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Medical Policy

BlueCross BlueShield of Kansas
An independent licensee of the Blue Cross Blue Shield Association

Title: Digital Breast Tomosynthesis

Professional
Original Effective Date: October 11, 2012
Revision Date(s): September 17, 2013; January 1, 2015; September 29, 2015; February 3, 2016; January 4, 2017; January 1, 2018; February 15, 2018; January 1, 2019
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Populations	Interventions	Comparators	Outcomes
Individuals: • Who are asymptomatic and at average risk for breast cancer	Interventions of interest are: • Digital breast tomosynthesis as an adjunct to mammography for screening	Comparators of interest are: • Mammography alone	Relevant outcomes include: • Overall survival • Disease-specific survival • Test accuracy • Test validity
Individuals: • Who are asymptomatic and at average risk for breast cancer	Interventions of interest are: • Digital breast tomosynthesis with synthesized mammography for screening	Comparators of interest are: • Mammography alone	Relevant outcomes include: • Overall survival • Disease-specific survival • Test accuracy • Test validity
Individuals: • With abnormal findings on breast imaging or clinical exam	Interventions of interest are: • Digital breast tomosynthesis as an adjunct to mammography for diagnosis	Comparators of interest are: • Mammography alone	Relevant outcomes include: • Test accuracy • Test validity • Treatment-related morbidity

DESCRIPTION

Digital breast tomosynthesis (DBT) uses modified digital mammography equipment to obtain additional radiographic data that are used to reconstruct cross-sectional "slices" of breast tissue. Tomosynthesis may improve the accuracy of digital mammography by reducing distortions caused by overlapping tissue. Tomosynthesis typically involves additional imaging time and radiation exposure, although recent improvements may change this.

OBJECTIVE

The objective of this policy are: (1) to determine whether digital breast tomosynthesis improves the net health outcome for women undergoing routine breast cancer screening compared with standard mammography; and (2) to determine whether adding tomosynthesis to other imaging modalities (mammography, ultrasound) improves the net health outcome for women undergoing a diagnostic workup following suspicious findings on breast imaging or clinical examination.

BACKGROUND

Conventional Mammography

Conventional mammography produces two-dimensional (2D) 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. The spot views are often used to evaluate microcalcifications, opacities or architectural distortions or to distinguish masses from overlapping tissue, as well as to view possible findings close to the chest wall or in the retro-areolar area behind the nipple.[1] The National

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Cancer Institute (NCI) reports 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 1,000 screening mammography examinations.[3] The Mammography Quality Standards Act audit guidelines anticipate 2-10 cancers detected per 1,000 screening mammograms.[4] Interval cancers, which are detected between screenings, tend to have poorer prognoses.[5]

Digital Breast Tomosynthesis

Digital breast tomosynthesis was developed to improve the accuracy of mammography by capturing three-dimensional (3D) images 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] Digital breast tomosynthesis produces a 3D image by taking 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 degree for each image in a 15-50 degree arc, acquiring 11-49 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 10 seconds per view. In one study in a research setting, the mean time to interpret the results was 1.22 (standard deviation [SD]=1.15) minutes for digital mammography and 2.39 (SD=1.65) for combined digital mammography 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.[7]

A machine equipped with breast tomosynthesis can perform 2D digital mammography, 3D digital mammography, or a combination of both 2D and 3D mammography during a single compression. The radiation exposure from tomosynthesis is roughly equivalent to a mammogram. Therefore, adding tomosynthesis to mammography doubles the radiation dose, although it still is below the maximum allowable dose established in the U.S. Mammography Quality Standards Act.

Studies typically compare 1-view (ie, mediolateral oblique [MLO] view), or more commonly, 2-view (MLO plus craniocaudal view) breast tomosynthesis alone or combined with standard 2D mammography with standard 2D mammography alone. A 2014 TEC Assessment[9] 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

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tomosynthesis is preferable to 1-view tomosynthesis (both used in combination with full-field digital mammography).[10]

In May 2013, the FDA approved new tomosynthesis software that will permit creation of a 2D image (called C view) from the tomosynthesis images.[11] As a result, the 2D mammography may become unnecessary, thereby lowering the radiation dose. In other words, it is possible that only the tomosynthesis procedure will be needed, with the ability to create both conventional 2D and DBT images. It is too early to gauge how traditional mammography plus tomosynthesis compares to the C-View plus tomosynthesis.

REGULATORY STATUS

Table 1 provides a summary of digital breast tomosynthesis (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 in order for a facility to use this module, the facility must apply to FDA for certification that extends to the tomosynthesis module. The U.S. Mammography Quality Standards Act requires interpreting physicians, radiologic technologists, and medical physicists to complete 8 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 P080003/S001 P080003/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

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Device	Manufacturer	Date Approved	PMA	Indications
				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	Siemens	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 an error that may occur during tomosynthesis reconstruction with breast thickness >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	P160009	Approved for 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.

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POLICY

Digital breast tomosynthesis is considered **experimental / investigational** in the screening or diagnosis of breast cancer.

RATIONALE

The most recent literature update was performed through July 21, 2017.

Assessment of a diagnostic technology typically focuses on 3 categories of evidence: (1) its technical reliability (test-retest reliability or interrater reliability); (2) clinical validity (sensitivity, specificity, and positive [PPV] and negative predictive values [NPV]) in relevant populations of patients; and (3) clinical utility (ie, demonstration that the diagnostic information can be used to improve patient outcomes).

Digital Breast Tomosynthesis for Screening

The question addressed in this portion of the evidence review is whether there is sufficient evidence that digital breast tomosynthesis (DBT), used to screen for breast cancer, improves the net health outcome compared with standard techniques. Specifically, is DBT as an adjunct to mammography or DBT plus synthesized 2-dimensional (2D) mammography superior to mammography alone, and is DBT instead of mammography at least as beneficial as mammography? For both interventions, are differences in accuracy likely to improve health outcomes via earlier diagnosis and treatment?

The following PICOTS were 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 DBT screening as an adjunct to mammography and DBT plus synthesized 2D mammography.

Comparators

The primary comparator of interest is mammography alone.

Outcomes

The outcomes of interest for clinical validity include test accuracy and test validity (ie, sensitivity, specificity). The primary outcomes of interest for the clinical utility are overall mortality and breast cancer–specific mortality. Specific primary outcomes reported in the current evidence include the number of cancers detected and the number of unnecessary recalls and biopsies. Improvement in sensitivity and specificity of testing is an intermediate outcome that may impact ultimate health outcomes but is not by itself sufficient to establish that outcomes are improved. If tomosynthesis is performed during screening, the number of unnecessary recalls may decline.

