Public Comments
Received before 12/13/13 (in order of receipt)

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December 8, 2013

Review of the ICER report for The New England Comparative Effectiveness Public Advisory Council in preparation for the Public Meeting – December 13, 2013.
I have reviewed only the first section of the ICER summary and have summarized some of the factual problems with their statement at the end of this summary.

FACTS:

1. Mammography screening for women ages 40 and over is the main reason that the death rate from breast cancer has declined by more than 30% since 1990.
2. Efforts are ongoing to try to reduce access for women to mammography screening.
3. Mammography does not find all cancers and does not find all cancers at a time when cure is possible, but full participation in screening could reduce the death rate by 50% or perhaps more.
4. The breast is composed of
    a. Glandular tissue
    b. Fibrous connective tissue
    c. Ducts
    d. Fat
    e. Skin.
5. Glandular tissue, fibrous connective tissue, ducts and skin are "dense" on mammograms. There is no correlation between breast tissue "density" and the firmness of the tissue on palpation. "Dense" tissue cannot be felt, it can only be determined by imaging.
6. Dense tissues cast shadows that can hide cancers which have similar "density" on mammograms. Although mammography finds most breast cancers, even in dense tissue, it is somewhat less sensitive when the tissues are dense.
7. Depending on how you measure density, as many as 65% of all women are classified as having moderate to high amounts of dense tissue. Breast density is far more common than breasts that are all fat.

8. There is a large body of literature that suggests that dense tissues raise the risk of breast cancer. These are, fundamentally, flawed since they relied on measurements that ignored the basic physics of mammography (1). There is probably a slight increase in risk for the extremely dense breasts compared to the all fat breasts, but each of these make up only 10% of women. Approximately 80% of women have somewhat fatty or heterogeneous dense tissues and there is no apparent difference in the risk of breast cancer for these women.

SCREENING FOR BREAST CANCER

The fact is that mammography screening is the main reason that the death rate from breast cancer has declined in the U.S. since 1990 following the onset of mammography screening at a National level in the mid 1980's (2). This is true for screening beginning at the age of 40. Even the US Preventive Services Task Force (USPSTF) and the American College of Physicians agree. The latter two organizations, however, have, unfortunately, imposed their own values and decided that they do not feel that the "harms" of screening are worth saving lives while women are in their forties. They have ignored the fact that more than 40% of the years of life lost to breast cancer are among women diagnosed in their forties (3). As noted below, there is no scientific or biological reason to delay screening until the age of 50. It is a completely arbitrary threshold, but women have been told that there is scientific support for waiting until the age f 50 when there is none. Nevertheless, there is a major effort underway to try to reduce access to mammography screening by using methodologically flawed analyses to drop support for screening women ages 40-49, and to increase the time between screens to every 2 years instead of annually. It makes no sense to allow cancers to grow for an extra year, and the papers supporting biennial screening over annual make no biological sense. Cancer does not stop and wait to grow, and to metastasize. Therapy has improved, but it is clear that therapy saves lives when breast cancers are treated earlier.

That said, mammography is far from the ultimate answer to breast cancer. Although annual screening from age 40 and up will result in a 30-50% reduction in deaths, there, tragically, are still women whose lives are not saved by mammography screening. Some of these women have cancers that spread to other organs before any test can find them. Some have cancers that are hidden by normal breast tissue like trying to find a birch tree in a pine forest. I invented, and my group developed, Digital Breast Tomosynthesis to eliminate some of the masking of tumors by normal breast tissue on mammograms. We hope that this will lead to an additional reduction in breast cancer deaths.

Dr. Priscilla Slanetz, in my group at the Massachusetts General Hospital, was the first to show that Magnetic Resonance Imaging could reveal breast cancers that are hidden on conventional mammograms. MRI screening could well drive down the death rate, but it is very expensive and it requires the intravenous injection of a contrast agent. In addition, the "false positive" rate is higher than mammography which is under attack for being too high. MRI screening is advised for women who are at very high risk, but it is unlikely to be useable for women at average risk who make up 75% of the women diagnosed with breast cancer each year.

Ultrasound is another test that can find some cancers that are not evident on mammograms because they are hidden by normal breast tissues. Since there have been no randomized

controlled trials of ultrasound screening, there is no proof that finding these lesions will, actually, save lives. In addition there are many more "lesions" found using ultrasound that raise concerns, but , ultimately, prove to not be cancer than there are similar lesions found on mammograms, yet mammography is being attacked for having too many "recalls". At this point in time, breast ultrasound screening is, primarily, accomplished using hand held probes and is completely operator dependent and time consuming. Automated screening devices, although being approved by the FDA, have yet to be tested in large, prospective trials. The biggest concern is the very high biopsy rate for what prove to be noncancerous findings resulting from these studies.

There is no objection to providing women with the radiologist's assessment of their tissue "density". Women and their doctors should know that this is a subjective assessment. Computer segmentation is more reproducible, but its true value is unproven. The problem will come if women are advised to have additional screening with ultrasound or MRI which will result in much higher health care costs, recalls for additional evaluations, and biopsies with benign results without clear proof of any benefit. Mammography screening is not the ultimate answer to breast cancer, but it has major scientific support. Before any new rules are developed, women need to be guaranteed access to mammography screening, annually beginning at the age of 40. If women lose access to screening mammography, then screening using ultrasound or MRI, with far less scientific support, will be eliminated as well.

PARTIAL REVIEW OF THE ICER DOCUMENT

Page 6:

The death rate from breast cancer has declined by over 30% since 1990. The 28% is an old figure from 2008.

ICER: "The median values from a series of models estimated that a little more than half of the decline was due to improvements in therapy for breast cancer and that a little less than half (46%) was due to early diagnosis from mammography."

FACTS: It should be noted that this was a summary of models. The results of models are determined by the assumptions programmed into the model, and these dictate the results. This is clearly seen by the fact that the 7 models varied in their estimates from 23%-65%. There is no justification for taking the average of models that do not reproduce "real-life". Actual data from patients suggests that the decline in deaths is likely due, predominantly, to screening (4,5,6,7,8,9,10,11,12,13,14). Therapy saves lives when cancers are found and treated earlier.

ICER: "Bleyer and Welch estimated that 31% of breast cancer diagnosed with mammography represents “overdiagnosis” (i.e. , identification of cancers unlikely to cause significant morbidity or mortality) and concluded that screening mammography has had, at best, only a small effect on breast cancer mortality.7"

FACTS: The summary of Bleyer and Welch is misleading and incomplete and should not be passed on as if it is factual. ICER appears to be unaware of the major methodological errors in that paper (15,16). There is little if any overdiagnosis of invasive breast cancers (17). ICER repeats the, completely, false suggestion that tens of thousands of cancers may be "overdiagnosed" each year. Those who suggest there is massive overdiagnosis claim that these cancers, if left undiscovered, would regress and disappear without treatment. If there were tens of thousands of these cancers every year, why is there not a single report of an invasive breast cancer regressing and disappearing on its own? The suggestion is totally without scientific merit.

ICER: "For average-risk women between the ages of 40 to 49 years, there remains significant controversy about whether the benefits of routine mammography outweigh the harms, but most guidelines recommend either routine mammography or a discussion of the benefits and risks of mammography".

FACTS: The controversy is completely manufactured (18). The trials of mammography screening have always shown a decline in breast cancer mortality for screening women ages 40 and over. None of the parameters of screening change abruptly at the age of 50 or any other age (19). The age of 50 has no biological or scientific reason to be used as a threshold (20). The models used by the US Preventive Services Task Force (USPSTF), and provided with the Task force statement, showed that the most lives are saved by annual screening beginning at the age of 40 (21). Using the same models that were used by the USPSTF, Hendrick and Helvie have shown that if women, now in their thirties, follow the USPSTF guidelines, as many as 100,000 lives will be lost that could be saved by screening annually beginning at the age of 40 (22).

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ICER: " Thus, across the United States, for every 1000 mammograms performed approximately 100 women will be recalled and 10 will have a biopsy to detect about 5 cancers. One of those cancers will be DCIS (~20%), four will be lymph node negative (~80%), and 3 or 4 (~75%) will be stage 0 or 1.74 These statistics will vary when looking at different subgroups of women or different screening technologies. For instance, younger women have more false positive mammography assessments and a lower risk for cancer, so their recall rate will be higher and the number of cancers detected will be lower."

FACTS: The ICER review provides no frame of reference for the reader.

1. The recall rate for mammography is the same as the recall rate for cervical cancer screening (Pap testing) - approximately 10%.
2. A biopsy rate yielding cancer at 30-50% is excellent. When a surgeon feels a lump and performs a biopsy based only on the physical examination, the yield of cancer is much lower at 15% (23) and the size of the cancers is larger and they are generally later stage and less likely to be cured than those detected by mammography.

