*Technical Brief Disposition of Comments Report*

**Research Review Title:** *Imaging Techniques for Treatment Evaluation for Metastatic Breast Cancer*

Draft review available for public comment from February 10, 2014 to March 5, 2014.

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## Comments to Research Review

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The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

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| Commentator & Affiliation | Section | Comment | Response |
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| **Peer Reviewer #1** | General Comments | This report is a thorough guide through the issues involving imaging capabilities for detecting metastatic breast cancer. It is refreshing to see concerns of patient anxiety and quality of life sharing the stage with the technical issues of the different imaging modalities. However, there is a very important concern with respect to quantitative imaging that is not discussed. Early measurement of response to therapy requires knowledge of the sources of noise and bias in imaging systems, especially if different devices are used in longitudinal imaging studies. No mention was made of how results from separate studies may have been influenced by different operating conditions of the devices (within a single imaging modality). If imaging methods are to gain acceptance across a wide range of users, the issues of harmonization must be addressed. | We reviewed each of the abstracted studies. Although none made mention of sources of noise or bias in the imaging systems described, most studies stated that the scans were conducted on the same machine for all patients. Additionally, one study (Kenny et al. 2007) presented results on the excellent reproducibility of FLT-PET scans in their patient population. We have added this result to pages 9-10.<br><br>We agree that this is an important issue and have added text to that effect to page 20 in the Summary and Implications section. |
| | Background | The Background information is informative and adequate. The objective is clearly stated on page 1 lines 52 - 54, stating that the comparative effectiveness of imaging modalities in terms of health outcomes, patient satisfaction, and cost have not been determined. This reviewer is concerned that without appropriate information on the quantitative characteristics of imaging devices (variance, bias, etc.) comparative effectiveness results will be difficult to obtain. | We agree with this point and, as described above, have added text to the document to address this issue. |
| | Guiding Questions | These guiding questions are sufficient to give structure to the technical brief. | We appreciate the comment. |
| | Methods | The Search Strategy for the data appears to be appropriate. The decision to exclude studies published before 2003 seems a bit arbitrary, but some date has to be picked. There is some confusion in table 1 of the Eligibility Criteria on page 4. Under “Indication for Imaging”, a criterion for exclusion is “Imaging used to detect recurrence following successful treatment”, yet under “Outcomes associated with imaging findings”, an inclusion criterion is “Recurrence-free survival”. This is a bit confusing. | We excluded studies that examined imaging that was used to detect recurrence after treatment had ended. In the studies that examined imaging to evaluate treatment, we abstracted data on whether the studies followed the treated women and reported on recurrence-free survival (we did not find any studies that reported this outcome). These studies would have had to have been longitudinal, reporting imaging used for treatment evaluation and following the women for some time after that to determine how long they survived without a recurrence. |

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| | Findings | The Overview section discusses the various PET tracer options (page 5, line 42). Responses from the Key Informants, given in Appendix B, were not always consistent or satisfying. For example, when asked how often imaging is used for treatment response evaluation for metastatic breast cancer, answers ranged from every 2-4 months to choice of intervals dictated by insurance.<br><br>A question is raised concerning evaluation of therapy response if on one visit the patient receives a PET scan and on the next visit receives a bone scan (Page B1 lines 24 - 30). How is response to therapy done?<br><br>It is questionable how the information in Tables 2 - 4 can be used. | Because we interviewed nine Key Informants, we occasionally received contradictory information. We attempted to convey the information they provided to us in a logical, summarized manner in the main text of the Technical Brief, but we wanted to present the full array of information we gained from the Key Informant interviews in the Appendix for completeness.<br><br>We agree that a change from one imaging modality at one visit to another modality at a subsequent visit is a possibility. However, it is unlikely that the same provider or institution would initiate such a change. None of the articles we reviewed identified this as an issue.<br><br>We have added information to Tables 2-4 to improve their usefulness. For example, we added the numbers of studies and patients to each of the cells of Table 2. We also added the estimated enrollment and eligibility criteria and the primary outcome measures to Table 4. |
| | Summary and Implications | There is nothing incorrectly stated in the Summary. Research on biomarkers for evaluation of therapy response is a goal that should be pursued, and will support the hope for eventual personalized medicine in the near future. Short of that, however, imaging offers non-invasive opportunities to monitor response to therapy for today's patients. | We agree with these statements and have conveyed these remarks in the Summary and Implications section. |
| | Next Steps | Certainly knowledge of long-term patient outcomes is important for studies of therapy evaluation of metastatic breast cancer. Although retrospective data can be used to gain some idea of long-term survival (overall, progression free, etc.), as therapies improve, the survival statistics with also change. Therefore, ongoing prospective studies are important, as stated on page 19. There is no indication in the report, however, as to how these studies should be performed. | We have added text to the "Intermediate and Long-Term Outcomes section" (beginning with "To research this, women with…) that describes how a prospective study might be conducted. |

