Evidence-based Practice Center Technical Brief Protocol

Project Title: Imaging Techniques for Treatment Evaluation for Metastatic Breast Cancer

I. Background and Objectives for the Technical Brief

Metastatic Breast Cancer

In spite of significant gains in detection and treatment, breast cancer continues to have a broad impact in the United States, with an estimated 234,580 individuals with new diagnoses in 2013.[1] About 33 percent of individuals with breast cancer diagnosed between 2001-2007 had regional metastases, with a 5-year relative survival rate of 84 percent. Approximately 5 percent were diagnosed with distant metastases, most commonly to the bones, lungs, liver, or brain, and had a 5-year relative survival rate of only 23 percent.[1]

Several imaging modalities, including ultrasound, magnetic resonance imaging (MRI), computed tomography (CT), positron emission tomography (PET), PET-CT, and bone scintigraphy, are used to evaluate the effects of treatment for metastatic breast cancer.[2] However, as outlined in guidelines from the National Comprehensive Cancer Network (NCCN) and the National Institute for Health and Clinical Excellence (NICE), evidence regarding the accuracy and effectiveness of these modalities to evaluate treatment of metastatic breast cancer is lacking, even though the type and results of imaging may strongly affect patient outcomes.[2, 3] Inappropriate use could lead to overtreatment. For example, use of MRI during breast cancer diagnosis and treatment planning is associated with longer time intervals from diagnosis to treatment[4, 5] and with potentially avoidable mastectomies.[6-8] Alternatively, inappropriate use of imaging may also lead to undertreatment if additional foci of disease are not identified and these lead to disease progression. Furthermore, imaging modalities vary substantially in cost, ranging in direct costs from about $115 for ultrasound to $1114 for PET-CT,[9, 10] increasing the need to determine whether more expensive tests result in improved patient outcomes.

Current Practices in Imaging Metastatic Breast Cancer

Healthcare providers generally rely on recommendations from professional societies such as NCCN, the American Society for Clinical Oncology (ASCO), and the European Society for Medical Oncology (ESMO), to guide the use of imaging techniques to assess treatment response in metastatic breast cancer. However, these recommendations are not based on robust data. Current practice recommendations for managing metastatic breast cancer include imaging of the chest, abdomen, and bone, in addition to obtaining medical histories, physical examinations, and relevant laboratory tests.[11, 12] The most commonly used imaging modalities are chest/abdomen/pelvis CT and bone scans. PET-CT[12] and abdominal ultrasound are also widely used.[11] For patients with bone-only metastases, bone scans are the most common imaging modality, with supplemental use of x-ray, CT, MRI and/or PET-CT to evaluate localized symptoms.[12, 13]

Objective of Technical Brief

Although multiple imaging modalities to evaluate metastatic breast cancer are used clinically, their comparative effectiveness in terms of health outcomes, patient satisfaction, or cost, has not

been determined. The purpose of this technical brief is to understand current utilization patterns of metastatic breast imaging modalities in the U.S., emerging technologies, research in progress, patient values, and study design issues, in order to summarize the current state of the science and inform a conceptual framework for future comparative effectiveness research in this area. We will also evaluate whether certain imaging technologies may be more suitable for some subpopulations and attempt to determine if the technologies are being used appropriately. Although we will ask Key Informants about the role of biomarkers in imaging for treatment evaluation of metastatic breast cancer, a thorough exploration of emerging biomarkers and other non-imaging tests is beyond the scope of this Technical Brief. We will combine information we obtain from published literature, grey literature, and key informants in order to provide context for appropriate comparative effectiveness studies on imaging for metastatic breast cancer in the near future.