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ICER: " It is currently impossible to know whether any particular patient whose cancer is detected by mammography is or is not at risk of the cancer being "overdiagnosed," and the true magnitude of overdiagnosis for breast cancer is unclear and controversial."

FACTS: It is misleading to imply that "overdiagnosis" and "overtreatment" are confined to mammographically detected cancers. There is legitimate discussion about the importance and treatment of DCIS lesions, but there are no data to suggest that mammographically detected invasive cancers have any less lethal potential than those that are clinically evident. The only difference is that mammographically detected lesions are treated at a smaller size and earlier stage and cure, although not guaranteed, is more likely.

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Continuation to previous comments from Dr. Kopans:

RADIATION RISK

1. All of the radiation risk estimates are based on extrapolations from high doses.

2. There is no direct proof that even high doses increase the risk of breast cancer for women ages 40 and over (Kopans DB. Just the facts: mammography saves lives with little if any radiation risk to the mature breast. Health Phys. 2011 Nov;101(5):578-82.).

3. Even the extrapolated risk is well below even the smallest reduction in breast cancer deaths (Mettler FA, Upton AC, Kelsey CA, Rosenberg RD, Linver MN. Benefits versus Risks from Mammography: A Critical Assessment. Cancer 1996;77:903-909.).

4. No one has ever been shown to develop a breast cancer from a mammogram

5. Since 1985 hundreds of millions of mammograms have been performed in the U.S. If mammography were causing cancers then the incidence of breast cancer should have increased in the late 1990's (10 year latency). Instead, the incidence of breast cancer began to decline in 1999.

6. Yaffe and Mainprize did not provide any frame of reference in their paper (Yaffe MJ, Mainprize JG. Risk of radiation-induced breast cancer from mammographic screening. Radiology. Jan 2011;258(1):98-105..) namely how many cancers would "naturally" occur and how many deaths would occur among the 100,000 women in the absence of mammography. I would estimate that among 100,000 women ages 40-75, used in their analysis, approximately 8250 cancers would occur among these women "naturally" and 4125 of these women would die in the absence of mammography vs. the estimated 86 possibly induced by mammography and 11 deaths. Assuming mammography reduces deaths by 30%, this would suggest that approximately 1200 lives would be saved by mammography

Thanks

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December 9, 2013

BY ELECTRONIC DELIVERY

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Chair
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RE: The Comparative Clinical Effectiveness and Value of Supplemental Screening Tests Following Negative Mammography in Women with Dense Breast Tissue

Dear Dr. Gruss:

The Medical Imaging & Technology Alliance (MITA) is pleased to submit comments on the New England Comparative Effectiveness Public Advisory Council (CEPAC)'s Draft Report entitled *The Comparative Clinical Effectiveness and Value of Supplemental Screening Tests Following Negative Mammography in Women with Dense Breast Tissue* ("Draft Report"). MITA has extensive knowledge of the substantial benefits afforded by medical imaging and radiation therapy to the health of Americans due to our role as the leading trade association representing medical imaging, radiation therapy, and radiopharmaceutical manufacturers. We support quality 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, diagnostic ultrasound, nuclear imaging (including positron emission tomography (PET)), magnetic resonance imaging (MRI), and related imaging acquisitions. Medical imaging is used to diagnose patients with disease, often reducing the need for costly medical services and invasive surgical procedures.[1] In addition, medical imaging equipment often is used to select, guide, and facilitate effective treatment, for example, by using image guidance for surgical or

[1] *See, e.g.*, Perrier, et al., "Multidetector-Row Computed Tomography in Suspected Pulmonary Embolism," *New England Journal of Medicine*, 352(2005): 1760-1768.

radiotherapeutic interventions.[2] MITA's members also develop and manufacture innovative radiotherapy equipment used in cancer treatment.

Our comments address five areas in the Draft Report: (1) General Comments, (2) Hand-Held Ultrasonography, (3) Automated Breast Ultrasound, (4) Magnetic Resonance Imaging (MRI), and (5) Analyses.

1. General Comments

Mammography has helped to reduce breast cancer mortality in the US; however, many patients require adjunctive imaging because they have dense breast tissue. We must continue to expand and provide patient access to adjunctive breast imaging. Limiting access may increase the likelihood that breast cancers will go undiagnosed.

2. Hand-Held Ultrasonography (HHUS)

MITA is concerned that CEPAC is delineating ultrasound systems by design features rather than functions. "Hand-Held" does not reflect the functionality of the system or any classification used by the Food and Drug Administration (FDA). The use of ultrasound needs to be assessed based on all the peer-reviewed published literature, regardless of the shape or size of the ultrasound. The systems used in included studies must be easily carried from one exam room to another. Also, some of the systems used in the studies should not be obsolete.

Since their introduction in 1999, ultrasound systems marketed under the term "hand-carried" or "hand-held" have undergone a transformation in their capabilities. The first generation of the hand carried ultrasound systems were limited in functionality; they did not have all of the major imaging modes, and their image quality, although diagnostic in many instances, was comparable with the lower end of the cart based, conventional ultrasound systems. Over several generations of products, all imaging modes have been added to the products and image quality is now equivalent to that of high performance cart based ultrasound systems. Therefore, making a distinction in equipment size versus functionality will only limit the number of studies that CEPAC could review. We recommend that CEPAC not delineate ultrasound systems based on design features.

3. Automated Breast Ultrasound (ABUS)

In 2012, FDA granted Premarket Approval (PMA) for an automated breast ultrasound device developed for adjunctive imaging. The product's device labeling is directly applicable to the CEPAC comparative effectiveness research as it 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 approval is supported by the pivotal Multi- Reader Multi- Case Clinical Retrospective Readers Study (CRRS-4) presented within the FDA Safety and Effectiveness Data (SSED) for the above PMA. This research was 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. The primary endpoint was the identification of any shifts in the

[2] *See, e.g.*, Jelinek, JS et al., "Diagnosis of Primary Bone Tumors with Image-Guided Percutaneous Biopsy: Experience with 110 Tumors." *Radiology*. 223(2002): 731-37.

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% when supplementing mammography with ABUS, versus mammography alone in the study population. Additionally, there was a 35.7% increase in cancer detection sensitivity. As a result, the FDA unanimously provided Premarket Approval on the safety and effectiveness of this ultrasound equipment.[3]

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.[4] This analysis demonstrated minimal inter-reader variability using ABUS as a screening tool and validated the use of ABUS for improved consistency in the clinical environment.

Two other prospective registry studies demonstrate robust preliminary results: the European Asymptomatic Screening Study (EASY) and the Somo INSIGHT Registry study (Ref: NCT00816530 / USI2008002) which have enrolled over 15,000 patients to date. These studies evaluate the sensitivity and specificity of ABUS in conjunction with mammography vs. mammography alone. These studies indicate improved sensitivity in identifying small, invasive and node-negative cancers.[5] Since these studies are pending submission for publication, it would be premature for CEPAC to formulate a final conclusion on the effectiveness of screening ultrasonography in this clinical environment.

4. Magnetic Resonance Imaging (MRI)

Studies have shown that diffusion-weighted (DWI) MRI improves the diagnostic accuracy of conventional breast MRI and has 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% from 37% compared to dynamic contrasted enhanced (DCE) MRI alone. Biopsies of 33% of the benign lesions could have been avoided without compromising cancer detection.[6]
Research by El Khouli et al., indicated that DWI improves the diagnostic performance of conventional MRI: area under the ROC curve improved from 0.89 to 0.98 and the false-positive rate diminished to 24% from 36% in the 25 benign lesions within the 93-patient study.[7]

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. Their results indicated an area under the curve (AUC) of 0.73 with sensitivity

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of 50% for DWI compared to 0.64 AUC and sensitivity of 40% for mammography. Combining DWI with mammography was found to increase sensitivity to 69%.[8]

Currently a 100-subject clinical trial has been initiated to investigate whether DWI can evaluate features more specific for breast cancer in high risk patients. We anticipate completion of this trial is January 2015 and would recommend that CEPAC defer any final decision until results are known.[9]

5. Analyses

With the growing evidence on mammography for women with dense breast tissue, we urge CEPAC to examine the breadth of available evidence without more heavily weighing any one study over others. In particular, meta-analysis published in the Annals of Internal Medicine (October 18, 2011) demonstrates a significant improvement in sensitivity with the use of digital mammography in women with dense breast tissue. Although there is improvement of detection with digital mammography, it does not surpass the sensitivity of mammography in women with fatty breast tissue, which the paper also demonstrates. This discrepancy brings into question the validity of this study and no other study demonstrates these discrepant findings. We are concerned that heavy reliance of the results of one study, albeit a meta-analysis, would undervalue the technologies capable of detecting anomalies in dense breast tissue.