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| | Clarity and Usability | This report is very clearly written and is an informative document regarding metastatic breast cancer and the role of imaging to monitor therapy response. The four guide questions structure the technical brief very well. There is a great deal of information in tables 2 - 4 that make extraction of useful information difficult. Because of that, there is a sense of "so what" after reading everything. Much of the results are obvious to lay readers of healthcare documents (newspapers, general pamphlets, etc.) Most of the technical information is contained in the tables, and they are difficult to concentrate on. | We believe that the most important message of this brief, both for lay and professional readers, is that very few research studies on the use of imaging to evaluate treatment response in metastatic breast cancer have been conducted in the past decade. Throughout the brief, we convey the importance of this information gap and describe some methods that could be used to gain more scientific knowledge in this area. |
| **Peer Reviewer #2** | Findings | Page 12 line 3 to 12: formulation of studies included is not clear. It is more accurate to talk of "metabolic response" or "anatomical / morphological response" instead of "tumor response as measured by tracer uptake"<br>Page 12 - line 3: Two contradictory number of studies, 16 and then 18 studies are mentioned.<br>Page 13 line 38: "physical and chemical" : not clear, rephrase.<br>Page 13 line 46-47: Bone scintigraphy and PET/CT do not assess the same extent of disease and therefore cannot be compared for substitution (for ex. liver metastasis cannot be assessed on bone scintigraphy). | The wording has been changed to metabolic or anatomic response as appropriate.<br>This has been corrected.<br>We have deleted "physical and chemical" in the bone scan description and now state that "bone scans are used to identify areas of damage to the bones…"<br>We agree that bone scans do not assess the extent of disease in the same manner as PET/CT. However, our Key Informants reported that they had seen situations in which patients without adequate insurance coverage received bone scans rather than PET/CT, possibly because of the greater expense of PET/CT, and that is the information we are conveying with that sentence. |
| | Findings (continued) | Page 13 line 48: Not entirely correct. Bone scintigraphy does not take less time.<br>- Imaging time is nearly the same between PET and BS.<br>- But average total time needed is slightly longer for bone scan: patients has to first arrive, Tc99m radiotracer is injected and images are performed in average 2-3 hours after injection.<br>Page 13 line 51 and 54: technitium is not a "contrast agent". In addition, 99mTc is the radiotracer labelling all bone scintigraphy. Those data need to be corrected.<br>Page 13 line 54: Technitium is not a contract agent, hence no allergic reaction.<br>Page 14 line 3: Literature review in insufficient and lacks references. (For instance, Hayashi, Clin Breast Cancer 2013.) | We have taken this sentence out.<br>We have corrected this wording.<br>We have removed mention of "contrast agent" when discussing technetium. Although allergic reactions to technetium are rare, they are still possible; thus, we have kept the language about this potential harm.<br>We have abstracted the Hayashi 2013 article and added the data to the relevant sections of the Technical Brief. |

