

# Appropriate Imaging for Breast Cancer Screening

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**Draft Key Questions: Public Comment & Response**

**August 22, 2014**

**Health Technology Assessment Program (HTA)**

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## **Response to Public Comments**

*The Institute for Clinical and Economic Review (ICER) is an independent vendor contracted to produce evidence assessment reports for the Washington HTA program. For transparency, all comments received during the public comment period are included in this response document. Comments related to program decisions, process, or other matters not pertaining specifically to the draft key questions, project scope, or evidence assessment are acknowledged through inclusion only.*

This document responds to comments from the following parties:

### **Draft Key Questions**

- Murray Rebner, MD, FACR, President, Society of Breast Imaging; Director, Section of Breast Imaging, Beaumont Hospitals; Professor, Diagnostic Radiology, Oakland University William Beaumont School of Medicine; and Daniel Kopans, MD, FACR, Director and Chair of Fellows, Society of Breast Imaging; Professor Radiology, Harvard Medical School; Senior Radiologist, Breast Imaging Division, Massachusetts General Hospital Avon Comprehensive Breast Evaluation Center
- Matthew Larson, MBA, Gig Harbor, WA
- Gail Rodriguez, PhD, Executive Director, Medical Imaging and Technology Alliance (MITA)
- William T. Thorwarth, MD, Chief Executive Officer, American College of Radiology; Barbara Monsees, MD, FACR, Chair, Commission on Breast Imaging; and Edward Sickles, MD, FACR, Chair, Committee on Screening and Emerging Technology – Breast Imaging

	Comment	Response
<p>Murray Rebner, MD, FACR, President, Society of Breast Imaging; Director, Section of Breast Imaging, Beaumont Hospitals; Professor, Diagnostic Radiology, Oakland University William Beaumont School of Medicine; and Daniel Kopans, MD, FACR, Director and Chair of Fellows, Society of Breast Imaging; Professor Radiology, Harvard Medical School; Senior Radiologist, Breast Imaging Division, Massachusetts General Hospital Avon Comprehensive Breast Evaluation Center</p>		
1	<p>There has been a great deal of misinformation that has crept into the medical literature. Guidelines panels should carefully review reports that suggest there is little benefit from screening.</p>	<p><i>Thank you for your comments. No changes to key questions. The scope of the review is not intended to evaluate the benefits of screening generally but instead compare the benefits and potential risks of different screening strategies.</i></p>
2	<p>It is not clear that “more fibrous tissue” or dense breasts is a major increased risk for breast cancer. The literature is scientifically flawed.</p>	<p><i>No changes to key questions. We will evaluate the evidence for supplemental screening approaches among women with dense breasts regardless of scientific rationale (i.e., whether for masking or heightened risk concerns).</i></p>
3	<p>The recall rate for mammography is the same as for cervical cancer screening (Pap testing). The number is 10% or less. It should be clear that these are recalls from screening, most of which are resolved by a few extra views or ultrasound. Calling them “false positives” is highly pejorative and misleading.</p>	<p><i>We have clarified the background section and key questions to attribute the term “false positives” to negative biopsy findings after positive screening. We will nevertheless include recall rate as an outcome of interest, as rates differ between screening technologies and recalls still represent additional costs to the system.</i></p>
4	<p>The comments on digital breast tomosynthesis are misleading, “versus those tumors not likely to grow”. Contrary to methodologically poor publications, there is little if any “overdiagnosis” of invasive cancers... The scientific evidence suggests that it is 10% or less and likely less than 1%.</p>	<p><i>No changes to key questions. While overdiagnosis is an area of controversy, we will nevertheless review the evidence and report on the range of estimates for each screening technology, as well as any issues with these estimates (e.g., lead time bias).</i></p>
5	<p>...why set an upper limit of 74 years. Numerous studies have proven a benefit of screening in the older population. If a woman is in good health age should not prevent her from receiving a potentially life-saving test.</p>	<p><i>No changes to key questions. Major screening studies have generally not included women over age 75, and most systematic reviews (as well as the U.S. Preventive Services Task Force) have concluded that the evidence is insufficient to assess benefits and harms in these women.</i></p>

	Comment	Response
6	Patient anxiety has been studied and is short lived. The risk of radiation to the breast for women 40 and older has been thoroughly studied and is negligible. Radiation risk is highest among teenage women and drops rapidly with age so that by age 40 there is likely little if any risk to the breast.	<i>No changes to key questions. If these variables have been thoroughly studied we will summarize the major conclusions on them in the available literature.</i>
7	[Referring to patient subgroups] It is hard to test these variables but it is not unreasonable. If breast density is measured it should be obtained with a computer software program and not by radiologist gestalt. BMI could also be added to the list. The “percent of the breast” that is dense is immeasurable since the denominator is the volume of breast and this cannot be determined. Any study should look at total volume of dense tissue.	<i>We have added BMI as a patient factor of interest to key question 4. We will document variability in technique used to measure breast density as the available evidence allows.</i>
<i>Matthew Larson, MBA, Gig Harbor, WA</i>		
1	[Key Question 1]: Three-dimensional mammography (digital breast tomosynthesis or DBT) has demonstrated the ability to improve net health outcomes in terms of increasing the detection of invasive cancer and reducing false positives. Since approval, more than 100 peer-reviewed publications and scientific presentations have reported findings from women in both investigational and non-investigational settings. The evidence pertaining to these improved health outcomes is summarized below and a full bibliography is also provided.	<i>Thank you for your comments and references. No changes to key question 1.</i>
2	[Key Question 2]: No comments.	
3	[Key Question 3]: Dose with breast tomosynthesis is at an allowed dose level, and is permitted without issue in the U.S. In addition, new software is commercially available to create synthesized 2D images from a 3D acquisition. This allows 2D + 3D information to be created at the same dose as U.S. average 2D dose levels (Ochs, 2013).	<i>No changes to key question 3. We will obtain all available data on radiation dose, including data from studies using synthesized 2D imagery.</i>
4	[Key Question 4]: Breast tomosynthesis is intended for the entire screening population and several studies have demonstrated the ability to improve performance in screening across the spectrum of breast density and age sub-groups seen in the entire screening population.	<i>No changes to key question 4.</i>
5	[Key Question 5]: A comprehensive financial analysis has been prepared and submitted for publishing by Truven Health Analytics. The model is based on data from over 70 million patient claims in the MarketScan Research Database. It evaluates the prevalence of, and costs associate with, recall following a new breast cancer screening mammogram among women ages 40-75. In addition the model estimated the mean	<i>No changes to key question 5. It is important to note, however, that we will be basing our conclusions primarily on published studies (as opposed to those submitted or otherwise in press).</i>

	Comment	Response
	<i>value of breast cancer costs</i> in the year following diagnosis (which was distributed by cancer stage using information from published literature).	
<i>Gail Rodriguez, PhD, Executive Director, Medical Imaging and Technology Alliance (MITA)</i>		
1	The majority of interval breast cancers, which arise in between mammography screening episodes, are attributable to increased breast density.	<i>Thank you for your comments. No changes to key questions. There is controversy about the role of breast density in cancer incidence, and our intent with this review is to assess the performance of supplemental screening technologies in women with dense breast tissue.</i>
2	Data support the effectiveness of supplemental imaging for detecting early stage cancers in women with dense breast tissue.	<i>No changes to key questions. Again, there is not uniform consensus on this statement, and so a review of the evidence in this population is appropriate.</i>
3	The art of breast imaging often relies on a patient-centered multimodality approach. An example of such an approach can be seen with the use of tomosynthesis to minimize false positives and the use of ultrasound to improve sensitivity in dense breast tissue. Combining techniques could optimize outcomes while containing costs and unnecessary workups. The days of a single approach for all patient populations are far behind us. By encouraging transparency, more women will have informed conversations with their physicians about their breast health and be appropriately managed.	<i>We intend to explore the clinical and economic effects of supplemental screening vs. digital mammography alone, as well as separately vs. tomosynthesis alone.</i>
<i>William T. Thorwarth, MD, Chief Executive Officer, American College of Radiology; Barbara Monsees, MD, FACR, Chair, Commission on Breast Imaging; and Edward Sickles, MD, FACR, Chair, Committee on Screening and Emerging Technology – Breast Imaging</i>		
1	The term “relatively large numbers” is misleading... The recall rate for screening mammography is similar to that of Pap test screening for cervical cancer. Data show the average recall rate for screening mammography to be slightly less than 10%. Either use the term “some”, as suggested, or alternatively use “approximately 10%” instead.	<i>Thank you for your comments. No changes to key questions. We have modified the background section of the document to avoid misleading language.</i>
2	... only a small percentage of recalled women undergo biopsy.	<i>No changes to key questions. Biopsy rates vary by study and screening methodology, and will be abstracted from all available studies.</i>