* * * *

MITA appreciates this opportunity to comment on the Draft Report. 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

[8] 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

[9] http://clinicaltrials.gov/ct2/show/NCT01938157

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December 10, 2013

Re: Supplemental Breast Cancer Screening for Women with Dense Breast Tissue – December 2013

To Whom It May Concern:

I have recently finished my active treatments for advanced breast cancer (stage 3C) that was not originally found by my mammogram due to my breast density. Even with my mother having had breast cancer at 42, my PCP, Gynecologist and the Radiologists who had read 33 years of my annual mammograms, never told me that, since I had breast density, I should get secondary screening to make sure my many mammograms were not false negative. (Breast density can mask a cancer tumor since both breast density and cancers are manifested as white on the mammogram, making the tumor indistinguishable from the breast density) After each mammogram, I received a letter that said my mammograms were "normal " with "no changes from the previous year" and that "routine mammogram screening was recommended". Each year, I was relieved with a false sense of security that, as a daughter of a mother who had breast cancer, I had made it through another year without any concerns of breast cancer.

In Dec 2012, when I was 58 years old and 6 months after my last mammogram report that stated I had ***"Dense breast tissue. No Evidence of malignancy. No significant change from prior exam. Routine annual screening recommended",*** my mammogram proved to be "false negative". I had found a hard and enlarged lymph node in my axilla that needed to be biopsied. When the lymph node biopsy returned as cancer, my first thought was that the cancer must not be coming from my breast since I was told that my most recent mammogram had shown no sign of cancer. It was my PCP who then told me, for the first time, that it could still be breast cancer even with a "negative" mammogram because of my breast density. Even as a medical professional (I am a physical therapist), my ignorance shocked me. I had always trusted that I couldn't have breast cancer if my mammogram was negative and none of my doctors seemed alarmed nor alerted to any concerns. In all my years of faithfully having annual mammograms and with a mother who had early age breast cancer, no one had ever educated me about my breast density until, much to my horror, it was too late. An ultrasound was ordered 8 days after the "negative" mammogram and the ultrasound did in fact reveal the source to be breast cancer. The cancer, having not been detected sooner with a recommendation of secondary screening, had already spread to 16 lymph nodes. I was now in Stage 3C breast cancer, leaving me at high risk for breast cancer Stage 4 with metastases. Not only did I have to endure the treatments of more extensive surgery, chemotherapy and radiation, I now live with the real fear, for the rest of my life, of developing stage 4

breast cancer. If someone with a medical background like me, who has a fair amount of medical knowledge and is relatively savvy navigating the complicated medical system, could be in the dark about breast density and its implications, what about the average woman that knows very little to nothing. I fully trusted my doctors to let me know if there was any concern, as do most patients with their mammograms.

My story is only one of the all too many stories of women with breast density who end up with delayed diagnosis of breast cancer because of false negative mammograms, some with stage 3 and some with Stage 4 who lose their battle with cancer. MDAC was founded by one such woman, Ellen Kelliher, who lost her life on July 1, 2013 to Stage 4 breast cancer because of her delayed diagnosis secondary to breast density.

I feel passionate about making sure that woman with breast density noted on mammogram receive notification, education, and recommendation for secondary screening, if deemed necessary, to protect many woman from delayed diagnosis with late stage cancer like myself. I believe this is a moral and ethical informed consent with “the right to know” for women (and men) with breast density. This notification and education of breast density has been purposefully kept from the patient due to concerns about provoking unnecessary anxiety for woman with false positives. All I can say is that I would take many false positives over just one false negative to save my life. Studies have shown that a majority of women feel as I do even with or without a post cancer diagnosis.

Please take into consideration the need for notification and education that can save women’s lives.

Thank You,

Cynthia Rowe Cardillo

First, Do No Harm

My name is Elizabeth Tyson-Smith; I live in Groton MA. I am a licensed and certified clinical mental health counselor who has treated many women with breast cancer over the past 24 years. I chose to treat breast cancer patients after my own experiences with it: the first in 1990 and the second14 years later, in 2004.

I had no risk factors at all for this disease so it was a completely shocking diagnosis. I did not know I had heterogeneous breast density and an increased risk of cancer until I became active in this committee this fall. Since neither my PCP nor my radiologists mentioned density at any time over all those years, I recently contacted my PCP and found it in my record, which had I had never seen. But I was lucky enough to have had ultrasounds after the mammograms which identified the two early-stage cancers. I thought everyone had ultrasounds after their mammogram.

It was due to my own experience through cancer that I decided to provide more support for other women with breast cancer. In 2000, I co-founded the Virginia Thurston Healing Garden, Inc., located in Harvard MA. We have continue to make available varieties of support services for cancer patients.

****

I would like to address the issue of supplemental testing as it pertains to women undergoing mammography, particularly in the light of a recommendation for additional testing due to high breast density.

It is essential women be aware if they have breast density, which is apparent to the radiologist reading the mammography films at the time. This information must be conveyed to the patient - hopefully during that appointment. It has been proven that dense breast tissue can mask small tumors in mammograms as well as perhaps raise the risk for malignancy. Therefore, when the patient who has density learns about this, recommendations should include taking into account her perspective and desires once she is informed of risks and benefits of more screening. That would be following the "rule out" diagnostic criteria, and if a malignancy is shown, treatment would be less arduous and less costly. It would be a preventive step.

Regarding disclosure, many who oppose allowing the patient to be informed of her breast density state their concern that she will be frightened or panicked – not only to learn about the density, but also to fear the additional testing and the possibility of a tumor. In my opinion, their position is extremely misguided and disrespectful of a normal reaction.

For the truth is every woman is anxious prior to her mammogram. They dread it. And those of us who have had breast cancer are even more anxious. But why wouldn't we be? If we know our level of density, and something shows up on the film, we want it identified. An ultrasound can show small tumors more clearly than a mammogram. We trust our medical providers to follow up any questionable mammogram reports. How dreadful to think they might breach this trust by not giving us all the information about our density and not suggest supplemental testing, for are we not trying to detect breast cancer earlier, avoid long arduous and expensive treatment, and death??

Yes, I have met with a lot of these unfortunate women. What can I say to help them cope with this terrible omission of critical information, so simple to share at the time of mammogram? All I can say is it was an unnecessary, unethical, painful tragedy.

Elizabeth Tyson-Smith, MA, LMHC, CCMHC

Breast Cancer survivor
MA Density Awareness Coalition
Co-Founder/former ED Virginia Thurston Healing Garden, Inc.

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Wendie Berg, MD, PhD, FACR
Professor, Department of Radiology, University of Pittsburgh

In general, this document should present an objective, data-driven review. This is a challenging topic. Sometimes objectivity is lacking in the wording. Sometimes data are not included or slightly misrepresented, but generally this is an excellent review.

1.1. Screening can only reduce breast cancer mortality among women participating in screening. Bleyer and Welch did not correct for this, and their analysis is given too much credence as presented. Take a look at Webb et al (1).

1.2. Nelson et al (2) in the 2009 USPSTF analysis concluded that the randomized trials showed a 15% mortality reduction in women age 40-49 at entry. The trials screened women every 2-3 years. In a meticulous modeling analysis of the impact of annual screening for such women, Hendrick and Helvie (3) show a far greater impact on mortality reduction could be achieved. Hendrick and Helvie also present a careful analysis of risks. The controversy is in the weighting of the harms of recall for additional testing or a needle biopsy. Educating women about the process of screening and recall, and the low likelihood of cancer even after recall (3-4%) will likely reduce the psychological stress of screening.

1.3. The phrasing is biased: MRI "has been most widely used" (more patients have been screened by ultrasound in the literature); ultrasound "has been promoted by some" (guidelines by the ACS and SBI suggest its use in high-risk women who cannot tolerate MR and in women with dense breasts, yet those are not cited here); and tomosynthesis holds "significant promise". There are no data from incidence screening tomosynthesis, and informal discussions would suggest that there is no significant supplemental cancer detection due to tomosynthesis after the first year; further, there are serious concerns about the performance of tomosynthesis in extremely dense breasts or areas of the breast. "Sestamibi" is the tracer used in breast-specific gamma imaging and molecular breast imaging. Positron emission mammography and thermography are not in the "early investigational phases" for screening. PEM should not be considered for screening due to radiation dose, minimum 60 minute circulation time, and shielding requirements. Thermography is insensitive to cancers 100 patients) and results from synthetic 2D images created from DBT have now been presented and approved by the FDA, eliminating the need for concurrent digital mammogram (and thereby added dose). One of the issues in question is the degree to which cancers are seen in dense breasts with tomo and whether ultrasound is still needed. Abstracts on this issue were presented at RSNA showing supplemental yield of ultrasound of 2 per 1000 even after tomo. Again, it is not yet clear that tomo will increase cancer detection for incidence screening.