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| | Findings (continued) | Page 14 line 11: Lack data regarding SPECT/CT in bone scintigraphy.<br>Lack data on 18F-FNa PET/CT<br><br>Page 14 line 28: Sentence incorrect.<br>As previously reported, technitium is not a “contrast agent” hence no allergic reaction is noted for bone scan. On the other hand, allergic reaction can be noted with Gadolinium, even though less frequent than with iodine contrast agent.<br><br>Page 14 line 45. Rephrase, not clear.<br><br>Page 15 line 3 to 11: This chapter is about computed tomography, but all studies described here assess the value of PET/CT. Results interpretations are incorrect. | Our systematic literature review was focused on treatment response. Therefore, even though SPECT and 18F-Na PET/CT are useful tools in demonstrating bony disease progression in cancer patients, they are not currently considered accurate for response to treatment. Our literature review did not identify any articles specific to 18F-Na PET/CT or SPECT with regards to metastatic breast cancer treatment response.<br><br>We have corrected this wording.<br>We have rephrased this for clarity.<br><br>The articles described in this section compare tracer uptake from PET/CT to anatomic changes as measured by CT. |
| | Findings (continued) | Page 15 line 14-15: description of PET is simplistic. More relevant scientific parameters are needed.<br>Page 15 line 17: FDG is not the only FDA approved tracer in oncology. For exemple, 18F-FNa (assessing bone metastasis) is also FDA approved. Need to precise if data concern only breast cancer.<br>Page 15 line 19-20: Shortcut. Rephrase.<br>Page 15 line 33: Which harmful contrast agent to you refer to? The reference listed (31) refers to CT-scan.<br>Page 15 line 38: PET has been used for the last decades. | We have added text to the first paragraph of this section to address this comment.<br><br>We have changed this to specify that FDG is the only FDA-approved tracer for breast cancer imaging.<br><br>We have rephrased this sentence and added language on how FDG is preferentially taken up by tumors.<br><br>The reference describes the doses of radiation from CT. We have removed reference to contrast agents from this sentence.<br><br>We meant to imply that PET technology is newer than say, bone scans, x-rays, mammograms, and ultrasounds, and therefore might be less appropriately utilized according to our Key Informants. |

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| | Findings (continued) | Page 15 line 47: What do you mean? Standardized international interpretation guidelines are used worldwide (EORTC, PERCIST, lymphoma scoring...)<br>Page 15 line 54: non relevant<br>Page 16 line 20: “level of uptake”: rephrase.<br>Page 17 line 5: usually low-dose coregistration CT-scans are used. “relatively large amount” is incorrect. | While guidelines are published worldwide, no enforcement mechanisms exist that require clinicians to follow them. Furthermore, no accrediting organization monitors the interpretation of PET/CT scans in the U.S.<br>We have clarified this sentence.<br><br>We believe that the fact that many physicians interpret a low volume of PET/CT scans that were performed to monitor treatment of metastatic breast cancer is an important point.<br><br>This has been rephrased to “standard uptake value.”<br><br>We have changed “relatively large amount of radiation” to “as much radiation” |
| | Summary and Implications | Page 24 line 10,20 and 26: bone scintigraphy is not an anatomical imaging.<br><br>Page 24 line 35: FDG is not the only FDA approved tracer | We have corrected this.<br><br>We have clarified that FDG is the only FDA-approved tracer for breast cancer imaging. |
| | Next Steps | Page 32 line 18-19: conclusion is surprising “because we bought PET/CT we might as well use them”: Neither relevant nor scientific.<br><br>Page 32 line 30-31: Sentence is not clear. Which parameter takes time?<br><br>Page 32 line 39-40: Too restrictive, since only bone is mentioned. Precise why other metastatic sites (liver, adrenal, brain, etc.) are not mentioned.<br><br>Page 34 line 26: Precise what does “waiting times” refer to. | The purpose of Appendix B is to provide a more detailed account of our conversations with the Key Informants. More than one brought up the fact that they believed that PET-CT scans were often used because the expensive technology had been paid for and was readily accessible to the ordering physicians. We believe that this feedback is relevant to the audience for this Technical Brief.<br><br>The Key Informants meant that the peer-to-peer discussions required by some insurance plans can be time-consuming.<br>We have clarified this sentence.<br><br>We have clarified this sentence in Appendix B in the section “When is PET-CT used versus bone scan?”<br><br>We have clarified “waiting times” to be the “long idle periods of time needed to allow radiotracer circulation.” |

