Author's response to reviews

Title: Cost-effectiveness of MRI compared to mammography for breast cancer screening in a high risk population

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To

Dr. Melissa Norton,

Editor-in-Chief, The BMC-series journals

Dear Dr Norton,

Thank you for considering our MS: 1543760476185532 titled “Cost-Effectiveness of MRI Compared to Mammography for Breast Cancer Screening in a High Risk Population” for publication in *BMC Health Services Research* journal. Also thank you for giving us the opportunity to revise and resubmit the manuscript and address the reviewers’ comments. We have made substantial changes to the manuscript based on the useful comments by the reviewers.

Below is the point-by-point response to the reviewers’ comments. Once again, thank you for your time and consideration. We hope that you find this second revision of the manuscript acceptable for publication in the *BMC Health Services Research* journal. Please contact me at (404) 778-5554 or at Christopher.Flowers@emoryhealthcare.org if you have any questions.

Regards,

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Response to comments raised by Reviewer 1

1. The evaluation of Cost-effectiveness of MRI compared to mammography for screening women at high risk for breast cancer is of great interest, as this procedure is now more and more adopted in many western countries. Study methodology and analysis is accurate and the study gives interesting information to evaluate the impact and cost-effectiveness of screening high risk women with MRI.

We would like to thank the reviewer for taking time to read our manuscript and provide this valuable feedback. We agree that assessing the cost-effectiveness of screening high risk populations of women with various screening methodologies is of considerable importance.

2. Nevertheless the AA should better explain the assumptions adopted in order to calculate the QALYs. We wonder why, given that we assume that mammography screening decline mortality from breast cancer by 7-23% and that mammography has a sensitivity of 25-36% compared to MRI sensitivity of 77-91%, the model estimates that mammography and MRI provided 23.39 and 23.57 QALYs respectively. Why the higher sensitivity of MRI do not provide benefit in term of further mortality reduction, following further advance of diagnosis. Are the benefit completely compensated by the quality of Life adjustment because of false positives cases produced by mammography and by discomfort of MRI examinations in women without a diagnosis of breast cancer?

The increased sensitivity of MRI does identify a limited number of women with node negative breast cancer who would not be identified by mammography. However, this benefit is offset by the increased number of false positives from MRI screening that leads to a temporary decrement in quality of life as a result of increased numbers of biopsies. Even in this high risk population mammography remains an adequate screening modality that must be improved upon by a more sensitive testing modality without adjustments for quality of life due to false positive results.

3. Would be interesting to know the results of cost-effectiveness analysis without adjustment for quality of life.

The authors agree with the reviewer’s comment. These are now included in the manuscript. When adjustments for quality of life were ignored MRI provided 23.9 life years compared to 23.8 life years for mammography producing and ICER of $144,045/life year. A sentence describing this finding was added to the first paragraph of the results section (page 9, ¶ 2).
4. The threshold of <$100,000/QALY is reported in Results (page 9 row 15) but is never used in the following discussion (to be checked)

The $100,000/QALY threshold is now included in our sensitivity analyses, net benefit analyses (page 10, ¶ 1), and addressed in the discussion section.
Response to comments raised by Reviewer 2

1. The use of “average” cost-effectiveness ratios can be misleading and should be removed from both the Abstract and the main body of the text. This is particularly the case because the comparator used is $0 cost and 0 QALY life expectancy. Such a comparator does not correspond to the status quo nor does it correspond to no treatment.

We do appreciate the reviewer’s comment. The revised version reports only the incremental cost effectiveness ratio. The term average cost-effectiveness has been removed in all instances.

2. The authors report the “net benefit” of MRI in the abstract and then whether MRI is cost-effective at a $50,000 QALY threshold. It would seem more appropriate to report net health benefit? Reporting the Net health benefit and its 95% CI for a given WTP or thresholds will provide a more accurate and standard representation of the uncertainty analysis performed. This also impacts how the conclusions of the abstract are reported.

We agree with the reviewer’s comment and report the net health benefit and its 95%CI in our revised version (page 10, ¶ 1).

3. Please detail how the model developed in this analysis differs from the breast models developed by others previously such as those from the CISNET collaboration. Please discuss the features of this model that make it more appropriate than using a previous model and specifically how the output of the model developed for this analysis was compared and validated against data not used in its construction (i.e., how does its out compare to SEER to observation or clinical trial data?).

The models developed by the CISNET collaboration were extensive in their analysis. We include discussion regarding the differences and its features in the revised version.

4. Please note the discount rate used in the methods section (page 7) and also note whether it was applied to costs and to quality adjusted life expectancy.

Both costs and QALYs were events that occurred based upon the screening strategy applied within that year and were not directly affected by the prior year’s screening. Neither costs nor outcomes were discounted in the model since costs and benefits all occurred within the year that resources were utilized and each strategy required the recurring costs of screening. A sentence was added to the methods section to clarify this point (page 8, ¶ 1).

5. While the paper states that the published literature was used to parameterize the model, neither the body of the paper nor Table 1 provides citations for sources of the model parameters. Are any of the probabilities mentioned (death from other causes for example) age-specific? Complete citations should be made
In aggregate, the model parameters address the probabilities of events (e.g., development of node positive breast cancer) for average high-risk women in our population of interest. Thus, these parameters account for age-specific risks for this population. The revised manuscript provides the citations for sources of the model parameters in Table 1.