II. Guiding Questions

The questions below will guide the data collection for this technical brief. Question 1 will lay the groundwork for the literature review by describing each of the imaging modalities currently in use for treatment evaluation for metastatic breast cancer. We will describe the accuracy, benefits and potential risks of each modality, including sensitivity and specificity, safety, costs, adverse effects, and other issues. Question 2 will provide the context for how each of the imaging modalities is currently used, including US Food and Drug Administration (FDA) approval status, need for additional equipment (e.g., contrast agents), and, when possible, we will describe reimbursement policies and how commonly each modality is used for metastatic breast cancer treatment evaluation. Using published studies and grey literature, Question 3 will describe the state of the current research on the use and safety of each imaging modality. Finally, in Question 4, we will identify important issues pertaining to metastatic breast cancer imaging, particularly areas of uncertainty surrounding ethical, economic, and safety issues, as well as areas of research that we expect to be pursued in the near future.

1. Overview of Different Imaging Modalities Currently Used to Evaluate Treatment of Metastatic Breast Cancer

- What are the imaging modalities currently used for metastatic breast cancer treatment evaluation in the United States?
- What are the advantages (e.g., sensitivity and specificity) and disadvantages (e.g., safety issues, cost) of each modality?

2. Context in which Different Imaging Modalities are Currently Used to Evaluate Treatment of Metastatic Breast Cancer

- What is the FDA status of each modality?
- What other resources (e.g., contrast agents) are commonly used with each modality?
- How commonly is each modality used?

3. Current Evidence for Each Imaging Modality

- What published and unpublished studies have reported on the use and safety of each modality? When describing each study, include:

     a. Patient population (inclusion/exclusion criteria, age, race, cancer characteristics)
     b. Study design/size
     c. Concurrent and prior imaging modalities used
     d. Length of followup
     e. Outcomes measured (survival, recurrence, others)
     f. Adverse events or harms reported

4. Important Issues and Future Directions of Metastatic Breast Cancer Imaging for Treatment Evaluation

- Given the current state of the science, what are the implications for future diffusion of the imaging modalities for metastatic breast cancer?
- What are the economic, ethical, and privacy considerations that impact the diffusion of each imaging modality?
- Who (e.g., primary oncologist, interpreting radiologist, or payers) should make final decisions about the types of imaging ordered for metastatic breast cancer treatment evaluation?
- What are important areas of uncertainty for metastatic breast imaging modalities?
- What research questions would have the greatest impact for women with metastatic breast cancer?

III. Methods

We will integrate discussions with Key Informants with searches of the published literature and the grey literature in this Technical Brief.

1. Data Collection

A. Discussions with Key Informants

We will work with the Key Informants to understand current utilization patterns, emerging technologies, research in progress, patient values, and study design issues, in order to help summarize the current state of the science and inform a conceptual framework for future comparative effectiveness research on imaging for metastatic breast cancer. For example, we will seek input from Key Informants to create a comprehensive list of imaging technologies, including technologies not commonly used but that are in development and may be used in the U.S. in the near future. We will use this list to guide assessments of utilization among U.S. patients with metastatic breast cancer. We will also seek input from Key Informants to determine whether some imaging technologies may be more appropriate for certain populations and subgroups, and will evaluate concordance with actual utilization. Input from Key Informants will also be sought to determine safety issues that may be associated with imaging technologies and methods for assessing outcomes of different imaging strategies, as well as contextual issues that may affect use, including policies related to coverage and reimbursement. We will seek input from Key Informants to identify values patients place on different outcomes and how they weigh various trade-offs (e.g., increased sensitivity but decreased specificity). We will also seek input from Key Informants to identify ongoing clinical trials and other research on imaging for metastatic breast cancer and will discuss possible ethical concerns associated with each technology. We plan to identify Key Informants who are clinical experts/practitioners in

radiology and oncology, representatives of patient perspectives, as well as payers, scientists, and members of professional societies.

Table 1 represents sample questions to be asked to each of the categories of Key Informants.