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| | Next Steps (continued) | Page 34 line 41: References are needed.<br><br>Page 34 line 46: incorrect. PET acquisition are standardized, yet reproducible. | Appendix B is reporting information that we received during the conversations with the Key Informants, not published literature which could be referenced.<br><br>This Key Informant was referring to a quantitative assessment of treatment response related to standard uptake value changes seen on PET, which he believed requires further research until an actual association can be validated and reproduced. We have clarified the wording in Appendix B under the question "What emerging technologies can we expect in the next five years or so?" |
| **Peer Reviewer #3** | General Comments | This is an excellent technical brief. There are no significant deficiencies. | We appreciate the comment. |
| | Background | The background is appropriate, well-summarized, and concise. The writing is very clear, and the guiding questions logically are derived from the background. | We appreciate the comment. |
| | Guiding Questions | Guiding questions are clear and logically derive from the background. | We appreciate the comment. |
| | Methods | This section is very strong. How key informants are used is very clear. How data from the literature was gathered is also clear. Well written and concise. | We appreciate the comment. |
| | Findings | Excellent summary of findings for each modality. There is limited information on cost for each modality, so this guiding question does not seem to have been answered as thoroughly, but it is clear that is due to gaps in the literature. This section summarizes what has been done, and what gaps need to be addressed. | We appreciate the comment. |
| | Summary and Implications | The summary is concise and consistent with the background and findings. | We appreciate the comment. |
| | Next Steps | The next steps are clearly laid out and are logically concluded from the findings and summary. In particular, the authors offer specific study designs (such as randomized trials) to answer gaps identified. | We appreciate the comment. |
| | Clarity and Usability | A real strength of this report is the organization and clarity with which the findings are reported. The conclusions can be used to inform future research. | We appreciate the comment. |
| **Peer Reviewer #4** | General Comments | Very good report overall. May benefit from more background on what an ideal or "gold standard" treatment evaluation tool would look or work like for the non-clinical or non-technical reader. The evidence seems very limited for such important decision-making processes. | We agree that a description of an ideal treatment evaluation tool is helpful to this brief and have added some text to address this to the introductory paragraph of the Next Steps section on page 19. |

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| | Background | The background section provides a good overview. More context information may be helpful with basic description of a treatment cycle, duration, timing of imaging. Some of this detail is in the key informant section. Perhaps more context on why imaging versus other tools. Also, it would be helpful to know in the background that the goal of treatment is to prolong survival as explained in the Next Steps section.<br><br>What is the typical (or an example) frequency of imaging during treatment? (page 1 paragraph 2) | We have addressed these points in the first paragraph of the "Current Practices in Imaging Metastatic Breast Cancer" section on page 1.<br><br>We have described this in the first paragraph of the "Current Practices in Imaging Metastatic Breast Cancer" section on page 1. |
| | Guiding Questions | Good. | We appreciate this comment. |
| | Methods | The 2003 cut-off date may be reasonable for PET but is it too limiting for scintigraphy, older technologies? | We considered looking at literature published earlier than 2003. However, we concluded that even though modalities like bone scintigraphy and CT were used earlier, both treatment regimens and imaging technologies were evolving so rapidly that older data would not be comparable to data collected from 2003-2014. |
| | Findings | Helpful and disappointing. Few prospective evaluations of very small numbers, no randomized evaluations of PET, yet clearly an important, maybe critical tool.<br><br>Would be helpful to know affiliations of key informants (page 5, paragraph 1), e.g., all academic (?), given perspective reported about variability and interpretation (Page 6, line 46). | We agree with this comment and have conveyed these sentiments in the Summary and Implications section.<br><br>We have added the affiliations of the Key Informants to the second paragraph of the Overview section on page 5. |
| | Summary and Implications | What evidence supports the statement that FDG PET / CT can provide critical information (Page 18, line11)? If it does, does it result in prolonged survival, or change in management, or ? Statement suggests the evidence is better than it appears.<br><br>There is a lot of focus on PET/CT in this section, and maybe for good reason. PET/CT seems like the best option as it gets both functional as well as anatomic information. It appears there is only very limited data suggesting improved survival. It seems this is a major gap in the evidence as noted page 19, line 4. | We have changed our wording to be more circumspect regarding the theoretical information PET/CT may provide regarding functional tumor response.<br><br>We agree this is a major gap in evidence and have described how this might be addressed in the Next Steps section on pages 19-21. |
| | Next Steps | Section is clear. More study is needed evaluating all outcomes. | We agree with this comment and have included some suggestions for how future studies might be conducted in the Next Steps section on pages 19-21. |