	Comment	Response
3	This is not the correct place to discuss “overdiagnosis”, because current breast screening in general and DBT in particular are not designed to assess tumor biology and differentiate more aggressive from less aggressive cancers.	<i>No changes to key questions. We have modified the document to place overdiagnosis and overtreatment in the appropriate context. While overdiagnosis is an area of controversy, we will nevertheless review the evidence and report on the range of estimates for each screening technology, as well as any issues with these estimates (e.g., lead time bias).</i>
4	Supplemental screening is not a generally accepted practice among women whose risk is limited to a personal history of breast cancer. However, it is generally accepted among women with very strong family history.	<i>No changes to key questions. We changed “personal history” to “significant family history” in the background and analytical framework to describe this subset of women where screening is appropriate.</i>
5	Why use an upper age limit of 74 years? There is evidence that screening is at least as effective in more elderly women, and many women older than age 74 have substantial life expectancy and little comorbidity to cause them to decline screening. If inclusion of more elderly women (no upper age limit, but using the 3.2 million exam 2008-2013 National Mammography Database data showing steady decline in usage beyond age 74) would severely confound your analysis, then indicate that the reason for using an upper age limit is to simplify analysis, not because that is widely recommended practice.	<i>No changes to key questions. Major screening studies have generally not included women over age 75, and most systematic reviews (as well as the U.S. Preventive Services Task Force) have concluded that the evidence is insufficient to assess benefits and harms in these women.</i>
6	Presumably you chose 1-2 years to bridge the range of recommended screening interval by many national medical organizations (annual) versus the USPSTF (biennial). However, be clear about how you will perform your analyses.	<i>We have removed language referencing screening intervals from key question 1 and clarified that we intend to stratify available studies by screening interval.</i>
7	Note that breast density assessment data from published clinical trials and observational studies is out-of-date, because the current (2014 going forward) approach to assessing density is based on potential masking of cancer by dense tissue, whereas the previous approach was quartile assessment of the volume of dense breast tissue.	<i>No changes to key questions. We will note that the change in approach to assessing breast density will affect comparability of studies moving forward, and will also document variability in technique used to measure breast density as the available evidence allows.</i>
8	Since you are assessing DBT as a “better mammogram”...you should also evaluate supplemental screening compared to DBT...	<i>Both key question 2 and the analytic framework have been modified to clarify that the comparators to supplemental screening will be both digital mammography alone and DBT alone.</i>

	Comment	Response
9	The term “unnecessary” biopsy is a misnomer (the correct term is false-positive biopsy).	<i>No changes to key questions. We used the terminology in the document to clarify for a broad audience that we are discussing a negative biopsy done as a result of a falsely-positive imaging test.</i>
10	Handheld ultrasonography may be performed in a variety of ways: solely by radiologist, solely by technologist, initially by technologist and then by radiologist as needed.	<i>We added clarifying language to key question 4 to show that we intend to explore, where the published literature allows, the differential effectiveness of how these tests are performed.</i>
11	What is meant by “safety”? What is meant by “imaging protocol”?	<i>As discussed in key question 3, “safety” refers to the potential harms of each screening strategy, as it would with any intervention. An example of “imaging protocol” is provided in the response to comment 10 above.</i>





July 24, 2014

WA State Health Care Authority  
Health Technology Assessment Program  
PO Box 42712  
Olympia, WA 98504-2712

Subject: Washington State Health Technology Assessment Program Appropriate Imaging for Breast Cancer Screening in Special Populations

Program Manager:

The Society of Breast Imaging wishes to comment on the Washington State Health Technology Assessment Program as related to appropriate imaging for breast cancer screening. This is an important topic which will affect many women in your state. It is important to begin with the right background information and then ask the correct questions. We hope the attached document will aid you in this process. Please do not hesitate to contact us with questions or comments.

*Murray Rebner MD FACR, FSBE*

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## SBI Comments for WA Health Technology Assessment

### Background

Mammography screening has been shown to reduce mortality from breast cancer for women ages 40-74 in randomized, controlled trials. When screening is utilized by the general public the death rate goes down. In the U.S. the death rate from breast cancer had been unchanged for 50 years. Screening began in the mid 1980's as evidenced by an abrupt increase in cancers detected. As expected there was an equally abrupt and parallel decline in breast cancer deaths that began, as expected, in 1990. As more and more women have participated in screening each year, the death rate has continued to decline so that each year there are now more than 30% fewer women dying of breast cancer. Therapy has improved, but therapy reduces deaths when breast cancers are treated earlier. Instead of declining, the death rate for men with breast cancer increased in 1990 despite access to the same therapies. It remained high and then returned to 1990 levels. Men have not seen the decline in breast cancer deaths seen among women. The difference is early detection - men are not screened for breast cancer.

There has been a great deal of misinformation that has crept into the medical literature. Guidelines panels should carefully review reports that suggest there is little benefit from screening. Virtually every one of these has failed to account for differences in risk between populations being compared, and did not account for the fact that most deaths in the early years of screening programs are due to cancers that occurred before screening was available. These women could not have benefited from screening and should not have been included in these analyses.

There are very few medical interventions that have been shown to be as effective in saving lives as mammography. Review panels need to be extremely careful in removing or reducing access to an intervention that is saving so many lives.

### SPECIFIC COMMENTS

It is not clear that "more fibrous tissue" or dense breasts is a major increased risk for breast cancer. The literature is scientifically flawed.

Kopans DB. Basic physics and doubts about relationship between mammographically determined tissue density and breast cancer risk. *Radiology* 2008; 246:348-53.

The recall rate for mammography is the same as for cervical cancer screening (Pap testing). It is not clear that this is a "relatively large number". The number is 10% or less. It should be clear that these are recalls from screening most of which are resolved by a few extra views or ultrasound. Calling them "false positives" is highly pejorative and misleading.

The comments on Digital Breast Tomosynthesis are misleading. "versus those tumors not likely to grow". Contrary to methodologically poor publications, there is little if any "overdiagnosis" of invasive cancers. In fact there is not a single reported case in the medical literature of an invasive cancer regressing or disappearing on its own. The scientific evidence suggests that it is 10% or less and likely less than 1%.

Puliti D, Duffy SW, Miccinesi G, de Koning H, Lynge E, Zappa M, Paci E; EUROSCREEN Working Group. Overdiagnosis in mammographic screening for breast cancer in Europe: a literature review. *J Med Screen* 2012;19 Suppl 1:42-56.

There are legitimate questions surrounding Ductal Carcinoma in Situ (DCIS), but DBT does not increase the detection of DCIS.

DBT is simply a better mammogram. Once there is no increased dose and 2D images can be synthesized, there is no reason to not use DBT for all screening. There is a legitimate question as to how many of the cancers found by ultrasound and/or MRI will be detected by DBT. It is likely that there will still be cancers that are not detected by x-ray imaging (DBT).

#### Key Questions:

1. What is the effectiveness of screening every 1-2 years with DBT vs. DM for women ages 40-74 who are at average risk for breast cancer?

Comment: Recent data has clearly demonstrated the advantages of DBT vs. DM - it is simply a better mammogram. However, if a trial were to be performed a randomized control trial comparing annual DBT vs. annual DM in women of average risk would be the best model. Furthermore, why set an upper limit of 74 years. Numerous studies have proven a benefit of screening in the older population. If a woman is in good health age should not prevent her from receiving a potentially life-saving test.

2. What is the comparative effectiveness of handheld ultrasound, automated ultrasound and MRI when used as a supplementary screening modality in women with dense breasts and a negative mammogram?

Comment: These are legitimate questions. There is little data regarding screening with these modalities in women of average risk for breast cancer.

3. What are the documented and potential harms with these imaging tests including overdiagnosis and overtreatment, false positive findings, patient anxiety and radiation exposure?

Comment: There is only a theoretical risk of overdiagnosis for invasive breast cancers - no reported case exists in the medical literature. DCIS warrants further study. The only way to prove this is to perform a randomized control trial and follow the groups for 30 years.

"False-positives" is a pejorative term. A recall for additional imaging (which happens in the majority of abnormal screening interpretations) is not a false-positive. It is reasonable to call a negative biopsy based on an abnormal screening interpretation a false positive.

Patient anxiety has been studied and is short lived. The risk of radiation to the breast for women 40 and older has been thoroughly studied and is negligible. Radiation risk is highest among teenage women and drops rapidly with age so that by age 40 there is likely little if any risk to the breast.

4. What is the differential effectiveness and safety of the test of interest according to such factors as age or ethnicity, comorbidities, breast density, classification, overall breast cancer risk, scan vendor and imaging protocol?

Comment: It is hard to test these variables but it is not unreasonable. If breast density is measured it should be obtained with a computer software program and not by radiologist gestalt. BMI could also be added to the list. The "percent of the breast" that is dense is immeasurable since the denominator is the volume of breast and this cannot be determined. Any study should look at total volume of dense tissue.

5. What are the costs and cost-effectiveness of the imaging modalities of interest?

Comment: These are reasonable questions.

To Whom It May Concern,

RE: Breast Cancer Screening

I wanted to take a few minutes to respond to some of the questions in your “DRAFT Key Questions” of “Appropriate Imaging for Breast Cancer Screening in Special Populations”. I have summarized my comments below and request they be considered during the public comment period.

Regards,

Matthew Larson, MBA  
Gig Harbor, WA  
[matthewllarson@gmail.com](mailto:matthewllarson@gmail.com)

- 1) What is the effectiveness of screening every 1-2 years with digital breast tomosynthesis vs. digital mammography among women aged 40-74 who are at average risk of breast cancer and are candidates for screening mammography?*

Three-dimensional mammography (digital breast tomosynthesis or DBT) has demonstrated the ability to improve net health outcomes in terms of increasing the detection of invasive cancer and reducing false positives. Since approval, more than 100 peer-reviewed publications and scientific presentations have reported findings from women in both investigational and non-investigational settings. The evidence pertaining to these improved health outcomes is summarized below and a full bibliography is also provided.

The major screening trials summarized above demonstrate favorable results when directly comparing the results of breast tomosynthesis to the use of 2D mammography alone. While results vary, they clearly show evidence of the improvement in outcomes when including 3D mammography in a screening paradigm.

It should be noted that 3D mammography is not indicated for screening use without concurrent use of traditional 2D mammography. Therefore, it can be reasonably expected that mammography with breast tomosynthesis will be at least as beneficial as 2D mammography alone. There have been no studies that demonstrate poorer outcomes using breast tomosynthesis, all have demonstrated an overall increase in invasive cancer detection and a reduction in recall rates when 3D mammography is added to screening.