6. The utilities used in the model are not specifically cited. This should be corrected in the body of the paper. Particular attention should be paid to not only citing but also explaining the utility value (0.89) for the temporary state of “False Positive” – is this due to factors other than anxiety? There are methodological discussions of temporary health states and their elicitation which may be useful to cite here.

Citations for utilities are now provided in Table 3. The false positive temporary health is due to the negative consequences of having a breast biopsy as well as the anxiety associated with a positive test result. These include pain, disability, and altered body view, among other consequences. Since this health state is temporary the overall adjustment in quality of life for the cycle when this occurs is minimal. For example, a woman who returns to screening following a false positive test would experience 0.982 QALYs during that year.

7. In reporting the results of the probabilistic sensitivity analysis, the following sentence appears problematic: “From the probabilistic sensitivity analysis, the ICER for the MRI was $151,890/QALY (95% confidence range: $130,233/QALY to $456,633/QALY).” From Figure 3, MRI sometimes costs more and provides less benefit which means that it is dominated (Quadrant II) which changes the interpretation of its incremental cost-effectiveness ratio. Computing an incremental cost-effectiveness ratio only for those times when a strategy is non-dominated can introduce bias. It would also be helpful for the authors to comment on the orientation of the confidence oval – what are the main factors that cause it to go from the upper left to the lower right (when MRI is less effective it is more costly)?

We agree with the reviewer’s comment and have deleted the above mentioned sentence from the results section. A discussion of the net health benefits of MRI screening and a net benefits acceptability curve have been added (page 10, ¶ 1).

8. Table 1 notes probabilities that exceed 1.0 (for example, True Negative and Live Node Negative). It is unclear how to properly interpret a probability >1.0 and hence it is unclear what this means for the analysis and its results. Is this a function of the normal distributions imposed for probabilistic sensitivity analysis? If so, beta distributions may be more appropriate as they bound the probability between 0 and 1.
We appreciate the reviewer’s comment and agree. We obtained probability ranges by constructing 95% CI for proportions derived from the literature using normal approximations to the binomial distribution. This was based on the paper by Hanley JA, Lippman-Hand A: If nothing goes wrong, is everything all right? Interpreting zero numerators. JAMA 1983, 249:1743-1745. The listed probabilities in the table were errors. These have been corrected in the current version of the manuscript.

9. It is concerning that False Positive (0.89) has a utility that is lower than Breast Cancer (0.95). Please provide the citation for how this value is arrived at and also please comment in the text about how sensitive results are to assumptions about utility of false positive. It would appear that this is likely an uncertain and highly influential parameter.

The utility of false positive is from the paper Haes JCJMd, Koning HJd, Oortmarssen GJv, Agt HMEv, Bruyn AEd, Maas PJvd: The impact of a breast cancer screening programme on quality-adjusted life-years. International Journal of Cancer 1991, 49:538-544. And that for breast cancer is from the paper van Roosmalen MS, Verhoef LCG, Stalmeier PFM, Hoogerbrugge N, van Daal WAJ: Decision Analysis of Prophylactic Surgery or Screening for BRCA1 Mutation Carriers: A More Prominent Role For Oophorectomy. J Clin Oncol 2002, 20:2092-2100. Please see the discussion of the temporary health state above. Because experiencing a false positive test result produces a temporary decrement in quality of life, a woman who returns to screening following a false positive test would experience 0.982 QALYs during that year. This exceeds the QALYs experienced by a woman with breast cancer during a one year period.

10. The model schematic appears incomplete as there are utilities for health states not shown in the model schematic — (utilities for health states such as False Positive and False Negative Node Positive). Furthermore, unilateral and bilateral mastectomies are mentioned; does the model then track the remaining breast for further cancer? Please provide a more detailed model description, list of assumptions, and a diagram that shows all transitions and states

We appreciate the reviewer’s comments. Accordingly, we have modified Figure 1. The model does track for the remaining breast. In such cases, the cost is adjusted to that of unilateral screening. However, the probabilities of cancer detection remain the same.

11. It appears from Table 1 that the probability of having a positive result is fixed in the model. Probability of positivity is not a test characteristic (like sensitivity and specificity) that does not depend on prevalence of underlying disease. Since the tests are used repeatedly on a population that develops cancer and dies, the remaining population may have a lower prevalence of disease and thus the probability of positivity may be lower over time. Please comment on this both to clarify what is meant by probability of positivity and how the tests are operationalized in the model.

**Minor Essential Revisions**

1. Please provide a citation for the following sentence: “Medicare reimbursement data for hospital, physician, and laboratory services according to the methodology described in recently published work.” (page 8)

The revised version now provides citation for the sentence.

2. Please comment on whether for the probabilistic sensitivity analysis, any correlation structure was assumed for the normal distributions. For example, when sensitivities are higher are specificities lower in studies of these screening technologies? If so, should such correlation be reflected in the analysis? This could be noted as a limitation in the discussion section if data on the relationship between uncertainty in parameters do not exist.

One of the limitations of our paper is that the data on the relationship between uncertainties in parameters are limited. We have included this in the discussion section in our revised version.

3. Given that the authors note differences of their results from other CEAs of MRI vs. Mammography, it might be appropriate to comment about differences in their model from the studies/models that provide divergent results.

We now include comments on the differences of our model from other studies in the discussion section.

4. Please provide the results for all univariate analyses in the appendix in table form for all model parameters.

All the univariate analysis results are now addition as in additional file 2

**Discretionary Revisions**

1. Please make the labels of probabilities in the figures and the tables less abbreviated (for example, “Birad03”) to facilitate easy reading

The revised version now states the abbreviations for BIRAD03 in the tables.