



EUROPEAN COMMISSION  
JOINT RESEARCH CENTRE

Directorate F - Health, Consumers & Reference Materials (Ispra)  
**Health in Society**

## European Commission Initiative on Breast Cancer (ECIBC): European guidelines on breast cancer screening and diagnosis

QUESTION	
Should screening using digital breast tomosynthesis vs. digital mammography be used in organised screening programmes for early detection of breast cancer in asymptomatic women?	
POPULATION:	Asymptomatic women attending an organised breast cancer screening programme
INTERVENTION:	screening using digital breast tomosynthesis (including synthesised 2D images)
COMPARISON:	digital mammography
MAIN OUTCOMES:	Breast cancer mortality, breast cancer stage, breast cancer detection, interval breast cancer, recall for assessment, quality of life, other-cause mortality, adverse effects (including radiation exposure, radiation induced cancers-related to radiation dose, overdiagnosis related adverse effects, false positive related adverse effects)
SETTING:	European Union
PERSPECTIVE:	Population (National Health System)
BACKGROUND:	<p>Breast cancer is the second most common cancer in the world and, by far, the most frequent cancer among women, with an estimated 2 088 849 new cancer cases diagnosed in 2018 (11.6% of all cancers) (Ferlay, 2018). Breast cancer ranks as the fourth cause of death from cancer overall (626 679 deaths) (Ferlay, 2018).</p> <p>Screening programmes play a crucial role in early breast cancer detection; it can increase the chance of survival as well as have an impact on breast cancer mortality. Digital mammography (DM) remains the best method to detect breast cancer in an early stage. DM is a technique of imaging which produces a 2D image of the 3D organ. Inevitably, this implies that lesions can be obscured by superposition of dense tissue. Indeed, the superposition of tissue can lead to false positives as well as false negatives.</p> <p>Digital breast tomosynthesis (DBT) is an imaging technique based on a series of low dose images of the breast taken from different angles and one compression, and has the potential to partly overcome tissue superposition thus improving detection of breast lesions through minimization of masking effects in DM (Rafferty EA, 2013, Gur D, 2009). The series of projections is then processed by a reconstruction algorithm to estimate the 3D appearance of the breast which can be viewed in successive slices. In screening trials, tomosynthesis has been used in addition to a 2D image done with 2D DM, regardless whether synthetic 2D images of the DBT series were available or not. In this question we compare DBT to DM, only if synthetic 2D from the DBT data set are available.</p> <p><b>This recommendation was updated in January 2020. Previous versions of the recommendation are available on the ECIBC website.</b></p>

<b>CONFLICT OF INTEREST:</b>	<p>Management of Conflicts of Interest (Col): Cols for all Guidelines Development Group (GDG) members were assessed and managed by the Joint Research Centre (JRC) following an established procedure in line with European Commission rules. GDG member participation in the development of the recommendations was restricted, according to Col disclosure. Consequently, for this particular question, the following GDG members were recused from voting: Jan Danes, Solveig Hofvind, Elsa Pérez, and Kenneth Young. Miranda Langendam was not allowed to vote due to the established rules for external experts.</p> <p>For more information please visit <a href="https://healthcare-quality.jrc.ec.europa.eu/discover-ecibc/governance/ecibc-working-groups">https://healthcare-quality.jrc.ec.europa.eu/discover-ecibc/governance/ecibc-working-groups</a></p>
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## ASSESSMENT

### Problem

Is the problem a priority?




JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <li>○ No</li> <li>○ Probably no</li> <li>○ Probably yes</li> <li>● Yes</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	<p>Breast cancer is the second most common cancer in the world and, by far, the most frequent cancer among women, with an estimated 2 088 849 new cancer cases diagnosed in 2018 (11.6% of all cancers), it ranks as the fourth cause of death from cancer overall (626 679 deaths) (Ferlay, 2018).</p> <p>DM is widely used in screening and diagnosis of breast cancer. However, some aspects such as superposition of breast tissue limits the sensitivity and specificity of mammography and false-positives and false negatives are an issue (JRC Technical Report PICO 1-3, contract FWC443094012015; available upon request). DBT might provide better imaging and discriminative capacity in these cases.</p>	

### Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <li>○ Trivial</li> <li>○ Small</li> <li>● Moderate</li> <li>○ Large</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	<p><b>Date of last search: January 2020</b></p>	<p>After reviewing the eligibility criteria, three studies previously included in this question (STORM and MBTST) are only included now in PICO 4 (DBT+DM vs. DM).</p> <p>The GDG agreed that the desirable outcomes are: breast cancer detection, false positive recall for assessment (reduction). Recall for assessment was not considered as a critical outcome because it is already included in the outcome "false positive recall for assessment".</p> <p>During the updating of the searches, in January 2020, one new randomised clinical trial (RCT) was identified (Hofvind 2019).</p> <p>During the update of January 2020, the panel decided to include also unpaired studies for all outcome. The</p>

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)		
				Risk with digital mammography	Risk difference with (Post-meeting) screening using digital tomosynthesis (including synthesised 2D images)	
Breast Cancer Detection <sup>a</sup>	432029 (10 observational studies) <sup>1,10,2,3,4,5,6,7,8,9,b,c</sup>	⊕⊕⊕○ MODERATE <sup>d</sup>	RR 1.36 (1.22 to 1.51)	Study population		<p>included studies, both paired (i.e. comparison made within participants, all participants underwent 2D mammography and DBT) and unpaired designs (i.e. comparison of separate groups that underwent DBT or 2D mammography), reported data for test performance outcomes. Results from both types of design were consistent across outcomes, and data was therefore pooled.</p> <p>Critical outcomes such as breast cancer mortality, quality of life, or other-causes of mortality are still not measured in the included studies.</p> <p>All included studies except one (Hovda Radiology 2019) only report data from first round DBT. We included only studies that reported both breast cancer detection rate and false positive recall for assessment. If needed we calculated the former using other available data (e.g. recall rate or specificity).</p> <p>Grade/tumour characteristics/prognostics might clarify the amount of possible overdiagnosis in this group. A systematic review of these characteristics was not pre-planned and results of such search and analysis are not available.</p> <p>From the total breast cancer detected a proportion will be a desirable health outcome and another proportion of the increased detection will be overdiagnosis. However, the panel suggested that detection rate is a desirable effect. Overdiagnosis, which is part of this number is considered an undesirable effect. The proportion of this is not known conclusively.</p> <p>The inconsistency of the results of interval cancer (not fitting with the expected direction of the results) suggests that a large proportion of detected cancers may be indeed overdiagnosis. Some members of the panel questioned if the observation of increased interval cancers are indeed creating an inconsistency because of the biology being possibly different.</p> <p>The GDG decided to include the outcome detection rate evaluated in a second round of screening. The lower detection rate of DBT compared with the first round suggests that tumour diagnosis might be anticipated through DBT rather than over-diagnosed.</p> <p>As consensus was not reached, voting was conducted</p>
				573 per 100,000	<b>206 more per 100,000</b> (126 more to 292 more)	
Breast cancer stage (inferred from invasive cancer detection rate)	217069 (5 observational studies) <sup>1,5,6,7,9,b,c</sup>	⊕⊕⊕○ MODERATE <sup>d,e</sup>	RR 1.34 (1.19 to 1.51)	Study population		
				464 per 100,000	<b>158 more per 100,000</b> (88 more to 237 more)	
Invasive cancer /total cancer	1398 (5 observational studies) <sup>1,5,6,7,9</sup>	⊕⊕⊕○ MODERATE <sup>d</sup>	RR 0.96 (0.66 to 0.97)	Study population		
				83 per 100	<b>3 fewer per 100</b> (28 fewer to 2 fewer)	
Breast cancer detection (second round screening with DM alone after a first round of DBT or DM)	72017 (1 observational study) <sup>11,f</sup>	⊕⊕⊕○ MODERATE <sup>d</sup>	RR 0.70 (0.56 to 0.88)	Study population		
				558 per 100,000	<b>167 fewer per 100,000</b> (245 fewer to 67 fewer)	

	False positive recall for assessment <sup>g</sup>	428802 (10 observational studies) <sup>1,10,2,3,4,5,6,7,8,9,b,c</sup>	 VERY LOW <sup>d,h</sup>	RR 0.80 (0.66 to 0.97)	Study population	
					4,382 per 100,000	<b>876 fewer per 100,000</b> (1,490 fewer to 131 fewer)
	Interval breast cancer <sup>i</sup>	784166 (8 observational studies) <sup>11,12,13,14,15,16,17,18,b</sup>	 VERY LOW <sup>d,j</sup>	RR 1.04 (0.90 to 1.20)	Study population	
					103 per 100,000	<b>4 more per 100,000</b> (10 fewer to 21 more)
	Radiation exposure	0 (3 observational studies) <sup>19,20,4,b</sup>	 LOW <sup>k,l</sup>	-	Radiation doses for DBT vary by manufacturer and protocol (Bernardi 2016, Paulis 2015, Wallis 2012). m	
	Breat cancer mortality - not reported	-	-	-	-	-
	Quality of life - not reported	-	-	-	-	-
	Radiation induced cancers-related to radiation dose - not reported	-	-	-	-	-
	Other causes of mortality - not reported	-	-	-	-	-
	<ol style="list-style-type: none"> <li>Houssami, N ,Lockie,Clemson,Pridmore,Taylor,Marr. Pilot trial of digital breast tomosynthesis (3D mammography) for population-based screening in BreastScreen Victoria. 2019.</li> <li>Skaane P, Bandos,Niklason,Sebuødegård,Østerås,Gullien,Gur,Hofvind. Digital Mammography versus Digital Mammography Plus Tomosynthesis in Breast Cancer Screening: The Oslo Tomosynthesis Screening Trial. Radiology; 2019.</li> </ol>					

among the GDG members to judge how substantial desirable effects are: 1 member voted “small”, **7 members voted “moderate”**, 2 members voted “large”, 6 members voted “don’t know” and 1 abstained.

3. Romero Martín S, Raya Povedano JL, Cara García M, Santos Romero AL, Pedrosa Garriguet M, Álvarez Benito M. Prospective study aiming to compare 2D mammography and tomosynthesis + synthesized mammography in terms of cancer detection and recall. From double reading of 2D mammography to single reading of tomosynthesis. *Eur Radiol*; 2018.
4. Bernardi D, Macaskill P, Pellegrini M, Valentini M, Fantò C, Ostilio L, Tuttobene P, Luparia A, Houssami N.. Breast cancer screening with tomosynthesis (3D mammography) with acquired or synthetic 2D mammography compared with 2D mammography alone (STORM-2): a population-based prospective study.. *Lancet Oncol*; 2016.
5. Hofvind S, Holen Hildegunn, Houssami Sebuødegård Moger Haldorsen Akslen. Two-view digital breast tomosynthesis versus digital mammography in a population-based breast cancer screening programme (To-Be): a randomised, controlled trial. *Lancet Oncol*; 2019.
6. Hofvind S, Hovda T, Holen ÅS, Lee CI, Albertsen J, Bjørndal H, et al. Digital Breast Tomosynthesis and Synthetic 2D Mammography versus Digital Mammography: Evaluation in a Population-based Screening Program. *Radiology*; 2018.
7. Freer, P. E., Riegert, J., Eisenmenger, L., Ose, D., Winkler, N., Stein, M. A., Stoddard, G. J., Hess, R.. Clinical implementation of synthesized mammography with digital breast tomosynthesis in a routine clinical practice. *Breast Cancer Res Treat*; 2017.
8. Bernardi, D., Gentilini, M. A., De Nisi, M., Pellegrini, M., Fanto, C., Valentini, M., Sabatino, V., Luparia, A., Houssami, N.. Effect of implementing digital breast tomosynthesis (DBT) instead of mammography on population screening outcomes including interval cancer rates: Results of the Trento DBT pilot evaluation. *Breast*; 2019.
9. Auiero, M. P., Gavenonis, S. C., Benjamin, R., Zhang, Z., Holt, J. S.. Clinical Performance of Synthesized Two-dimensional Mammography Combined with Tomosynthesis in a Large Screening Population. *Radiology*; 2017.
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11. Hovda, T., Holen, A. S., Lang, K., Albertsen, J. L., Bjørndal, H., Brandal, S. H. B., Sahlberg, K. K., Skaane, P., Suhrke, P., Hofvind, S.. Interval and Consecutive Round Breast Cancer after Digital Breast Tomosynthesis and Synthetic 2D Mammography versus Standard 2D Digital Mammography in BreastScreen Norway. *Radiology*; 2019.
12. Bernardi D, Gentilini, De Nisi, Pellegrini, Fanto, Valentini, Sabatino, Luparia, Houssami. Effect of implementing digital breast tomosynthesis (DBT) instead of mammography on population screening outcomes including interval cancer rates: Results of the Trento DBT pilot evaluation. *The Breast*; 2019.
13. Alsheik, N. H., Dabbous, F., Pohlman, S. K., Troeger, K. M., Gliklich, R. E., Donadio, G. M., Su, Z., Menon, V., Conant, E. F.. Comparison of Resource Utilization and Clinical Outcomes Following Screening with Digital Breast Tomosynthesis Versus Digital Mammography: Findings From a Learning Health System. *Acad Radiol*; 2018.
14. Bahl M, Gaffney S, McCarthy AM, Lowry KP, Dang PA, Lehman CD. Breast Cancer Characteristics Associated with 2D Digital Mammography versus Digital Breast Tomosynthesis for Screening-detected and Interval Cancers. *Radiology*; 2018.
15. Houssami, N., Bernardi, D., Caumo, F., Brunelli, S., Fanto, C., Valentini, M., Romanucci, G., Gentilini, M. A., Zorzi, M., Macaskill, P.. Interval breast cancers in the 'screening with tomosynthesis or standard mammography' (STORM) population-based trial. *Breast*; 2018.

	<p>16. McDonald, E. S., Oustimov, A., Weinstein, S. P., Synnestvedt, M. B., Schnall, M., Conant, E. F.. Effectiveness of Digital Breast Tomosynthesis Compared With Digital Mammography: Outcomes Analysis From 3 Years of Breast Cancer Screening. JAMA Oncol; 2016.</p> <p>17. Skaane, P., Sebuodegard, S., Bandos, A. I., Gur, D., Osteras, B. H., Gullien, R., Hofvind, S.. Performance of breast cancer screening using digital breast tomosynthesis: results from the prospective population-based Oslo Tomosynthesis Screening Trial. Breast Cancer Res Treat; 2018.</p> <p>18. Conant, E. F., Barlow, W. E., Herschorn, S. D., Weaver, D. L., Beaber, E. F., Tosteson, A. N. A., Haas, J. S., Lowry, K. P., Stout, N. K., Trentham-Dietz, A., diFlorio-Alexander, R. M., Li, C. I., Schnall, M. D., Onega, T., Sprague, B. L.. Association of Digital Breast Tomosynthesis vs Digital Mammography With Cancer Detection and Recall Rates by Age and Breast Density. JAMA Oncol; 2019.</p> <p>19. Wallis MG, Moa E,Zanca F,Leifland K,Danielsson M. Two-view and single-view tomosynthesis vs. full-field digital mammography: high-resolution X-ray imaging observer study. Radiology; 2012.</p> <p>20. Paulis LE, Lobbes MB,Lalji UC,Gelissen N,Bouwman RW,Wildberger JE,et al. Radiation exposure of digital breast tomosynthesis using an antiscatter grid compared with full-field digital mammography. Invest Radiol; 2015.</p> <p>a. Calculated as the total number of women with positive screening/overall number of screening examinations</p> <p>b. Cohort studies provided partial diagnostic information. The risk of bias was assessed using an ad-hoc modified QUADAS-2 tool</p> <p>c. Hofvind 2019 was a randomised prospective trial</p> <p>d. Concerns for risk of bias due to reference standard was not blinded to the index tests. Additionally, there was variability in the number of readings, readers' experience and number of readers (i.e. single or double) across studies.</p> <p>e. Downgraded due to scarce number of events</p> <p>f. Hovda Radiology 2019 was included to assess detection rate outcome evaluated in a second round screening.</p> <p>g. Calculated as the number of false positives/overall number of screening examinations - total number of cancers</p> <p>h. Important unexplained heterogeneity (I<sup>2</sup>=97%)</p> <p>i. Calculated as the number of false positives/overall number of screening examinations - total number of cancers</p> <p>j. Wide 95%CI and low number of events</p> <p>k. Radiation exposure is a surrogate outcome of "other cancer related to radiation".</p> <p>l. Results were consistent independently of the technology used (Hologic Selenia Dimensions or Siemens Mammomat Inspiration).</p> <p>m. Doses levels are known to vary (diagnostic reference levels are typically country/region and system specific).</p>	
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## Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE					ADDITIONAL CONSIDERATIONS	
<div>○ Large</div> <div>○ Moderate</div> <div>● Small</div> <div>○ Trivial</div> <div>○ Varies</div> <div>○ Don't know</div>	Date of last search: January 2020					<p>The GDG agreed that the undesirable outcomes are: interval breast cancer, overdiagnosis, and radiation exposure.</p> <p>As consensus was not reached, voting was conducted among the GDG members to judge how substantial undesirable effects are: <b>7 members voted “small”</b>, 1 member voted “moderate”, 4 members voted “trivial”, 1 member voted “varies”, 3 members voted “don’t know” and 1 abstained.</p>	
	Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects * (95% CI)		
					Risk with digital mammography		Risk difference with (Post-meeting) screening using digital tomosynthesis (including synthesised 2D images)
	Breast Cancer Detection <sup>a</sup>	432029 (10 observational studies) <sup>1,10,2,3,4,5,6,7,8,9,b,c</sup>	⊕⊕⊕○ MODERATE <sup>d</sup>	RR 1.36 (1.22 to 1.51)	Study population		
					573 per 100,000		<b>206 more per 100,000</b> (126 more to 292 more)
	Breast cancer stage (inferred from invasive cancer detection rate)	217069 (5 observational studies) <sup>1,5,6,7,9,b,c</sup>	⊕⊕⊕○ MODERATE <sup>d,e</sup>	RR 1.34 (1.19 to 1.51)	Study population		
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	Invasive cancer /total cancer	1398 (5 observational studies) <sup>1,5,6,7,9</sup>	⊕⊕⊕○ MODERATE <sup>d</sup>	RR 0.96 (0.66 to 0.97)	Study population		
83 per 100					<b>3 fewer per 100</b> (28 fewer to 2 fewer)		



	Breast cancer detection (second round screening with DM alone after a first round of DBT or DM)	72017 (1 observational study) <sup>11,f</sup>	⊕⊕⊕○ MODERATE <sup>d</sup>	RR 0.70 (0.56 to 0.88)	Study population	
					558 per 100,000	<b>167 fewer per 100,000</b> (245 fewer to 67 fewer)
	False positive recall for assessment <sup>g</sup>	428802 (10 observational studies) <sup>1,10,2,3,4,5,6,7,8,9,b,c</sup>	⊕○○○ VERY LOW <sup>d,h</sup>	RR 0.80 (0.66 to 0.97)	Study population	
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					103 per 100,000	<b>4 more per 100,000</b> (10 fewer to 21 more)
	Radiation exposure	0 (3 observational studies) <sup>19,20,4,b</sup>	⊕⊕○○ LOW <sup>k,l</sup>	-	Radiation doses for DBT vary by manufacturer and protocol (Bernardi 2016, Paulis 2015, Wallis 2012). <sup>m</sup>	
	Breast cancer mortality - not reported	-	-	-	-	-
	Quality of life - not reported	-	-	-	-	-
	Radiation induced cancers-related to radiation dose - not reported	-	-	-	-	-
	Other causes of mortality - not reported	-	-	-	-	-

	<ol style="list-style-type: none"> <li>1. Houssami, N ,Lockie,Clemson,Pridmore,Taylor,Marr. Pilot trial of digital breast tomosynthesis (3D mammography) for population-based screening in BreastScreen Victoria. 2019.</li> <li>2. Skaane P, Bandos,Niklason,Sebuødegård,Østerås,Gullien,Gur,Hofvind. Digital Mammography versus Digital Mammography Plus Tomosynthesis in Breast Cancer Screening: The Oslo Tomosynthesis Screening Trial. Radiology; 2019.</li> <li>3. Romero Martín S, Raya Povedano JL,Cara García M,Santos Romero AL,Pedrosa Garriguet M,Álvarez Benito M. Prospective study aiming to compare 2D mammography and tomosynthesis + synthesized mammography in terms of cancer detection and recall. From double reading of 2D mammography to single reading of tomosynthesis. Eur Radiol; 2018.</li> <li>4. Bernardi D, Macaskill P,Pellegrini M,Valentini M,Fantò C,Ostillo L,Tuttobene P,Luparia A,Houssami N.. Breast cancer screening with tomosynthesis (3D mammography) with acquired orsynthetic 2D mammography compared with 2D mammography alone (STORM-2): a population-based prospective study.. Lancet Oncol; 2016.</li> <li>5. Hofvind S, Holen Hildegunn Houssami Sebuødegård Moger Haldorsen Akslen. Two-view digital breast tomosynthesis versus digital mammography in a population-based breast cancer screening programme (To-Be): a randomised, controlled trial. Lancel Oncol; 2019.</li> <li>6. Hofvind S, Hovda T,Holen ÅS,Lee CI,Albertsen J,Bjørndal H,et al. Digital Breast Tomosynthesis and Synthetic 2D Mammography versus Digital Mammography: Evaluation in a Population-based Screening Program. Radiology; 2018.</li> <li>7. Freer, P. E., Riegert, J., Eisenmenger, L., Ose, D., Winkler, N., Stein, M. A., Stoddard, G. J., Hess, R.. Clinical implementation of synthesized mammography with digital breast tomosynthesis in a routine clinical practice. Breast Cancer Res Treat; 2017.</li> <li>8. Bernardi, D., Gentilini, M. A., De Nisi, M., Pellegrini, M., Fanto, C., Valentini, M., Sabatino, V., Luparia, A., Houssami, N.. Effect of implementing digital breast tomosynthesis (DBT) instead of mammography on population screening outcomes including interval cancer rates: Results of the Trento DBT pilot evaluation. Breast; 2019.</li> <li>9. Aujero, M. P., Gavenonis, S. C., Benjamin, R., Zhang, Z., Holt, J. S.. Clinical Performance of Synthesized Two-dimensional Mammography Combined with Tomosynthesis in a Large Screening Population. Radiology; 2017.</li> <li>10. Caumo, F., Zorzi, M., Brunelli, S., Romanucci, G., Rella, R., Cugola, L., Bricolo, P., Fedato, C., Montemezzi, S., Houssami, N.. Digital Breast Tomosynthesis with Synthesized Two-Dimensional Images versus Full-Field Digital Mammography for Population Screening: Outcomes from the Verona Screening Program. Radiology; 2017.</li> <li>11. Hovda, T., Holen, A. S., Lang, K., Albertsen, J. L., Bjørndal, H., Brandal, S. H. B., Sahlberg, K. K., Skaane, P., Suhrke, P., Hofvind, S.. Interval and Consecutive Round Breast Cancer after Digital Breast Tomosynthesis and Synthetic 2D Mammography versus Standard 2D Digital Mammography in BreastScreen Norway. Radiology; 2019.</li> <li>12. Bernardi D, Gentilini,De Nisi,Pellegrini,Fanto,Valentini,Sabatino,Luparia,Houssami. Effect of implementing digital breast tomosynthesis (DBT) instead of mammography on population screening outcomes including interval cancer rates: Results of the Trento DBT pilot evaluation. The Breast; 2019.</li> <li>13. Alsheik, N. H., Dabbous, F., Pohlman, S. K., Troeger, K. M., Gliklich, R. E., Donadio, G. M., Su, Z., Menon, V., Conant, E. F.. Comparison of Resource Utilization and Clinical Outcomes Following Screening with Digital Breast Tomosynthesis Versus</li> </ol>	
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	<p>Digital Mammography: Findings From a Learning Health System. Acad Radiol; 2018.</p> <ol style="list-style-type: none"> <li>14. Bahl M, Gaffney S, McCarthy AM, Lowry KP, Dang PA, Lehman CD. Breast Cancer Characteristics Associated with 2D Digital Mammography versus Digital Breast Tomosynthesis for Screening-detected and Interval Cancers. Radiology; 2018.</li> <li>15. Houssami, N., Bernardi, D., Caumo, F., Brunelli, S., Fanto, C., Valentini, M., Romanucci, G., Gentilini, M. A., Zorzi, M., Macaskill, P.. Interval breast cancers in the 'screening with tomosynthesis or standard mammography' (STORM) population-based trial. Breast; 2018.</li> <li>16. McDonald, E. S., Oustimov, A., Weinstein, S. P., Synnestvedt, M. B., Schnall, M., Conant, E. F.. Effectiveness of Digital Breast Tomosynthesis Compared With Digital Mammography: Outcomes Analysis From 3 Years of Breast Cancer Screening. JAMA Oncol; 2016.</li> <li>17. Skaane, P., Sebuodegard, S., Bandos, A. I., Gur, D., Osteras, B. H., Gullien, R., Hofvind, S.. Performance of breast cancer screening using digital breast tomosynthesis: results from the prospective population-based Oslo Tomosynthesis Screening Trial. Breast Cancer Res Treat; 2018.</li> <li>18. Conant, E. F., Barlow, W. E., Herschorn, S. D., Weaver, D. L., Beaber, E. F., Tosteson, A. N. A., Haas, J. S., Lowry, K. P., Stout, N. K., Trentham-Dietz, A., diFlorio-Alexander, R. M., Li, C. I., Schnall, M. D., Onega, T., Sprague, B. L.. Association of Digital Breast Tomosynthesis vs Digital Mammography With Cancer Detection and Recall Rates by Age and Breast Density. JAMA Oncol; 2019.</li> <li>19. Wallis MG, Moa E, Zanca F, Leifland K, Danielsson M. Two-view and single-view tomosynthesis vs. full-field digital mammography: high-resolution X-ray imaging observer study. Radiology; 2012.</li> <li>20. Paulis LE, Lobbes MB, Lalji UC, Gelissen N, Bouwman RW, Wildberger JE, et al. Radiation exposure of digital breast tomosynthesis using an antiscatter grid compared with full-field digital mammography. Invest Radiol; 2015.</li> </ol> <ol style="list-style-type: none"> <li>a. Calculated as the total number of women with positive screening/overall number of screening examinations</li> <li>b. Cohort studies provided partial diagnostic information. The risk of bias was assessed using an ad-hoc modified QUADAS-2 tool</li> <li>c. Hofvind 2019 was a randomised prospective trial</li> <li>d. Concerns for risk of bias due to reference standard was not blinded to the index tests. Additionally, there was variability in the number of readings, readers' experience and number of readers (i.e. single or double) across studies.</li> <li>e. Downgraded due to scarce number of events</li> <li>f. Hovda Radiology 2019 was included to assess detection rate outcome evaluated in a second round screening.</li> <li>g. Calculated as the number of false positives/overall number of screening examinations - total number of cancers</li> <li>h. Important unexplained heterogeneity (I<sup>2</sup>=97%)</li> <li>i. Calculated as the number of false positives/overall number of screening examinations - total number of cancers</li> <li>j. Wide 95%CI and low number of events</li> <li>k. Radiation exposure is a surrogate outcome of "other cancer related to radiation".</li> <li>l. Results were consistent independently of the technology used (Hologic Selenia Dimensions or Siemens Mammomat Inspiration).</li> <li>m. Doses levels are known to vary (diagnostic reference levels are typically country/region and system specific).</li> </ol>	
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## Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <li>● Very low</li> <li>○ Low</li> <li>○ Moderate</li> <li>○ High</li> <li>○ No included studies</li> </ul>		Due to imprecision and inconsistency of the estimates for the critical outcomes prioritised by the GDG the certainty of the evidence is very low.

## Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <li>● Important uncertainty or variability</li> <li>○ Possibly important uncertainty or variability</li> <li>○ Probably no important uncertainty or variability</li> <li>○ No important uncertainty or variability</li> <li>○ No known undesirable outcomes</li> </ul>	<p><b>Date of last search: April 2016</b></p> <p>No specific studies focusing in DBT were identified. The findings, all from mammography studies (JRC Technical Report PICO 10-11, contract FWC443094012015; available upon request), however, are likely to be generalisable to DBT, as both screening tests are associated with similar desirable and undesirable effects.</p> <p>A systematic review shows that participants in mammography screening programmes place a low value on the psychosocial and physical effects of false positive results and overdiagnosis (JRC Technical Report PICO 10-11, contract FWC443094012015). Women generally consider these undesirable effects acceptable (low certainty). However, these findings are of limited value, mainly given the significant concerns regarding the adequacy of the information provided to women, in order to make an informed decision about participation. Also, acceptability of false positive results is based on studies of participants who had already received a false positive result. Their preference may differ from the general population. Another finding is that breast cancer screening represents a significant burden for some women due to the associated psychological distress and inconvenience.</p> <p>Regarding breast cancer diagnosis, there is very limited data available on women' views. One of the main themes identified in the literature is that people disvalue highly the anxiety caused by delays in the receipt of results of diagnostic procedures, or by a lack of understanding of the tests due to suboptimal communication with physicians (moderate certainty). Also, people have a higher overall preference towards more comfortable, brief diagnostic procedures (moderate certainty).</p>	From the studies reviewed there was not much confidence in the findings and there is, therefore, uncertainty in how much people value the main outcomes. The GDG agreed that the increase in breast cancer detection, as well as the variation in recall rate, and the increase in radiation exposure are likely to be valued very differently by women.

## Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?





JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <li>○ Favors the comparison</li> <li>○ Probably favors the comparison</li> <li>○ Does not favor either the intervention or the comparison</li> <li>● Probably favors the intervention</li> <li>○ Favors the intervention</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>		<p>To help the panel make a decision on the balance of effects, in addition to the criteria above (desirable and undesirable effects and values), and taking into account that most outcomes were diagnostic accuracy ones, the criteria below from the diagnostic framework were considered:</p> <p>1) Test accuracy: how accurate is the test?</p> <p><b>High accuracy due to a high detection rate (true positives), low false positive recall for assessment (false positives), and no relevant increase in interval cancer rate (false negatives)</b></p> <p>2) Desirable effects: how substantial are the desirable anticipated effects?</p> <p><b>Moderate</b></p> <p>3) Undesirable effects: how substantial are the undesirable anticipated effects?</p> <p><b>Small</b></p> <p>4) Certainty of the evidence of test accuracy: what is the overall certainty of the evidence of test accuracy?</p> <p><b>Very low</b></p> <p>5) Certainty of the evidence of test's effects: what is the overall certainty of the evidence for any critical or important direct benefits, adverse effects or burden of the test?</p> <p><b>Low</b></p> <p>6) Certainty of the evidence of management's effects: what is the overall certainty of the evidence of effects of the management that is guided by the test results?</p> <p><b>High from Treatment studies</b></p> <p>7) Certainty of the evidence of test result/management: how certain is the link between test results and management decisions?</p>