1.4 Statistics. The BI-RADS 5th edition defines a positive screen as BI-RADS 0, 3, 4, or 5. BI-RADS 3 was not previously considered test positive, and should not be used on screening mammography, but it can be used on other modalities. False negatives are not limited to interval cancers, as false negative mammograms, for example, may include cancers found by supplemental imaging. Many false negatives will go undetected if mammography is its own gold standard. Interval cancers typically only include those detected because of clinical abnormalities in the interval between recommended screens. Interval cancers are important in women with dense breasts as interval cancer rates are higher in such women and outcomes are worse for interval cancers. Again, see Webb et al (1) for discussion of outcomes from interval cancers as a function of age.

p. 13, Overdiagnosis—really "overtreatment". The magnitude of overtreatment decreases with longer follow-up as some slow-growing cancers that can be diagnosed early eventually come to be clinically detected. It is much more of an issue for low-grade DCIS on the prevalent screen than for any invasive cancer or new DCIS. A nice analysis by Yen et al (17) should be cited, which indicates that for every 11 cancers diagnosed by mammographic screening, one represents overdiagnosis, two are life-saving, and 8 would have been detected with or without screening. This is also much more of an issue for older women than for young women as older women have less time during which the benefit of screening might be realized.

p. 15, the visually estimated percent dense is no longer part of the language of BI-RADS 5th edition (to be published Jan 2014), but the terminology remains the same, together with standard phrasing on the impact of such density. Use of numeric categories 1-4 to describe density is discouraged as they can be confused with final assessment categories. Use: A-fatty; B-scattered fibroglandular tissue; C-heterogeneously dense parenchyma which could obscure detection of small masses; and D-extremely dense which lowers the sensitivity of mammography.

p. 19, It should be clearly stated that the Gail model should not be used to determine lifetime risk for purposes of determining who qualifies for MR screening (see online appendix to Saslow et al (18)). The link provided: https://tools.bcsc-scc.org/BC5yearRisk/calculator.htm does not work. It is just https://tools.bcsc-scc.org/BC5yearRisk/calculator. Importantly, this model does not consider the age at diagnosis of affected relatives nor provide any estimate of mutation risk and should not be used to determine eligibility for MR screening. This model will overestimate risk when first-degree relatives were diagnosed late in life. Early in this section, it should be stated that these models predict risk of invasive breast cancer.

Section 3. In keeping with prior sections, would organize with MR first, then ultrasound, then tomosynthesis. Medicare recently issued a policy statement on tomosynthesis indicating it could be included within codes for digital mammography. This may be revised, but the discussion should reflect the current status.

Section 5, p. 31, it is unclear how the 3% 5-year risk threshold was determined as "high risk", and it is not clearly stated that this uses the BCSC 5-year risk calculator, but I suspect it does.

In Table 8 and related discussion, it should be clarified that the Hooley, Weigert, and Parris studies (as well as Kaplan 2001) analyzed technologist-performed handheld ultrasound. The sensitivity may be slightly lower as a result, or the prevalence of disease may be lower in those broader populations. For the ACRIN 6666 study by Berg et al, only 20% of participants meet "high-risk" criteria of Saslow/ACS. The results/conclusions do not differ if those women are excluded. Further, results were the same in the subset of women with digital vs. film mammography. PPV3 and biopsy rates were reported in years 2/3 in JAMA 2012 and should not be listed as "NR" in Table 10. I am not sure what numbers Table 10 is reporting in general as none of the ones listed for the Berg 2012 paper agree with Table 3 in the JAMA paper. Are these the results of combined mammography plus ultrasound, or the difference between mammography plus ultrasound and mammography alone or the results of ultrasound alone? The table needs explanation and correction. P. 62 and 63 again indicate that the ACRIN 6666 population was "high risk" but this overstates it (and the risks are summarized in detail in the 2008 and 2012

publications). At end of p. 62, “by the third” should be rephrased to simply indicate “incidence screening results in the second and third rounds”.

In the Weigert 2012 paper, 4 cases with only atypical results were included among cancers and should not have been. The Hooley 2012 paper included patients with whole breast ultrasound at the time of diagnostic mammography.

Interval cancer rates are reported in Berg 2012 and Corsetti 2011 (19) papers and should be described here as they are quite favorable at 1.2 per 1000 and 1.1 per 1000 respectively in women with dense breasts having both screening ultrasound and mammography. The rate in women with nondense breasts in Corsetti et al was 1.0 per 1000.

Table 11 is also puzzling as the size of cancers on mammography and number lymph node negative are clearly stated in Berg 2012 JAMA paper in Table 2 yet are listed as “NR” here.

p. 61, unless the authors are aware of compelling evidence that invasive cancers represent overdiagnosis, these statements should be revised to indicate that overdiagnosis is unlikely among invasive cancers with long-term follow-up.

Table 12 and previously, the incremental biopsy rate in ACRIN 6666 for incidence screens, attributable to ultrasound, was 50 per 1000, not 88 (see Table 3, JAMA 2012).

p. 66—As noted above, the methodology of the Kelly study of semi-automated breast ultrasound was different from other studies using a large (15 cm) footprint transducer. Consider including the results for ABUS presented at RSNA 2012 (Brem, listed below).

p. 76 mentions concerns about operator dependence of HHUS. With adequate training, operator dependence of HHUS is not worse than with any other breast imaging. See Berg et al (20). Bosch et al reported favorable results from resident-performed screening US, similar to attendings with up to 20 years’ experience (21).

DBT estimates of incremental cancer detection rates (ICDR) are high. Skaane’s study directly compared patients and the ICDR was 1.9 per 1000. At the very least, would consider an average of the Ciatto and Skaane results. Further, as mentioned above, the ICDR may be much lower if any for incidence screens. This would seem to be critical information, but its lack is not mentioned. Note that the Ciatto study started at age 48 and the Skaane study at age 50, and that biennial screening is the norm in Italy and Norway respectively, compromising generalizability of results to USA and younger women.

p. 83 ff risk models. It should be considered that a 9-10-year horizon is needed to see a benefit from screening. As such, a 5-yr risk may not be ideal—10-yr risk would be far more appropriate. 5-yr risk increases dramatically as women age, and all women over age 60 with prior biopsy would be eligible for supplemental “high-risk” screening even though they have fewer potential years of life to save. Indeed, the worst outcomes from current screening are in women age 40-49, where the 5-year risk will not typically exceed the 3% threshold proposed, and where annual mammography is more important, especially in women with dense breasts, yet these issues are not discussed (see Kerlikowske (22).

p. 95, even though there are more cancers that can be detected with MR even after mammography plus US (ACRIN 6666), the interval cancer rate was low (also low in the analysis of Ciatto et al 2011). Consider this more clearly in Table 26 and throughout.

p. 96 ff, if Medicare continues to indicate no additional payment for DBT, the results of the modeling will change. This at least merits discussion. How facilities will offer it and stay in business (especially if they stop charging patients outside of Medicare) is not clear.

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BBDC
BOSTON BREAST
DIAGNOSTIC CENTER

September 16, 2013

The Honorable James T. Welch, Senate Chair
The Honorable Steven M. Walsh, House Chair
The Joint Committee on Health Care Financing
Massachusetts State House
Boston, MA 02133

Dear Chairman Welch, Chairman Walsh and Members of the Committee,

I am writing this letter in support of House Bill 1050. I am a board certified radiologist with fellowship training in breast imaging which has been the sole focus of my practice for over twenty years. Advances in technology and our knowledge base have improved our diagnostic capabilities and treatment options but current techniques can always be optimized to improve patient care.

Radiologists have long been aware of the limitations of mammography due to dense breast tissue and recent studies have also shown that breast density is an independent risk factor for developing breast cancer. Conflicting screening recommendations and mixed messages have led to a decline in screening mammography in recent years.

Breast MRI is advised for women who carry the BRCA gene mutation regardless of breast density but this population only accounts for 5-10% of women diagnosed with breast cancer. Breast MRI is also advised for women with a lifetime risk of >20-25%. The high sensitivity and negative predictive value of MRI makes it a valuable tool for high risk patients but the time and cost of the exam precludes its use for the low and average risk patient.

Whole breast ultrasound has been used as a supplemental screening technique for women with dense breasts. The American College of Radiology Imaging Network 6666 trial increased the cancer detection rate at prevalent screening from 7.6/1000 with mammography alone to 11.8/1000 with mammography and whole breast ultrasound. The additional cancers found were primarily invasive with a median size of 10mm and 89% were lymph node negative. Although there are no randomized controlled trials of whole breast screening ultrasound, there is no reason to believe that these early stage breast cancers would not have the same good prognosis as a mammographically detected breast cancer.

Currently, radiologists are required to send a mammography results letter which could be modified to include their breast density. There is commercially available software that can quantify breast density on digital mammography systems which will help standardize breast density reporting.

California breast imagers and breast cancer risk specialists launched a website (www.breastdensity.info) to help educate radiologists and referring physicians regarding the challenges posed by the breast density notification laws. This document addresses the questions about the efficacy and benefits as well as the potential harms of supplementary screening tests.