Conventional 2D mammography has two major limitations. First, the sensitivity in detecting breast cancers is relatively low, estimated by some to be as low as 70% (Pisano, Gastonis, & Hendrick, 2005). Second, recall rates in U.S. institutions are frequently above the 10%

threshold recommended by the American College of Radiology (Rauscher, Murphy, Orsi, Dupuy, Grabler, & Weldon, 2014). The primary reason for the low sensitivity and high recall rates of 2D mammograms is attributed to the superimposition of overlapping breast tissue (Bird, Wallace, & Yankaskas, 1992). 3D mammography overcomes the limitations of conventional 2D mammography by eliminating artifacts and distortions created by tissue superimposition. Mammography with breast tomosynthesis is addressing the weaknesses raised in the heightened debate on the value of screening mammography, by significantly improving sensitivity, specificity, and positive predictive value. Perhaps rather than looking at DBT as a replacement for digital mammography, it would be wise to consider DBT an alternative covered service with the recommendation that it be reimbursed at an increased rate, above digital mammography alone.

### Earlier Detection

There is a large body of data available demonstrating the value of breast tomosynthesis. In terms of the impact of breast tomosynthesis on cancer detection, several recent peer reviewed publications (Skaane, et al., 2013; Ciatto, et al., 2013; Rose, Tidwell, Bujnoch, Krushwaha, Nordmann, & Sexton, 2013; Haas, Kalra, Geisel, Raghu, Durand, & Philpotts, 2013; Destounis, Arieno, & Morgan, 2014) have demonstrated that breast cancer screening with breast tomosynthesis finds significantly more cancers than 2D alone. These are summarized in Table 1 below.

**Table 1**

Study	Cancer Detection:		% Increase with BT	P-value
	Breast Tomosynthesis	2D alone		
Skaane (Norwegian)	8.0/1000	6.1/1000	27%*	0.001
Ciatto (Italian)	8.1/1000	5.3/1000	53%	<0.0001
Rose	5.4/1000	4.0/1000	35%	0.18
Haas	5.7/1000	5.2/1000	10%	0.70
Destounis	5.7/1000	3.8/1000	50%	Not Reported
Friedewald (JAMA)	5.4/1000	4.2/1000	29%	<0.001

\*Adjusted for reader specific performance

Four studies also report the *invasive cancer* detection rate and all report an increase in detection with breast tomosynthesis (Table 2). *Invasive* cancer detection is important because it is known to progress more rapidly than non-invasive cancers (ie: DCIS) and requires more aggressive treatment.

**Table 2**

Study	Invasive Cancer Detection:		% Increase with BT	P-value
	Breast Tomosynthesis	2D alone		
Skaane (Norwegian)	6.4/1000	4.4/1000	40%*	<0.001
Ciatto (Italian)	7.1/1000	4.8/1000	48%	Not Reported
Rose	4.3/1000	3.8/1000	54%	0.07
Friedewald (JAMA)	4.1/1000	2.9/1000	41%	<0.001

\*Adjusted for reader specific performance

The magnitude of additional cancers detected in the studies reported in Tables 1 & 2 should be considered a significant increase. Advances in screening seek to do what breast tomosynthesis has accomplished, an increase in both sensitivity and specificity. More importantly, published data also reports a significant improvement in positive predictive value with breast tomosynthesis.

### Reduced False Positives

Data demonstrates that a reduction in the false-positive rate represents an improvement in health outcomes in terms of a reduction in unnecessary diagnostic imaging procedures and biopsies where cancer is not found.

3) *What are the documented and potential harms associated with these imaging tests, including overdiagnosis and overtreatment, false-positive findings, patient anxiety, and radiation exposure?*

Study	Recall/FPR:	Recall/FPR:	% Reduction in Recall/FPR	p-value
	Breast Tomosynthesis	2D alone		
Skaane (Norwegian)	5.3%*	6.1%*	15%*	<0.001
Ciatto (Italian)	4.3%*	5.0%*	17%*	<0.01
Rose	5.5%	8.7%	37%	<0.001
Haas	8.4%	12.0%	30%	<0.01
Destounis	4.2%	11.5%	63%	<0.0001
Friedewald (JAMA)	9.1%	10.7%	15%	<0.001

\*False positive rates for the European studies were estimated based on the % of cases sent to arbitration.

### Dose with Breast Tomosynthesis

Dose with breast tomosynthesis is at an allowed dose level, and is permitted without issue in the U.S.

In addition, new software is commercially available to create synthesized 2D images from a 3D acquisition. This allows 2D + 3D information to be created at the same dose as U.S. average 2D dose levels (Ochs, 2013).

Two recent publications have documented the usefulness of two dimensional mammograms synthesized from tomosynthesis acquisitions.

The Norwegian trial (Skaane et al) evaluated 24,901 women where both traditional 2D mammograms and 2D mammograms synthesized from breast tomosynthesis acquisitions were available (Skaane, et al., 2014). In the 12,270 women for which the latest version of the synthesized 2D algorithm was used, there was no significant difference in cancer detection using traditional 2D + 3D (7.8 cancers/1000 exams) vs synthesized 2D + 3D (7.7 cancers/1000 exams) or false positive scores (4.6% for traditional 2D + 3D vs 4.5% for synthetic 2D + 3D).

Zuley et al performed a “fully crossed, mode-balanced multicase ( $n = 123$ ), multireader ( $n = 8$ ), retrospective observer performance study” in order to “assess interpretation performance and radiation dose when two-dimensional synthesized mammography (SM) images versus standard full-field digital mammography (FFDM) images are used alone or in combination with digital breast tomosynthesis images.” [13] This study found that probability of malignancy-based mean AUCs for SM and FFDM images alone were statistically similar ( $p=0.85$ ) and that mean AUC for SM plus DBT and FFDM plus DBT were also statistically similar ( $p=0.19$ ).

- 4) *What is the differential effectiveness and safety of the tests of interest according to such factors as age, race or ethnicity, comorbidities, breast density classification, overall breast cancer risk, scan vendor, and imaging protocol?*

#### **Use of Tomosynthesis in Sub-groups (Age, Breast Density)**

Breast tomosynthesis is intended for the entire screening population and several studies have demonstrated the ability to improve performance in screening across the spectrum of breast density and age sub-groups seen in the entire screening population.

The Italian (Ciatto) study reported a statistically significant increase in cancer detection with breast tomosynthesis versus 2D alone in women under the age of 60 ( $p=0.016$ ) as well as those 60 and older ( $p<0.0001$ ). This study also demonstrated an increased cancer detection with mammography using breast tomosynthesis in subgroups of women with low breast density and high breast density, though the increased detection in the subgroup with high density was not statistically significant ( $p=0.25$ ), potentially due to the small number of cancers in this subgroup.

Haas et al reported a decrease in recall rate with breast tomosynthesis versus 2D alone across all age subgroups (<40, 40-49, 50-59, 60-69, 70+), with the decrease being statistically significant in all sub-groups except the 70+ subgroup ( $p=0.38$  for the 70+ subgroup). Similarly, this study reported a decrease in recall rate with breast tomosynthesis versus 2D alone across all breast density sub-groups (predominantly fatty, scattered fibroglandular, heterogeneously dense, extremely dense), with the decrease being statistically significant in all sub-groups except the predominantly fatty subgroup ( $p=0.12$  for the predominantly fatty sub-group).



Finally, Haas et al reported a 30% or more reduction in recall rate with breast tomosynthesis versus 2D alone across all age subgroups (<50, 50-64, 65+) and all breast density subgroups (BIRADS density 1-4).

5) *What are the costs and cost-effectiveness (e.g., cost per cancer detected) of the imaging modalities of interest?*

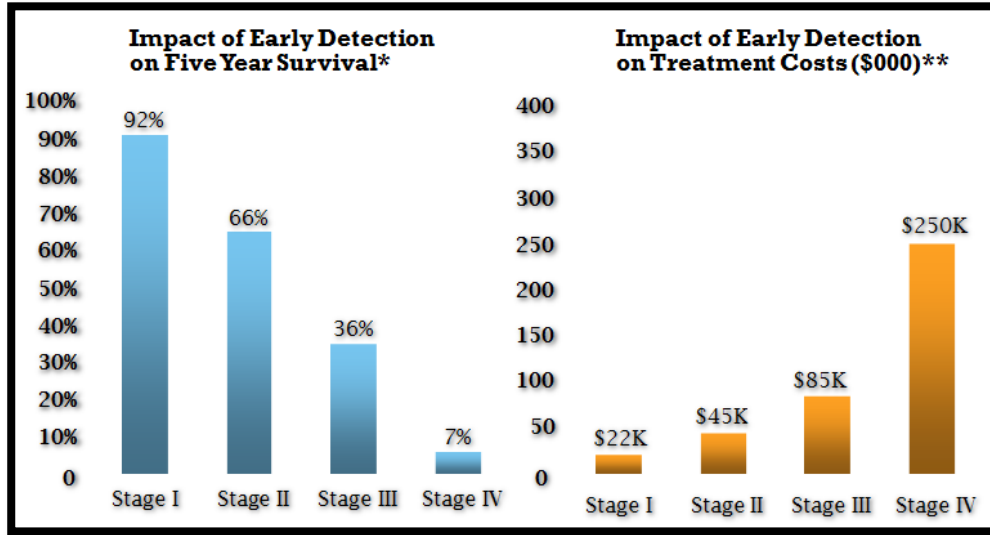
A comprehensive financial analysis has been prepared and submitted for publishing by Truven Health Analytics. The model is based on data from over 70 million patient claims in the MarketScan Research Database. It evaluates the prevalence of, and costs associate with, recall following a *new breast cancer screening mammogram* among women ages 40-75. In addition the model estimated the mean *value of breast cancer costs* in the year following diagnosis (which was distributed by cancer stage using information from published literature). Finally, both a study authored Dr. Gary Levine and data from SEER agree on the costs associated with treating one cancer, as displayed in the Chart 1 & 2, by stage.