Table 1. Sample questions for Key Informants

Key Informant Category	Potential Questions
Clinical Experts/Clinical Researchers **[n=5]**	1. In general, what are the specific clinical indications (e.g., PET-CT for neoadjuvant chemotherapy response) for imaging following initial treatment for patients with metastatic breast cancer? For each of these indications, what imaging technologies do you most often recommend and how often do you recommend they be used? 2. What are the advantages and disadvantages of each of the types of imaging you use for treatment evaluation of metastatic breast cancer? Why do you choose one over another? Please feel free to provide examples. 3. What are some imaging technologies that are not commonly used now but have the potential to be widely used in the U.S. in the next 5 years or so for the evaluation of treatments for metastatic breast cancer? Do you think these new technologies will replace or be added onto existing technologies? 4. What imaging technologies do you feel are being appropriately and inappropriately used for treatment evaluation for metastatic breast cancer patients? 5. Please describe how each of the following influences your choice of imaging for treatment evaluation of metastatic breast cancer: (a) clinical practice guidelines (if you use these, which ones do you use?); (b) health insurance policies; (c) patient preferences. Do any other ***NON-CLINICAL*** factors influence your choices of imaging? 6. In your experience, what role do accreditation programs have on the types of imaging that are offered and used? 7. Is the type of imaging used for treatment evaluation for metastatic breast cancer different in an academic compared to a community setting? If so, why? 8. Can you direct us to any abstracts or conference proceedings on this topic that have not been published yet? 9. Can you comment on the search terms and exclusion criteria for the literature search? 10. What research topics for imaging of treatment evaluation for metastatic breast cancer are most urgent? Please focus on studies that would help you when you make decisions for your patients.
Patient Advocates **[n=3]**	1. What factors are most important to patients regarding imaging following treatment for metastatic breast cancer? Examples include (a) how accurate the imaging test is; (b) how invasive the test is; (c) the expense of the test; (d) the harms associated with the test. 2. In your opinion, which of the above factors regarding imaging for metastatic breast cancer are important for patients to know, but they may not be aware of? For example, are patients aware that the accuracy of these imaging tests varies? 3. What types of expectations do the patients you work with have regarding imaging following treatment for metastatic breast cancer? 4. Is it clear to patients why they obtain certain imaging exams and when the exams are specifically meant to evaluate spread of cancer to other areas of the body? 5. What types of imaging do you most often hear metastatic breast cancer patients discuss? What experiences with imaging do these patients most often share with you? 6. Do any themes, such as cost, accuracy of tests, or discomfort, inconvenience, often arise when metastatic breast cancer patients discuss their experiences with imaging? 7. Do patients generally know how much they will have to pay out of pocket for imaging tests? What resources do they use to get that information (e.g., contacting insurance company, contacting clinic where test is performed, friends/family, others)?

Key Informant Category	Potential Questions
Payers/Hospital Administrators **[n=2]**	1. What policies do payers put in place to influence use of imaging for treatment evaluation of metastatic breast cancer? 2. How are decisions to purchase imaging equipment used to evaluate treatment for metastatic breast cancer made at your institution? 3. What are the major trends in imaging to evaluate treatment for the metastatic breast cancer population? In general, is imaging use for metastatic breast cancer increasing, decreasing, or staying the same? 4. What are some research questions about imaging for treatment evaluation for metastatic breast cancer that you would like answered? 5. What types of imaging is most commonly reimbursed for treatment evaluation of metastatic breast cancer? What are the advantages and disadvantages of these types of imaging? 6. Are you considering new policies to improve the use of imaging in this population? If so, please describe them.
Product Developers/Industry Representatives **[n=2-3]**	1. What are the major trends in imaging to evaluate treatment for the metastatic breast cancer population? In general, is imaging use for metastatic breast cancer increasing, decreasing, or staying the same? 2. What issues (e.g., cost, accuracy, patient discomfort) with imaging for treatment evaluation for metastatic breast cancer do you see as most important to address? 3. What are some imaging technologies that are not commonly used now but have the potential to be widely used in the U.S. in the next 5 years or so for treatment evaluation of metastatic breast cancer? Do you think these new technologies will replace or be added onto existing technologies? 4. What types of imaging technologies are you developing for the assessment of treatments for metastatic breast cancer? 5. What do you believe will be the role of biomarkers for the assessment of treatments for metastatic breast cancer? 6. What topics regarding imaging for treatment evaluation for metastatic breast cancer do you see as the most important areas for further research?