Patient and physician education is vital in order for patients to make informed decisions so screening can be optimized based on breast density and other risk factors. In my experience, patients worry more about a false negative (missed breast cancer) than about the potential of additional testing and a possible false positive. The best phone call I make is when I can tell the patient her biopsy was benign.

Thank you for your time and attention to this matter. Please feel free to contact me at my office at (617) 553-5300 with any questions or concerns.

Sincerely,

Elsie Levin MD

Elsie Levin, M.D.
Medical Director
Boston Breast Diagnostic Center

December 11, 2013

BY ELECTRONIC DELIVERY

Claudia Gruss, MD, FACP, FACG, CNSC
Chair
New England Comparative Effectiveness Public Advisory Council
One State Street, Suite 1050
Boston, MA 02109

RE: The Comparative Clinical Effectiveness and Value of Supplemental Screening Tests Following Negative Mammography in Women with Dense Breast Tissue

Dear Dr. Gruss:

We thank the New England Comparative Effectiveness Public Advisory Council for the opportunity to submit comments regarding the draft report titled *Comparative Clinical Effectiveness and Value of Supplemental Screening Tests Following Negative Mammography in Women with Dense Breast Tissue.*

As a leading developer, manufacturer and supplier of premium diagnostic products, surgical products and medical imaging systems, with an emphasis on serving the healthcare needs of women, Hologic:

- Support the right of women with dense breasts and their healthcare providers to have access to effective imaging technology, to improve breast cancer screening, and provide confident diagnosis.
- Believe that all women should have access to digital breast tomosynthesis (DBT) as a first line screening technology. In addition, the use of digital breast tomosynthesis as a first line screening tool is advantageous specifically in women with dense breasts by providing better review of the architecture of the breast, and thus improved breast cancer diagnosis in dense breasts.

Approximately 46% of women in New England are estimated to have heterogeneously dense or extremely dense breast tissue. While the CEPAC review focuses on 'supplemental screening', we believe that a treatment pathway which includes additional imaging to supplement the initial exam in almost 50% of women undergoing a screening mammogram will dramatically increase healthcare utilization and expenditure. Hologic proposes the most cost effective and clinically beneficial approach for screening women with dense breasts is to provide digital breast tomosynthesis (DBT) as their initial modality for annual screening. Although DBT has been demonstrated to provide benefits to women of all breast densities, its ability to visualize areas of tissue superimposition (which are responsible for "masking" in 2D mammography) is what makes DBT particularly valuable as a primary screening modality in women with dense breasts. One of the issues of this current assessment is the need to define more clearly the term "supplemental imaging". If a woman is having her standard mammogram, then any follow up and additional imaging is considered to be a diagnostic exam. This is an important distinction in how the patient

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is treated, how Insurers cover additional testing and additional out of pocket expenses for the patient. It is also important in defining the best pathway for treating women with dense breasts.

Digital breast tomosynthesis is widely available. There are currently 64+ sites throughout New England offering annual mammography exams using FDA approved DBT systems. In doing so, their patients are already aware that they have received the most accurate mammogram available when they receive their results and notification of dense breasts. A single visit is far more convenient and cost effective for the patient, who would have otherwise had to schedule a second appointment to have supplemental screening performed, and incur additional out of pocket costs for supplemental imaging. Moreover, utilization of DBT as the primary screening method helps ensure the appropriate utilization of supplemental technologies like ultrasound and MRI, potentially reducing overall imaging cost while reducing the number of biopsies performed on a false positive image.

A cost effective pathway of managing women with dense breasts would be to recommend that physicians request a mammogram with DBT when referring women known or likely to have dense breasts for her yearly exam. In reviewing the prior year's mammography report, a physician should be able to advise his patient that he is ordering a 3D mammogram to enable better able visualization of the architecture of her dense breasts.

Digital breast tomosynthesis was developed in order to address the limitations of current 2D mammography, and provide all women with a better standard of care. However, women with dense breasts have the most to gain when it comes to the clinical impact of this new technology. Given 3D mammography's seamless integration into the breast cancer screening work flow and minimal budgetary impact, digital breast tomosynthesis represents the best option for improving the quality and value of healthcare for women, providers, and payers.

As you complete your final assessment, we ask that you please take into valuable consideration the following comments regarding the use of advanced screening technology for women with dense breasts.

Pg. 7: CEPAC statement regarding 3D's potential as a next generation screening technology:

"Finally, digital breast tomosynthesis (DBT), a 3-dimensional extension of digital mammography, has been viewed as holding significant promise in breast cancer screening"

Comment:

Hologic agrees with your assessment. Please note that there are numerous studies which have been published regarding DBT's clinical benefits for all women, not just those with dense breasts. We ask that the Panel consider the topic of DBT as an alternative to FFDM (2D Digital Mammography).

Pg. 9: Digital Breast Tomosynthesis (DBT)

"Digital breast tomosynthesis (DBT) uses a conventional x-ray source that sweeps along an arc around the breast to acquire multiple two-dimensional (2-D) digital images.[54,56,69] *Breast compression is performed using the same device and technique as conventional mammography. The procedure to obtain each digital view is complete in less than 20*

seconds. One of the advantages of DBT is that the images can be acquired immediately following the digital mammogram without needing additional compression. Like MRI, computational algorithms synthesize the resulting 2-D digital images to create tomograms (i. e. , slices) allowing for a 3-D reconstruction of the breast. The tomograms can be displayed individually (similar to enhanced conventional mammograms) or in a dynamic movie mode.

There are several drawbacks to DBT. The dose of ionizing radiation for each DBT view is about the same as that used for a conventional mammogram. Currently, a standard digital image is also acquired, so the total dose is approximately twice that of digital mammography alone.[54,55] The technology and algorithms used for DBT are still in evolution. [54,56,69] One of the crucial areas is the development of techniques to biopsy lesions that are only seen on DBT.[70] The reading time for DBT is also about twice that required for digital mammography.[54,55] "

Comment:

Compression Time & Radiation Dose:

We recognize the concerns about dose exposure in women with mammographically dense breasts. While the dose of a combined breast tomosynthesis and digital mammography exam is under the MQSA and EUREF limits and deemed safe, in May 2013, Hologic received FDA approval to use its C-View software enhancement to construct 2D images from a 3D data set **in place** of the conventional FFDM 2D x-rays required as a part of a tomosynthesis screening exam. Supporting clinical data shows that the combination of Hologic's breast tomosynthesis technology and C-View 2D images results in superior results compared to 2D mammography alone. C-View provides an improved patient experience — lower radiation exposure and a faster exam time — without compromising the clinical superiority of the tomosynthesis screening exam. The American College of Radiology (ACR) issued guidance saying that 2D constructed images should be billed in the same way as conventional 2D images. Each image takes only 4 seconds, so the use of tomosynthesis is completely compatible with high throughput screening applications. With the FDA approval and integration of the C-view enhancement to the current 3D technology, it drops the radiation dose level back to that of the current 2D digital Mammography; performing a DBT with C-view reconstruction of 2D Digital will have the same radiation dose level as 2D mammography. This dose is at 1.3 mGy or .5 mSv. This alleviates CEPAC's statement and concerns that the dose is twice that of Digital Mammography. In fact, the use of DBT with reconstructed 2D will, on average, reduce the dose to the population, not increase it, due to the demonstrated reduction in callback rates when using DBT in screening. This enhancement is currently available on all of our tomosynthesis equipment on the market.

Convenience, Compliance & Cost:

(Same CEPAC reference as above: Pg. 9: DBT Overview)

Performing DBT during a woman's yearly mammogram enhances patient comfort, and avoids the need for "supplemental" imaging, thereby ensuring compliance. Additionally, when used as a primary screening technology, DBT reduces the unnecessary radiation, anxiety, and inconvenience associated with supplemental screening & additional diagnostic testing. By doing so, DBT can reduce costs to both the patient, and the payer. If DBT is performed as the annual screening mammogram the cost to the patient is limited to only the portion not covered by her insurance. However, if a woman gets a 2D mammogram for her

yearly screening, and then goes on to get MRI, ultrasound, or additional imaging, it is likely that she will incur more significant out of pocket costs. Providing DBT as the primary screening technology for women with dense breast, reduces both patient and payer costs.