**Chart 1**

Staging			
Stage 0-I			
Screening Mammography	75%	Rosenberg, et al., <i>Radiology</i> , 2006, Apdx.	
Symptomatic Referrals	0%		
ABUS	100%	Kelly, et al, <i>Eur Radiol</i> , 2010	
Stage II-IV			
Screening Mammography	25%	Rosenberg, et al., <i>Radiology</i> , 2006, Apdx	
Symptomatic Referrals	100%	Assumption (size greater than 2cm	
ABUS	0%	Kelly, et al, <i>Eur Radiol</i> , 2010	
Costs			
Screening Mammography	\$150	Medicare 2011	
Density Assessment	\$10		
Screening Ultrasound	\$300		
Diagnostic Mammography	\$150	Medicare 2011, rounded	
Diagnostic Ultrasound	\$95	Medicare 2011, rounded	
Mammography Based Biopsy	\$943	Medicare 2011 (combined stereo/US)	
Symptomatic Biopsy	\$969	Medicare 2011, US	
ABUS Biopsy	\$969	Medicare 2011, US	
Stage 0-I Cancer	\$50,000	Surgery + Radiation	
Stage II-IV Cancer	\$250,000	Surgery + Radiation+ Chemotherapy	

Howlader N, Noone AM, Krapcho M, et al. (eds). *SEER Cancer Statistics Review, 1975-2008*, National Cancer Institute. Bethesda, MD, [http://seer.cancer.gov/csr/1975\\_2008/](http://seer.cancer.gov/csr/1975_2008/), based on November 2010 SEER data submission, posted to the SEER web site, 2011.

Chart 2



Ries LAG, Kosary CL, Hankey BF, Miller BA, Clegg L, Edwards BK (eds). SEER Cancer Statistics Review, 1973-1996, National Cancer Institute. Bethesda, MD, 1999.  
 Levine, Gary. "The Benefits of Breast Tomosynthesis As The Primary Screening Modality for Mammography." Lecture and presentation, Marlborough, MA, June, 2011.

If the model were applied to a health plan with 500,000 lives and DBT were reimbursed an additional \$50 over digital mammography the results are astounding; a savings of more than \$1.2M annually with significant reductions in PMPM costs.

Recalls		Patients Recalled per Year		PMPM		Per-Member, Per-Month Costs	
Current Scenario		4,990		Current Scenario		\$ 3.49	
Revised Scenario		2,994		Revised Scenario		\$ 3.29	
Patients not recalled due to DBT use			1,996	Savings PMPM due to DBT			\$ 0.21
Total Costs		Total Annual Costs		Per-Patient Costs		Total Annual Cost Per Screened Patient	
Current Scenario		\$ 20,954,074		Current Scenario		\$ 646.73	
Revised Scenario		\$ 19,713,340		Revised Scenario		\$ 608.44	
Total cost savings due to use of DBT			\$ 1,240,734	Per-patient cost savings due to DBT			\$ 38.29
<b>Attributions:</b>				<b>Attributions:</b>			
Additional expense of DBT in screenings			\$ (1,620,000)	Additional expense of DBT in screenings			\$ (50.00)
Attributable to reduction in recalls			\$ 2,405,566	Attributable to reduction in recalls			\$ 74.25
Attributable to earlier detection			\$ 455,168	Attributable to earlier detection			\$ 14.05

If the model were applied to the state of Washington, the results would be even more impressive, with a reduced burden to the entire health system. Access to DBT in Washington is very good and this is not an unreasonable future scenario.

## Conclusion and Other

All published data to date demonstrate the value of breast tomosynthesis on improving net health outcome. While exact results may vary based on screening protocol, baseline recall rates with digital mammography, and baseline cancer detection with digital mammography, all studies report an increase in invasive cancer detection and a decrease in false-positive recall rates when breast tomosynthesis is implemented. Mammography with breast tomosynthesis in a screening environment addresses the limitations of digital mammography and supports healthcare initiatives aimed at improving patient outcomes, increasing quality measures for providers, streamlining care, and reducing unnecessary costs/resource use. I request you support

## Medical Society Support

On July 22<sup>nd</sup>, 2014 the American College of Radiology released the “ACR Statement on Breast Tomosynthesis” that concluded the following key points in support of DBT:

- *Breast tomosynthesis has shown great promise as an advance over digital mammography, with higher cancer detection rates and fewer patient recalls for additional testing. This is extremely important. The medical community has long sought ways to improve breast cancer screening accuracy. Better sensitivity will likely translate into more lives saved. Lower recall rates result in fewer patients who may experience short-term anxiety awaiting test results.*
  - ✓ This is a key statement in that the ACR shows support for DBT and the value of DBT’s improved breast screening accuracy. It points out that they have been searching for a technology to improve accuracy. The ACR supports DBT as an advance over digital mammography and agrees it has better cancer detection rates and fewer recalls. This statement also shows the support for DBT regarding the patient experience and patient satisfaction.
- *Availability is greatly impacted by reimbursement for the service provided. The College urges the Centers for Medicare and Medicaid Services (CMS) and private insurers to facilitate access to these exams by covering beneficiaries for tomosynthesis - now that it has been shown to improve key screening parameters compared to digital mammography.*
  - ✓ This is the most powerful statement from the ACR as they implore both Private and Government insurers to cover DBT as a mammography screening technology based on proven clinical data supporting improvements compared to digital mammography.
- *It is fairly clear that tomosynthesis represents an important advance in breast imaging.*
  - ✓ This final statement by the ACR shows that based on the clinical data and information on DBT, the ACR feels without question that DBT is the next evolution and important advancement in breast cancer screening.

Additionally, the 2013 The American Society of Breast Disease “Statement on Digital Breast Tomosynthesis” concludes

- *Mammography plus tomosynthesis is an advanced imaging technology for breast cancer screening and diagnosis. The mammography plus tomosynthesis technology produces cross-sectional images*

*by using multiple, low-dose acquisitions with total radiation exposure and breast compression similar to that used for conventional 2D digital mammography.*

- *The addition of mammography plus tomosynthesis to conventional DM improves the accuracy of diagnostic mammographic interpretation. This improvement in diagnostic accuracy can be achieved by enhanced detection of lesion, improvement in the analysis of the margins of a lesion and precise localization of a lesion.*
- *Mammography plus tomosynthesis with DM has a higher sensitivity than DM alone. Published studies showed an increase cancer detection rate of 27 - 30% at screening.*
- *Single center studies have shown that mammography plus tomosynthesis and DM have increased specificity compared to DM alone. Multiple studies noted reduction in the recall rates of screening mammography with the addition of mammography plus tomosynthesis. Recent studies suggest that young women with dense mammographic breast tissue may benefit the most from mammography plus tomosynthesis and may have the greatest reduction in the recall rates.*
- *The three largest published mammography plus tomosynthesis screening studies demonstrate a 40-50% increase in cancer detection rates.*

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July 29, 2014

Dorothy F. Teeter, M.H.A.  
Director  
Health Technology Assessment Program  
P.O. Box 42712  
Olympia, WA 98504-2712

RE: Washington State Health Care Authority Health Technology Assessment draft key questions on Appropriate Imaging for Breast Cancer Screening in Special Populations.

Dear Director Teeter:

The Medical Imaging and Technology Alliance (MITA) is pleased to submit comments on the Washington State Health Care Authority (HCA) Health Technology Assessment (HTA) Draft Key Questions on Appropriate Imaging for Breast Cancer Screening in Special Populations.

Every woman has specific screening needs based on a variety of factors including age, family history, and breast density. It is of the utmost importance that access to the most appropriate screening technology remains intact. This access to screening options based on evidence is a key factor in achieving optimal quality of care and outcomes.

As the leading trade association representing medical imaging, radiotherapy, and radiopharmaceutical manufacturers, we have in-depth knowledge of the significant benefits to the health of Americans that medical imaging and radiotherapy provide. We support efforts that foster appropriate use of these technologies for the early detection, diagnosis, staging, therapy monitoring, and surveillance of many diseases.

Medical imaging encompasses X-ray imaging, computed tomography (CT) scans, related image acquisitions, diagnostic ultrasound, nuclear medicine imaging (including positron emission tomography (PET)), and magnetic resonance imaging (MRI). Medical imaging is used to diagnose patients with disease, often reducing the need for costly medical services and invasive surgical procedures.<sup>1</sup> In addition, medical imaging equipment often is used to select, guide, and facilitate effective treatment,

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<sup>1</sup> See, e.g., Perrier, A et al. "Multidetector-Row Computed Tomography in Suspected Pulmonary Embolism." *New England Journal of Medicine*, 352 (2005) No 17: 1760-1768.

for example, by using image guidance for surgical or radiotherapeutic interventions.<sup>2</sup> MITA's members also develop and manufacture innovative radiotherapy equipment used in cancer treatment.

According to The National Breast Cancer Foundation, 98 percent of breast cancer patients survive – if detection occurs early. There are multiple factors contributing to breast cancer in women. Today, thanks to innovation in imaging, women benefit from a variety of screening options that tailor screening to the patient's unique needs, rather than taking a one-size fits all approach. In addition, for cancers that are detected, imaging informs staging and treatment for improved care.

Our comments address breast density and associated increased risk, screening and its benefits, and current technology used for alternative or additional screening to traditional mammography.