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| | Clarity and Usability | The report is well structured. More contextual information in the background will help readers unfamiliar with the condition and treatment.<br><br>In the summary and implications or in the evidence summary for PET/CT a clear statement about the knowns and unknowns in the literature and the strengths and limitations of the evidence will improve understanding. Key informant information is very helpful, but only few and small studies appear to provide good information on utility. | We have added some contextual information about the typical frequency and goals of imaging to the Background section on page 1.<br><br>We have discussed the strengths and limitations of the PET/CT literature in the third paragraph of the Summary and Implications section and we have highlighted how few studies exist that have evaluated the use of imaging to evaluate treatment in women who have metastatic breast cancer. |
| **Peer Reviewer #5** | General Comments | Good description of current studies on multiple tests. Less clear what the critical questions that remain to be answered are and what the appropriate conceptual framework would be to engage in ongoing research. | We have expanded the Next Steps section to outline the next steps more clearly. For example, in the first paragraph, we now describe the ideal tool that could be used to evaluate treatment progress in women with metastatic breast cancer. We also describe the intermediate and long-term outcomes that warrant further research and describe studies that could provide information about these on pages 19 and 20. Finally, we have also added text on how research could be conducted to result in improved communication with patients on page 20. |
| | Abstract | Findings do not include conclusion /main outcomes from the small studies.<br><br>Future studies should address lack of appropriate clinical outcomes as well as patient centered outcomes.<br><br>Unclear why advocacy for novel radiotracers and biomarkers was included. | We have added a sentence to the Findings section of the Abstract that summarizes the conclusions from the published literature.<br><br>We agree with this and have added clinical outcomes (including progression-free and overall survival) to this sentence.<br><br>We included novel radiotracers and biomarkers because they arose in both the published literature search and in almost all of our discussions with Key Informants as important areas of future research. |
| | Background | Solid background and summary information on potential for over, under, and misuse. Adding comments on importance of information in treatment planning would be helpful (included in implications and next steps section). | We have added information on the importance of imaging for treatment planning (in that imaging can identify treatment regimens that are not working and allow women to change treatments) in the first sentence in the “Current Practices in Imaging Metastatic Breast Cancer” section on page 1. |
| | Guiding Questions | Seem appropriate to objective of paper. | We appreciated this comment. |
| | Methods | Search and exclusion criteria seem appropriate. Unclear why a payer representative was not included in key informant group given background. | Thank you for this suggestion. We did include a payer on the peer review panel, but it would have been helpful to have one as a key informant. |

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| | Findings | Good overview/summary of findings. Great context of number of study participants compared to use. Could use more information about the impact of not including certain outcomes -especially changes in treatment decision if that is the primary purpose of the test.<br><br>Summary of trend - could use comments on general description of trend being stable or increased compared to known impact of use from studies.<br><br>Unclear payer comments when payers weren't a key informant - perhaps can be reframed as questions or issues that were raised. | We agree that this point is important and have added a sentence to the last sentence of the second paragraph of the Summary and Implications section on page 18 to highlight the lack of reporting of changes in treatment decisions in the published literature.<br><br>While the paucity of published literature prevented us from formally analyzing the trends of use of the modalities, our Key Informants did provide some information on their sense of the current and near-future trends of use of imaging for treatment evaluation of metastatic breast cancer (see pages 6-7).<br><br>We have clarified this: the clinician, product purchaser, and patient advocate Key Informants, not payers themselves, commented on their experiences with reimbursement and the use of Radiology Benefit Managers. |
| | Findings (continued) | What are the implications of access and usage trends given evidence from studies?<br><br>Individual modality summary - it would be helpful to have a common set of items (gleaned from the context gathering of most important information) for each one: e.g. number of study participants, gold standard accuracy, studied test accuracy, key outcome results, comparator issues, common advantage and disadvantages categories). | We qualitatively report the opinions of the Key Informants on these issues, but none of the published studies that we identified commented on issues of access and usage trends. We also report on the Key Informants' opinions about access to imaging modalities. For example, on page 10, we report that our Key Informants felt that breast cancer patients in community care centers might have less access to advanced imaging such as PET/CT.<br><br>We have added the number of study participants for each modality, broken down by county, study type, comparators used, and outcomes evaluated, to Table 3. We have described the advantages and disadvantages of each modality within the individual modality summaries because they were too large to fit into the table. |
| | Summary and Implications | It would be helpful to include what the critical issues and appropriate conceptual framework would be here. | In the first paragraph, we list the critical issues with the current literature: all published studies were limited to small, nonrandomized studies. Throughout this section, we describe potential research approaches to add to the body of knowledge on this topic. |