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Other relevant screening outcomes, not available or estimable from current evidence, include (1) breast cancer–specific mortality, (2) interval cancer rates, and (3) overdiagnosis or detection of cancers that would not otherwise become symptomatic or lead to mortality.

Timing

DBT would be performed at routine screening; timing can be guided by national guidelines on breast cancer screening. For example, the United States Preventive Services Task Force has recommended biennial screening for average-risk women 50 to 74 years of age.

Setting

The test would be performed in an outpatient imaging setting.

Technical Reliability

A number of products are commercially available to perform DBT, and the technical reliability of these devices has been evaluated by the Food and Drug Administration as part of its 510(k) process.

DBT as an Adjunct to Mammography

Clinical Validity

Key studies addressing the diagnostic accuracy of DBT for screening are summarized in Table 2.

Table 2. Studies of DBT for Breast Cancer Screening

Study	No. Cancers/ No. Patients	Recalls/1000 Screens (95% CI)	PPV for Recalls (95% CI), %	Cancers Detected/1000 Screens (95% CI)	PPV for Biopsies (95% CI), %
Prospective Studies					
Patients served as their own controls					
Skaane (2013)[12]	121/12,621				
Mammo		NR	28.5	6.1	NR
Mammo + DBT			29.1	8.0	
p value				0.001	
STORM[13,14,a]	59/7292				
Mammo		45	11	5.3 (3.8 to 7.3)	NR
Mammo + DBT		30	19	8.1 (6.2 to 10.4)	
p value				<0.001	
MBTST (2016)[15] (exploratory results)	68/7500				
Mammo		17	24	6.3 (4.6 to 8.3)	NR
Mammo + DBT		24	24	8.9 (6.9 to 11.3)	
p value				<0.001	
Sumkin (2015)[16]	6/1074				
Mammo		384	Small number of cancers (see text)		
Mammo + DBT		274			
Rafferty (2013)[17,b] Study 1	51/997	Reported separately for cancer and			
Mammo		noncancer cases	43	NR	NR

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Study	No. Cancers/ No. Patients	Recalls/1000 Screens (95% CI)	PPV for Recalls (95% CI), %	Cancers Detected/1000 Screens (95% CI)	PPV for Biopsies (95% CI), %
Mammo + DBT			56		
Study 2					
Mammo			47	NR	NR
Mammo + DBT			50		
S2D mammo					
Bernaldi (2016; STORM-2)[18]	90/9672			NR	
Mammo		False-positive recall, %		6.3 (4.8 to 8.1)	
Mammo + DBT		3.42 (3.07 to 3.80)		8.5 (6.7 to 10.5)	
s2D mammo + DBT		3.97 (3.59 to 4.38) 4.45 (4.05 to 4.89)		8.8 (7.0 to 10.8)	
Retrospective studies					
Multireader study; patients apparently served as their own controls					
Good (2008)[19] Gur (2009)[8] (2011)[20] DM alone DBT alone DM before DBT DM + DBT	35/125	Reported separately for cancer and noncancer cases	NR	NR	NR
Patient or provider choice to receive tomosynthesis and did not serve as their own controls					
Geiss (2017)[21]					
Mammo	26/14,180	103	1.8	1.8	NR
DBT	37/9,817	107	3.6	3.8	
p value		0.26	0.006	0.005	
Powell (2017)[22]					
Mammo	54/10,477	160	3	5.2	25.1
Mammo + DBT	18/2,304	140	5.6	7.8	29.5
p value	0.127	0.017	0.032	NR	0.689
Destounis (2014)[23]	5/1048				
Mammo		114	16.7	3.8	NR
Mammo + DBT		42	50.0	5.7	
p value		<0.001		NR	
Durand (2015)[24,c]	105/17,955				
Mammo alone		123 (117 to 130)	NR	5.7	NR
Mammo + DBT		78 (73 to 84)		5.9	
p value		<0.001		*NS*	
Greenberg (2014)[25,d]	321/59,617				
Mammo alone		155 (138 to 175)	3.0 (2.6 to 3.4)	4.9 (4.2 to 5.7)	21.5 (18.9 to 24.5)
Mammo + DBT		134 (119 to 152)	4.5 (3.8 to 5.4)	6.2 (5.2 to 7.5)	22.7 (19.5 to 26.6)
p value		<0.001	<0.006	0.041	*NS*
Haas (2013)[26,c]	71/13,158				
DM		120 (113 to 128)	NR	5.2	NR
DM + DBT		84 (77 to 91)		5.7	
p value		<0.01		0.70	

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Study	No. Cancers/ No. Patients	Recalls/1000 Screens (95% CI)	PPV for Recalls (95% CI), %	Cancers Detected/1000 Screens (95% CI)	PPV for Biopsies (95% CI), %
Pre-/postimplementation of tomosynthesis					
Friedewald (2014)[27,d]	2157/454,850	107 (89 to 124)	4.3	4.2 (3.8 to 4.7)	24.2
Mammo alone		91 (73 to 108)	6.4	5.4 (4.9 to 6.0)	29.2
Mammo + DBT		<0.001	<0.001	<0.001	<0.001
p value					
Lourenco (2015)[28]	113/25,498				
DM		93 (88 to 99)	5.8	5.4	30.2
DM + DBT		64 (60 to 68)	7.2	4.6	23.8
p value		<0.001	*NS*	*NS*	
McCarthy (2014)[29]	134/26,299				
DM		104 (98 to 109)	4.4 (3.2 to 5.6)	4.6 (3.3 to 5.8)	24.7 (18.6 to 30.9)
DM + DBT		88 (83 to 92)	6.2 (4.9 to 7.5)	5.5 (4.3 to 6.6)	25.4 (20.6 to 30.2)
p value		<0.001	0.047	*NS*	*NS*
Rose (2013)[30,e]	107/23,357				
DM		87	4.7	4.0	NR
DM + DBT		55	10.1	5.4	
p value		<0.001		*NS*	
McDonald (2016)[31]	NR/23,958				
DM		104	4.4	4.6	NR
DBT (year 1)		88	6.2	5.5	
DBT (year 2)		90	6.5	5.8	
DBT (year 3)		92	6.7	6.1	
p value (vs DM years 1, 2, 3)		<0.001, <0.001, <0.003	0.06, 0.03, 0.02	*NS*	*NS*, *NS*, *NS*
Conant (2016)[32,f]	NR/198,881				
DM		104	4.1	5.9	NR
DM + DBT		87	6.4	4.4	
p value		<0.001	<0.001[g]	0.003	
Sharpe (2016)[33]	311/85,852				
DM		75	NR	3.5	NR
DBT		61		5.4	
p value		<0.001		<0.002	
S2D mammo					
Freer (2017)[34]					
DM	126/21435	87		5.9	30.4
DM + DBT	7/1019	70		6.9	38.9
s2D+ DBT	56/9525	58	NR	5.9	37.8
p value		<0.001 (s2D+DBT vs DM)		0.66 (s2D+DBT vs DM)	0.3 (s2D+DBT vs DM)
		0.25 (s2D+DBT vs DM+DBT)		0.9 (s2D+DBT vs DM+DBT)	0.98 (s2D+DBT vs DM+DBT)
Aujero (2017)[35]					