Breast cancer is the most common cancer diagnosed in women, affecting 1 in 8 women in their lifetimes; almost 300,000 women were diagnosed with breast cancer in 2013.<sup>3</sup> Since the introduction of mammography screening, mortality from breast cancer has decreased by 30 percent;<sup>4</sup> however it is still the second most common cause of cancer death in women and almost 40,000 died from it in 2013.<sup>5</sup>

#### *Dense Breast Tissue and Associated Increased Risks*

Breasts are made up of glandular and fatty tissue. Breast density refers to the amount of glandular tissue (which absorbs x-rays and hence appears white on mammographic images, so is called 'x-ray dense' tissue) as opposed to fatty tissue (which appears dark on mammographic images); breast density is not related to the firmness of a woman's breasts, it is a factor of how much x-ray energy is absorbed.

Breast density is determined by the appearance of the breast tissue on a mammogram and is categorized on a BI-RADS (Breast Imaging Reporting and Data System) scale of 1 to 4; BI-RADS 1 breasts have less than 25 percent dense tissue, BI-RADS 2 have between 26 and 50 percent, BI-RADS 3 have 51 to 75 percent, and BI-RADS 4 have over 75 percent dense tissue.

Younger women usually have dense breasts; however, as women age their breast density often decreases. Despite this, dense breasts (BI-RADS 3 or 4) persist as a normal finding in approximately 50 percent of American women who qualify for mammography<sup>6</sup>. One of the challenges in dense breasts is the overlapping tissue that can mask cancer resulting in a false negative, or in some cases mimic cancer, resulting in a false positive.

Compounding the decrease in sensitivity of mammography in women with dense breasts is the fact that the risk of developing breast cancer increases with breast density; the risk of developing breast cancer is four to six times higher in women with dense breast tissue when compared to women with

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<sup>2</sup> See, e.g., Jelinek, JS et al. "Diagnosis of Primary Bone Tumors with Image Guided Percutaneous Biopsy: Experience with 110 Tumors." *Radiology*. 223 (2002): 731-737.

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<sup>5</sup> American Cancer Society. Cancer Facts and Figures 2013-2014 <http://www.cancer.org/research/cancerfactsstatistics/allcancerfactsfigures/index>

<sup>6</sup> <http://breastscreening.cancer.gov/>.



predominately fatty breast tissue.<sup>7,8</sup> Recent research has begun to better understand the underlying pathophysiology of this increased risk.<sup>9</sup>

### *Screening and its Benefits*

Mammography has proven to be effective in significantly reducing mortality,<sup>10</sup> however, in some cases, additional screening tools may be appropriate, especially for women with dense breasts.

The majority of interval breast cancers, which arise in between mammography screening episodes, are attributable to increased breast density.<sup>11</sup> A recent study demonstrates that 81 percent of cancers detected by screening ultrasonography were not seen on mammography, even in retrospective analysis.<sup>12</sup> Breast cancers found in women with dense breast tissue are routinely more advanced and more aggressive than cancers found in women without dense breasts,<sup>13,14,15</sup> hence they have a worse prognosis and require more extensive and more expensive treatments.

The five-year survival rate for breast cancer is 99 percent for localized disease; however, the survival rate dramatically drops with advanced disease.<sup>16</sup> Therefore, early detection of breast cancer results in better outcomes. Data support the effectiveness of supplemental imaging for detecting early stage cancers in women with dense breast tissue. For example, with the use of screening ultrasonography, mostly small, invasive, lymph node negative breast cancers and, hence, early stage cancers, are predominantly identified.<sup>17,18</sup> Even though the benefits of mammography are evident, a screening process should be equally effective for all women, not just the segment of women with fatty breast tissue.

### *Imaging Options*

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<sup>18</sup> U-systems PMA P110006 FDA's Summary of Safety and Effectiveness Data - Multi- Reader Multi- Case Clinical Retrospective Readers Study (CRRS-4) Sept 2012

### **Automated Breast Ultrasound (ABUS)**

In 2012, FDA granted Premarket Approval (PMA) for an automated breast ultrasound device specifically developed for adjunctive imaging. The device is indicated as an adjunct to mammography for breast cancer screening in asymptomatic women for whom screening mammography findings are normal or benign with dense breast parenchyma. This is the first and only medical device specifically FDA-approved for women with dense breast tissue.

This result is supported by the pivotal Multi-Reader Multi-Case Clinical Retrospective Readers Study (CRRS-4) presented within the FDA Safety and Effectiveness Data (SSED) designed to evaluate reader performance when ABUS was used in conjunction with mammography as opposed to mammography alone in asymptomatic women with dense breast tissue.<sup>19</sup> Seventeen radiologists evaluated 200 consecutive cases from the Somo INSIGHT Registry study. The primary endpoint was the identification of any shifts in the Receiver Operating Characteristic (ROC) Curve and the secondary endpoints addressed sensitivity and specificity differences. The area under the ROC Curve was found to increase by 21.5 percent when supplementing mammography with ABUS versus mammography alone in the population indicated for use. Additionally, there was a 35.7 percent increase in cancer detection sensitivity with a 2 percent decrease in specificity. As a result, the FDA unanimously provided Premarket Approval on the safety and effectiveness of this product.

Additionally, a sub-analysis of these data titled *Interreader Scoring Variability in an Observer Study Using Dual-Modality Imaging for Breast Cancer Detection in Women with Dense Breasts* (by Drukker K et al.) was published in the July 2013 edition of *Academic Radiology*.<sup>20</sup> This analysis demonstrated minimal inter-reader variability using ABUS as a screening tool. This study validates the use of ABUS for improved consistency in the clinical environment.

Two other prospective registry studies demonstrate robust preliminary results. These studies are the European Asymptomatic Screening Study (EASY) and the Somo INSIGHT Registry study (Ref: NCT00816530 / USI2008002) which have enrolled over 15,000 patients to date.<sup>21</sup> These studies evaluate the sensitivity and specificity of ABUS in conjunction with mammography vs. mammography alone. Both studies indicate improved sensitivity in identifying small, invasive and node-negative cancers.

### **Magnetic Resonance Imaging (MRI)**

Studies have shown that diffusion-weighted (DWI) MRI imaging may improve the diagnostic accuracy of conventional breast MRI and have the potential to be used as a non-contrast adjunctive imaging. A study by Partridge, et al, noted that DWI increased positive predictive value (PPV) to 47 percent from 37 percent compared to dynamic contrasted enhanced (DCE) MRI alone. Biopsies of 33 percent of the benign lesions could have been avoided without compromising cancer detection.<sup>22</sup> Research by El Khouli et al, indicated that DWI improves the diagnostic performance of conventional MRI where area under the ROC curve improved from 0.89 to 0.98 and the false-positive rate diminished to 24 percent from 36

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<sup>19</sup> FDA. PMA P110006: Summary of Safety and Effectiveness Data (SSED). Retrieved from: [http://www.accessdata.fda.gov/cdrh\\_docs/pdf11/P110006b.pdf](http://www.accessdata.fda.gov/cdrh_docs/pdf11/P110006b.pdf)

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<sup>22</sup> Partridge SC, et. al., Quantitative diffusion-weighted imaging as an adjunct to conventional breast MRI for improved positive predictive value, *AJR*, December 2009, Vol. 193, No 6, pgs 1716-1722

percent in the 25 benign lesions within the 93-patient study.<sup>23</sup> In a noted study with 42 asymptomatic subjects with non-palpable breast cancer, Yabuuchi et al concluded that the addition of DWI could be useful for screening patients when contrast medium is contraindicated.<sup>24</sup> Their results indicated an area under the curve (AUC) of 0.73 with sensitivity of 50 percent for DWI compared to 0.64 AUC and sensitivity of 40 percent for mammography. Combining DWI with mammography was found to increase sensitivity to 69 percent.

### **Breast Tomosynthesis (3D Mammography)**

Breast tomosynthesis was FDA approved in February, 2011 with an indication of clinically superior to 2D mammography for screening.<sup>25</sup> Breast tomosynthesis is a three-dimensional imaging technology that involves acquiring images of a stationary compressed breast at multiple angles during a short scan. The individual images are then reconstructed into a series of thin high-resolution slices that can be displayed individually or in a dynamic ciné mode. Reconstructed tomosynthesis slices reduce or eliminate the problems caused by tissue overlap and structure noise in single slice two-dimensional mammography imaging.

Breast tomosynthesis is an advance in mammography technology that significantly improves the screening of women in all age brackets and addresses some of the current limitations of 2D mammography. This is especially useful for women with dense breasts because the technology has the ability to visualize areas of tissue superimposition. As a front-line screening tool, it will do this through two key clinical benefits that have been shown in studies published in peer-reviewed journals. Large-scale, peer-reviewed clinical research shows that breast cancer screening with breast tomosynthesis finds up to 40 percent more invasive cancers than conventional 2D mammography.<sup>26</sup> Additionally, breast tomosynthesis increases diagnostic accuracy and reduces unnecessary callbacks up to 40 percent.<sup>27</sup> These findings were recently validated in the *Journal of the American Medical Association (JAMA)*, the largest study to date with a total of 454,850 examinations (281,187 conventional mammograms compared to 173,663 3D mammography exams). The results confirmed that breast tomosynthesis finds significantly more invasive cancers than a traditional mammogram – an improvement of 41 percent.<sup>28</sup> The researchers also found that 3D mammography reduces the number of women called back for unnecessary testing due to false alarms by 15 percent. That reduces anxiety, as well as health care costs.