Biopsy:
(Same CEPAC reference as above: Pg. 9: DBT Overview)
Earlier this year, the FDA approved Affirm tomosynthesis guided biopsy procedure allows radiologists to locate and accurately target regions of interest for biopsy using tomosynthesis imaging, thus alleviating the concern of how to biopsy a lesion only visible on DBT. This offers a number of advantages over 2D stereotactic biopsy procedures including:

- Ease of targeting lesions, particularly those visible only in tomosynthesis images
- Streamlined procedure steps and faster targeting, resulting in improved workflow and shorter patient procedure time
- Fewer required number of x-ray exposures

The availability of DBT guided biopsy procedures should ease CEPAC's concern regarding *"the development of techniques to biopsy lesions that are only seen on DBT".*

Technology & Algorithms:
(Same CEPAC reference as above: Pg. 9: DBT Overview)
In reference to CEPAC's statement *"The technology and algorithms used for DBT are still in evolution",* we recognize that many systems are working to optimize the integration of DBT into their existing screening paradigms. However, with wide spread adoption, we respectfully disagree with the statement that the technology and algorithms used for DBT are still in evolution. DBT has been commercially available in the U.S. for 3 years as of February 2013 and in Europe for over 7 years. In this time, standard algorithms for treatment have been defined and the technology has been implemented by more than 800 facilities nationwide and 1200+ facilities around the world. Many academic and private institutions and facilities have added DBT as their primary mammography screening technology. Any further evolutions to the technology will only serve to improve the performance beyond the currently demonstrated improvements in cancer detection and reduction in callback rates. Published data consistently proves the efficacy of this technology. While other breast tomosynthesis systems remain in development, this should not impact the outlook on the current commercially available technology which demonstrates both a significant reduction in recall and an increase in cancer detection. All digital technology continues to evolve, making systems more efficient, and producing better images at lower doses. The proven published efficacy using current 3D technology does not warrant calling 3D, or 2D technology into question.

Read Time:
(Same CEPAC reference as above: Pg. 9: DBT Overview)
Finally in this section, CEPAC discusses the increase in Radiologist read time of a DBT being twice that of the standard read time for FFDM. While there may be a learning curve initially associated with reviewing DBT image sets, in routine practices, radiologists report a reduction in read-time after 3 months. . This initial increase and subsequent reduction is similar to the experience observed with the conversion from Analog to FFDM. While radiologists may spend more time reading a breast tomosynthesis screening exam, it is alleviating the need for further diagnostic work ups in 40% of cases (which on average take 3

x longer to read than a screening mammogram), which is in essence allowing radiologists to function more efficiently by focusing on screening exams rather than often unnecessary diagnostic exams. ABUS has a much longer screening time as many times it is often followed by a Handheld US.

Pg. 13: Harms of screening: False Positive Results

Comment:

The data regarding false positives which CEPAC presents in this section are not specific to dense breasts. For that reason, we want to bring to your attention that DBT has been clinically proven consistently to reduce false positives across all breast densities and age groups, while at the same time increasing sensitivity across all these cohorts. In fact, DBT has been proven to increase the PPV of both imaging and biopsy, meaning that women who are going on to supplemental screening are more likely to have a cancerous lesion, and those that are biopsied are more often confirmed to have cancer. It is also important to recognize that while DBT increases cancer detection, this is detection of *invasive* cancers, which will progress and require treatment. In summary, breast tomosynthesis decreases false positives, increases PPV and increases detection of invasive cancer. The ability to "see through" tissue superimposition using 3D mammography makes it especially valuable as a primary screening method for women with dense breasts. It prevents those who do not need ultrasound or MRI from having any unnecessary supplemental imaging (with high false positive recall rates) performed, and then undergoing a biopsy which could have been avoided.

Pg. 23: Clinical Guidelines Section-CEPAC statement:

2.4 Digital Breast Tomosynthesis (DBT)

National Comprehensive Cancer Network (NCCN)
http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

Under breast screening considerations, the NCCN guidelines state, *"Early studies show promise for DBT mammography. Currently, there is insufficient evidence to recommend routine use for screening or diagnosis at this time."*[129]

Comment:

This statement was made prior to a significant amount of the compelling clinical data on DBT being published in May to present of 2013. This includes, Rose, Ciatto, Skaane, Rafferty, Zuley and Haas clinical papers.

Pg. 26: Medicaid, Medicare, National and New England Private Insurance Coverage Policies

3.3 Digital Breast Tomosynthesis (DBT)

Medicare:

No NCDs or LCDs were available for coverage of DBT

Comment:

Because breast cancer screening is federally legislated as a preventive service for all Medicare patients and women with private insurance, the Centers for Medicare and Medicaid

Services recently posted an FAQ explaining that breast tomosynthesis is considered mammography service for screening and diagnosis.

http://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/PhysicianFeeSched/Downloads/FAQ-Mammography-Services-Coding-Direct-Digital-Imaging.pdf

Regarding Private insurance, many of the health plan medical policies referenced have not taken into consideration, the DBT data published during a significant portion of 2013. The majority of the policies cited by CEPAC as investigational or experimental were created in advance of the most recent 2013 publications. The studies that were not considered include, Rose, Ciatto, Skaane, Rafferty, Zuley and Haas clinical papers. In some cases, the Health Plan Policies based their decision, in part, on clinical data derived from studies performed using non-FDA approved equipment. In the upcoming 2014 review cycle it is anticipated that as payers perform their annual technology assessments, , medical policies for mammography will be updated to include DBT as an alternative to 2D for all women as a covered benefit. Additionally, it is expected that CMS will develop a unique code for DBT, and establish coverage and compensation guidelines in the early half of 2014.

Pg. 55: DBT Studies-CEPAC review

Comment:

Additional large scale studies have recently been published regarding DBT (such as the Rafferty study, *Radiology* 1/2013), but were not included in this technology assessment. Most of these studies looked at breast cancer detection among all women receiving mammograms, not specifically those with dense breasts, and the published results represent the benefit of using 3D mammography as a primary screening method for women of all breast densities demonstrating that screening provides the most beneficial use for all densities.

Pg. 75 Summary

DBT, on the other hand, decreased the recall rate in the four studies considered in this assessment, particularly in women with high breast density.[55,159-162] *At the same time, DBT increased the cancer detection rate by about 2 per 1000 examinations compared to digital mammography alone. One of the studies also reported that the biopsy rate decrease from 15.2 to 10.6 per 1000 examinations.*[161] *In the subgroup of women with dense breasts and negative mammograms, DBT identified an additional 2.7 cancers per 1000 examinations with a recall rate of 21.3 per 1000 examinations. This is an equivalent cancer detection rate to HHUS with a much lower recall rate. DBT has the advantage of being easy to incorporate into routine mammography screening, requiring little extra time from the woman being screened.*[55] *However, it uses additional ionizing radiation (about the same amount again as digital mammography).*[54,55] *And there are also technical aspects that are still under development, such as accurate biopsy techniques for abnormalities identified on DBT, but not visible on the digital mammogram.*[70]

Comment:

Dose & Biopsy:

Please refer to comments on Dose on page 2 and Biopsy on page 3.

Pg. 79: Model of Clinical and Economic Outcomes of Supplemental Screening in Women with Dense Breast

Tissue-CEPAC statement:
Supplemental modalities considered included HHUS, ABUS, MRI, and DBT. While DBT's eventual use may be as a first-line screening test in all women and it is not yet widely available, it nevertheless represents an additional supplemental screening option for women with dense breast tissue that clinicians may wish to consider.

Comment:

The CEPAC report raised a potential concern regarding the availability of DBT and access for women. As previously mentioned, DBT is currently available at 64 locations throughout New England, making it more widely available for primary screening, and more cost effective, than other supplemental screening technologies under consideration. Currently, we understand that there are a limited number of ABUS systems in the nation. At the 64 DBT sites, DBT is primarily used as the first line screening method for all patients. There are over 800+ tomo units nationwide & over 1200 worldwide, with DBT screening exams being performed on women in 49 states. There have currently been over 3 million DBT screening exams done. With all of the clinical data published over the past 6 months, it is anticipated that as payers perform their yearly re-review of policies, they will update their medical policies to include DBT as a covered benefit as an **alternative** to 2D mammography and compensate providers for making this service available to their members. Additionally, it is expected that CMS will develop a specific code for DBT in the early half of 2014. As reimbursement becomes more prevalent for DBT it is expected that more sites will convert to DBT.

Pg. 81: Economic Model Assumptions-CEPAC review:

For these analyses of supplemental screening, digital mammography was assumed for initial screening, as evidence indicates it is the current screening standard.
We had to make several broad assumptions in designing the model that are important because they limit the ability of the model to capture the nuances of patient behavior and the many variations in clinical care patterns that occur for individual patients. For example, we assumed perfect compliance for both mammography and supplemental screening in this analysis. While it is the case that actual compliance is always less than 100%, differences across studies in the definition of the time interval within which women are considered compliant as well as considerations of what constitutes screening vs. diagnostic mammography [183] precluded our use of a uniform, widely-accepted estimate for compliance across different imaging modalities.

The model assumes that supplemental screening would occur immediately after a negative mammography result, and that one year of follow-up is available as the reference standard for both mammography and supplemental screening results.