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Study	No. Cancers/ No. Patients	Recalls/1000 Screens (95% CI)	PPV for Recalls (95% CI), %	Cancers Detected/1000 Screens (95% CI)	PPV for Biopsies (95% CI), %
DM	169/32,076	87	6.0	5.3	22.2
DM + DBT	194/30,561	58	10.9	6.4	28.5
s2D+ DBT	98/16,173	43	14.3	6.1	40.8
p value		<0.001 (DM vs DM+DBT) <0.001 (DM+DBT vs s2D+DBT)	<0.001 (DM vs DM+DBT) 0.02 (DM+DBT vs s2D+DBT)	0.08 (DM vs DM+DBT) 0.71 (DM+DBT vs s2D+DBT)	0.01 (DM vs DM+DBT) 0.001 (DM +DBT vs s2D+DBT)
Zuckerman (2016)[36]					
DM +DBT	NR/15,571	88	6.2	5.45	27.0
s2d + DBT	NR/5366	71	7.1	5.0	38.6
p value		<0.001	0.548	0.723	0.053

BI-RADS: Breast Imaging Reporting and Data System; CI: confidence interval; DBT: digital breast tomosynthesis; DM: digital mammography; Mammo: mammography; MBTST: Malmö Breast Tomosynthesis Screening Trial; NR: not reported; PPV: positive predictive value; s2D: synthesized 2D mammography; STORM: Screening with Tomosynthesis OR standard Mammography.
[a] Data from Ciatto (2013) and Houssami (2014).
[b] Twenty-seven women with no follow-up not included in results.
[c] Patient samples overlap in the Durand (2015) and Haas (2013) studies.
[d] Adjusted estimates reported in this table.
[e] Recalls at BI-RADS=0.
[f] Data overlap with in McDonald (2016).
[g] PPV defined as some cancers diagnosed per number of positive screens.

Prospective Studies: The strongest evidence for using mammography plus DBT for screening women for breast cancer comes from results of a large trial published in 2013 by Skaane et al in Norway.[12,37] The Skaane analysis is 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 12,621 women with 121 cancers detected on routine screening. The cancer detection rate was 6.1 per 1000 screenings for mammography alone and 8.0 per 1000 screenings for mammography plus DBT. Cancers missed by DBT were missed due to reading errors, either detection or interpretation.[38] After adjusting for reader differences, the ratio of cancer detection rates for mammography plus DBT vs mammography alone was 1.27 (98.5% confidence interval [CI], 1.06 to 1.53; p=0.001). The authors did not ascertain any improvement in detecting ductal carcinoma in situ (DCIS) by adding breast tomosynthesis (ie, additional cancers detected were mostly invasive). The false-positive rate was 61.1 per 1000 screenings for mammography alone and 53.1 per 1000 screenings for mammography plus DBT. A reduction in the false-positive rate would decrease the number of women recalled after screening for additional imaging or biopsy. In Norway, as in much of Europe, women are screened every other year, and 2 readers independently interpret the images, which differs from usual practice in the United States. 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<0.001). For this analysis, only limited data were available about interval cancers, so "conventional absolute sensitivity and specificity" could not be estimated.

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The second study (STORM [Screening with Tomosynthesis OR standard Mammography]) 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.[13,14] 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. Mammography plus DBT revealed all 59 cancers; 20 (34%) were missed by traditional mammography ($p<0.001$). 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 ($p<0.001$). In preplanned analyses, combined results of mammography and DBT yielded more cancers in both age groups (<60 vs ≥60 years) and breast density categories (1 [least dense] and 2 vs 3 and 4 [most dense]).

In both of the above studies, follow-up of women with negative imaging findings was insufficient to confirm results.

In 2016, Lång et al 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 digital mammography [DM]) with 2-view DM.[15] The Malmö Breast Tomosynthesis Screening Trial is a 1-arm, single institution, prospective study. Randomly selected women in Malmö, Sweden (age range, 40-74 years) were offered 1-view DBT and 2-view DM. A sample size of 15,000 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. The primary outcomes were cancer detection rates, recall rates, and PPVs. Six experienced readers interpreted images (mean experience, 26 years; range, 8-41). Blinded double reading was carried out for DBT and DM with rule-based arbitration for disagreements. Pathologic findings after abnormal imaging (additional DM, ultrasound, and indicated biopsy) were the basis for outcomes. Women in this exploratory analysis were followed at least 1 year for the development of cancer ascertained through the South Swedish Cancer Registry. Of 10,547 women invited, 71.1% participated with 20% undergoing their first screening test. Cancers were detected in 47 of the DM and 67 of the DBT reading arms (21 by DBT alone; 1 by DM alone; 46 by both modalities). The detection rate for DBT was 8.9 per 1000 screens (95% CI, 6.9 to 11.3) and for DM was 6.3 per 1000 screens (95% CI, 4.6 to 8.3; $p<0.001$). 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; $p<0.001$). PPVs were similar for both modalities at 24%.

In these "explorative" Malmö Breast Tomosynthesis Screening Trial results, DBT achieved a higher cancer detection rate. In contrast to other studies, however, recall rates were lower for DM. Tomosynthesis-detected cancers were generally smaller, of lower grade, more often node negative, and found among women somewhat younger. Regarding this finding, the authors noted, "It is not clear whether this represents earlier diagnosis and/or overdiagnosis from DBT

screening since the present study was not designed to address these issues." Additionally, DBT alone detected cancers tended to be in women with dense and fatty breasts. Although the findings are from an explorative analysis, the authors stated that "...one-view DBT may be feasible as a stand-alone technique for breast cancer screening." The partial results include only half of the planned sample accrual with follow-up insufficient to assess interval cancer rates. Experienced readers were used, and all studies read independently by 2 readers. Final results will require consideration of broader applicability.