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<sup>23</sup> El Khouli RH, et al., Diffusion-weighted Imaging Improves the Diagnostic Accuracy of Conventional 3.0-T Breast MR Imaging, *Radiology*, July 2010, Vol 256, No 1, pgs 64-73

<sup>24</sup> Yabuuchi H, et. al., Detection of non-palpable breast cancer in asymptomatic women by using unenhanced diffusion-weighted and T2-weighted MR imaging: comparison with mammography and contrast-enhanced MR imaging, *European Radiology*, January 2011, Vol 2, No 1, pgs 11-17

<sup>25</sup> Rafferty et. Al Assessing Radiologist Performance using Combined Digital Mammography and Breast Tomosynthesis Compared with Digital Mammography Alone *Radiology*: Volume 266: Number 1-January 2013

<sup>26</sup> Skaane P, Bandos A, Gullien R, et al. "Comparison of Digital Mammography Alone and Digital Mammography Plus Tomosynthesis in a Population-based Screening Program." *Radiology*. 2013 Apr; 267(1):47-56. Epub 2013 Jan 7. 2013.

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<sup>28</sup> Friedewald S, Rafferty E, et al. "Breast Cancer Screening Using Tomosynthesis in Combination with Digital Mammography." *Journal of the American Medical Association*. 2014 Jun; 311(24): 2499-2507.

Further evidence demonstrates that breast tomosynthesis is effective in all age groups and breast densities in reducing the recall rate. In the Rose study, while the average reduction in false positive results is 37 percent, all age populations realized in improvement in the recall rate as follows:

< 50 years old 37.2 percent  
50-64 years old 32.9 percent  
≥ 65 years old 46.6 percent

Breast tomosynthesis has demonstrated to provide benefits to women of all breast densities, with its ability to visualize areas of tissue superimposition (which are responsible for “masking” in 2D mammography) making breast tomosynthesis especially valuable for women with dense breasts.


The art of breast imaging often relies on a patient-centered multimodality approach. An example of such an approach can be seen with the use of tomosynthesis to minimize false positives and the use of ultrasound to improve sensitivity in dense breast tissue. Combining techniques could optimize outcomes while containing costs and unnecessary workups. The days of a single approach for all patient populations are far behind us. By encouraging transparency, more women will have informed conversations with their physicians about their breast health and be appropriately managed.

These technologies bring an increase in quality of care to women’s health, and access to screening options need to be protected. MITA encourages HCA to examine all evidence including relevant peer-reviewed literature, as they review this technology.

\* \* \* \*

MITA appreciates this opportunity to comment on the 2014 selection of technologies for future review by the Health Technology Assessment (HTA) program. We would be pleased to answer any questions you might have about these comments. Please contact me at (703) 841-3235 if MITA can be of any assistance.

Sincerely,



Gail Rodriguez, Ph.D.  
Executive Director, MITA



QUALITY IS OUR IMAGE

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July 22, 2014

WA State Health Care Authority  
Health Technology Assessment Program  
PO Box 42712  
Olympia, WA 98504-2712

Subject: Washington State Health Technology Assessment Program Appropriate Imaging for Breast Cancer Screening in Special Populations

Program Manager:

The American College of Radiology Committee on Screening and Emerging Technology for Breast Imaging has provided the attached comments of the draft assessment of Appropriate Imaging for Breast Cancer Screening in Special Populations. The committee stresses the importance on not only the text, but the comments in the margin as well. Thank you for the opportunity to review these documents. If you have any questions please feel free to contact me 800-227-6440, x-4595.

Sincerely,

William T. Thorwarth, MD  
Chief Executive Officer  
American College of Radiology

Barbara Monsees, M.D., FACR  
Chair, Commission on Breast Imaging

Edward A. Sickles, M.D., FACR  
Chair, Committee on Screening and Emerging Technology – Breast Imaging

Enclosures (2)

cc: Pamela Wilcox  
Priscilla Butler  
Pamela Platt

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## Draft Key Questions and Background

### Appropriate Imaging for Breast Cancer Screening in Special Populations COMMENTS FROM THE AMERICAN COLLEGE OF RADIOLOGY

Public comments on the draft Key Questions will be accepted until 5 pm, July 29, 2014

#### Background

It is estimated that about one in eight women in the United States will develop invasive breast cancer in her lifetime; breast cancer is also the second-leading cause of cancer death among women, behind only lung cancer (BreastCancer.org, 2014). Some women have an elevated risk of breast cancer, including those who have a personal or family history of the disease, genetic abnormalities (particularly carriers of the BRCA1 and BRCA2 gene mutations), previous instances of chest radiation therapy, or the presence of denser, ~~more fibrous~~ breast tissue.

Early detection is widely considered essential to reduce the risk of breast cancer mortality. Population-based screening with x-ray mammography is considered the standard of care for women over 40 in the United States. Mammography has evolved from film-based to ~~digitally reconstructed two-dimensional imagery~~ full field digital, which has ~~resulted in improved~~ been shown to increase overall visual precision and better sensitivity diagnostic accuracy in some women (Pisano, 2005). However, even digital mammography results in some missed cancers and requires relatively large numbers of some women to be “recalled” for additional screening diagnostic imaging to eliminate concern for cancer, and/or ~~Despite diagnostic imaging, a few women also must undergo needle~~ biopsy, most of whom are ultimately judged not to have cancer (i.e., false positives). In 2011, the FDA approved the use of digital breast tomosynthesis (DBT), ~~a three-dimensional form of an advanced application of digital~~ mammography that has ~~the shown~~ promise of improved cancer detection and lower recall rates in comparison to digital mammography. In addition, the FDA’s recent approval of specialized imaging software has eliminated the need to generate ~~2D and 3D both planar (conventional full field digital) and tomosynthesis~~ images separately, which ~~in effect had~~ doubled the radiation dose to the patient. Now, ~~2D planar~~ images can be generated directly from DBT data, and ~~early~~ recent study suggests that ~~equal-dose~~ results are comparable to the older ~~combination double-dose~~ procedure (Zuley, 2014). Despite this promise, however, questions remain about DBT’s performance over the long-term, ~~its ability to discriminate between early aggressive cancers versus those tumors not likely to grow (i.e., “overdiagnosis”)~~ such as whether it reduces breast cancer mortality, as well as its ~~characteristics relative utility~~ in specific patient subpopulations.

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**Comment [EAS6]:** Changes made to indicate that only a small percentage of recalled women undergo biopsy.

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Imaging technologies used for this purpose typically include magnetic resonance imaging (MRI), as well as ultrasonography. Traditional ultrasounds are is performed using a handheld transducer wand, but a relatively new variant on this technology involves use of an automated transducer that also produces three- dimensional images (Kelly, 2011). As with DBT, there are also questions about the impact of these supplemental screening approaches on cancer detection, overdiagnosis recalls, and false-positive rates.

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There are two major policy considerations surrounding the use of advanced imaging approaches in breast cancer screening. The first is the potential for DBT to replace digital mammography as a frontline screening tool in asymptomatic women. Because this is a new technology, the evidence base is expected to be limited, particularly with respect to long-term patient outcomes.

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Supplemental screening is a generally-accepted practice among women with very strong risk factors for breast cancer, such as BRCA mutations or a personal-significant family history of the disease. However, these represent a small proportion of screened women. In contrast, dense breast tissue is present in nearly 50% of adult-screening-age women (ICER/CTAFBI-RADS, 2013). While the presence of dense breast tissue has also been acknowledged as an independent (although modest) risk factor for breast cancer and denser tissue may mask tumors on standard mammography, little is known about the potential impact of supplemental screening if it were to be expanded to all women with dense breast tissue regardless of overall breast cancer risk.

Nevertheless, within the last decade 5 years, 18 states have passed legislation requiring physicians to notify women if they have dense breast tissue, largely as a result of patient advocacy efforts fueled by situations of missed cancer on mammography (Are You Dense Advocacy, 2014). Some of these mandates also require insurers to cover supplemental screening in such women. Many patient advocacy groups have commended these efforts, stating historically poor communication between the medical community and patients about the limitations of mammography (Lee, 2013). Others are concerned that such mandates are premature, as the current literature does not provide evidence of the benefits of supplemental screening in such a large and diverse

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### Project Scope

This review will involve an evaluation of the evidence within two distinct constructs: (a) use of digital breast tomosynthesis versus digital mammography as a frontline general population screening tool; and (b) use of automated and handheld ultrasound as well as magnetic resonance imaging for supplemental screening in women with dense breast tissue. This project will be an expansion of a previously-conducted systematic review of the published literature on supplemental screening for women with dense breasts (ICER/CTAF, 2013). Specific details on the proposed scope of the updated literature search (Population, Intervention, Comparators, and Outcomes, or PICO) are detailed in the following sections.

### Populations

As described above, the population of interest for the assessment of DBT will include all women age 40-74 who are at average breast cancer risk and are candidates for screening mammography every 1-2 years. The target population for the comparison of supplemental screening modalities will include women with dense breast tissue and a normal mammography result. We will examine clinical trials and observational studies that include women in the BI-RADS categories of “c” (heterogeneously dense) or “d” (extremely dense) (ACR BI-RADS® Atlas, 2013). Both populations will be stratified by a number of important characteristics as the available evidence allows, including age, race/ethnicity, overall breast cancer risk, and others.

### Interventions

We will evaluate the effectiveness, costs, and cost-effectiveness of magnetic resonance imaging (MRI), handheld ultrasonography (HHUS), automated ultrasonography (ABUS), and digital breast tomosynthesis (DBT). Data on these technologies will be collected regardless of manufacturer, imaging protocol, or other test characteristics. Note that, while the focus of attention on supplemental screening technologies will be findings in women with dense breast tissue, results from major clinical studies will also be abstracted to provide overall context for test performance.

### Comparators

The comparator of interest for frontline screening with DBT will be digital mammography. Studies that use film mammography as the primary screening tool will

**Comment [EAS17]:** Why use an upper age limit of 74 years? There is evidence that screening is at least as effective in more elderly women, and many women older than age 74 have substantial life expectancy and little comorbidity to cause them to decline screening. If inclusion of more elderly women (no upper age limit, but using the 3.2 million exam 2008-2013 National Mammography Database data showing steady decline in usage beyond age 74) would severely confound your analysis, then indicate that the reason for using an upper age limit is to simplify analysis, not because that is widely recommended practice.