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| | Next Steps | Intermediate and long term outcomes - well defined outcomes and potential research approaches. Personalized medicine and blood tests - unclear whether advocacy for research for these is related to an inherent deficiency in imaging modalities given that they appear to be beyond scope. | While we agree that personalized medicine and blood tests are not relevant imaging modalities, they were discussed, sometimes extensively, by almost all of our Key Informants as tools that will add to or possibly replace imaging to evaluate treatment progress for women with metastatic breast cancer. We therefore believe that these issues warrant mention when discussing the future directions of treatment evaluation of metastatic breast cancer. |
| | Clarity and Usability | Generally well organized for large, comparative topic. Having a section that describes and categorizes key considerations and applies to each modality would be useful. The more specific the future research needs can be tied to issues raised by current diffusion or science gaps, the better. | In the section on Intermediate and Long-term Outcomes, we have outlined specific approaches for future studies that could begin to narrow the gaps in knowledge about metastatic breast cancer imaging. |
| **Peer Reviewer #6** | General Comments | 1. Imaging is used to diagnose metastatic disease (and then a biopsy is indicated) and also used to follow response. I believe this review is intended to examine literature to follow response only. This should be clarified.<br><br>In addition the issue of how much imaging is needed for restaging is unknown. For example, if the patient has a liver lesion as their only site of metastasis, should that site alone be imaged in follow up, or do we need to image the whole body every time the patient is restaged? I believe this answer is not known, and could be a consideration for future study.<br><br>2. Patients with some types of breast cancer do better than others (ER+ and/or bone dominant have longer OS than ER- visceral dominant, with HER2+ in between, due to advances in therapy). There is the possibility that these types of clinical scenarios merit different types of imaging. | Yes, this review is intended to examine response to treatment following diagnosis only. We have clarified this throughout the Brief.<br><br>We agree with this point and have addressed it in the first paragraph of the Intermediate and Long-Term Outcomes section on page 20.<br><br>We agree with this and have added a sentence to the first paragraph of the Intermediate and Long-Term Outcomes section on page 20 to address this point. |

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| | General Comments (continued) | 3 references cited target the “bone dominant” group (De Giorgi et al, Huyge et al and Specht et al). This is an important group for whom the disease is indolent and particularly challenging to follow by traditional imaging. Responding patients may have more uptake by bone scan or CT- an apparent “flare” which is really healing bone, and treatment may be INAPPROPRIATELY changed based on this finding. It is possible that these patients would be better managed by FDG PET (without diagnostic CT) or by less frequent imaging.<br><br>4. For clinical trials, RECIST is limited (MDACC bone met study Hamaoka JCO 2004) and these trials set a standard which gets followed in practice. Specifically how to follow bone metastasis is unclear, and the exclusion of the bone dominant patients from clinical trials makes it difficult to learn how best to follow patients in practice. | We have added language to allude to this valid point in the second paragraph of the Summary and Implications section.<br><br>We agree, and have added language to allude to this knowledge gap at the end of the second paragraph of the Summary and Implications section. |
| | Background | Well done save the context of the challenge of imaging bone and more indolent disease. | As stated above, we now allude to this area for further research in the Summary and Implications section. |
| | Guiding Questions | Appropriate | We appreciate this comment. |
| | Methods | Logical. They may have benefited from more clinicians (by clinicians were they speaking with medical oncologists or imagers?) | We have added their specialties (3 were medical oncologists and 2 were radiologists) as well as their affiliations to the second paragraph of the Findings, Overview section on page 5. |
| | Findings | Appropriate and thoughtful. May want to consider looking at whether fluoride bone scan differs from traditional technetium scan. Findings are limited by the lack of studies done to determine utility of imaging in a particular instance, and a lack of evaluation of quantitative imaging vs qualitative imaging. These are limitations of the current literature, not limitations of the review. | We agree that there are limitations with the current literature. While the use of fluoride bone scans is increasing for determining disease extent, we did not find any articles about the use of fluoride bone scans evaluating treatment response in metastatic breast cancer patients. |
| | Summary and Implications | The literature is lacking studies of imaging which could guide clinical practice regarding utility of each imaging tool for a particular situation, overlap of imaging technologies, and considerations of how we could use less imaging in some situations, to reduce costs, patient exposure and over diagnosis/misdiagnosis. | We agree with this comment and have conveyed these ideas throughout the Summary and Implications section. |

