Author's response to reviews

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

Authors:

Susan G Moore (smoore@gmail.com)
Laura Fanucchi (lcfanuc@learnlink.emory.edu)
John W Tumeh (jtumeh@gmail.com)
Pareen J Shenoy (pkamat3@emory.edu)
Christopher R Flowers (Christopher.Flowers@emoryhealthcare.org)

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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. However, we are sorry to inform you that at this point of time, we have been unable to complete some of the planned analysis due to software glitches and unavailability of some of the authors due to their schedules. We do hope that we would be able to address the rest of the comments in the near future and would be thankful if you grant us some more time.

Below is the point-by-point response to the reviewers’ comments. For those points which we have still not been able to address, we have also indicated what we intend to do in order to address the comments. Once again, thank you for your time and consideration. We will notify you when we have all the revisions complete. We look forward to receiving your reply and hope that you grant us additional time.

Regards,

Christopher Flowers, MD, MS
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 give us valuable feedback.

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 flase positives cases produced by mammography and by discomfort of MRI examinations in women without a diagnosis of breast cancer?

   Yes, this is due to compensation by quality of life adjustment because of false negative form mammography and false poitive from MRI screening.

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. We do intend to provide the cost-effectiveness analysis without adjustment for quality of life as soon as we fix our software glitches.

4. The threshold of <$100,000/QALY is reported in Results (pag 9 row 15) but is never used in the following discussion (to be cheked)

   Again, this would be checked in our next revised version.
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.

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 will report the net health benefit and its 95% CI in our next revised version.

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 shall include discussion regarding the differences and its features in our next 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.

We intend on using a 5% discount rate to costs and quality adjusted life expectancy in our revised version.

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 the body of the paper. Also, the probabilities and age-specific probabilities should be further documented in the appendix.
The revised version now provides the citations in Table 1. We shall address the age-specific probabilities in our next revision.

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. We shall include discussion on temporary health states and their elicitations in our next version.

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 $151890/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.

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. In our earlier version, 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. In our next version, we intend to use β distribution.

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.


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 probability remains 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)
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 if data on the relationship between uncertainty in parameters do not exist. We shall include this in the discussion section in our next 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.

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.