**Comment [EAS18]:** Presumably you chose 1-2 years to bridge the range of recommended screening interval by many national medical organizations (annual) versus the USPSTF (biennial). However, be clear about how you will perform your analyses. Will you separately assess annual versus biennial screening, will you assume an average of every 1.5 year screening, or will you do it some other way?

**Comment [EAS19]:** Note that breast density assessment data from published clinical trials and observational studies is out-of-date, because the current (2014 going forward) approach to assessing density is based on potential masking of cancer by dense tissue, whereas the previous approach was quartile assessment of the volume of dense breast tissue. The effect of this (clinically relevant) change in approach to density assessment is unknown, but may be substantial. Your review will have to acknowledge this limitation.



be excluded, as nearly 95% (12,790/13,523) of all US mammography machines accredited by the U.S. Food and Drug Administration are now full-field digital (FDA, 2014). We will evaluate supplemental screening technologies against each other, and individually against additional follow-up (with any method) or no follow-up examination in women with dense breasts. In addition, we will consider studies utilizing clinical breast examinations (CBEs) or self-exams following normal prior to mammography.

### Outcomes

Specific outcomes of interest will be focused on the test characteristics of the modalities of interest, including rates of sensitivity and specificity, positive predictive value, recall, and biopsy. Where available, we will also collect data on the impact of screening modality on breast cancer mortality and health-related quality of life. Finally, potential harms of interest will include false-positive findings and unnecessary biopsy, overdiagnosis and overtreatment, missed cancers, and radiation exposure. Information on the costs and cost-effectiveness of each screening method will also be collected where available.

### Analytic Framework

The proposed analytic frameworks for this project are depicted below and on the following page. As is the case for many screening or diagnostic tests, it is expected that data linking screening modalities to direct patient outcomes will be limited, requiring instead a series of conceptual links between test characteristics and the major outcomes of interest.

### Analytic Framework: Breast Cancer Screening

#### Search A

Excluded patients: high-risk patients defined as having personal history, genetic susceptibility, previous chest radiation at age < 30 years, substantial family history

Study patients: all asymptomatic women age 40-74 at average breast cancer risk

Study arms: Screening with digital breast tomosynthesis (DBT) versus screening with digital mammography (DM)

Outcomes: sensitivity, specificity, PPV, recall rate, biopsy, breast cancer mortality, health related quality of life

Harms: false-positive findings, unnecessary and biopsy, overdiagnosis and overtreatment, missed cancers, radiation exposure

#### Search B

**Comment [EAS20]:** Since you are assessing the utility of DBT as a "better mammogram" (to be used instead of digital mammography), you also should evaluate supplemental screening compared to DBT (by modeling data acquired in studies that compare supplemental screening to digital mammography). This is very relevant because if DBT is validated, supplemental screening will have less potential for increase cancer detection; also, the excess of recalls from supplemental screening and DBT will be much greater than it is between supplemental screening and digital mammography.

**Comment [EAS21]:** Clinical breast exam and/or breast self-exam, if performed, should precede (not follow) mammography. Women with palpable lumps at breast exam should undergo diagnostic rather than screening mammography. Women with palpable lumps should be excluded from screening studies (if palpation is performed prior to mammography), or the studies will be seriously flawed).

**Comment [EAS22]:** The term "unnecessary" biopsy is a misnomer (the correct term is false-positive biopsy). When imaging raises suspicion of malignancy that cannot be eliminated by other means, biopsy is necessary for ultimate diagnosis, to exclude the possibility of malignancy.

**Comment [EAS23]:** [1] Overdiagnosis (and downstream overtreatment) must be defined precisely. Since overdiagnosis cannot be measured directly, it is critical to evaluate published studies in the context of whether appropriate adjustments were made for lead time and underlying incidence trends (see the attached PDF of the most recent article describing the strengths and limitations of various approaches to estimating overdiagnosis: Smith RA. J Am Coll Radiol 2014; 11(7):648-652).

**Comment [EAS24]:** Personal history deleted, as per comment #12.

**Comment [EAS25]:** Previous chest radiation is associated with increased cancer risk only if exposure is at age < 30 years.

**Comment [EAS26]:** Substantial family history added, as per comment #12.

**Comment [EAS27]:** See comment #15 about use of age 74 as the upper age limit for study.

**Comment [EAS28]:** "Unnecessary" deleted, as per comment #20.

Excluded Patients: [high-risk patients defined as having personal history](#), genetic susceptibility, previous chest radiation [at age < 30 years](#), [substantial family history](#). [Also non-dense breast tissue](#)

Study patients: all [asymptomatic](#) women age 40-74 with "heterogeneously" or "extremely" dense breast tissue who have no abnormalities detected at screening with digital mammography

Study arms: Follow-up screening with magnetic resonance imaging (MRI) versus follow-up screening with hand-held ultrasonography (HHUS) versus follow-up screening with automated whole breast ultrasonography (ABUS) versus no follow-up screening

Outcomes: sensitivity, specificity, PPV, recall rate, biopsy, breast cancer mortality, health related quality of life; [compare outcomes with each type of supplemental screening versus no follow-up screening using \[1\] digital mammography and \[2\] digital breast tomosynthesis](#)

Harms: false-positive findings, [unnecessary and](#) biopsy, overdiagnosis and overtreatment, missed cancers, radiation exposure

### DRAFT Key Questions

A number of key questions are felt to be of importance for this project. Each question is listed below, along with the type of evidence that will be examined.

- 1) What is the [effectiveness](#) of screening every 1-2 years with digital breast tomosynthesis vs. digital mammography among women aged 40-74 who are at average risk of breast cancer and are candidates for screening [mammography](#)?
- 2) What is the comparative effectiveness of handheld [ultrasonography](#), automated ultrasonography, and magnetic resonance imaging when used as supplemental screening modalities in women with dense breast tissue and a negative [mammogram](#)?
- 3) What are the documented and [potential harms](#) associated with these imaging tests, including overdiagnosis and [overtreatment](#), false-positive findings, patient anxiety, and radiation exposure?
- 4) What is the differential effectiveness and safety of the tests of interest according to such factors as age, race or ethnicity, comorbidities, breast density classification, overall breast cancer risk, scan vendor, and imaging [protocol](#)?
- 5) What are the costs and cost-effectiveness (e.g., cost per cancer detected) of the imaging modalities of interest?

### REFERENCES:

Agency for Healthcare Research & Quality (AHRQ). Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Rockville, MD: Department of Health and Human

**Comment [EAS29]:** Personal history deleted, as per comments #12 and #22.

**Comment [EAS30]:** Text added about age of exposure to chest radiation, as per comment #23.

**Comment [EAS31]:** Substantial family history added, as per comments #12 and #24.

**Comment [EAS32]:** This exclusion is used because there is no substantial cancer masking at mammography by non-dense breast tissue (dense tissue is not a substantial risk factor).

**Comment [EAS33]:** See comment #15 about use of age 74 as the upper age limit for study.

**Comment [EAS34]:** Text added, as per comment #18.

**Comment [EAS35]:** "Unnecessary" deleted, as per comments #20 and #26.

**Comment [EAS36]:** For all these key questions it will be key to define "effectiveness". As currently written several outcomes are analyzed, but it is unclear how "effectiveness" will be defined.

**Comment [EAS37]:** You are asking two questions here: DBT versus digital mammography and screening annually versus biennially. This will confound analysis of outcomes. It would be far better to ask two separate questions.

**Comment [EAS38]:** Handheld ultrasonography may be performed in a variety of ways: solely by radiologist, solely by technologist, initially by technologist and then by radiologist as needed. Somewhat different outcomes are reported for these different approaches (higher cancer detection rate if physicians perform the exam), but the data are sparse.

**Comment [EAS39]:** As per comments #18 and #32, comparative effectiveness should be assessed versus digital mammography and also versus DBT (because DBT is being assessed as a replacement for digital mammography).

**Comment [EAS40]:** You must understand (and communicate to your readers) that lengthening the age at which screening starts and/or lengthening the interval between screening exams will have no effect on the frequency of overdiagnosis (and overtreatment). So long as [any](#) screening is performed after a screening exam averted out of concern about overdiagnosis, each and every "overdiagnosed" cancer whose detection was averted will still be present, mammographically visible, and ripe for overdiagnosis when screening is performed later. You must make it clear in your report that although overdiagnosis may be one of the harms of screening, little can be done to overcome it apart from recommending no screening at all (equivalent to throwing out the baby with the bath water). Hence, overdiagnosis is an ...

**Comment [EAS41]:** What is meant by "safety"? What is meant by "imaging protocol"?

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Public Comment & Response

See Key Question Public Comment and Response document published separately. [For additional information on key questions and public comments.](#)

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relative to the potential harms of patient anxiety, overdiagnosis, and false-positive findings.

### Project Scope

This review will involve an evaluation of the evidence within two distinct constructs: (a) use of digital breast tomosynthesis versus digital mammography as a frontline general population screening tool; and (b) use of automated and handheld ultrasound as well as magnetic resonance imaging for supplemental screening in women with dense breast tissue. This project will be an expansion of a previously-conducted systematic review of the published literature on supplemental screening for women with dense breasts (ICER/CTAF, 2013). Specific details on the proposed scope of the updated literature search (Population, Intervention, Comparators, and Outcomes, or PICO) are detailed in the following sections.

### Populations

As described above, the population of interest for the assessment of DBT will include all women age 40-74 who are at average breast cancer risk and are candidates for screening mammography every 1-2 years. The target population for the comparison of supplemental screening modalities will include women with dense breast tissue and a normal mammography result. We will examine clinical trials and observational studies that include women in the BI-RADS categories of “c” (heterogeneously dense) or “d” (extremely dense) (ACR BI-RADS® Atlas, 2013). Both populations will be stratified by a number of important characteristics as the available evidence allows, including age, race/ethnicity, overall breast cancer risk, and others.