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| | Next Steps | Further studies would benefit from considerations of types of measurable and nonmeasurable disease (bone dominant is tough to measure with RECIST, but it is different from effusion based disease, which is also non measurable).<br>Correlation with blood markers or other biomarkers is desirable, but likely beyond the scope of the review.<br>While each imaging tool could be qualified, it will be difficult to compare head to head without specification of what tumor type is under consideration. For example, a patient with predominantly lung nodules, never with tumor outside of the lung, would not benefit from serial bone scans... | Thank you for this comment. We agree that comparative studies will have to limit the inclusion criteria and be very specific to the anatomic location of the disease. |
| **Public Reviewer #1 (Gail Rodriguez)** | General Comments | **1) Imaging modalities have varied functions and uses in a clinical setting. As such, comparative analyses of modalities are of limited value, especially when removed from the particular clinical setting and circumstances of the individual patient.**<br><br>Medical imaging includes multiple modalities and each modality provides unique and many times complementary value in better understanding the clinical situation. In fact, outside the context of a particular episode of clinical care, comparisons of modalities do not appropriately value the contribution of each modality to healthcare. Rather, imaging modalities should be considered in the context of the information they add to the clinical situation and how they add value in establishing appropriate care for the individual patient. AHRQ notes studies in which imaging modalities are compared. However, these differences in technology are of limited meaning outside the context of patient care. Currently, no single imaging technology provides all necessary information to care for every patient in every clinical setting. | While we agree that no single imaging modality can provide all the information to care for every patient in every clinical setting, we do not agree that comparative analyses of modalities are of limited value. The main message conveyed by this Technical Brief is that more research is needed to identify the optimal use of the imaging modalities for treatment evaluation of women with metastatic breast cancer, and we suggest that this information could be obtained by randomized trials or, more realistically, pragmatic trials or prospective studies to determine the clinical characteristics of women who would benefit from each imaging modality. |

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| | General Comments (continued) | Access to appropriate imaging is necessary to inform clinical decisions related to the proper diagnosis and treatment of disease. In order to better direct the optimal use of imaging, physician societies and other provider groups have developed appropriate use criteria and practice guidelines specific to individual clinical indications. These clinical decision-support tools are based on research and evidence, and aid physicians to determine the appropriate scans to be used for specific clinical indications.<br><br>The American College of Radiology (ACR) has clinical practice guidelines on breast cancer. The guidelines outline the efficacious use of imaging modalities for informing care at various intervals: diagnosis, staging and extent of disease, and post-therapy monitoring. In addition, the guidelines address post-operative imaging. For example, postoperative mammography should document complete excision of malignancy. However, to evaluate residual disease in patients with positive margins at lumpectomy prior to re-excision, MRI may be considered. These guidelines appropriately acknowledge that clinical value of each imaging modality is determined by how it informs specific clinical care, not how it ranks in comparison to other modalities. | We did not find that clinical decision-support tools are based on evidence specific to treatment evaluation for women with metastatic breast cancer. As this Brief reports, very little evidence exists on the use of imaging for this indication in this disease population. |
| | General Comments (continued) | MITA advocates the development and use of physician-developed appropriateness criteria to guide treatment decisions and training of hospital and imaging facility personnel who perform medical imaging exams. In order to provide optimal care and prevent medical errors, physicians and technologists must account for the patient's individual needs. By providing proper training and adhering to these standards and initiatives, physicians can ensure that patients receive the life-saving benefits of medical imaging technology.<br><br>**2) Outcomes related to the use of imaging must be defined to reflect the unique contribution of imaging to clinical decisions.** The Draft Technical Brief points to lack of studies on "clinical and patient centered outcomes". This is cited as a gap in evidence. However, we offer that this is not a gap, but rather includes endpoints which are inappropriate to evaluate diagnostic imaging in the context of patient care. | We agree that it can be challenging to determine the effects of any one type of imaging on outcomes when so many other variables such as treatment options, comorbidities, and patient demographic and genetic characteristics are involved. We also agree that the intermediate endpoints such as treatment choices are therefore very important and perhaps easier to study. However, the most important endpoints to patients are clinical and patient-centered outcomes such as survival time and quality of life; therefore we have included a discussion of these in the Technical Brief. |