Rafferty et al (2013) compared results of mammography alone with mammography plus DBT among 997 patients with mixed indications: 780 women were undergoing routine screening, and 217 were scheduled for a biopsy.[17] Two reader studies were conducted. Some of these results were included in the submission to the U.S. Food and Drug Administration for pre marketing application approval of Hologic's Selenia Dimensions tomosynthesis system. Readers were trained in interpreting tomosynthesis images, and training was augmented between the first and second reader studies to emphasize how to read certain lesions that were often misinterpreted in the first reader study. In both reader studies, the area under the receiver operating characteristic curve for mammography plus DBT was greater than for mammography alone; the difference for the second study was 6.8% (95% CI, 4.1% to 9.5%; $p<0.001$). For noncancer cases, adding DBT to mammography changed the mean recall rate across readers for study 2 from 48.8% (12.3%; 95% CI, 28.2% to 69.1%) to 30.1% (7.6%; 95% CI, 19.8% to 41.3%) for the combined modalities. Almost all of the improvement among readers was attributable to noncalcification cases, including masses, asymmetries, and architectural distortions. Risk of bias was considered high due to substantial patient dropout (16%) after enrollment, use of an investigational tomosynthesis system during the early part of the study that may have yielded results different from the U.S. Food and Drug Administration–approved system, and enrichment of the screening sample by the inclusion of biopsy cases.

Sumkin et al (2015) enrolled women ages 34 to 56 years of age undergoing baseline screening mammography at a single institution.[16] High-risk women were preferentially included. All women underwent DM and DBT (Selenia Dimension). DM and DBT images were interpreted by different radiologists (from a group of 14 having 5-28 years of experience) who "were instructed 'not' to discuss" the evaluation with each other until completed. A total of 1074 women (mean age, 42.03 years) were studied; the number invited to participate was not reported. Just over half (50.8%) had a Breast Imaging Reporting and Data System (BI-RADS) rating of 3, and 40.1% a BI-RADS rating of 2. The recall rate based on DM alone was 38.4% vs 25.5% with DM and DBT. Changes in recall rates varied among radiologists—5 of 11 who interpreted more than 15 images demonstrated statistically significant improvements with DBT. Two invasive cancers were detected—one by DM alone and one by DBT. Four cases of DCIS were found—all by both modalities. Among a younger and generally higher risk target population undergoing an initial exam, the recall rate was high for either modality. Although the addition of DBT reduced the recall rate, there was considerable variability among radiologists. Only 2 invasive cancers were detected (one by each modality) preventing conclusions concerning cancer detection rates. Also, using patients as controls, a strength of the study was conduct in a U.S. setting. Lack of follow-

up, no report of exclusions and possible selection bias, and adequacy of blinding in interpretation are potential limitations.

Retrospective Studies: In 3 related articles, Good et al (2008) and Gur et al (2009, 2011) compared the diagnostic performance of DM alone with DM plus tomosynthesis.[8,19,20] One study reported that the recall rate among noncancer cases was 42% (95% CI, 38% to 45%) for DM alone and 28% (95% CI, 25% to 31%) for DM plus breast tomosynthesis ($p<0.001$).[8] Analogous rates for cancer cases were 88% (95% CI, 84% to 91%) for DM alone and 93% (95% CI, 90% to 96%) for DM plus breast tomosynthesis. The sensitivity of DM alone was 60% and increased to 72% when breast tomosynthesis was added ($p=0.034$, but authors noted the small number of positive findings). These reports did not describe the sample, the time between DM and breast tomosynthesis, or how the reference standard was verified. Therefore, the risk of bias is unknown.

In 2016, McDonald et al compared the diagnostic performance of DM prior with the introduction of DBT, to years 1, 2, and 3 of DBT.[31] As shown in Table 2, breast cancer detection rates were not significantly higher with DBT than with DM. Recall rates, and the PPV of recalled cases were significantly higher with DBT than with DM.

Also in 2016, Conant et al reported on screening data from 3 centers participating in the PROSPR consortium.[32] Data from this study may overlap with data from the 2016 McDonald study (data collected for both studies at the same center). The analysis compared the diagnostic accuracy of DM alone and DM plus DBT in asymptomatic women presenting for breast cancer screenings. Outcomes, shown in Table 2, were reported for cases with at least 1 year of follow-up. The study, which included 198,881 women, found significantly higher cancer detection rates and lower recall rates with DM plus DBT vs DM alone.

Sharpe et al (2016) analyzed diagnostic accuracy of breast cancer screening before and after the introduction of tomosynthesis.[33] The authors reported on 85,852 asymptomatic women undergoing breast cancer screening, 80,149 (93.4%) women were screened with mammography and 5703 (6.6%) screened with DBT. The study found significantly higher cancer detection rates and lower recall rates with DBT compared with mammography, although the subgroup of patients who received DBT also included "a higher proportion of patients with risk factors for breast cancer and baseline examinations."

A large reading study was conducted in the U.K. National Health Service.[39,40] Because the 2015 study included a mix of screening and diagnostic patients, case-selection bias limits extrapolation of the results to a screening population. The TOMosynthesis with digital MammographY (TOMMY) trial compared the performance of DM plus tomosynthesis with DM alone among women at moderate-to-high risk for breast cancer undergoing screening (n=1040 including 2 cancers) and women who had been recalled for a diagnostic workup after having a screening mammogram (n=6020 including 1158 cancers). After enrollment, these women had a mammogram and tomosynthesis; a synthesized mammogram (C-View) was also reconstructed from the tomosynthesis results. Comparisons were DM alone vs DM plus tomosynthesis vs synthetic

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mammogram plus tomosynthesis. The reference standard was pathology results for women who had a biopsy; the report did not note follow-up for other subjects. Sensitivity was 87% (95% CI, 85% to 89%) for DM only, 89% (95% CI, 25% to 91%) for DM plus tomosynthesis, and 88% (95% CI, 86% to 90%) for C-View images plus tomosynthesis. None of these differences were statistically significant. Specificity was 58% (95% CI, 56% to 60%) for DM alone, 69% (95% CI, 67% to 71%) for DM plus tomosynthesis, and 71% (95% CI, 69% to 73%) for C-View images plus tomosynthesis. Specificity for each of the combined modalities was statistically greater compared with DM alone (p<0.001). This result also held for all age and breast density groups. When breast density was divided into 2 groups (more or less than 50% density), sensitivity for women with greater breast density was improved with DM plus tomosynthesis compared with DM alone (93% vs 86%; p=0.03).