B. Grey Literature Search

We will conduct a search of the grey literature, which will be identified using advice from our Key Informants as well as Internet searches (e.g., clinicaltrials.gov, NIH Reporter, Google Scholar, ProQuest Dissertations and Theses, and/or PQDT Open). We will search for professional society consensus statements, conference abstracts and proceedings, and other preliminary, unpublished study findings. Professional societies may include American Society for Clinical Oncology (ASCO), the American College of Radiology (ACR), the American Cancer Society (ACS), the National Comprehensive Cancer Network (NCCN), and others.

C. Published Literature Search

Inclusion and exclusion criteria for our search of published literature are shown in Table 2.

Table 2. Inclusion and exclusion criteria for imaging of metastatic breast cancer published literature search

Criterion	Inclusion	Exclusion
Population	Age 19 and above Females Diagnosed with metastatic (stage IV) breast cancer	Age 18 and below Males Diagnosed with stages I-III breast cancer
Intervention	Imaging for treatment evaluation	Diagnostic imaging or imaging used to assess stage
Comparator	Comparison of multiple imaging modalities No comparator	None
Outcomes	Tumor response Changes in treatment decisions Changes in patient decisions Recurrence-free survival Overall survival Quality of life Cost and resource utilization Adverse events	None
Timing	All timing	None
Setting	All care settings	None
Study design	Systematic reviews Randomized control trials Non-randomized control trials Cohort studies (prospective and retrospective) Case-control studies Case series	Case reports Opinions Commentaries Letters to the editor with no primary data
Other	English language	Non-English language

We will systematically search, review, and analyze the available information for each guiding question. To identify articles for this review, we will conduct focused searches of PubMed and the Cochrane Library. An experienced research librarian will use a pre-defined list of search terms and medical subject headings (MeSH). Table 3 lists search terms and limits. We will also review the reference lists of identified publications and add any previously unidentified papers.

Table 3. Search terms for imaging of metastatic breast cancer treatment evaluation

Search #	Query	Number of Items Found
1	exp Diagnostic Imaging	1737346
2	exp Breast Neoplasms/dh, dt, pc, rt, su, th [Diet Therapy, Drug Therapy, Prevention & Control, Radiotherapy, Surgery, Therapy]	101054
3	exp Neoplasm Metastasis	157923
4	secondary.fs.	127206
5	3 or 4	256416
6	exp Prognosis	1098484
7	exp "Outcome and Process Assessment (Health Care)"	726373
8	exp Mortality	283847
9	mo.fs.	421173
10	exp survival analysis/	190795
11	6 or 7	1163519
12	1 and 2 and 5 and 11	632
13	exp *Breast Neoplasms/dh, dt, pc, rt, su, th	64661
14	1 and 5 and 11 and 13	252
15	exp "Outcome Assessment (Health Care)"	703145
16	1 and 5 and 13 and 15	127
17	((treat$ or therap$ or interven$ or regimen$ or pharmacother$ or chemother$ or radiother$ or surger$ or surgic$) adj7 (effectiv$ or work$ or reduc$ or shrink$ or shrank or shrunk)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	560424
18	1 and 5 and 13 and 17	90
19	18 not 16	70
20	limit 19 to english language	35
21	((assess$ or determin$ or evaluat$ or discover$ or learn$ or discern$) adj7 (effectiv$ or success$ or reduc$ or remission$ or shrink$ or shrank or shrunk)).mp.	187310
22	1 and 5 and 13 and 21	8
23	limit 22 to english language	7
24	16 or 20 or 23	166

We will update the literature review by repeating the initial search during the peer review process. Any literature suggested by the Peer Reviewers or public comment respondents will be investigated and, if appropriate, incorporated into the final review. We will also study the reference lists of any systematic reviews that do not meet the inclusion criteria but are pertinent to our topic to identify additional studies that should be considered for this literature search. These "hand-searched" studies will also be evaluated against the inclusion and exclusion criteria outlined in Table 2.