### Interventions

We will evaluate the effectiveness, costs, and cost-effectiveness of magnetic resonance imaging (MRI), handheld ultrasonography (HHUS), automated ultrasonography (ABUS), and digital breast tomosynthesis (DBT). Data on these technologies will be collected regardless of manufacturer, imaging protocol, or other test characteristics. Note that, while the focus of attention on supplemental screening technologies will be findings in women with dense breast tissue, results from major clinical studies will also be abstracted to provide overall context for test performance.

### Comparators

The comparator of interest for frontline screening with DBT will be digital mammography. Studies that use film mammography as the primary screening tool will be excluded, as nearly 95% (12,790/13,523) of all US mammography machines accredited by the U.S. Food and Drug Administration are now full-field digital (FDA, 2014). We will evaluate supplemental screening technologies against each other, and individually against additional follow-up (with any method) or no follow-up examination

**Comment [EAS16]:** Why use an upper age limit of 74 years? There is evidence that screening is at least as effective in more elderly women, and many women older than age 74 have substantial life expectancy and little comorbidity to cause them to decline screening. If inclusion of more elderly women (no upper age limit, but using the 3.2 million exam 2008-2013 National Mammography Database data showing steady decline in usage beyond age 74) would severely confound your analysis, then indicate that the reason for using an upper age limit is to simplify analysis, not because that is widely recommended practice.

**Comment [EAS17]:** Presumably you chose 1-2 years to bridge the range of recommended screening interval by many national medical organizations (annual) versus the USPSTF (biennial). However, be clear about how you will perform your analyses. Will you separately assess annual versus biennial screening, will you assume an average of every 1.5 year screening, or will you do it some other way?

**Comment [EAS18]:** Note that breast density assessment data from published clinical trials and observational studies is out-of-date, because the current (2014 going forward) approach to assessing density is based on potential masking of cancer by dense tissue, whereas the previous approach was quartile assessment of the volume of dense breast tissue. The effect of this (clinically relevant) change in approach to density assessment is unknown, but may be substantial. Your review will have to acknowledge this limitation.

in women with dense breasts. In addition, we will consider studies utilizing clinical breast examinations (CBEs) or self-exams prior to mammography.

### Outcomes

Specific outcomes of interest will be focused on the test characteristics of the modalities of interest, including rates of sensitivity and specificity, positive predictive value, recall, and biopsy. Where available, we will also collect data on the impact of screening modality on breast cancer mortality and health-related quality of life. Finally, potential harms of interest will include false-positive findings and biopsy, overdiagnosis and overtreatment, missed cancers, and radiation exposure. Information on the costs and cost-effectiveness of each screening method will also be collected where available.

### Analytic Framework

The proposed analytic frameworks for this project are depicted below and on the following page. As is the case for many screening or diagnostic tests, it is expected that data linking screening modalities to direct patient outcomes will be limited, requiring instead a series of conceptual links between test characteristics and the major outcomes of interest.

### Analytic Framework: Breast Cancer Screening

#### Search A

Excluded patients: high-risk patients defined as having genetic susceptibility, previous chest radiation at age < 30 years, substantial family history

Study patients: all asymptomatic women age 40-74 at average breast cancer risk  
Study arms: Screening with digital breast tomosynthesis (DBT) versus screening with digital mammography (DM)

Outcomes: sensitivity, specificity, PPV, recall rate, biopsy, breast cancer mortality, health related quality of life

Harms: false-positive findings and biopsy, overdiagnosis and overtreatment, missed cancers, radiation exposure

#### Search B

Excluded Patients: high-risk patients defined as having genetic susceptibility, previous chest radiation at age < 30 years, substantial family history. Also non-dense breast tissue

**Comment [EAS19]:** Since you are assessing the utility of DBT as a "better mammogram" (to be used instead of digital mammography), you also should evaluate supplemental screening compared to DBT (by modeling data acquired in studies that compare supplemental screening to digital mammography). This is very relevant because if DBT is validated, supplemental screening will have less potential for increase cancer detection; also, the excess of recalls from supplemental screening and DBT will be much greater than it is between supplemental screening and digital mammography.

**Comment [EAS20]:** Clinical breast exam and/or breast self-exam, if performed, should precede (not follow) mammography. Women with palpable lumps at breast exam should undergo diagnostic rather than screening mammography. Women with palpable lumps should be excluded from screening studies (if palpation is performed prior to mammography), or the studies will be seriously flawed).

**Comment [EAS21]:** The term "unnecessary" biopsy is a misnomer (the correct term is false-positive biopsy). When imaging raises suspicion of malignancy that cannot be eliminated by other means, biopsy is necessary for ultimate diagnosis, to exclude the possibility of malignancy.

**Comment [EAS22]:** [1] Overdiagnosis (and downstream overtreatment) must be defined precisely. Since overdiagnosis cannot be measured directly, it is critical to evaluate published studies in the context of whether appropriate adjustments were made for lead time and underlying incidence trends (see the attached PDF of the most recent article describing the strengths and limitations of various approaches to estimating overdiagnosis: Smith RA. J Am Coll Radiol 2014; 11(7):648-652).

**Comment [EAS23]:** Personal history deleted, as per comment #12.

**Comment [EAS24]:** Previous chest radiation is associated with increased cancer risk only if exposure is at age < 30 years.

**Comment [EAS25]:** Substantial family history added, as per comment #12.

**Comment [EAS26]:** See comment #15 about use of age 74 as the upper age limit for study.

**Comment [EAS27]:** "Unnecessary" deleted, as per comment #20.

**Comment [EAS28]:** Personal history deleted, as per comments #12 and #22.

**Comment [EAS29]:** Text added about age of exposure to chest radiation, as per comment #23.

**Comment [EAS30]:** Substantial family history added, as per comments #12 and #24.

**Comment [EAS31]:** This exclusion is used because there is no substantial cancer masking at mammography by non-dense breast tissue (dense tissue is not a substantial risk factor).



Study patients: all asymptomatic women age 40-74 with "heterogeneously" or "extremely" dense breast tissue who have no abnormalities detected at screening with digital mammography

Study arms: Follow-up screening with magnetic resonance imaging (MRI) versus follow-up screening with hand-held ultrasonography (HHUS) versus follow-up screening with automated whole breast ultrasonography (ABUS) versus no follow-up screening

Outcomes: sensitivity, specificity, PPV, recall rate, biopsy, breast cancer mortality, health related quality of life; compare outcomes with each type of supplemental screening versus no follow-up screening using [1] digital mammography and [2] digital breast tomosynthesis

Harms: false-positive findings and biopsy, overdiagnosis and overtreatment, missed cancers, radiation exposure

### DRAFT Key Questions

A number of key questions are felt to be of importance for this project. Each question is listed below, along with the type of evidence that will be examined.

- 1) What is the effectiveness of screening every 1-2 years with digital breast tomosynthesis vs. digital mammography among women aged 40-74 who are at average risk of breast cancer and are candidates for screening mammography?
- 2) What is the comparative effectiveness of handheld ultrasonography, automated ultrasonography, and magnetic resonance imaging when used as supplemental screening modalities in women with dense breast tissue and a negative mammogram?
- 3) What are the documented and potential harms associated with these imaging tests, including overdiagnosis and overtreatment, false-positive findings, patient anxiety, and radiation exposure?
- 4) What is the differential effectiveness and safety of the tests of interest according to such factors as age, race or ethnicity, comorbidities, breast density classification, overall breast cancer risk, scan vendor, and imaging protocol?
- 5) What are the costs and cost-effectiveness (e.g., cost per cancer detected) of the imaging modalities of interest?

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**Comment [EAS32]:** See comment #15 about use of age 74 as the upper age limit for study.

**Comment [EAS33]:** Text added, as per comment #18.

**Comment [EAS34]:** "Unnecessary" deleted, as per comments #20 and #26.

**Comment [EAS35]:** For all these key questions it will be key to define "effectiveness". As currently written several outcomes are analyzed, but it is unclear how "effectiveness" will be defined.

**Comment [EAS36]:** You are asking two questions here: DBT versus digital mammography and screening annually versus biennially. This will confound analysis of outcomes. It would be far better to ask two separate questions.

**Comment [EAS37]:** Handheld ultrasonography may be performed in a variety of ways: solely by radiologist, solely by technologist, initially by technologist and then by radiologist as needed. Somewhat different outcomes are reported for these different approaches (higher cancer detection rate if physicians perform the exam), but the data are sparse.

**Comment [EAS38]:** As per comments #18 and #32, comparative effectiveness should be assessed versus digital mammography and also versus DBT (because DBT is being assessed as a replacement for digital mammography).

**Comment [EAS39]:** You must understand (and communicate to your readers) that lengthening the age at which screening starts and/or lengthening the interval between screening exams will have no effect on the frequency of overdiagnosis (and overtreatment). So long as any screening is performed after a screening exam averted out of concern about overdiagnosis, each and every "overdiagnosed" cancer whose detection was averted will still be present, mammographically visible, and ripe for overdiagnosis when screening is performed later. You must make it clear in your report that although overdiagnosis may be one of the harms of screening, little can be done to overcome it apart from recommending no screening at all (equivalent to throwing out the baby with the bath water). Hence, overdiagnosis is an unavoidable and uncorrectable harm of all types of screening.

**Comment [EAS40]:** What is meant by "safety"? What is meant by "imaging protocol"?

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Public Comment & Response

See Key Question Public Comment and Response document published separately. [For additional information on key questions and public comments.](#)