Comment:

The only screening protocol which would produce 100% compliance among women with dense breasts, is when DBT is performed as the primary component of the annual screening exam. On a DBT mammogram, the radiologist is better positioned to review the areas of

density with greater clarity than the FFDM all in the primary screening exam. We are also seeing a growing trend of radiologists moving the patient straight to Ultrasound or MRI and foregoing additional diagnostic mammograms when they can clearly see the cancer, thus improving the patient treatment pathway. Given the patient inconvenience associated with having to schedule an ultrasound or MRI test following a negative mammogram, and the fact that most payers, including Medicare and Medicaid, will not cover supplemental screening for these costly tests, 100% compliance with these technologies would not be realistic.

Pg. 76: CEPAC's approximation of DBT sensitivity

Information on DBT sensitivity in women with dense breast tissue and negative digital mammography is available,[159] but is overstated at 100% because of lack of interval follow-up. The rate of interval cancers in most screening populations is approximately 1 per 1,000 women screened.[112,192] Applying this rate to the Ciatto data yields a sensitivity of 75%, which was used for DBT in our model.

Comment:

CEPAC assumed DBT sensitivity of 75%, which we feel is overly conservative, and does not properly adjust for gains in specificity. While it is unfortunate that no single modality will attain 100% sensitivity (without a considerable loss in specificity) our experience with DBT in the United States supports a slightly less conservative estimate of 80-85%. Underestimating DBT's sensitivity will also underestimate the number of earlier stage cancers detected, something which is especially important in women with mammographically dense breasts. Furthermore, this negatively impacts the comparative clinical effectiveness and economic value of DBT.

Tables: 22,23,24,25

Comment:

The circled figures represent a cost comparison between the different screening methods, but with DBT performed as the primary screening method --removing the duplicated 2D mammography costs from their figures. The circled figures represent a cost comparison between the different supplemental imaging methods. It is important to note that the true cost of DBT is inflated in the model, because the assumptions about the pathway of care are not indicative of true clinical practice. In true clinical practice, many women with dense breasts are already getting digital breast tomosynthesis as their initial screening exam. This adds ~$50 to their screening mammogram over 2D alone. It is very likely that women with dense breasts receiving a screening mammogram with breast tomosynthesis would not require another supplemental tomosynthesis exam at $50 and certainly would not require another 2D+breast tomosynthesis exam at a combined cost of $199. If a woman receives a screening mammogram with 2D alone, it is also possible that she may return for a diagnostic work up and receive a breast tomosynthesis exam alone (not another 2D exam with her breast tomosynthesis exam).

Table 22: Clinical outcomes and costs of supplemental screening in New England in all women with dense breast tissue and negative mammography: vs. digital mammography alone.

Outcome (per 1,000 screened)	*DM+HHUS/ABUS*	*DM+MRI*	*DM+DBT*	*DM Alone*
Biopsies Performed	63.2	48.4	31.8	17.8
Incremental	*45.4*	*30.6*	*14.0*	
Cancers Detected (True Positives	8.1	10.2	7.7	4.2
Incremental	*3.9*	*6.0*	*3.5*	
Adjusted for potential overdiagnosis (low)	*3.5*	*5.4*	*3.1*	
Adjusted for potential overdiagnosis (high)	*2.7*	*4.2*	*2.4*	
False Positive Biopsy	55.1	38.2	24.1	13.6
Incremental	*41.5*	*24.6*	*10.5*	
Cancers Missed (Interval Cancers)	0.2	0.1	0.3	0.9
Incremental	*(0.7)*	*(0.8)*	*(0.6)*	
Cost (per Woman Screened, $)	333/416	856	403	191
Incremental	*142/225*	*665*	*212*	

DM: Digital mammography; HHUS: Handheld ultrasound; ABUS: automated breast ultrasound; MRI: magnetic resonance imaging; DBT: digital breast tomosynthesis

Table 23: Clinical outcomes and costs of supplemental screening in New England in women at low overall breast cancer risk with dense breast tissue and negative mammography: vs. digital mammography alone.

Outcome (per 1,000 screened)	*DM+HHUS/ABUS*	*DM+MRI*	*DM+DBT*	*DM Alone*
Biopsies Performed	31.3	28.7	13.9	6.2
Incremental	*25.1*	*22.5*	*7.7*	
Cancers Detected (True Positives)	3.4	5.0	3.1	1.6
Incremental	*1.8*	*3.4*	*1.5*	
Adjusted for potential overdiagnosis (low)	*1.6*	*3.0*	*1.3*	
Adjusted for potential overdiagnosis (high)	*1.2*	*2.4*	*1.0*	
False Positive Biopsy	27.9	23.7	10.8	4.6
Incremental	*23.3*	*19.1*	*6.2*	
Cancers Missed (Interval Cancers)	0.1	0.1	0.1	0.4
Incremental	*(0.3)*	*(0.3)*	*(0.3)*	
Cost (per Woman Screened, $)	309/391	842	391	185
Incremental	*124/206*	*657*	*206*	

DM: Digital mammography; HHUS: Handheld ultrasound; ABUS: automated breast ultrasound; MRI: magnetic resonance imaging; DBT: digital breast tomosynthesis

Table 24: Clinical outcomes and costs of supplemental screening in New England in women at moderate overall breast cancer risk with dense breast tissue and negative mammography: vs. digital mammography alone.

Outcome (per 1,000 screened)	*DM+HHUS/ABUS*	*DM+MRI*	*DM+DBT*	*DM Alone*
Biopsies Performed	66.8	48.1	31.7	15.5
Incremental	*51.3*	*32.6*	*16.2*	
Cancers Detected (True Positives	8.3	10.4	8.0	3.9
Incremental	*4.4*	*6.5*	*4.1*	
Adjusted for potential overdiagnosis (low)	*4.0*	*5.8*	*3.7*	
Adjusted for potential overdiagnosis (high)	*3.1*	*4.5*	*2.9*	
False Positive Biopsy	58.5	37.7	23.8	11.6
Incremental	*46.9*	*26.1*	*12.2*	
Cancers Missed (Interval Cancers)	0.2	0.1	0.3	1.1
Incremental	*(0.9)*	*(1.0)*	*(0.8)*	
Cost (per Woman Screened, $)	341/424	859	407	193
Incremental	*148/231*	*666*	*214*	

DM: Digital mammography; HHUS: Handheld ultrasound; ABUS: automated breast ultrasound; MRI: magnetic resonance imaging; DBT: digital breast tomosynthesis

Table 25: Clinical outcomes and costs of supplemental screening in New England in women at high overall breast cancer risk with dense breast tissue and negative mammography: vs. digital mammography alone.

Outcome (per 1,000 screened)	*DM+HHUS/ABUS*	*DM+MRI*	*DM+DBT*	*DM Alone*
Biopsies Performed	102.9	73.7	51.8	31.1
Incremental	*71.8*	*42.6*	*20.7*	
Cancers Detected (True Positives	14.7	18.5	14.1	7.9
Incremental	*6.8*	*10.6*	*6.2*	
Adjusted for potential overdiagnosis (low)	*6.1*	*9.5*	*5.6*	
Adjusted for potential overdiagnosis (high)	*4.7*	*7.4*	*4.3*	
False Positive Biopsy	88.2	55.1	37.7	23.2
Incremental	*65.0*	*31.9*	*14.5*	
Cancers Missed (Interval Cancers)	0.3	---	0.4	2.1
Incremental	*(1.8)*	*(2.1)*	*(1.7)*	
Cost (per Woman Screened, $)	366/449	875	418	199
Incremental	*167/250*	*676*	*219*	

DM: Digital mammography; HHUS: Handheld ultrasound; ABUS: automated breast ultrasound; MRI: magnetic resonance imaging; DBT: digital breast tomosynthesis

Comment Summary:
The assumptions used in the CEPAC economic model are limited by a one-year term, meaning they only looked at women who were diagnosed as having dense breasts for the first time. If CEPAC had contemplated a model beyond the one year mark, it would have included women previously identified as having dense breasts, for who DBT would have emerged as a cost effective and clinically preferable option for primary long term screening. The cost of performing a (2D + 3D) digital breast tomosynthesis exam at the time of her regular yearly screening would be $149 + $50= $199. This represents a significantly lower cost than a scenario in which a woman has her 2D mammography and then goes on to have a MRI, U/S or ABUS. Utilizing DBT as the preferred screening pathway for women with dense breasts should reduce the need for supplemental imaging and provide subsequent reductions in recall rates while maintaining similar rates of cancer detection.

Conclusion:
Thank you again to the CEPAC panel for calling attention to the importance of accurate mammographic screening and diagnosis in women with dense breasts. Access to the most accurate imaging technology is of importance to all women and their families. Digital breast tomosynthesis represents a valuable screening technology, which is compatible, but may significantly limit the need for many supplemental screening modalities. We thank the committee for its consideration.

Should you have any questions or if Hologic could be of further assistance, please do not hesitate to contact me at 508-263-8958.

Sincerely,

Margaret Eckenroad
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Patricia Connors, Patient Advocate

I am a member of the Massachusetts Density Awareness Coalition (MDAC) which actively supports the enactment of House Bill 3733, An Act Relative To Breast Cancer Early Detection, currently pending before the Massachusetts state legislature. This bill would require that physicians who interpret mammograms provide notice to their patients if they have dense breast tissue and also a determination as to whether additional testing is recommended. It was inspired by the death of a friend from breast cancer who had no known risk factors for breast cancer (other than dense breast tissue) and was not given any recommendation to obtain additional testing even though her mammogram showed that she had dense breast tissue.

December 10, 2013

New England Comparative Effectiveness Public Advisory Council (CEPAC)
The Institute for Clinical and Economic Review (ICER)
Re: Draft CEPAC Report on Supplemental Breast Cancer Screening for Women with Dense Breast Tissue
Public Meeting: December 13, 2013

Dear CEPAC members and attendees:

Please accept this correspondence in place of my in-person testimony at the CEPAC meeting on Friday, December 13, 2013. By way of introduction, in 2004 I was diagnosed, within 6 weeks of my 11th normal mammogram, with advanced stage IIIC breast cancer which metastasized to 13 lymph nodes. When I questioned my medical team as to why my cancer was not seen by mammogram but, that same day, a quarter-size lesion was illuminated by ultrasound, I was informed that I **my extremely dense breast tissue** hid my cancer for 4 to 5 years. I was shocked to discover that **radiologists have been reporting density to a woman's referring doctor for years**- but that information is seldom shared with the patient. Each of my 11 yearly mammography reports read, "**Patient has extremely dense breasts. No change from prior exam**."

At such a vulnerable time of my life, I uncovered a decade of scientific studies dating back from 1995 confirming **that breast density is the strongest predictor of the failure of mammographic screening to detect cancer** (1). I shared the research with my doctors. Their refusal to report density to patients compelled me to get this most critical breast health information to the person to whom it matters most – the woman with the dense breasts.

I began working with the Connecticut legislature and since my diagnosis we **spearheaded three laws through the legislature** – ultrasound screening coverage as an adjunct to mammography for women with dense breast tissue, density reporting through the mammography report and MRI coverage for women who meet the 20% lifetime risk for breast cancer. I also founded two nonprofit organizations, **Are You Dense, Inc. & Are You Dense Advocacy, Inc.,** which became the driving forces behind the education of the public of the impact of density on the accuracy of a mammogram and the advocacy movement for density reporting to the patient. As of this correspondence, **thirteen states have enacted density reporting laws and another dozen legislatures are considering density reporting legislation.** The state of Massachusetts has introduced a density reporting law and Vermont, Maine & New Hampshire are in discussions to introduce density reporting legislation in 2014. The interest of our global mission extends beyond the border of the United States.

Report Considerations: There were minimal discussions or acknowledgement in the draft report of the **"harms" of missed positives** because of the masking effect of dense tissue. **Those of us with later stage cancer would exchange a false positive for a missed positive any day.** The results of two national surveys (2, 3) and a survey conducted by Stanford researchers (4) report that the majority of women do not know their dense tissue and want to know. Women in the Stanford study also reported that interest in knowing their dense breast tissue persisted despite the possibility of an increased likelihood of undergoing invasive procedures, increase in false positives, and additional out-of-pocket expenses. **The literature suggests that women are willing to be recalled for a non-invasive or invasive procedure if it might increase the chance of detecting cancer earlier** (5).

Data from Connecticut practices since our density reporting legislation in 2009 report **more than a 70% increase in early invasive cancers by adding ultrasound to mammography** for the general screening population of women with otherwise normal mammograms and dense breast tissue (6, 7).

Additionally, women with dense breast tissue compared with women with fatty breasts are at a greater likelihood of **interval cancer, delayed diagnoses and advanced disease** (1,8-13) which convey less treatment options and worse survival outcomes (14-16). Additionally, there is no research to suggest that cancers not visible by mammogram and detected by other screening tests are less clinically significant (17). These scientific facts are not reassuring to women with dense breast tissue who experience delayed diagnoses in spite of yearly normal mammograms.

Shouldn't patients have an opportunity to be part of the discussion of whether supplemental tests may be appropriate for them after reviewing the potential risks and benefits of a screening test? To determine, **by policy,** that women that fall into the "*low risk: BI-RADS density 3 or 4, age 40-49, no close family history (corresponds to 5-year risks generally <1.7%). Risk assumed in the model: 1% (0.2% per year*)" should terminate their screening at a digital mammogram fails to acknowledge that 85% of breast cancer is sporadic. **Let the woman decide, after consulting with her doctors, whether the benefits of a screening test outweigh the risks after considering the masking risk of her dense tissue.**

A premenopausal woman at age 49 with extremely dense breast tissue in the 'low' causal risk category may be at a greater risk (because of the causal risk of extremely dense breast tissue) than a post-menopausal woman at age 51 with heterogeneously dense breast tissue in the 'low ' or 'moderate' causal risk category.

Recommendations in this report should encourage a woman to have discussions with her breast health-care providers about her dense breast tissue and the potential risk and benefit of secondary surveillance screening regardless of whether she falls in the low, moderate or high risk category. These conversations must exist independent of screening codes, false positives and anxiety concerns**. If EARLY detection matters then women with dense breast tissue must have the same access as women with fatty breasts to reliable screening tests.**

Respectfully submitted by: Nancy M. Cappello, Ph.D. Dec. 13, 2013

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Please accept my written comment on the draft report Re: supplemental screening options for women with dense breast tissue for the CEPAC meeting on December 13, 2013.

I am a nurse and member of the Massachusetts Density Awareness Coalition (MDAC) which supports MA House Bill 3733, An Act Relative To Breast Cancer Early Detection. This bill would require that radiologists inform patients when they have dense breast tissue and recommend additional screening, i.e., ultrasound and/ or MRI.

Dense breast tissue is comprised of less fat and more connective tissue which appears white on a mammogram. Cancer also appears white on a mammogram therefore tumors are often hidden behind the dense tissue.

Women with dense breast tissue have a GREATER risk of having cancer and are LESS likely to have cancer detected by mammography alone. Breast density is a stronger risk factor of breast cancer than having a mother or sister with breast cancer. The likelihood of a radiologist seeing a tumor on mammography is reduced from 80% in a fatty breast to 40% in a dense breast. This often leads to a delayed diagnosis and advanced cancer.

I became involved in the coalition because despite no family history of breast cancer I was diagnosed with stage 3A lobular cancer in 2011. Breast cancer staging goes from Stage 0 to 4. Mine was stage 3 A due to it's size (3.5") and metastasis to the sentinel node. Survival decreases as the size of a tumor increases.

For 20 years I had received letters informing me my annual mammograms were normal. No mention to me of my dense breast tissue though it was documented in the radiologists' reports all those years. I had received just such a letter only 6 months before finding a large lump in my left breast. Even after I found the lump it was not seen on repeat mammogram or on ultrasound.

The first time I heard of dense breast tissue was at the surgeon's office when he was reviewing the mammogram with my husband and me. How could that be? I've been an RN for 37 years and pride myself in being a patient advocate but I did not have this information to advocate for myself. There were brochures about breast MRIs in the surgeon's office. When I inquired about having an MRI he said insurance wouldn't cover it. That all changed when the needle biopsy showed malignant cells. I had the MRI which confirmed the cancer I knew in my heart was there. I was out of work for 9 months as an ER nurse being treated with a double mastectomy, reconstruction, 8 weeks of chemotherapy and 6 1/2 weeks of radiation treatments. I was worried about losing my job during that time, too. I am continuing treatment with a daily dose of Arimidex, an estrogen lowering medication, which may increase my risk of stroke, blood clots and developing osteoporosis (weak bones) that could lead to fractures.

If House Bill 3733 had been in effect prior to 2011 I would have been informed by the radiologists of the dense breast tissue and its significance. I am a nurse and a researcher at heart. I would have been

online educating myself about dense breast tissue BEFORE the diagnosis, not after. My doctors and I could have been more vigilant. Alternative screening could have been recommended. I could have been diagnosed at an earlier stage, required less treatment and reduced my risk for metastasis. I would not still be feeling side effects from those treatments to this day. I would not be waiting for the other shoe to drop.

Oral Comments

Members of the public who delivered oral remarks during the December 13, 2013 CEPAC meeting are listed below:

1. **Daniel B. Kopans, MD**
   Professor of Radiology, Harvard Medical School
   Senior Radiologist, Breast Imaging Division
   Department of Radiology, Massachusetts General Hospital

2. **JoAnn Pushkin**
   Co-founder, D.E.N.S.E
   Founder, D.E.N.S.E NY

3. **Elizabeth Tyson-Smith, LMHC, CCMHC**
   MA Density Coalition