Characteristics of Detected Cancers: In 2017, Yun et al published a meta-analysis of the characteristics of cancers detected with DM alone vs DM plus DBT during routine breast cancer screening.[41] Eleven studies were included in the meta-analysis, 4 prospective and 7 retrospective observational studies, all of which are described in Table 2, above. Reviewers evaluated study quality using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) 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.

In a pooled analysis, the overall cancer detection rate was significantly higher with DM plus DBT than with DM alone (relative risk [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=1.39l 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 may have been underpowered. The findings of this meta-analysis were limited by the potential biases of the included studies (eg, many are retrospective and studies had insufficient confirmatory data on negative imaging results).

Clinical Utility

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

Chain of Evidence: Given that the utility of breast cancer screening with mammography has been established, a chain of evidence should demonstrate that DBT used as an adjunct to screening

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improves screening performance compared with standard mammography alone. Available studies have reported that adding DBT to mammography may increase cancer detection and reduce recalls. However, performance characteristics are uncertain due to limitations described below, and thus it is not possible to construct a chain of evidence.

- The higher quality, prospective studies compare DBT plus mammography with mammography alone in the same patients, so that patients served as their own controls for purposes of comparative performance. However, these studies had insufficient data on negative imaging findings and interval cancers to calculate sensitivity and specificity rates. Further, the higher quality studies were conducted in Europe, where screening practices differ markedly from those in the United States, so that performance consequences for U.S. settings would need to be explicated.
- Retrospective studies have included mixed populations of patients or unclear indications for screening and inadequate reference standards such as historical controls, which introduce potential sources of bias that limit the usefulness of these results to inform screening performance estimates.
- Prospective and statistically robust studies, preferably in the U.S. setting, comparing DBT plus mammography with mammography alone in the appropriate comparison population, with complete reporting of performance indicators, are needed.

Section Summary: Screening with DBT as an Adjunct to Mammography
Current evidence has suggested that 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. Results from half of the anticipated sample of the Malmö Breast Tomosynthesis Screening Trial demonstrated improved sensitivity with 1-view DBT, but not lower recall rates. A decrease in the false-positive rate would reduce unnecessary diagnostic workups and their consequences. However, the potential for overdiagnosis cannot be ascertained because of the study designs, and interval cancer rates are not yet available. In other retrospective case reviews, patients had mixed or unclear indications for screening. Prospective and large retrospective studies have reported modestly higher cancer detection rates with reduced false-recall rates. The nonrandomized designs lack long-term follow-up to assess false-negative results. A 2017 meta-analysis has provided some data on the potential for overdiagnosis with DBT. In a pooled analysis of 11 screening studies, reviewers found a significantly higher rate of invasive cancer detection with DBT plus DM than with DM alone. However, the analysis is subject to the same methodologic limitations as the included studies.

The long-term effects of additional radiation exposure also are unknown. Adding tomosynthesis to mammography may increase the radiation dose depending on the specific equipment and protocols used, although it still is below the maximum allowable dose established in the U.S. Mammography Quality Standards Act.

There is also 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.

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Due to limitations in the studies on diagnostic accuracy, it is not possible to construct a chain of evidence.

DBT Plus Synthesized 2D Mammography

Clinical Validity

In 2016, Bernardi et al published findings of the prospective population-based STORM-2 study comparing DBT with acquired (standard) mammography images to synthesized 2D (s2D) mammography images (see Table 2).[18] The study included asymptomatic women attending a breast cancer screening program in Italy. Synthetic mammography images, using this technique, do not require 2 sets of images, which reduces exposure to radiation. Double reading was conducted for mammography images. The cancer detection rate did not differ significantly in the DBT plus acquired mammography and DBT plus synthesized 2D mammography groups. The percentages of examinations with false-positive recalls were significantly higher in both DBT groups compared with mammography alone.

Several retrospective studies have been published. In a single-center study published in 2016, Zuckerman et al compared the performance of DBT with s2D mammography to a historical control group that received DBT plus 2D mammography.[36] In the analysis, DBT with synthesized 2D mammography had a similar cancer detection as DBT with acquired mammography (5.03 per 1000 vs 5.45 per 1000, respectively) and a lower recall rate (8.8% vs 7.1%, respectively; $p<0.001$).

In 2017, Aujero et al compared the diagnostic accuracy of s2D plus DBT, DBT-DM, and DM alone in a retrospective analysis of breast cancer screening data from a single institution in the United States.[35] The study took place during the institution's transition from DM to DBT and then DBT plus synthesized 2D between 2011 and 2016. Single reading was done for mammography images. All DBT plus synthesized 2D images were acquired between 2015 and 2016 after radiologists had several years of experience with DBT and thus interpretation of those images may have been impacted by the learning curve effect. The cancer detection rate did not differ significantly among the 3 groups (see Table 2). The recall rates were significantly lower in both DBT groups compared with DM alone, and significantly lower in the DBT plus synthesized 2D group compared with the DBT plus DM group. The database used to collect study data did not include the reasons for recalls. Moreover, data on confirmation of negative findings using a reference standard test or long-term follow-up to assess false-negative results were not available.

A second single institution retrospective study in 2017 was published by Freer et al, who reported on the diagnostic accuracy of synthesized 2D plus DBT, DBT plus DM, and DM alone for screening breast cancer.[34] In this study, the cancer detection rate did not differ significantly between the DBT plus synthesized 2D and either of the other groups. The recall rate was significantly lower in the DBT plus s2D group than in the mammography alone group and was similar in the DBT plus synthesized 2D group and the DBT plus mammography groups. As with the Aujero study, data on confirmation of negative findings were not available.

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Clinical Utility
Direct Evidence: There are is no direct evidence from trials comparing health outcomes in patients screened for breast cancer using DBT and mammography.

Chain of Evidence: Given that the utility of breast cancer screening with mammography has been established, a chain of evidence should demonstrate that DBT plus synthesized 2D is equivalent to screening performance of standard mammography alone. Available studies have reported that replacing mammography with DBT plus synthesized 2D might increase cancer detection and reduce recall rates. However, performance characteristics are uncertain due to 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.

Section Summary: Screening with DBT Plus Synthesized 2D Mammography
One prospective and 3 retrospective studies assessed DBT plus synthesized 2D mammography, which has lower radiation exposure than DBT plus DM. Two studies found higher detection rates with DBT plus synthesized 2D compared with DM, one found similar detection rates with DBT plus synthesized 2D compared with DM, and one found similar detection rates with DBT plus synthesized 2D compared with DBT plus DM. When comparing the recall rate of DBT plus synthesized 2D with DM alone, the prospective study found a higher recall rate in the former, 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.

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.