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| | General Comments (continued) | One consideration is that it is difficult to isolate the contribution of diagnostic imaging from the larger care paradigm, and in fact, due to the incremental value of diagnostic imaging within the delivery of healthcare, diagnostic imaging's value outside the care paradigm would be of limited meaning. Models that attempt to extract diagnostic imaging from the care that it informs neglect to reflect the reality of healthcare delivery. In fact, in clinical practice, a patient may have multiple diagnostic tests, with additional value from each test used to inform the complex clinical decision process in unique and inimitable ways. In addition, some diagnostics tests are synergistic and are ordered to better evaluate findings from a prior imaging test. For example, a CT scan may be ordered in follow up to an ultrasound scan that shows a mass or nodule.<br>Additionally, as the science of cancer diagnosis and staging progresses, diagnostic imaging may inform decision-making in concert with other tests including biomarker identification, genomic studies, and other assays. | |
| | General Comments (continued) | A more appropriate endpoint for diagnostic imaging would be similar to that which AHRQ considers as "intermediate outcomes" including effects on diagnostic thinking and clinical decision making. That is, changes in therapeutic management or stage reclassification are appropriate terminal points when considering the impact of diagnostic imaging on healthcare. A recent article on the topic suggests "the outcomes, or endpoints, appropriate to assessing whether diagnostic interventions are reasonable and necessary are best characterized as "change in clinical management." This is distinct from the outcomes, or endpoints, classically applied in assessing whether therapeutic interventions are reasonable and necessary."<br><br>**3) Innovative, dose-lowering imaging technologies support quality care.**<br>The Draft Technical Brief also points to radiation dose as a potential harm of CT and PET. In recent years, innovative, dose-lowering technologies have limited dose while maintaining imaging quality. Due to lower dose and high clinical efficacy, the CT and PET/CT benefit-to-risk profiles have improved. | Thank you for highlighting these important endeavors to reduce radiation dose. We have added language about these positive advances in the "Improving Communication with Patients" section, where we encourage improved provider-patient communication regarding the balance between benefits and risks (including those related to radiation) of medical imaging for evaluating treatment response. |

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| | General Comments (continued) | Dose efficiency and dose reduction have been important design considerations for CT for many years. The focus on these design considerations has grown and intensified in more recent years, and has yielded a variety of new and innovative hardware and software features that directly help physicians both reduce and monitor dose for CT exams. The CT industry has developed new features that enable both the dose to be displayed prior to scanning, and to alert operators to potentially higher than expected doses, as well as enabling electronic recording of the CT dose in the patient record. These features are important for both the patient as well as facilities, since they provide facilities with the ability to compare the dose of their CT protocols and establish optimized reference values.<br><br>The dose monitoring/reduction features described below play a significant role in helping to reduce the dose for CT exams, while maintaining diagnostic quality and the capability to report and record dose. For example:<br>Automatic Exposure Control helps optimize dose for each patient for the given diagnostic task. This feature adjusts the exposure to use only what is needed to maintain a constant image quality. This feature is now standard on CT systems. | Thank you for this information. |

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| | General Comments (continued) | Wider coverage detectors minimize the amount of x-ray that falls outside of the active detector region, thereby reducing dose to the patient without impacting image quality. Systems are now available in a range of wide coverage designs.<br>"Shutter" modes block unused x-ray at the beginning and end of helical scans and therefore do not degrade image quality. This feature is now standard on many CT systems and is "built in" to each helical acquisition.<br>Advanced electronics in data acquisition systems result in better imaging performance and less noise, thereby enabling equal performance at a lower dose.<br>First generation CT iterative reconstruction results in a significant dose reduction potential, while maintaining diagnostic image quality, and is well suited to CTC studies.<br>Iterative reconstruction is available on new systems and also as an upgrade to many installed base systems.<br>More advanced second generation CT iterative reconstruction provides even further dose reduction potential, where some expert users are able to achieve some exams approaching 1 mSv levels for combined supine and prone CTC scans, while still maintaining diagnostic image quality. This feature is becoming widely available on new systems. | Thank you for this information. |
| | General Comments (continued) | The DICOM Dose Structured Report allows the exam dose to be electronically captured with the patient record. This feature is now standard on all new CT systems and has also been implemented on newer installed base systems. | Thank you for this information. |