 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 oncotype dx, vs AOL).

Response to reviewer: we have added the following text on page 4 “A validated software program Adjuvant!Online (AOL) has been developed that projects outcomes at 10 years to assist oncologists in adjuvant decision-making process. However, AOL is also based on histopathologic measures”.

6. Reviewer’s comment: Page 6: it should be highlighted that these are also HER-2 negative patients.
Response to reviewer: we added the following text on page 8 in order to clarify this issue: “Although data on human epidermal growth factor receptor 2 (HER2) status were not collected by the registry during this time frame, the majority of these women are likely HER2 negative since women with HER2 positive are only found in approximately 10% to 15% of endocrine positive breast cancers such as those in our study population”.

7. Reviewer’s comments: 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.

Response to reviewer: we added the following sentence on page 17 to recognize this limitation “Although several studies have found that clinical practice patterns and therapies employed in the selected time periods in Manitoba reflect practice in other jurisdictions in Canada [4-6], differences in clinical practice for women with ER+/PR+ LN- ESBC and its associated costs across Canadian provinces may still exist”. Regarding the reviewer’s concern that “willingness to pay may be different across provinces”, we would like to clarify that we have provided the cost effectiveness acceptability curves” in figure 2 to account for any possible differences in willingness to pay.

8. Reviewer’s comment: 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).

Response to reviewer: In our model, the time spent in each disease state depends on transition probabilities out of the state. The information shown in table 1 under the column “duration” is to explain treatment administration and cost application over time in each health state. For instance, a duration of “One Time” for the cost of surgery indicates that this is a one-time expense, and a duration of “48 months” for tamoxifen indicates that patients would receive tamoxifen for up to 48 months.

9. The reviewer’s comment: 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.

Response to reviewer: We have included a new table “Table 2” to show the comparison between the 2000-2002 and 2003-2005 time periods.

10. Reviewer’s comment: page 10: comment should be made that these chemo regimes are older regimens 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 regimens was not found, you must clarify explicitly why these regimens were chosen (over others).

Response to reviewer: We first clarify that our choice of chemotherapy regimens was based on what was recommended in Canada from 2000 to 2002, as mentioned on page
10. To highlight the reviewer’s concern regarding the possible differences between the regimens used in this study compared to current regimens, we added the following sentence on page 17 to recognize this limitation “outcomes of therapies given in the 2000-2002 population may not necessarily reflect the possible benefits of other types of adjuvant therapies or dosing schedules used in current practice”.


Response to reviewer: We have added the following sentence on p. 17 to recognize this limitation: “Our analysis did not account for growing data on long term side effects of primary adjuvant chemotherapy such as cardiomyopathy, neuropathy, leukemia [7] “.

12. Reviewer’s comment: page 15: describe more clearly what “limitations” were noted in Tsoi paper.

Response to reviewer: We added the following text on page 15 to address this issue “and modeling the current experience of ER+/ PR+ LN- ESBC population was not based on Canadian data and real world clinical practice”.

13. Reviewer’s comment: 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.

Response to reviewer: we have addressed these concerns previously in our responses to points 6, 7 and 10.

14. Reviewer’s comment: figure 1: more accurately should state vs Canadian clinical practice (based on…what recommendations?)

Response to reviewer: We added the following sentence in the footnote of figure 1 “The risk classification criteria in the Canadian clinical practice arm was based on the Canadian clinical practice guidelines for adjuvant systemic therapy for women with node-negative breast cancer”.

15. Reviewer's comment: Table 2: aromataZe inhibitors (spelling).

Response to reviewer: we have fixed this.

Minor Essential Revisions

1. Reviewer’s comment: page 4 – need an extra “space” after most of the periods.

Response to reviewer: we have fixed this.
2. Reviewer’s comment: pg 4. Consider changing “…adjuvant chemotherapy may be considered when the benefits of treatment outweigh toxicities of therapy” (instead of “reduced recurrence”).

   Response to reviewer: we have fixed this.

3. Reviewer’s comment: 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).

   Response to reviewer: we have fixed this.

4. Reviewer’s comment: page 5: is the comment on the significance in the Asian population needed?

   Response to reviewer: we thought to be specific as for which population the clinical significance of the RS-assay has been reported.

5. Reviewer’s comment: page 5: response to adjuvant therapy should be, as above, benefit from adjuvant therapy

   Response to reviewer: we have fixed this.

6. Reviewer’s comment: page 7: specific why pre vs post menopausal distinction was made (ie: differences in outcomes/treatment modalities, cite some data.)

   Response to reviewer: we originally included table 2 in order to address this issue. We also discussed this issue in the discussion section page 15. We cite the Canadian guidelines and added the following sentence “as recommended by Canadian guidelines” on page 15 to highlight why pre vs. post-menopausal distinction is necessary.

7. Reviewer’s comment: extrapolate under “Costs” the modalities of treatment that were considered (Chemo, radiation, etc.).

   Response to reviewer: A detailed description of all costs is included in the footnote of table 1.

8. Reviewer’s comment: page 12…highlight HER-2 negative or unknown given the time frame used (2002).

   Response to reviewer: we have addressed this in point 6.
9. Reviewer’s comment: page 13: why was threshold of 100,000/QALY used as willingness to pay threshold. Explain.

Response to reviewer: we have originally explained this on page 14.

Discretionary Revisions


Response to reviewer: we thought to add “incremental” before “cost and effect”.


References: