Medical Policy

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***Current Policy Effective Date: 5/1/25**
(See policy history boxes for previous effective dates)

Title: Digital Breast Tomosynthesis (3-D Mammography)

Description/Background

CONVENTIONAL MAMMOGRAPHY

Conventional mammography produces 2-dimensional (2D) digital images of the breast. Overlapping tissue on a 2D image can mask suspicious lesions or make benign tissue appear suspicious, particularly in women with dense breast tissue. As a result, women may be recalled for additional mammographic spot views. Inaccurate results may lead to unnecessary biopsies and emotional stress, or to a potential delay in diagnosis. Spot views often are used to evaluate microcalcifications, opacities, or architectural distortions; to distinguish masses from overlapping tissue, and to view possible findings close to the chest wall or in the retroareolar area behind the nipple.[1] The National Cancer Institute has reported that approximately 20% of cancers are missed at mammography screening.[2] Average recall rates are approximately 10%, with an average cancer detection rate of 4.7 per 1000 screening mammography examinations.[3] The U.S. Mammography Quality Standards Act audit guidelines anticipate 2 to 10 cancers detected per 1000 screening mammograms.[4] Interval cancers, which are detected between screenings, tend to have poorer prognoses.[5]

DIGITAL BREAST TOMOSYNTHESIS

Digital breast tomosynthesis (DBT) was developed to improve the accuracy of mammography by capturing a group of tomograms of the breast, further clarifying areas of overlapping tissue. Developers proposed that its use would result in increased sensitivity and specificity, as well as fewer recalls due to inconclusive results.[6] DBT produces multiple low-dose images per view along an arc over the breast. During breast tomosynthesis, the compressed breast remains stationary while the x-ray tube moves approximately 1° for each image in a 15° to 50° arc, acquiring 11 to 49 images.[7] These images are projected as cross-sectional "slices" of the breast, with each slice typically 1-mm thick. Adding breast tomosynthesis takes about ten seconds per view. In a study in a research setting, Gur et al (2009) reported a mean time

(standard deviation) for interpretation of results was 1.22 (1.15) minutes for digital mammography (DM) and 2.39 (1.65) minutes for combined DM and breast tomosynthesis.[8]

With conventional 2D mammography, breast compression helps decrease tissue overlap and improve visibility. By reducing problems with overlapping tissue, compression with breast tomosynthesis may be reduced by up to 50%. This change could result in improved patient satisfaction.[9]

A machine equipped with breast tomosynthesis can perform 2D digital mammography, DBT, or a combination of both 2D mammography and DBT during a single compression. Radiation exposure from tomosynthesis is roughly equivalent to mammography. Therefore, adding tomosynthesis to mammography doubles the radiation dose, although it still is below the maximum allowable dose established in the Mammography Quality Standards Act.

Digital breast tomosynthesis can be performed in combination with digital mammography or can be acquired alone with a synthetic two-dimensional (2D) mammogram artificially generated from the 3D image acquisition.

Studies typically compare 1-view (ie, mediolateral oblique view), or more commonly, 2-view (mediolateral oblique plus craniocaudal view) breast tomosynthesis either alone or combined with standard 2D mammography, against standard 2D mammography alone. A TEC Assessment (2014) focused on 2-view tomosynthesis. The U.S. Food and Drug Administration (FDA), which reviewed this new modality in 2011, recommended that 2-view breast tomosynthesis is preferable to 1-view tomosynthesis (both used in combination with full-field DM).[10]

The FDA (2013) approved new tomosynthesis software that permits the creation of 2D images (called C-View) from images obtained during tomosynthesis. As a result, the performance of separate 2D mammography may become unnecessary, thereby lowering radiation dose. It is too early to gauge how conventional 2D mammography plus tomosynthesis compares with C-View plus tomosynthesis.

Regulatory Status

Table 1 provides a summary of DBT systems approved by the FDA through the premarket approval process. FDA product code: OTE. The tomosynthesis portion of the mammography unit is considered a separate mammographic module, and for a facility to use this module, the facility must apply to the FDA for certification that extends to the tomosynthesis module. The Mammography Quality Standards Act requires interpreting physicians, radiologic technologists, and medical physicists to complete eight hours of DBT training and mandates a detailed mammography equipment evaluation before use.

Table 1. FDA-Approved DBT Systems

Device	Manufacturer	Date Approved	PMA	Indications
Selenia Dimensions 3D System	Hologic	Feb 2011 May 2013 May 2017	P080003 P08003/S001 P08003/S005	• Used to acquire 2D and 3D mammograms for screening and diagnosis of breast cancer. Screening mammogram may consist of 2D or 2D and 3D image set. • A hardware and software upgrade to the FFDM conventional mammography system. A 2D image can be generated from 3D image set. • Approval for the added indication of screening for women with dense breasts using 3D plus 2D imaging, where the 2D image can be either synthesized 2D or FFDM image vs FFDM alone
SenoClaire DBT System Senographe Pristina 3D	GE Healthcare	Aug 2014 Mar 2017	P130020 P130020/S002	• A hardware and software upgrade to FFDM conventional mammography system. Same clinical applications as traditional mammography for screening mammography. A screening examination will consist of: a 2D image set consisting of a craniocaudal view and of a mediolateral oblique view, or a 2D craniocaudal view and 3D mediolateral oblique image set. • Approval for multiple projection views to produce 3D digital mammography images for screening and diagnosing breast cancer. Senographe uses similar DBT technology as SenoClaire and consists of software and hardware upgrade to reconstruct tomosynthesis images.
Mammomat Inspiration with Tomosynthesis Option	Seimens	Apr 2015 Jan 2016 Mar 2017	P140011 P140011/S002 P140011/S003	• A software upgrade to FFDM conventional mammography system. It produces multiple low-dose x-ray images used to create cross-sectional views. Indication is for a 2D image set or a 2D and 3D image set screening and diagnosing breast cancer. • Software update resolving any error that may occur during tomosynthesis reconstruction with breast thickness greater than 90 mm • A software upgrade indicated for use with the EMPIRE reconstruction algorithm for acquisition of 2D and 3D digital mammography images, to be used in screening and diagnosis of breast cancer
Aspire Cristalle Digital Breast Tomosynthesis Option	Fujifilm Medical Systems USA	Jan 2017	P160031	Approved for screening and diagnosing breast cancer consisting of images acquired in (1) FFDM mode only or (2) FFDM image set and DBT image set acquired in the ST (standard) mode. FFDM image set and DBT image set must be acquired with normal dose setting and may be acquired in 1 compression (Tomo Set mode) or separate compressions (FFDM and DBT modes).

PowerLook® Tomo Detection Software	iCAD	Mar 2017	P16009	Approved software device intended for radiologists while reading GE SenoClaire breast tomosynthesis exams. It detects up to 5 soft tissue densities (masses, architectural distortions, asymmetries) in the 3D tomosynthesis images and then blends with the standard 2D image. These images may be confirmed or dismissed by the radiologist in the DBT images.

DBT: digital breast tomosynthesis; FDA: Food and Drug Administration; FFDM: full-field digital mammography; PMA: premarket approval; 2D: 2-dimensional; 3D: 3-dimensional.

Medical Policy Statement

Digital breast tomosynthesis (DBT) 3-D Mammography is considered **established** as a screening or diagnostic modality for breast cancer in individuals meeting criteria.

Inclusionary and Exclusionary Guidelines

Inclusions:
Digital breast tomosynthesis (DBT) (3-D mammography) is considered established for screening. It is considered an acceptable alternative to 2D mammography alone**.**

The use of Digital breast tomosynthesis (DBT) (3-D mammography) as a diagnostic tool in the evaluation of suspicious findings for breast cancer is established.

Exclusions:
- Those not meeting the above criteria.

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

77061 77062 77063 G0279*

Other codes (investigational, not medically necessary, etc.):

N/A

***G0279 is for Medicare billing only**

Note: Individual policy criteria determine the coverage status of the CPT/HCPCS code(s) on this policy. Codes listed in this policy may have different coverage positions (such as established or experimental/investigational) in other medical policies.

Rationale

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

DIGITAL BREAST TOMOSYNTHESIS FOR SCREENING

Clinical Context and Test Purpose

The purpose of 3-dimensional (3D) DBT in patients who are being screened for breast cancer is to inform a decision whether to recall women for further diagnostic testing.

The following PICO was used to select literature to inform this review.

Patients

The relevant population of interest is asymptomatic individuals being screened for breast cancer.

Interventions

The intervention of interest is 3D DBT screening as an adjunct to 2D mammography and 3D DBT plus synthesized 2D mammography. DBT devices approved in the U.S. are summarized in Table 1.

Comparators

The primary comparator of interest is mammography alone.

Outcomes

The reference standard is histopathology or at least one-year follow-up for women with negative findings.

The health outcomes of interest are:

- Overall and breast cancer-specific survival
- Quality of life
- Recall rates, which may lead to unnecessary follow-up testing and possibly unnecessary biopsies and treatment
- Cancer risk from radiation exposure.

For breast cancer, the most important health outcome is an overall survival from the disease. DBT, as any breast screening test, may not directly improve breast cancer-specific survival; however, the higher sensitivity of breast DBT could lead to earlier cancer detection, which may, in turn, lead to improved health outcomes if earlier treatment is more effective. Although there is indirect evidence that earlier detection improves health outcomes, possible over detection also needs to be taken into account. Over detection would subject women to testing and treatment that does not improve health outcomes. When screening leads to diagnosis at

an early stage, it may also affect the quality of life by permitting the use of less invasive or otherwise less difficult to tolerate treatments for breast cancer. If using breast DBT reduces the false-positive rate, it would reduce recalls for a diagnostic workup or for biopsy. Fewer unnecessary recalls would, in turn, have a positive impact on patient's quality of life by avoiding the anxiety and additional imaging associated with recalls. Finally, adding breast DBT to traditional mammography doubles the radiation dose, even though the combined dose remains below the limit set in the Mammography Quality Standards Act of 1992. The increased dose might be offset in part by fewer diagnostic tests if the recall rate falls. If synthesized mammography permits the use of tomosynthesis to create both 2D and 3D images, then the dose would be roughly equivalent to a single mammogram and increased radiation exposure would no longer be an issue.

Study Selection Criteria
For the evaluation of the clinical validity of DBT, studies that met the following eligibility criteria were preferred:

- Prospective studies (preferably in a U.S. setting);
- Comparing DBT plus mammography with mammography alone;
- Including asymptomatic individuals being screened for breast cancer;
- Including performance characteristics such as screening sensitivity and specificity (ie, follow-up of negative findings and interval cancers for at least one year).

Several studies did not meet the preferred selection criteria, in particular, most lacked data on the follow-up of negative findings and interval cancers. The prospective studies without sufficient follow-up of negative findings are summarized briefly in tabular form following the discussion of studies with follow-up of negative findings.

3D DBT as an Adjunct to 2D Mammography

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Prospective Studies With Long-Term Follow-Up of Negative Findings
Characteristics of prospective studies with follow-up of negative findings are shown in Table 2. The table includes three publications of previously reported prospective studies that have provided additional data including follow-up for interval cancers.

Houssami et al (2018) reported on the results from STORM (Screening with Tomosynthesis OR standard Mammography) study, which assessed interval breast cancers, based on ascertainment at 2-year follow-up from screening examinations.[11] STORM examined comparative cancer detection for traditional mammography with or without DBT in a general population of 7292 asymptomatic Italian women being screened for breast cancer. In the initial screening of STORM, women were recalled if either of two independent readers recorded a positive result at either mammography alone or mammography plus DBT. Previous reports of STORM have summarized initial findings of one round of screening and partial follow-up of the cohort (summarized in the following section). The 2018 report focused on screening measures requiring completed ascertainment of interval cancers, ie, interval cancer rates and screening sensitivity, including 2 years of follow-up. Interval cancers were identified using a combination of checking local hospital and pathology databases; and checking with the local cancer registry for cancer notifications. Interval cancer rates for

concurrent Italian cohorts screened with 2D-mammography alone were provided for descriptive purposes. The study was not powered for formal comparisons of mammography alone to mammography plus DBT.

Similarly, Skaane et al (2018) reported performance indicators and characteristics of screen-detected and interval cancers from 24301 women in the Oslo Tomosynthesis Screening Trial (OTST) administered by the Norwegian Cancer Registry.[12,13] The OTST was designed to compare four different reading modes for mammography with or without DBT. The results reported in the 2018 publication include the double-reading mammography plus DBT and double-reading mammography alone arms. Decisions regarding recalls from the initial screens were made by consensus conference review of images that were rated by any reader as any score other than negative or definitely benign. Previous reports from the OTST included initial results of one round of screening without the follow-up of negative results (summarized in the following section). The 2018 publication reported a comparison of mammography plus DBT in women from the OTST who had 2 years of follow-up with 2 previous mammography screening rounds in Oslo using data from the Norwegian Cancer Registry. The OTST (2019) publication reports final results of the OTST, including the sensitivity and specificity of all 4 arms.

Zackrisson et al (2018) reported final results of the Malmö Breast Tomosynthesis Screening Trial (MBTST; NCT01091545), a population-based screening study of 14851 women ages 40–74 years attending a national breast cancer screening in Malmö, Sweden between 2010 and 2015.[14] Preliminary results have been reported previously and are discussed in the following section. The 2018 publication included follow-up of participants for at least 2 years. MBTST was designed to compare one-view DBT to standard two-view digital mammography (DM). Decisions regarding recalls were made by consensus conference review of images that were rated by reading groups as any score other than negative or definitely benign.

Table 2. Characteristics of Prospective Studies with Long-Term Follow-Up of Negatives

Study	Study Population	Reference Standard	Threshold for Positive Index Test	Timing of Reference and Index Tests	Blinding of Assessors	Comment
STORM	Asymptomatic women ≥48 y attending biennial screening in Italy, 2011 to 2012	Pathology; 2-y follow-up of negatives	Double-reading by radiologists experienced in mammography	Within 24 mo of screening episode	Yes	STORM was not designed to compare interval cancer data
OTST	Women ages 50-69 y invited biennially for screening in Norway, 2010 to 2012	Pathology; 2-y follow-up of negatives	Consensus decision of multiple radiologists	Within 24 mo of screening episode	Yes	Comparison group in 2018 paper was not concurrent
MBTST	Women ages 40–74 y, invited to attend national breast cancer screening in Sweden, 2010 to 2015. Ages 40 to 54 are screened every 18 m; ages 55 to 74 are	Pathology or record matching using national cancer registry; follow-up of negatives to next	Local procedures; no central review	Within 18 or 24 mo of screening episode	Yes	MBTST was not designed to compare interval cancer data

	screened every 24 m	screening (18 m or 2 y)				

OTST: Oslo Tomosynthesis Screening Trial; MBTST: Malmö Breast Tomosynthesis Screening Trial; STORM: Screening with Tomosynthesis OR standard Mammography

Results of prospective studies meeting with sufficient follow-up are shown in Table 3. Nine interval cancers were detected in STORM; three were diagnosed within one year of screening and the remaining six were diagnosed between one and two years after screening. STORM reported an interval breast cancer rate in mammography plus DBT screening participants that were numerically lower (and screening sensitivity numerically higher) than the rate in 2D-screened women although confidence intervals (CIs) overlapped. These findings should be interpreted with caution given that STORM was not designed to compare interval cancer data and there were a small number of interval cases. Specificity was not reported in the publication; however, based on the information provided and the data on mammography plus DBT test results in the previous publications, it appears that the specificity was 96.6% (95%CI, 96.2% to 97.0%) in the STORM participants.

Interval cancer rates were similar in women who received mammography alone and DBT plus mammography in the report including the OTST participants. The OTST also reported numerically but not statistically higher sensitivity while also reporting statistically higher specificity of mammography plus DBT compared with mammography alone. Most of the additional DBT-detected cancers in the OTST were reported to be small node-negative invasive cancers of molecular subtypes known to have a good prognosis.
MBTST was a paired design and the 2018 results did not compare to a non-MBTST cohort (as in STORM and OTST reports). Therefore interval cancers were reported overall and not by screening modality; 139 breast cancers were detected in 137 (less than 1%) of 14,848 women; 89 were detected by both DBT and DM, 42 were detected only by DBT, and 8 were detected only DM. Most of the cancers detected by DBT and DM were invasive, and nearly all cancers detected by DBT only were invasive. DBT detected a higher number of invasive lobular cancers.

Table 3. Results of Prospective Studies with Long-Term Follow-Up of Negatives

Study	**N**	**Interval Cancer Rate (95% CI)**	**Clinical Validity (95% CI), %**			
			Sensitivity	**Specificity**	**PPV**	**NPV**
STORM[11]						
Mammo-only concurrent cohort	25,058	1.61/1000 negative screens (1.15 to 2.18)	77.3 (70.4 to 83.2)	NR	NR	NR
STORM participants	7292	1.24/1000 negative screens (0.57 to 2.36)	85.5 (75.0 to 92.8)	NR	NR	NR
OTST						
Mammo-only non-current cohorts	59,877	2.0/1000 screens	76.2	96.4	NR	NR
OTST participants	24,301	2.1/1000 screens	80.8	97.5	NR	NR
Difference		0.1 (-0.5 to 0.8)	4.6 (-1.4 to 10.5)	1.2 (0.91 to 1.40)		
OTST only						
Mammo only, single reading			54.1	94.2	9.9	99.4
DBT+Mammo, single reading			70.5	95.0	14.1	99.6
MBTST						

Overall	14,848	1.48 cancers /1000 screened (0.93 to 2.24)				
Mammo-only (double view)	14,848	NA	60.4 (52.3 to 68.0)	98.1 (97.9 to 98.3)	25.9 (21.6 to 30.7)	99.6 (99.4 to 99.7)
DBT (single view) + Mammo	14,848	NA	81.1 (74.2 to 86.9)	97.2 (97.0 to 97.5)	24.1 (20.5 to 28.0)	99.8 (99.7 to 99.9)

CI: confidence interval; DBT: digital breast tomosynthesis;mammo: mammography; MBTST: Malmö Breast Tomosynthesis Screening Trial; NR: not reported; NPV: negative predictive value; OTST: Oslo Tomosynthesis Screening Trial; PPV: positive predictive value; STORM: Screening with Tomosynthesis OR standard Mammography.
[a] STORM participants were screened with both mammography and digital breast tomosynthesis. Women were recalled if either of two independent readers recorded a positive result at either mammography alone or mammography plus digital breast tomosynthesis

The purpose of the limitations tables (Tables 4 and 5) is to display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence and provides the conclusions on the sufficiency of the evidence supporting the position statement. STORM, OTST, and MBTST were not conducted in a U.S. setting and screening practices differ in European countries. While STORM and OTST included a prospective cohort of women receiving DBT plus mammography, the comparison group in the OTST study for the purposes of the 2018 publication was a cohort previously screened with mammography alone (ie, not concurrent) and few details were provided on selection of the women included in that cohort.

Table 4. Relevance Limitations of Prospective Studies with Long-Term Follow-Up of Negatives

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
STORM[11]	4. Italian setting; screening practices differ from those in the U.S.			3. Only screening sensitivity is reported in 2018 paper	
OTST[12,15]	4. Norwegian setting; screening practices differ from those in the U.S.	3. Uses consensus of multiple readers unlike single-reader relevant to U.S. clinical setting			
MBTST[14]	4. Swedish setting; screening practices differ from those in the U.S	3. Uses consensus of multiple readers unlike single-reader relevant to U.S. clinical setting			1: Younger women followed for only 18 m

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.
OTST: Oslo Tomosynthesis Screening Trial; MBTST: Malmö Breast Tomosynthesis Screening Trial; STORM: Screening with Tomosynthesis OR standard Mammography.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true-positives, true-negatives, false-positives, false-negatives cannot be determined)

Table 5. Study Design and Conduct Limitations of Prospective Studies with Long-Term Follow-Up of Negatives

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
STORM[11]						2. Comparisons not provided because study not powered to make comparisons for interval cancers
OTST[12]	2. Unclear if cohort from cancer registry was consecutive or randomly selected in 2018 publication		2. Compared with previous rounds of mammography in 2018 publication			
MBTST[14]						2: Because of paired design, rates of interval cancers cannot be compared

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.
OTST: Oslo Tomosynthesis Screening Trial; MBTST: Malmö Breast Tomosynthesis Screening Trial; STORM: Screening with Tomosynthesis OR standard Mammography.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (ie, convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison with other tests not reported.

Prospective Studies Without Long-Term Follow-Up of Negative Results

Other prospective studies assessing the diagnostic accuracy of DBT for screening are summarized in Table 6. The table is subdivided by the characteristics of study designs. Select studies are summarized briefly following the table. In general, these studies do not have follow-up sufficient to capture interval cancers and therefore traditional measures of sensitivity and specificity are not provided.

Table 6. Prospective Studies of DBT for Breast Cancer Screening Without Long-Term Follow-Up of Negatives

Study	No. Cancers/ Patients	Recalls per 1000 Screens (95% CI)	PPV for Recalls (95% CI), %	Cancers Detected per 1000 Screens (95% CI)	PPV for Biopsies (95% CI), %
Randomized controlled trials					
Pattacini et al (2018)[16]					
Mammo	44/9783	35	13	4.5	NR
Mammo plus DBT	83/9777	35	24	8.6	
p			less than 0.001		
Maxwell et al (2017)[17]	11/1227				
Mammo		28	NR	9.0	NR
Mammo plus DBT		27		10.6	

p					
Prospective observational studies					
Patients served as their own controls					
MBTST (2016)[18] (exploratory results)	68/7500				
Mammo		26 (23 to 30)	24	6.3 (4.6 to 8.3)	NR
Mammo plus DBT		38 (33 to 42)	24	8.9 (6.9 to 11.3)	
p		less than 0.001		less than 0.001	
Sumkin et al (2015)[19]	6/1074	[b]			
Mammo		384	NR	4.7	NR
Mammo plus DBT		274		4.7	
OTST[20]	121/12,621				
Mammo		NR	28.5	6.1	NR
Mammo plus DBT			29.1	8.0	
p				0.001	
STORM[21,22a]	59/7292				
Mammo		42	11	5.3 (3.8 to 7.3)	NR
Mammo plus DBT		36	19	8.1 (6.2 to 10.4)	
p				less than 0.001	
			Noncancer Cases[d]		
Rafferty et al (2013)[23c]	51/997				
Study 1 (range)					
Mammo		551 (223-798)[e]	43	NR	NR
Mammo plus DBT		167 (76-284)[e]	56		
Study 2 (range)					
Mammo		488 (282-691)[e]	47	NR	NR
Mammo plus DBT		301 (198-413)[e]	50		
Includes s2D mammo		**False-Positive Recall, %**			
Bernardi et al (2016; STORM-2)[24]	90/9672				
Mammo		3.42 (3.07 to 3.80)		6.3 (4.8 to 8.1)	NR
Mammo plus DBT		3.97 (3.59 to 4.38)		8.5 (6.7 to 10.5)	NR
s2D mammo plus DBT		4.45 (4.05 to 4.89)		8.8 (7.0 to 10.8)	NR

CI: confidence interval; DBT: digital breast tomosynthesis; Mammo: mammography; MBTST: Malmö Breast Tomosynthesis Screening Trial; NR: not reported; OTST: Oslo Tomosynthesis Screening Trial; PPV: positive predictive value; s2D: synthesized 2D mammography; STORM: Screening with Tomosynthesis OR standard Mammography.
[a] Data from Ciatto et al (2013) and Houssami et al (2014).
[b] U.S. population; high-risk preferentially included.
[c] Twenty-seven women with no follow-up not included in results.
[d] U.S. population; sample enriched with women referred for biopsy (22%).
[e] Range across 12 radiologists in study 1 and 15 radiologists in study 2.

Randomized Controlled Trials

Two RCTs have compared screening with mammography alone with mammography plus DBT. Pattacini et al (2018) reported on the preliminary results from the Reggio Emilia Tomosynthesis trial, which compare mammography plus DBT with mammography alone in women in Italy ages 45 to 74 who had previously been screened with mammography.[16] The trial is designed to enroll 40000 women and compare interval cancers with a cumulative incidence of advanced cancer and had 4.5 years of follow-up. The 2018 publication focuses on the preliminary results for the baseline screen of 19560 women recruited from 2014 to 2016, including cancers diagnosed within 9 months from recruitment and, as such, cannot yet provide data on interval cancers and confirmation of negative findings. Results are shown in Table 6.

Maxwell et al (2017) reported on the results of a trial of asymptomatic women from 2 centers in the U.K. ages 40 to 49 years who had previously undergone mammography for an increased risk of breast cancer.[17] Participants were randomized in a crossover design to screening with 2D mammography followed by 2D mammography plus DBT a year later, or vice versa. The trial was designed to compare recall rates. Results are shown in Table 6. The crossover design limits the utility of collecting long-term results.

In summary, recall rates did not differ for mammography alone vs mammography plus DBT in either RCT. Maxwell et al (2017) also reported no statistically significant difference in cancer detection rate. However, preliminary results from Reggio Emilia Tomosynthesis trial would suggest an almost 90% increase in detection rate for mammography plus DBT compared with mammography (relative risk [RR], 1.89; 95% CI, 1.31 to 2.72) and an increase in the PPV for recalls from 13.0% to 24.1%. The gain in cancer detection was observed for all classes of cancers except for very large or late cancers. There were more instances of ductal carcinoma in situ (DCIS) with mammography plus DBT (+1 per 1000), benign lesions (+1 per 1000), and invasive cancers (+3 per 1000). There was also an increase in the risk of surgery for mammography plus DBT (RR=1.90; 95% CI, 1.35, 2.68; risk difference, 5 per 1000; 95% CI, 2 to 7).

Prospective Observational Studies

Lång et al (2016) reported exploratory results from the first half of the Malmö Breast Tomosynthesis Screening Trial, comparing 1-view (mediolateral oblique) DBT (a lower radiation dose than DM) with 2-view DM.[18] The Malmö Breast Tomosynthesis Screening Trial is a 1-arm, single institution, prospective study. Randomly selected women in Sweden (age range, 40-74 years) were offered 1-view DBT and 2-view DM. A sample size of 15000 was specified to detect an improvement in cancer detection sensitivity from 63% to 88% (power, 80%); 7500 were included in the exploratory analysis. In Sweden, breast cancer screening is offered to women between ages 40 and 55 every 18 months and every 24 months after that to age 74. Six experienced readers interpreted images (mean experience, 26 years; range, 8-41 years). Blinded double-reading was carried out for DBT and DM with rule-based arbitration of disagreements women in this exploratory analysis were followed at least one year for the development of cancer ascertained through the South Swedish Cancer Registry. Of 10547 women invited, 71.1% participated with 20% undergoing their first screening test. Results are shown in Table 6. DCIS detection rates were similar between both modalities. Following arbitration, the recall rate was lower for DM (2.6%; 95% CI, 2.3% to 3.0%) than for DBT (3.8%; 95% CI, 3.3% to 4.2%; p less than 0.001).

The results of the analysis of a cohort from a large trial, the OTST comparing 4 different reading modes, was published by Skaane et al (2013) in Norway.[20,25] The Skaane et al (2013)

analysis was a preplanned interim analysis of 2 arms in a larger 4-arm trial; findings of the other 2 arms are not relevant to this topic. The sample included 12621 women with 121 cancers detected during routine screening.[26] Results are shown in Table 6. After adjusting for reader differences, the ratio of cancer detection rates for mammography plus DBT vs mammography alone was 1.27 (98.5% CI, 1.06 to 1.53; p=0.001). The trialists did not ascertain any increase in detecting DCIS by adding breast tomosynthesis (ie, additional cancers detected were mostly invasive). In Norway, as in much of Europe, women are screened every other year, and two readers independently interpret the images, which differs from usual practice in the U. S. After adjusting for differences across readers, the ratio of false-positive rates for mammography plus DBT vs mammography alone was 0.85 (98.5% CI, 0.76 to 0.96; p less than 0.001).

The STORM study examined comparative cancer detection for traditional mammography with or without DBT in a general population of 7292 asymptomatic Italian women being screened for breast cancer.[21,22] The reference standard was pathology results for women undergoing biopsies; women with negative results on both mammography and DBT were not followed so neither sensitivity nor specificity could be calculated. Results are shown in Table 6. Mammography plus DBT revealed all 59 cancers; 20 (34%) were missed by traditional mammography (p less than 0.001). In the original report, incremental cancer detection by using both modalities was 2.7 cancers per 1000 screens (95% CI, 1.7 to 4.2). There were 395 false-positive results: 181 were false-positive using either mammography or both imaging modalities together; an additional 141 occurred using mammography only, and 73 occurred using mammography and DBT combined (p less than 0.001). In preplanned analyses, combined results of mammography and DBT yielded more cancers in both age groups (less than 60 vs ≥60 years) and breast density categories (1 [least dense] and 2 vs 3 and 4 [most dense]). In a follow-up report including available data on interval cancers diagnosed in the first year of follow-up (note, screening was repeated at two years), six additional interval cancers had been diagnosed. The cancer detection rates including the 6 additional cancers were 4.8 (95% CI, 3.3 to 6.7) vs 7.5 (95% CI, 5.7 to 9.8) for mammography vs mammography plus DBT, for an incremental cancer detection rate of 2.7 (95% CI, 1.6 to 4.2; p less than 0.01).

Retrospective Studies

Several retrospective studies have also been performed, many of which included several thousand patients and 3 of which included more than 100,000 patients. Many of the retrospective studies have included mixed populations or unclear indications for screening and inadequate reference standards such as historical controls and are therefore not discussed. Retrospective studies have, in general, suggested increases in the rates of cancer detection and decreases in recall and false-positive rates.

Systematic Reviews

Marinovich et al (2018) reported results of a systematic review that included prospective and retrospective studies published through 2017.[27] The review does not include the prospective studies with long-term follow-up.

Characteristics of Detected Cancers

Yun et al (2017) published a meta-analysis assessing the characteristics of cancers detected with DM alone vs DM plus DBT during routine breast cancer screening.[28] Eleven studies were included in the meta-analysis, four prospective and seven retrospective observational studies, all of which are described in Table 2 (above). Reviewers evaluated study quality using the

Quality Assessment of Diagnostic Accuracy Studies tool and found an overall satisfactory risk of bias, but all studies had a high risk of bias concerning the reference standard as well as flow and timing because patients who were not recalled did not have a reference standard test (ie, did not have biopsy-confirmed negative findings).

In a pooled analysis, the overall cancer detection rate was significantly higher with DM plus DBT than with DM alone (RR=1.29; 95% CI, 1.16 to 1.43; I^2=0%). Moreover, the detection of invasive cancer was significantly higher in the DM plus DBT group compared with DM alone group (RR=1.33; 95% CI, 1.17 to 1.51; I^2=7%). The rate of carcinoma in situ detection did not differ significantly between the DM plus DBT group and the DM alone group (RR=1.20; 95% CI, 0.94 to 1.52; I^2=29%). Fewer studies reported on cancer detection by T and/or N stage. In a pooled analysis of 5 studies, there was a significantly higher rate of detecting T1 cancers with DM plus DBT than with DM alone (RR=1.39; 95% CI, 1.14 to 1.70; I^2=0%), but no significant difference for detecting stage T2 or larger cancer (RR=1.39; 95% CI, 0.90 to 2.16; I^2=0%). Similarly, there was a significantly higher rate of detection of stage N0 cancers with DM plus DBT than with DM alone (RR=1.45; 95% CI, 1.21 to 1.74; I^2=0%) and no significant difference in the detection of stage N1 or higher cancers (RR=1.34; 95% CI, 0.92 to 1.99; I^2=0%). The numbers of more advanced cancers were relatively small, and the pooled analyses of T2 or higher and N1 or higher cancers might have been underpowered. The findings of this meta-analysis were limited by the potential biases of the included studies (eg, many were retrospective and studies had insufficient confirmatory data on negative imaging results).

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs. There is no direct evidence from trials comparing health outcomes in patients screened for breast cancer using DBT and mammography.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

A chain of evidence should demonstrate that DBT used as an adjunct to screening improves screening performance compared with standard mammography alone. Available studies have reported that adding DBT to mammography may increase cancer detection and reduce unnecessary recalls. Even if adding breast tomosynthesis simply maintained the same sensitivity as mammography, a decline in the false-positive rate would reduce the substantial number of unnecessary diagnostic workups in the U.S.

Three prospective studies (STORM, OTST, MBTST) with a two-year follow-up for interval cancers have been published although none were conducted in the U.S. The OTST had prospective data on the mammography plus DBT cohort but compared outcomes with previously screened cohorts from a cancer registry. None were powered to compare interval

cancer rates. STORM reported an interval breast cancer rate in mammography plus DBT screening participants that were numerically lower (and screening sensitivity numerically higher) than the rate in 2D screened women although CIs overlapped. The OTST also reported numerically but not statistically higher sensitivity. However, the OTST did report statistically significantly higher specificity of mammography plus DBT compared with DBT alone. MBTST reported statistically higher sensitivity but not specificity.

- Two RCTs without sufficient follow-up to detect interval cancers have reported no difference in recall rates between DBT plus mammography and mammography alone. However, 1 RCT reported approximately a 90% increase in detection rate for DBT plus mammography compared with mammography with more instances of DCIS with mammography plus DBT (+1 per 1000), benign lesions (+1 per 1000), and invasive cancers (+3 per 1000) and an increase in the PPV for recalls from 13.0% to 24.1%. This RCT is ongoing and is designed to compare interval cancers and cumulative incidence of advanced cancer with 4.5 years of follow-up at completion.
- While the incremental radiation per individual is not large, the aggregate impact of that increased radiation dose over a large group can raise greater concern. Although any elevated dose, related to DBT may be offset by fewer diagnostic images required for women who are recalled for further evaluation, it needs to be considered. Synthesized mammography may resolve this issue (discussed in the following section).
- There has been widespread debate over the value of mammography that hinges in large part on beliefs about whether there is substantial over detection of breast cancer during screening. An argument in favor of tomosynthesis is that the probability of over detection is lower because most of the additional cancers detected are invasive. On the other hand, mammography is included with tomosynthesis in part because of concern that readers of tomosynthesis images may miss microcalcifications, some of which are malignant.

In summary, estimates of sensitivity and specificity of DBT plus mammography from studies with adequate follow-up of negative results are available from three studies. The sensitivity of DBT plus mammography is likely to be at least as high as mammography alone. One study with limitations reported the specificity of DBT plus mammography was significantly higher than mammography alone but another reported no difference in specificity. An increase in specificity (corresponding to a decrease in the false-positives) would reduce unnecessary diagnostic workups and their consequences. Two RCTs with short follow-up reported similar recall rates for DBT plus mammography and mammography alone but one of the RCTs reported a significant increase in cancer detection rate, including invasive cancer and DCIS.

Subsection Summary: Screening With 3D DBT as an Adjunct to 2D Mammography

There is a lack of direct evidence on the clinical utility of 3D DBT from screening trials comparing health outcomes in patients screened for breast cancer with 3D DBT vs 2D mammography. Current evidence would suggest that the use of mammography plus breast tomosynthesis may modestly increase the number of cancers detected, with a potential decrease in the number of women who undergo unnecessary recalls or biopsies. A 2017 meta-analysis including a pooled analysis of 11 screening studies found a significantly higher rate of invasive cancer detection with 3D DBT plus 2D DM than with 2D DM alone. Preliminary data from an RCT also found higher rates of invasive cancer with 3D DBT plus DM.

3D DBT Plus Synthesized 2D Mammography

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

No prospective studies with sufficient follow-up for interval cancers and negative findings were identified.

One systematic review of 3D DBT plus 2D vs DM plus DBT for breast cancer screening has been published. Characteristics are shown in Table 7. Houssami et al (2018) included studies that evaluated s2D plus DBT compared with DM plus DBT for population screening and provided quantitative data on screening detection measures (cancer detection and recall measures).[29] Five studies were identified.[24,30,31,32,33] The studies included in the Houssami et al (2018) systematic review, with the exception of Skaane et al (2014),[33] all included a comparison of DM and DM plus DBT in addition to the synthesized digital mammography (sDM) plus DBT arm and as such were included in Table 6.

Table 7. Characteristics of Systematic Reviews of DBT Plus s2D Mammography

Study	Dates	Studies	Participants	N (Range)	Design	Duration
Houssami et al (2018)[29],	Through Aug 2017	5	Received s2D or DM with DBT for population breast cancer screening	NR	Any design Eligible (included 2 prospective, 3 retrospective)	NR

DBT: digital breast tomosynthesis; DM: digital mammography;NR: not reported; s2D: synthesized 2-dimensional.

Results of the systematic review are shown in Table 8. Meta-analyses were not conducted; instead, qualitative summaries were provided. Cancer detection rates appear similar between DM plus DBT (range, 5.45 to 8.5 per 1000 screens) and s2D plus DBT (range, 5.03-8.8 per 1000 screens). The recall rates appear heterogeneous across included studies. The mean glandular dose for s2D plus DBT was 55% to 58% of DM plus DBT. The systematic review did not include a risk of bias or quality assessment. However, all of the included studies had limitations similar to the studies in the previous setting, ie, lack of follow-up for interval cancers or confirmation of negative results.

Table 8. Results of Systematic Reviews of DBT Plus s2D Mammography

Study	Breast Cancer Detect Rate (per 1000 screens)	Recall, %	Mean Glandular Dose, mGy
Houssami et al (2018)[29]			
Range of N	NR (5 studies)	NR (5 studies)	NR (3 studies)
Range of effect sizes			
DM	5.3 to 6.3/1000	3.42 to 8.7[a]	1.36 to 3.77
DM plus DBT	5.45 to 8.5/1000	3.97 to 8.8[a]	1.87 to 4.88
s2D plus DBT	5.03 to 8.8/1000	4.3 to 7.1[a]	3.22 to 7.97

DBT: digital breast tomosynthesis; DM: digital mammography; NR: not reported; s2D: synthesized 2-dimensional.
[a] Two studies reported recall and three studies reported false-positive recall.

The Skanne et al (2014) study from the systematic review and other studies published following the systematic review are briefly summarized in Table 9.[33] None has sufficient follow-up to evaluate interval cancers.

Table 9. Other Studies of DBT plus sDM for Breast Cancer Screening

Study	No. Cancers/ Patients	Recalls per 1000 Screens (95% CI)	PPV for Recalls (95% CI), %	Cancers Detected per 1000 Screens (95% CI)	PPV for Biopsies (95% CI), %
Randomized controlled trials					
Aase et al (2018)[34]; Hofvind et al (2019)[35]; To-Be trial (NCT02835625)					
DM (double)	87 / 14369	40 (37 to 43)	15.2 (12.3 to 18.2)	61 (48 to 73)	32.1 (26.5 to 37.7)
sDM plus DBT (double)	95 / 14380	31 (28 to 34)	21.4 (17.6 to 25.2)	66 (53 to 79)	37.7 (31.7 to 43.7)
P	0.56	less than 0.001	0.011		0.18
Prospective observational studies					
Romero Martin et al (2018)[36]	98/16,067				
DM (double)		50	9.4	4.7	39.4
sDM plus DBT		29	18.0	5.4	46.0
P		less than 0.001	less than 0.001	0.043	0.189
Caumo et al (2018)[37]					
DM	78/14,423	4.2	12.9	9.3	NR
sDM plus DBT	155/16,666	4.0	23.3	5.4	
P		0.32	less than 0.001	less than 0.001	
Retrospective observational studies					
Ambinder et al (2018)[38,39]					
DBT plus DM	41/7813	76	6.9	5.3	29.2
sDM plus DBT	82/14,722	71	8.0	5.6	36.7
P		0.04	0.33	0.75	0.16
Skaane et al (2014)[33]					
Period 1					
DBT plus DM		28	28.5	8.0	
s2D plus DBT		25	30.3	7.4	
P			0.61		
Period 2					
DBT plus DM		24	32.1	7.8	
s2D plus DBT		22	34.9	7.7	
P			0.47		

CI: confidence interval; DBT: digital breast tomosynthesis; DM: digital mammography; PPV: positive predictive value; sDM: synthesized digital mammography; s2D: synthesized 2-dimensional

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

There is no direct evidence from trials comparing health outcomes in patients screened for breast cancer using DBT and mammography.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Given that the utility of breast cancer screening with mammography has been established, a chain of evidence should demonstrate that screening performance of DBT plus synthesized 2D is equivalent to that of standard mammography alone. Available studies have reported that replacing mammography with DBT plus s2D might increase cancer detection and reduce recall rates. However, performance characteristics are uncertain due to the limitations described above in the section on the clinical utility of DBT plus acquired mammography, and thus it is not possible to construct a chain of evidence.

Subsection Summary: Screening With 3D DBT Plus Synthesized 2D Mammography
Preliminary results of one RCT, two prospective and three retrospective studies have assessed 3D DBT plus s2D mammography, which has lower radiation exposure than 3D DBT plus DM. In the RCT, the rate of cancers detected was similar for DBT plus s2D compared to DM but recall rates were lower. Two observational studies found higher detection rates with 3D DBT plus s2D compared with DM, one found similar detection rates with 3D DBT plus s2D compared with DM, and two found similar detection rates with 3D DBT plus s2D compared with 3D DBT plus DM. When comparing the recall rate of 3D DBT plus s2D with DM alone, one prospective observational study and one RCT found a higher recall rate for DM and one prospective study found similar rates, while the retrospective studies had mixed findings. However, the potential for overdiagnosis cannot be ascertained because of the study designs, and interval cancer rates are not yet available. The nonrandomized designs lack long-term follow-up to assess false-negative results. The RCT is designed to continue follow-up for 2 years with completion expected in 2022.

There is a lack of direct evidence on the clinical utility of DBT from screening trials comparing health outcomes in patients screened for breast cancer with DBT vs mammography. Due to limitations in the studies on diagnostic accuracy, it is not possible to construct a chain of evidence.

3D DBT for Diagnosis

Clinical Context and Test Purpose
The purpose of 3D DBT in patients who have screen-detected abnormalities suspicious for breast cancer is to inform a decision whether to biopsy.

The following PICO was used to select literature to inform this review.

Patients

The relevant population of interest is individuals with abnormal findings on breast imaging or a clinical examination.

Interventions
The intervention of interest is 3D DBT as an adjunct to 3D mammography for diagnosis.

Comparators
The comparators of interest are standard diagnostic methods. Diagnosis includes both physical examination and imaging. Diagnostic imaging may include diagnostic mammography and ultrasonography.

Outcomes
The beneficial outcomes of a true-negative test result, are an avoidance of invasive procedures (eg, biopsy or mastectomy). The beneficial outcomes of a true-positive test result are reductions in overall mortality and breast cancer-specific mortality.

The harmful outcomes of a false-negative test result are a delay in treatment and a potential increase in mortality. The harmful outcomes of false-positive test results are unnecessary invasive procedures.

Study Selection Criteria
For the evaluation of the clinical validity of DBT, studies that met the following eligibility criteria were selected:

- Prospective studies (preferably in a U.S. setting).
- Comparing DBT plus mammography with diagnostic evaluation alone;
- Appropriate reference standard (histopathology);
- Including performance characteristics (eg, sensitivity, specificity).

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Prospective Studies
As per the selection criteria, the characteristics of prospective studies are described in Table 10. The reference standard used for all included studies was histopathology. These prospective studies were conducted in Europe and Asia. Heywang-Kobrunner et al (2017)[40] and Thibault et al (2013)[41] used single-view DBT while Seo et al (2016)[42] used double-view.

Table 10. Characteristics of Prospective Studies of DBT Diagnostic Performance

Study	Study Population	Reference Standard	Threshold for Positive Index Test	Timing of Reference and Index Tests	Blinding of Assessors
Heywang-Kobrunner et al (2017)[40]	Germany • Ages 50-69 y with a screen-detected abnormality • Percent with calcifications NR	Histopathology and 2-y follow-up of negatives and registry matching	• Reading by experienced Radiologists; rating of BIRADS 0, 3, 4, or 5 • Single-view	NR	No
Seo et al	Korea	Histopathology and		NR	Yes

(2016)[42]	• Signs and symptoms of suspicious findings on screening mammography or ultrasonography • 10% with calcifications	2-y follow-up of negatives	• Reading by experienced radiologists; rating of BIRADS 4 or 5 • Double-view		
Thibault et al (2013)[41]	France • Ages ≥40 y with screening recalls with unresolved mammographic or ultrasound workup or with breast symptoms • 31% with calcifications	Histopathology or minimum 2-y follow-up	• Reading by experienced radiologist; rating of BIRADS 4 or 5 • Single-view	NR	Yes
Teertstra et al (2010)[43]	Netherlands • Abnormal screening mammogram, with clinical symptoms, or referred from other hospitals for a second opinion • Percent with calcifications NR	Histopathology with 1.5-2 y follow-up of negatives	Reading by experienced Radiologist; rating of BIRADS 0, 3, 4, or 5	NR	Yes

BIRADS: Breast Imaging Reporting and Data System; DBT: digital breast tomosynthesis; NR: not reported.

Results of the studies meeting selection criteria are shown in Table 11. Precision estimates for performance characteristics such as sensitivity and specificity were only provided in Teertstra et al (2010)[43] in which the diagnostic performance of DBT was very similar to DM and Seo et al (2016),[42] who reported that the sensitivity of DM plus DBT was significantly higher than DM alone (p less than 0.001). Only Thibault et al (2013) compared DBT with DM plus ultrasonography; adding DBT to DM plus ultrasound did not improve the estimated area under the curve.[41]

Table 11. Results of Prospective Studies of DBT Diagnostic Performance

Study	**Initial N**	**Final N**	**Excluded Samples**	**Prevalence of Condition, %**	**Clinical Validity (95% Confidence Interval)**			
					Sensitivity	**Specificity**	**PPV**	**NPV**
Heywang-Kobrunner et al (2017)[40]	NR	311	Unclear	18				
DM					91	42	25	96
DBT					96	57	32	97
DM plus DBT					96	54	31	99
Seo et al (2016)[42]	219	203	Surgical clip in breast or history of vacuum- assisted breast biopsy	63				
DM					73	61	NR	NR
DBT					78	63	NR	NR
DM plus DBT					80	64	NR	NR
Thibault et al (2013)[41]	156	131	Incomplete mammographic data for review	42				

DM					73	53	53	74
DM plus US					81	48	53	78
DBT					66	64	57	72
DM plus DBT					68	64	58	73
DM+US+DBT					81	52	55	79
Teertstra et al (2010)[43]	513	513	0	37				
DM					93	86	48	99
					(87 to 96)	(84 to 88)	(41 to 54)	(98 to 99)
DBT					93	84	45	99
					(87 to 96)	(92 to 87)	(38 to 52)	(98 to 99)

DBT: digital breast tomosynthesis; DM: digital mammography; NPV: negative predictive value; NR: not reported; PPV: positive predictive value; US: ultrasonography.

The studies included in the tables above were prospective, consecutively enrolled participants, and used an appropriate reference standard. Notable limitations identified in each study are shown in Tables 12 and 13. Only one study compared DBT with DM plus ultrasonography and one study provided precision estimates for performance characteristics such as sensitivity and specificity.

Table 12. Relevance Limitations of Prospective Studies of DBT Diagnostic Performance

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Heywang-Kobrunner et al (2017)[40]		1. BIRADS 0 and 3 included as positive	3. Ultrasonography not included		
Seo et al (2016)[42]			3. Ultrasonography not included	3. PPV and NPV not reported	
Thibault et al (2013)[41]					
Teertstra et al (2010)[43]		3. Intervention was DBT without DM	3. Ultrasonography not included		

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.
BIRADS: Breast Imaging Reporting and Data System; DBT: digital breast tomosynthesis; DM: digital mammography; NPV: negative predictive value; PPV: positive predictive value.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Classification thresholds not defined or not standard; 2. Version used unclear; 3. Not intervention of interest.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true-positives, true-negatives, false-positives, false-negatives cannot be determined).

Table 13. Study Design and Conduct Limitations of Prospective Studies of DBT Diagnostic Performance

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective	Data	Statistical[f]

				Reporting[d]	Completeness[e]	
Heywang-Kobrunner et al (2017)		1. No blinding	1. Timing of imaging tests and reference standard not described		1. No description of whether there were inadequate images	1. CIs not reported
Seo et al (2016)			1. Timing of imaging tests and reference standard not described			1. CIs not reported
Thibault et al (2013)			1. Timing of imaging tests and reference standard not described		2. 16% of breasts had incomplete mammographic data	1. CIs not reported
Teertstra et al (2010)			1. Timing of imaging tests and reference standard not described			

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.
DBT: digital breast tomosynthesis; CI: confidence interval.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (ie, convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison with other tests not reported.

Systematic Reviews

Lei et al (2014) conducted a meta-analysis of 7 studies (N=2014 patients; N=2666 lesions) that compared DBT with DM in patients who had breast lesions graded as category 2 or higher using the Breast Imaging Reporting and Data System (BI-RADS). All studies were rated high quality by reviewers using the Quality Assessment of Diagnostic Accuracy Studies-2 tool. However, only two studies were prospective. As shown in Table 14, compared with histologic diagnosis, the performance of both imaging modalities was approximately similar; PPVs were low (57% for breast tomosynthesis versus 50% for DM), and NPV were high. Statistical heterogeneity among these analyses was considerable (I^2≈90%). Studies used both 1-view (n=4) and 2-view (n=3) breast tomosynthesis. Pooled sensitivity and specificity for only 1-view breast tomosynthesis studies were 81% and 77%, respectively; for 2-view studies, pooled sensitivity and specificity were 97% and 79% respectively.[45]

Table 14. Side-by-Side Comparison of DBT and DM Diagnostic Performance with Histologic Diagnosis: Pooled Results

Outcomes	Pooled Estimates (95% Confidence Interval), %	
	DBT	DM
Sensitivity, %	90 (87 to 92)	89 (86 to 91)
Specificity, %	79 (77 to 81)	72 (70 to 74)
Positive predictive value, %[a]	57 (53 to 61)	50 (46 to 53)
Negative predictive value, %[a]	96 (95 to 97)	95 (94 to 97)

Diagnostic odds ratio[b]	26.04 (8.70 to 77.95)	16.24 (5.61 to 47.04)
LR+	3.50 (2.31 to 5.30)	2.83 (1.77 to 4.52)
LR-	0.15 (0.06 to 0.36)	0.18 (0.09 to 0.38)
Summary AUROC	0.867	0.856

Adapted from Lei et al (2014)
AUROC: area under the receiver operating characteristic curve; DBT: digital breast tomosynthesis; DM: digital mammography; LR+: positive likelihood ratio (ratio of the probability of positivity in cases to the probability of positivity in controls = sensitivity/[1 - specificity]); LR-: negative likelihood ratio (ratio of the probability of a negative result in cases to the probability of a negative result in controls = [1 - sensitivity]/specificity).
[a] Calculated by BCBSA.
[b] Calculated as the ratio of the odds of positivity in cases to the odds of positivity in controls = [LR+]/[LR-], where LR is the likelihood ratio.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

There is no direct evidence from trials comparing health outcomes in patients using DBT with another technique (eg, mammography, ultrasonography) for diagnosing breast cancer.

Chain of Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

A chain of evidence should establish that DBT incrementally improves diagnosis compared with standard management and the additional diagnostic information could be used to change management decisions so that the net health outcome is improved. However, performance characteristics are uncertain due to the limitations described below, and thus it is not possible to construct a chain of evidence.

- For women with suspicious lesions (eg, BI-RADS category 4), a consistently high NPV for DBT would be needed before DBT would likely be used to avoid biopsy. For women with lesions that have a lower BI-RADS category (eg, BI-RADS 3 [probably benign finding]), a high PPV for DBT might result in a change in management from continued surveillance to biopsy. The BI-RADS classification system supports the classification of imaging findings into categories that can be meaningfully linked to recommendations for further clinical management. For example, BI-RADS 3 may be recommended for shorter interval follow-up to assess for stability. If DBT were proposed for diagnostic use in this setting, the chain of evidence would need to clarify assumptions about how DBT results would be used to change management and how those changes would affect health outcomes. The chain cannot be established due to a lack of certainty about performance characteristics and intended use population.
- The mixed patient populations of the validation studies reflect the lack of clarity about who might benefit from this mode of imaging. The intended use population should be defined

based on clinical characteristics such as BI-RADS category, calcifications, breast density, asymmetry in densities or distortions, irregular margins, and prior biopsy or treatment.
- Mixed patient populations make it difficult to draw conclusions from the studies on the diagnostic performance of DBT. Also, some concerns have been raised about the classification of microcalcification clusters with DBT alone.
- Prospective studies, preferably in the U.S. setting, with an appropriate reference standard and comparison to relevant diagnostic evaluation, are needed to establish performance characteristics.

Section Summary: 3D DBT for Diagnosis
Mixed patient populations make it difficult to draw conclusions from the available studies on the diagnostic performance of 3D DBT. Few prospective studies have addressed whether the addition of 3D DBT improves diagnosis over mammography alone or mammography plus ultrasonography. Also, some concerns have been raised about the classification of microcalcification clusters with 3D DBT alone. There is no direct evidence on the clinical utility of 3D DBT from trials comparing health outcomes in patients diagnosed with breast cancer with 3D DBT vs mammography. Due to limitations in the studies on diagnostic accuracy, it is not possible to construct a chain of evidence.

SUMMARY OF EVIDENCE

Screening
For individuals who are asymptomatic and at average risk of breast cancer who receive DBT as an adjunct to mammography for screening, the strongest evidence comes from Norwegian and Italian studies in which women served as their own controls. The available studies have provided evidence that adding breast tomosynthesis to mammography may increase the numbers of cancers detected (increased sensitivity), while potentially reducing the number of women who are recalled unnecessarily (decreased false-positive rates).

Diagnosis
Digital breast tomosynthesis has the potential, when utilized in addition to mammography, to reduce the number of women who undergo biopsy by screening out some women with false-positive results. Complicating this analysis is the use of additional modalities of ultrasound or MRI as diagnostic adjuncts. Additional studies are warranted to assess the incremental value of tomosynthesis in comparison to current standard diagnostic modalities; as well as its value in the full range of findings, opposed to only differentiating masses from calcifications.
It is clear from the Rationale Section's summary of studies that the available evidence is not perfect. However, the currently available data does appear to clearly trend toward a conclusion that the use of DBT may increase the number of cancers identified and reduce the number of unnecessary call backs.

SUPPLEMENTAL INFORMATION

PRACTICE GUIDELINES AND POSITION STATEMENTS

American College of Radiology
The American College of Radiology's (ACR) 2014 statement on breast tomosynthesis included the following:[46]

> "… breast tomosynthesis has shown to be an advance over digital mammography, with higher cancer detection rates and fewer patient recalls for additional testing…. 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 important evidence that tomosynthesis will have a positive impact on patient care."

While the ACR has encouraged the additional study of breast tomosynthesis, focusing on long-term clinical outcomes and better definition of subgroups, it concluded that "To be clear: tomosynthesis is no longer investigational. Tomosynthesis has been shown to improve key screening parameters compared to digital mammography."

ACR's Appropriateness Criteria, last reviewed in 2023, gave digital breast tomosynthesis (DBT) a rating of "usually appropriate" for use with women at high risk, intermediate risk, as well as average risk for breast cancer.[47]

The ACR's Appropriate Criteria for palpable breast masses last reviewed in 2022, gave DBT the following ratings:[48]
"usually appropriate" for

- women 40 years of age or older, initial evaluation
- short-interval follow-up for women 40 years of age or older, mammography findings probably benign, next examination to perform
- women younger than 30 years of age, U.S. findings suspicious for malignancy. Next examination to perform
- women 30 to 39 years of age, initial evaluation.

"usually not appropriate" for

- short-interval follow-up for women 40 years of age or older, mammography findings suspicious for malignancy, next examination to perform
- short-interval follow-up for women 40 years of age or older, mammography findings benign (like lipoma) at site of palpable mass.
- Next examination to perform
- women 40 years of age or older, mammography findings negative. Next examination to perform women younger than 30 years of age, initial evaluation
- women younger than 30 years of age, U.S. findings probably benign. Next examination to perform
- women younger than 30 years of age, U.S. findings benign (like simple cyst). Next examination to perform
- women younger than 30 years of age, U.S. findings negative. Next examination to perform.

American Society of Breast Surgeons
In a position statement on screening mammography, the American Society of Breast Surgeons (2019) made the following recommendations regarding tomosynthesis:[49]
"Where available, 3D mammography is the preferred sole modality for women with an average risk for breast cancer."

American College of Obstetricians and Gynecologists
In a Practice Bulletin on breast cancer screening, the American College of Obstetricians and Gynecologists (2017) did not discuss tomosynthesis.[50]

A 2015 committee opinion on the management of women with dense breasts identified by mammography stated: "The American College of Obstetricians and Gynecologists does not recommend routine use of alternative or adjunctive tests to screening mammography in women with dense breasts who are asymptomatic and have no additional risk factors."[51] Breast tomosynthesis or thermography were not cited in the document as alternative tests.

National Comprehensive Cancer Network

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology, Breast Cancer Screening and Diagnosis (v.2.2024) state.[52]

- Those with Average Risk greater or equal to 40 Years of Age: "Tomosynthesis can decrease call back rates and improve cancer detection compared with 2D mammography alone."
- Screening Mammography: ”More recently, combined use of digital mammography (two-dimensional, 2D) in conjunction with digital breast tomosynthesis (DBT) improves cancer detection and reduces false-positive call-back rates.”
- Rationale for Mammographic Screening Starting at Age 40 “The NCCN Panel emphasizes adopting strategies and research to reduce the harms of screening (false positives and overdiagnosis) rather than raising the age to initiate screening to potentially delay these issues. This includes newer imaging modalities that improve the detection of breast cancer with fewer recalls (eg, tomosynthesis).”

Further, NCCN states to “consider” tomosynthesis in many of the recommendations for annual mammograms.

The NCCN also suggests that tomosynthesis be considered whenever an annual screening mammogram is recommended.

International Agency for Research on Cancer

In 2014, the benefits and harms of different methods of breast cancer screening were assessed by a panel of experts from 16 different countries, convened by the International Agency for Research on Cancer.[53]

Table 15 summarizes the panel's conclusions on the available evidence for the use of tomosynthesis with mammography.

Table 15. Recommendations on Use of Tomosynthesis with Mammography

Method	Strength of Evidence[a]
Mammography with tomosynthesis vs mammography alone	
Reduces breast cancer mortality	Inadequate
Increases the detection rate of in situ and invasive cancers	Sufficient
Preferentially increases the detection of invasive cancers	Limited
Reduces the rate of interval cancer	Inadequate
Reduces the proportion of false-positive screening outcomes	Limited

Adapted from Lauby-Secretan et al (2015).[54]
[a] Rating system detailed at http://handbooks.iarc.fr/workingprocedures/index.php

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

In 2024, U.S. Preventive Services Task Force (USPSTF) updated its recommendations for breast cancer screening.[55]

The USPSTF recommends biennial screening mammography for women aged 40 to 74 years. (B recommendation) The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening mammography in women 75 years or older. (I statement) The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of supplemental screening for breast cancer using breast ultrasonography or MRI in women identified to have dense breasts on an otherwise negative screening mammogram

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Government Regulations

National:

There is no national coverage determination (NCD).

Medicare – Digital Breast Tomosynthesis is a covered service effective 1/1/15.
CMS Medicare Claims Processing
Transmittal 3844 August 18, 2017; November 21, 2017

- CPT code 77063 (screening digital breast tomosynthesis) should be listed separately in addition to code from primary procedure 77067
- HCPCS code G0279 (diagnostic digital breast tomosynthesis) should be listed separately in addition to the primary service mammogram code 77066 or 77065

Local:

There is no local coverage determination (LCD).

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Computer-Aided Detection of Malignancy with Magnetic Resonance Imaging of the Breast (retired)
- Digital Mammography (Retired)
- Fiberoptic Ductoscopy of the Breast (retired)
- Magnetic-Resonance Imaging for Breast Cancer
- Scintimammography and Gamma Imaging of the Breast and Axilla
- Ultrasound for Breast Cancer Screening

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 1/3/25, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
11/1/08	9/15/08	8/19/08	• Joint policy established
1/1/11	10/12/10	10/27/10	• Routine maintenance
7/1/11	4/19/11	5/3/11	• Routine maintenance
5/1/13	4/16/13	4/22/13	• Routine maintenance • Title changed from “Digital Tomosynthesis” to “Digital Breast Tomosynthesis”.
3/1/15	12/9/14	12/29/14	• Routine maintenance • Code updates, added 77061, 77062 and 77063
5/1/15	2/17/15	2/27/15	• Code 77063 payable for Medicare with effective date 1/1/15 • Government Regulations updated • Benefit Determinations updated to reflect payment for BCNA members
5/1/16	2/16/16	2/16/16	• Routine maintenance • Updated per BCBSA policy • Updated Regulatory Status, Rationale, Practice Guidelines & Position Statements, References
3/1/17	12/13/16	12/13/16	• Routine maintenance • Added 3-D mammography to policy title and policy statement
3/1/18	1/31/18	1/31/18	• Policy status change to established • Updated MPS, rationale and references
3/1/19	12/11/18		• Routine maintenance
3/1/20	12/17/19		Routine maintenance References updated
3/1/21	12/15/20		Routine maintenance
3/1/22	12/14/21		Routine maintenance
3/1/23	12/20/22		Routine maintenance (jf) Vendor: NA

3/1/24	12/19/23		Routine maintenance (jf) Vendor Managed: NA
3/1/25	12/17/24		Routine maintenance (jf) Vendor Managed: NA • Edit to MPS and inclusions. -Removal of “may be” and added “is”.
5/1/25	2/18/25		Routine maintenance (jf) Vendor Managed: NA • Edits made to inclusions.

Next Review Date: 1st Qtr, 2026

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: DIGITAL BREAST TOMOSYNTHESIS (3-D MAMMOGRAPHY)

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered when criteria met
BCNA (Medicare Advantage)	See Government Regulations section.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.