DBT for Diagnosis

Clinical Context and Test Purpose
The question addressed in this portion of the evidence review is whether there is sufficient evidence that DBT used to detect breast cancer in patients with abnormal findings on breast imaging or clinical exam improves the net health outcome compared with standard techniques. Specifically, is DBT at least as accurate as standard methods for diagnosing breast cancer and is this degree of increased accuracy likely to improve health outcomes via earlier diagnosis, better patient management decisions, and more appropriate treatment?

The following PICOTS were 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.

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Interventions
The intervention of interest is DBT for diagnosis.

Comparators
The comparator of interest is mammography alone.

Outcomes
Outcomes of interest for diagnostic accuracy include test accuracy and test validity (ie, sensitivity, specificity). The primary outcomes of interest for the clinical utility are avoidance of invasive procedures (eg, biopsy or mastectomy), overall mortality, and breast cancer–specific mortality.

Timing
DBT for diagnosis would be performed after a positive breast cancer screening examination.

Setting
The test would be performed in an outpatient imaging setting.

Technical Reliability
A number of products are commercially available to perform DBT, and the technical reliability of these devices has been evaluated by the U.S. Food and Drug Administration as part of its 510(k) process.

Clinical Validity
Lei et al (2014) conducted a meta-analysis of 7 studies (total N=2014 patients; total N=2666 lesions) that compared DBT with DM in patients with breast lesions at BI-RADS category 2 or higher.[42] All studies were rated high quality by reviewers using the QUADAS-2 tool. As shown in Table 3, compared with histologic diagnosis, the performance of both imaging modalities was approximately similar; PPVs were low (57% for breast tomosynthesis vs 50% for DM), and negative predictive values were high. Statistical heterogeneity among these analyses was considerable ($I^2 \approx 90\%$). 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.[43]

Table 3. Side-by-Side Comparison of DBT and DM Diagnostic Performance With Histologic Diagnosis: Pooled Results[42]

	Pooled Estimates (95% CI), %	
Outcomes	**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)

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Outcomes	Pooled Estimates (95% CI), % DBT	DM
LR–	0.15 (0.06 to 0.36)	0.18 (0.09 to 0.38)
Summary AUROC	0.867	0.856

AUROC: area under the receiver operating characteristic curve; CI: confidence interval; 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 the author.
[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.

The 2014 TEC Assessment identified 6 studies that addressed the use of breast tomosynthesis in the diagnostic setting (ie, when there are suspicious findings on screening mammography or when the woman is symptomatic).[9] Findings of these studies are displayed in Table 4.

Table 4. Studies of Diagnostic DBT in 2014 TEC Assessment

Study (Year)	N	AUC	Sensitivity, %	Specificity, %	PPV, %	NPV, %
Bernardi et al (2012)[44]	158					
Screening mammo plus DBT			100	74	38	100
Brandt et al (2013)[4]	146					
Diagnostic mammo plus ultrasound		0.94	100	94		
DBT plus ultrasound						
Reader 1		0.94	100	94		
Reader 2		0.93		93		
Reader 3		0.89	88	89		
Tagliafico et al (2012)[1]	52					
Mammo spot view		0.96	100	94		
DBT		1.00	100	100		
Zuley et al (2013)[45]	182					
BI-RADS 3-5 = positive						
Screening plus diagnostic mammo		0.83	96	15		
Screening mammo plus DBT		0.87	96	26		
BI-RADS 4-5 = positive						
Screening plus diagnostic mammo			89	43		
Screening mammo plus DBT			90	52		
BI-RADS 5 = positive						
Screening plus diagnostic mammo			33	98		
Screening mammo plus DBT			39	98		
Michell et al (2012)[46]	738					
Film plus digital mammo		0.90	98	51	42	98
Film plus digital mammo plus DBT		0.97	100	74	59	100

AUC: area under the curve; BI-RADS: Breast Imaging Reporting and Data System; DBT: digital breast tomosynthesis; mammo: mammography; NPV: negative predictive value; PPV: positive predictive value.

Studies varied considerably by types of suspicious mammographic findings (eg, calcifications vs noncalcifications); patient samples; and comparators to breast tomosynthesis (eg, 2-view mammography, mammographic spot views, ultrasound).

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In a study of 158 women consecutively recalled after screening mammography, Bernardi et al (2012) evaluated breast tomosynthesis as a possible triage tool to reduce the number of false-positive results.[44] Results of diagnostic assessment (including ultrasound and needle biopsy when performed) were used as the reference standard. Breast tomosynthesis eliminated 102 (65%) of 158 recalls, all of which were unnecessary (ie, false-positive results on mammography). No cancers were missed on breast tomosynthesis. Performance of breast tomosynthesis did not vary by breast density or age group, but the reduction in recalls was greater for asymmetric densities and distortions, and nodular opacities with regular margins. As noted by the authors, the observed decline in recall rates after breast tomosynthesis exceeded that observed in blinded comparisons of DM and breast tomosynthesis.

Tagliafico et al (2012) compared the performance of mammographic spot views with DBT among 52 consecutive recalled women with a BI-RADS rating on initial screening of 0 (which means "Need Additional Imaging Evaluation and/or Prior Mammograms for Comparison").[1] Women with calcifications were excluded. The study was designed as a noninferiority analysis of the area under the receiver operating characteristic curve (AUROC), sensitivity, and specificity, with a noninferiority margin of the delta of 0.05, so that if DBT were noninferior to mammographic spot views, DBT could be performed right after screening mammography to avoid a recall. Sensitivity and specificity were extremely high for both modalities, and there was no statistically significant difference between them.

Brandt et al (2013) compared diagnostic mammography with DBT among 146 women with abnormalities on screening mammography with no calcifications in a "simulated clinical setting."[4] Breast tomosynthesis rating was based on readers' ratings and their confidence that no additional studies were needed, as well as ultrasound results in some cases. The reference standard was either results of the entire clinical workup, including biopsy if performed, or follow-up for women not undergoing biopsy (86% of the entire sample). There was no statistically significant difference in sensitivity or specificity between diagnostic mammography and DBT.