We will develop forms that will be used to screen titles, abstracts, and full reviews and to gather information about study characteristics and the PICOTS (**p**opulation, **i**ntervention, **c**omparator, **o**utcomes, **t**iming, and **s**etting) of each study. All titles and abstracts identified through searches will be independently reviewed for eligibility against our inclusion/exclusion criteria by a trained member (LG) of the research team. Studies marked for possible inclusion by any reviewer will undergo a full-text review. For abstracts without adequate information to determine inclusion or exclusion, we will retrieve the full text and then make the determination. All results will be tracked in an EndNote® database (Thomson Reuters, New York, NY). Each full-text article will be independently reviewed by two trained members of the research team (LG, CL) for inclusion or exclusion on the basis of the eligibility criteria described

earlier. If all reviewers agree that a study does not meet the eligibility criteria, the study will be excluded. If the reviewers disagree, conflicts will be resolved by discussion and consensus or by consulting another member of the review team. Results will be tracked in an EndNote® database. We will record the reason that each excluded full-text publication did not satisfy the eligibility criteria.

For studies meeting inclusion criteria, we will design data abstraction forms to gather pertinent information from each article, including characteristics of study populations, interventions, comparators, outcomes, study designs, settings, and methods. All data abstractions will be reviewed for completeness and accuracy by another member of the team.

D. Data Organization and Presentation

1. Data Organization

Fields we will use for data abstraction are listed in Table 4. Data from the published literature will be integrated with information from the gray literature and discussions with Key Informants.

Table 4. Proposed fields for data abstraction

Data Element	Endnote Reference Number, Author, Year
Study characteristics	Study design Inclusion/exclusion criteria Sample size at recruitment and followup rates
Population characteristics	Age (mean, range) Race (Percentages) Other cancer characteristics
Intervention characteristics	Type(s) of imaging described
Comparator	Type(s) of comparators, if any
Outcomes measured	Tumor response Changes in treatment decisions Changes in patient decisions Recurrence-free survival Overall survival Quality of life Cost and resource utilization Adverse events Others
Timing	Timing of outcome measurement(s)
Setting	Setting of imaging (clinic, hospital, other) Geographic location

2. Data Presentation

We will present our findings in the order of the guiding questions. We will summarize findings from the grey literature and the Key Informant interviews qualitatively. For guiding questions that have empirical evidence, we will present our findings in tables that describe the state of the evidence in terms of study characteristics, intervention characteristics, comparators, and the types of outcomes.

We will also present some of our findings graphically using a bubble graph similar to that published by Trikalinos, et al.[14] This will allow readers to visually understand the research to date on these breast imaging modalities.

IV. References

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V. Definition of Terms

Not applicable to this research.

VI. Summary of Protocol Amendments

No amendments have been made to the current version of this protocol.

VII. Key Informants

Because so little research has been conducted on this topic, Key Informants will be an integral part of the Technical Brief process. They will serve as a resource to offer insight into the clinical context of the technology/intervention, including how it is currently used and how it will be used in the near future. For this Technical Brief, Key Informants will include clinical experts, breast cancer patient advocates, device manufacturers, breast cancer researchers, payers, and hospital administrators. Differing viewpoints are expected and encouraged. Information gained from Key Informant interviews is identified as such in the report; they will not contribute to the writing of the report. Also, they will not review the report, except as given the opportunity to do so through the public review mechanism.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Key Informants, and those who present with potential conflicts may be retained. AHRQ and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

VIII. Peer Reviewers

Peer Reviewers will be invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC will consider peer review comments on the preliminary draft in preparing the final draft of the report. Peer Reviewers do not participate in writing or editing the final report or other products. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will be published 3 months after the publication of the Evidence report.

Potential Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than $10,000. Peer Reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

IX. EPC Team Disclosures

EPC core team members must disclose any financial conflicts of interest greater than $1,000 and any other relevant business or professional conflicts of interest. Related financial conflicts of interest which cumulatively total greater than $1,000 will usually disqualify EPC core team investigators.