Two[1,4] of these 3 studies found no difference in sensitivity and specificity between DBT and a clinical workup comprising diagnostic mammographic images or a more comprehensive diagnostic workup. The third study examined the use of DBT to triage women recalled after screening and reported a substantially reduced recall rate.[44]

Michell et al (2012) evaluated 738 women (comprising 759 lesions) recalled after screening with film mammography.[46] This unblinded study assessed the incremental value of DBT added to film and DM. The reference standard was pathology results or follow-up for 18 to 36 months. The addition of DBT to film and DM increased the area under the receiver operating characteristic curve from 0.895 (95% CI, 0.871 to 0.919) to 0.967 (95% CI, 0.957 to 0.977; p=0.001). Complete sensitivity (ie, counting ratings of 3-5 as positive) increased from 39.7% for DM to 58.3% when DBT was added; confidence interval or p values were not reported. Specificity increased from 51% to 74.2% when DBT was added to DM. The difference in AUROCs after the addition of DBT was statistically significant for soft tissue lesions, but not for microcalcifications.

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Zuley et al (2013) compared diagnostic mammography images with 2-view DBT in 217 lesions (72 [33%] malignant) among 182 women.[45] This retrospective study included women who had undergone diagnostic mammography and DBT. The sample included women with clinical symptoms such as a palpable lump, or findings on mammography, ultrasound, or magnetic resonance imaging. Women with only calcifications were excluded. The area under the receiver operating characteristic curve was 0.83 (95% CI, 0.77 to 0.83; range across readers, 0.74-0.87) for diagnostic mammography, and 0.87 (95% CI, 0.82 to 0.92; range across readers, 0.80-0.92) for DBT ($p<0.001$).

Skaane et al (2012), authors of the Norse screening trial, wrote about their initial experience with DBT in a clinical setting.[47] Their study sample included 129 women with a palpable lump (23%) or abnormal findings on screening mammography (42%), and women undergoing surveillance after prior biopsy or breast conservation surgery (35%). Twenty-five cancers were diagnosed with DBT, including 18 invasive cancers, 5 DCIS, and 2 other cancers. Thirty-eight percent of the women had dense breasts (BI-RADS density categories of 3 or 4). Of the 50 women in the reader study, 23 had cancer, 5 of which were DCIS. All 3 readers missed 2 of the DCIS cases. Two cancers were detected in women with dense breasts, increasing cancer detection by 8%.

Several studies assessing diagnostic DBT have been published after the TEC Assessment. They are summarized in Table 5. Several of the studies reported significantly higher rates of sensitivity with DM plus DBT than with DM alone; none reported significant differences in specificity. Differences in test performance between studies (ie, between Rafferty et al [2014][48] and Thibault et al [2013][49]) are likely due not only to the difference in technologies studied (2-view DM plus 1-view DBT vs 1-view DM plus 1-view DBT, respectively), but also to differences in sample sizes (310 vs 130), settings (U.S. vs Europe), patient population (screen-detected abnormalities vs signs or symptoms of breast cancer); and number (15 vs 7) and training (150 cases vs 20 cases) of readers.

Table 5. Studies of Diagnostic DBT 2014 to Present

Outcome (Year)	N	AUROC	Sensitivity, %	Specificity, %	PPV, %	NPV, %
Rafferty et al (2014)[48]	310					
DM		0.828	63	86	47	92
DM + 1-view DBT		0.864[a]	71[a]	86	50	94
DM + 2-view DBT		0.895[b]	79[b]	85	50	95
Gennaro et al (2013)[50]	463					
DM		NR	76	NR	NR	NR
1-view (CC) DM + 1-view DBT		NR	79	NR	NR	NR
Thibault et al (2013)[49]	130					
DM		0.756	73	53	53	74
1-view (CC) DM + 1-view DBT		0.780	68	64	58	73
DM + 1-view DBT + ultrasound		0.763	81	52	55	79
Cornford et al (2015)[51]	322					
DM + SCV		0.922	92	71	95	93
DM + 2-view DBT		0.946	94	72	95	93
Seo et al (2016)[52]	203					
DM		NR	73	61	NR	NR

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Outcome (Year)	N	AUROC	Sensitivity, %	Specificity, %	PPV, %	NPV, %
2-view DBT			78[a]	61		
DM + 2-view DBT			80[a]	64		

Note: One-view DBT is MLO unless noted otherwise.
AUROC: area under the receiver operating characteristic curve; CC: craniocaudal; DBT: digital breast tomosynthesis; DM: digital mammography (2-view unless noted otherwise); MLO: mediolateral oblique; NPV: negative predictive value; NR: not reported; PPV: positive predictive value; SCV: supplemental assessment views.
[a] Statistically significant difference from DM.
[b] Statistically significant difference from 1-view DBT.

Clinical Utility

Direct Evidence

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

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 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 (probably benign finding) 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 for how DBT results would be used to change management and how those changes would affect health outcomes. The chain cannot be established due to 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, differences in reference standards, use of different imaging tests to compare with DBT, and variations in follow-up make it difficult to draw conclusions from the studies on the diagnostic performance of DBT. Also, some concerns have been raised concerning the classification of microcalcification clusters with DBT alone.

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- 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: DBT for Diagnosis
Mixed patient populations, differences in reference standards, use of different imaging tests to compare with DBT, and variations in follow-up make it difficult to draw conclusions from the available studies on the diagnostic performance of DBT. Also, some concerns have been raised about the classification of microcalcification clusters with DBT alone. There is 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.

SUMMARY OF EVIDENCE

For individuals who are asymptomatic and at average risk of breast cancer who receive DBT as an adjunct to mammography for screening, the evidence includes results from several studies in which women served as their own controls and separate observational studies. Relevant outcomes are overall survival, disease-specific survival, test accuracy, and test validity. The available studies have provided evidence that adding breast tomosynthesis to mammography may increase accuracy (and possibly sensitivity) of screening while potentially reducing the number of women who are recalled unnecessarily. However, studies had methodologic limitations, including retrospective designs, inadequate follow-up of women with negative screening results, use of historical controls, and screening practices in Europe that differ from those in the United States. There is also a lack of data concerning interval cancers and breast cancer mortality. Therefore, the performance of DBT in the screening setting cannot be determined with certainty. There is a lack of direct evidence on the clinical utility of DBT from screening trials comparing health outcomes in patients screened using DBT and mammography. Due to limitations in the studies on diagnostic accuracy, it is not possible to construct a chain of evidence. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are asymptomatic and at average risk of breast cancer who receive DBT with synthesized mammography for screening, the evidence includes several nonrandomized comparative studies. Relevant outcomes are overall survival, disease-specific survival, test accuracy, and test validity. Two studies found higher detection rates with DBT plus synthesized 2-dimensional mammography than with digital mammography, 1 study found similar detection rates with DBT plus synthesized 2D mammography than with digital mammography, and the other found similar detection rates between DBT plus synthesized 2D mammography and DBT plus digital mammography. When comparing the recall rate of DBT plus synthesized 2D mammography with digital mammography alone, the prospective study found a higher recall rate in the former 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. There is a lack of direct evidence on the clinical utility of DBT from screening trials

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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. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have abnormal findings on breast imaging or clinical exam who receive DBT as an adjunct to mammography for diagnosis, the evidence includes multiple observational studies and a meta-analysis. Relevant outcomes are test accuracy, test validity, and treatment-related morbidity. Mixed patient populations, differences in reference standards, use of different imaging tests to compare with DBT, and variations in follow-up make it difficult to draw conclusions from the available studies on the diagnostic performance of DBT. Also, some concerns have been raised about the classification of microcalcification clusters with DBT alone. 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. The evidence is insufficient to determine the effects of the technology on health outcomes.

PRACTICE GUIDELINES AND POSITION STATEMENTS

American College of Radiology

The American College of Radiology's (ACR) November 2014 statement on breast tomosynthesis included the following[54]:

> "… breast tomosynthesis has shown to be an advance over digital mammography, with higher cancer detection rates and fewer patient recalls for additional testing. This is extremely important. The medical community has long sought ways to improve breast cancer screening accuracy. Better sensitivity will likely translate into more lives saved. Lower recall rates result in fewer patients who may experience short-term anxiety awaiting test results. This is important evidence that tomosynthesis will have a positive impact on patient care.…."

While ACR has encouraged 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 Appropriate Criteria, last reviewed in 2016, gave digital breast tomosynthesis (DBT) a rating of 9 ("usually appropriate") for use with women at high risk, intermediate risk, as well as average risk for breast cancer.[54] The ACR screening recommendations for breast cancer risk are:

- For high-risk women, screen those "with BRCA gene mutations and their untested first-degree relatives as well as women with a lifetime risk of breast cancer of ~20% or greater. Also included … are women who have received radiation therapy to the chest between the ages of 10–30…."
- For intermediate-risk women, screen those "with a lifetime risk of 15%–20%, a personal history of breast cancer, or … lobular neoplasia or ADH [atypical ductal hyperplasia]…."

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- For average-risk women, screen those with a "<15% lifetime risk of breast cancer [and] breasts [that are] not dense."

American College of Obstetricians and Gynecologists
In a 2011 practice bulletin on breast cancer screening, the American College of Obstetricians and Gynecologists noted that DBT is one of several screening techniques that were considered, but not recommended, for routine screening.[55]

A 2015 committee opinion on the management of women with dense breasts identified by mammography states, "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."[56] Breast tomosynthesis or thermography are not cited in the document as alternative tests.

American Academy of Family Physicians
In 2016, the American Academy of Family Physicians issued a clinical preventive service recommendation on breast cancer.[57] The recommendation stated that there is insufficient evidence for an assessment of the benefits and harms of DBT as a primary screening method for breast cancer. The recommendation also states that there is insufficient evidence for an assessment of benefits and harms of DBT as adjunctive screening for breast cancer in women identified as having dense breast tissue on an otherwise negative screening mammogram.

National Comprehensive Cancer Network
Current National Comprehensive Cancer Network guidelines (v.1.2017) state: "Multiple studies show tomosynthesis appears to improve cancer detection and decreased call back rates. Of note, most studies used double the dose of radiation. The radiation dose can be minimized by synthetic 2-D reconstruction."[58]

The National Comprehensive Cancer Network 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. Table 6 summarizes the panel's conclusions on the available evidence for the use of tomosynthesis with mammography.[59]

Table 6. Recommendations on Use of Tomosynthesis with Mammography[59]

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

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Method	Strength of Evidence[a]
Mammography with tomosynthesis vs mammography alone	
Reduces the proportion of false-positive screening outcomes	Limited

[a] Rating system detailed at http://handbooks.iarc.fr/workingprocedures/index.php.

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

In 2016, the U.S. Preventive Services Task Force (USPSTF) updated its recommendations on breast cancer screening.[60] USPSTF recommended biennial screening mammography in women ages 50 to 74 years (grade B recommendation) and that the decision to start screening mammography before age 50 should be individualized (grade C recommendation).

For all women, USPSTF stated, "...the current evidence is insufficient to assess the benefits and harms of digital breast tomosynthesis (DBT) as a primary screening method for breast cancer" (grade I recommendation). For women with dense breasts, USPSTF stated "…the current evidence is insufficient to assess the balance of benefits and harms of adjunctive screening for breast cancer using… DBT, or other methods in women identified to have dense breasts on an otherwise negative screening mammogram" (grade I recommendation).

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently unpublished trials that might influence this policy are listed in Table 7.

Table 7. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT01091545[a]	Malmö Breast Tomosynthesis Screening Trial	15,000	Dec 2017
NCT02698202	Screening for Breast Cancer With Digital Breast Tomosynthesis	40,000	Dec 2018
NCT02590315	Tomosynthesis Versus Digital Mammography in a Population-based Screening Program (ProteusDonna)	92,000	Dec 2019
NCT02835625	The Tomosynthesis Trial in Bergen (TOBE)	37,000	Jan 2022

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

CPT/HCPCS

77061	Digital breast tomosynthesis; unilateral
77062	Digital breast tomosynthesis; bilateral
77063	Screening digital breast tomosynthesis, bilateral (List separately in addition to code for primary procedure)
G0279	Diagnostic digital breast tomosynthesis, unilateral or bilateral

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- There are specific CPT codes for this imaging: 77061, 77062, 77063.
- Medicare established an add-on HCPCS G code specific to diagnostic breast tomosynthesis: G0279.

DIAGNOSIS
Experimental / investigational for all diagnoses related to this policy.

REVISIONS

10-11-2012	Policy added to the bcbsks.com web site.
09-17-2013	Updated Description section.
	Updated Rationale section.
	Updated Reference section.
01-01-2015	Policy posted 01-16-2015.
	In Coding section: ▪ Added CPT/HCPCS Codes: 77061, 77062, 77063, G0279 (Effective January 1, 2015) ▪ Deleted CPT Code: 77649 (Effective January 1, 2015)
09-25-2015	Updated Description section.
	Updated Rationale section.
	Updated References section.
02-03-2016	Updated Description section.
	Updated Rationale section.
	In Coding section: ▪ Revised coding bullets.
	Updated References section.
01-04-2017	Updated Description section.
	Updated Rationale section.
	In Coding section: ▪ Updated coding bullets.
	Updated References section.
01-01-2018	In Coding section: ▪ Revised nomenclature to HCPCS code: G0279.
02-15-2018	Updated Description section.
	Updated Rationale section.
	Updated References section.
01-01-2019	Policy archived.

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