		<p><b>High within programs</b></p> <p>8) Certainty of effects: what is the overall certainty of the evidence of effects of the test?</p> <p><b>Very low</b></p> <p>9) How much people value the main outcomes?</p> <p><b>Important uncertainty or variability</b></p> <p>As consensus was not reached, voting was conducted among the GDG members to judge if the balance between desirable and undesirable effects favours the intervention or the comparison: 4 members voted “does not favour either”, <b>9 members voted “probably favours the intervention”</b>, 3 members voted “don’t know” and 1 abstained.</p>
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## Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS																									
<div><div>○ Large costs</div><div>● Moderate costs</div><div>○ Negligible costs and savings</div><div>○ Moderate savings</div><div>○ Large savings</div><div>○ Varies</div><div>○ Don't know</div></div>	<div><div>Cost and resources used</div><table><thead><tr><th>Study</th><th>Screening using DBT</th><th>Screening using DM</th><th>Variation</th><th>Quality</th></tr></thead><tbody><tr><td colspan="5">Cost per screened woman (equipment, examination and reading time)</td></tr><tr><td>1 Cost-consequences trial-based study<sup>1</sup></td><td>Not reported<sup>b</sup></td><td>Not reported<sup>b</sup></td><td>Increase of 8.5 € (8.4–8.6)</td><td><div><div>○○○●</div>MODERATE<sup>a</sup></div></td></tr><tr><td colspan="5">Cost per screened woman (equipment, examination, reading time, and recall assessment if needed)</td></tr><tr><td>1 Cost-consequences trial-based study<sup>1</sup></td><td>Not reported<sup>b</sup></td><td>Not reported<sup>b</sup></td><td>Increase of 6.2 € (4.6–7.9)</td><td><div><div>○○○●</div>MODERATE<sup>a</sup></div></td></tr></tbody></table></div>	Study	Screening using DBT	Screening using DM	Variation	Quality	Cost per screened woman (equipment, examination and reading time)					1 Cost-consequences trial-based study <sup>1</sup>	Not reported <sup>b</sup>	Not reported <sup>b</sup>	Increase of 8.5 € (8.4–8.6)	<div><div>○○○●</div>MODERATE<sup>a</sup></div>	Cost per screened woman (equipment, examination, reading time, and recall assessment if needed)					1 Cost-consequences trial-based study <sup>1</sup>	Not reported <sup>b</sup>	Not reported <sup>b</sup>	Increase of 6.2 € (4.6–7.9)	<div><div>○○○●</div>MODERATE<sup>a</sup></div>	<div><div>Four studies assessing cost and resources used to screen with DBT vs. DM were included (Alsheik2019, Houssami2019, Miglioretti2019, Moger2019). One cost-consequences study (Moger2019) was based on data observed in the To-Be trial from Norway. One cost study (Houssami2019) was based on observational data from a pilot study from Australia. And, two observational studies were performed in the USA.</div><div>The GDG discussed that the resources required for moving from digital mammography to tomosynthesis includes: costs of the technology, capacity for data storage, and additional time for radiologists to read tomosynthesis images. However, these costs are expected to reduce in the future. Besides, these costs vary depending on the country context. In addition, the evidence is not conclusive regarding potential savings that may occur with DBT due to a reduced recall rate. Therefore, extra costs mentioned above (equipment, additional radiologists time, etc) would probably not be outweighed with a reduction in recall rate.</div></div>
Study	Screening using DBT	Screening using DM	Variation	Quality																							
Cost per screened woman (equipment, examination and reading time)																											
1 Cost-consequences trial-based study <sup>1</sup>	Not reported <sup>b</sup>	Not reported <sup>b</sup>	Increase of 8.5 € (8.4–8.6)	<div><div>○○○●</div>MODERATE<sup>a</sup></div>																							
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	<b>Use of additional DM in recalled women</b>				
	2 Cost studies <sup>1,2</sup>	<u>Norway</u>  81.4% (n= 403 / 495) of recalls had a DM	<u>Norway</u>  82.2% (n= 514 / 625) of recalls had a DM	Non-significant decrease (1.2%) in the use of DM in recalled women	 LOW <sup>c,d</sup>
		<u>USA</u>  The DBT group was less likely to have a DM as workup			
	<b>Use of additional DBT in recalled women</b>				
	1 Cost-consequences trial-based study <sup>1</sup>	11.5% (n= 57 / 495) of recalls had a DBT	23.2% (n= 145 / 625) of recalls had a DBT	Decrease of 11.7% in the use of DBT in recalled women	 MODERATE <sup>a</sup>
	<b>Use of additional Ultrasound (US) in recalled women</b>				
	1 Cost-consequences trial-based study <sup>1</sup>	96.4% (n= 477 / 495) of recalls had an US	97.9% (n= 612 / 625) of recalls had an US	Non-significant decrease of 1.5% in the use of US in recalled women	 MODERATE <sup>a</sup>
	<b>Use of biopsy in recalled women</b>				
	2 Cost studies <sup>1,2</sup>	<u>Norway</u>  52.3% (n= 259 / 495) of recalls had a biopsy	<u>Norway</u>  43.7% (n= 273/625) of recalls had a biopsy	Increase of 4.5% to 8.6% in the use of biopsy in recalled women	 LOW <sup>c</sup>
		<u>USA</u>  16.3% (n= 2,822/17,165) of recalls had a biopsy	<u>USA</u>  11.8% (n= 1,708/14,415) of recalls had a biopsy		

As consensus was not reached, voting was conducted among the GDG members to judge how large are the resources required: **15 members voted “moderate costs”**, 1 member voted “negligible costs and savings” and 1 abstained

As consensus was not reached, voting was conducted among the GDG members to judge how large are the resources required: **15 members voted “moderate costs”**, 1 member voted “negligible costs and savings” and 1 abstained

Reading time per screen mammography				
1 Pilot prospective trial <sup>3</sup>	67 seconds (interquartile range 46 – 105)	16 seconds (interquartile range 10 – 29)	Increase of 51 seconds per mammogram	⊗⊗⊗○ MODERATE <sup>e,f</sup>
Reading time per double reading of mammography				
1 Cost-consequences trial-based study <sup>1</sup>	132 (SD 91) seconds	79 (SD 94) seconds	Increase of 53 seconds per double reading	⊗⊗⊗○ MODERATE <sup>a</sup>
Time of consensus				
1 Cost-consequences trial-based study <sup>1</sup>	170 (SD 106) seconds	124 (SD 124) seconds	Increase of 46 seconds per consensus	⊗⊗⊗○ MODERATE <sup>a</sup>
Impact of reading volume on the recall rate				
1 Observational study <sup>4</sup>	<p>Regardless of reading volume in two years, the recall rate remained lower with DBT:</p> <p><u>400–799 studies</u>: OR = 0.80 (95% CI: 0.75, 0.85)</p> <p><u>800–1199 studies</u>: OR = 0.81 (95% CI: 0.76, 0.87)</p> <p><u>1200–1599 studies</u>: OR = 0.78 (95% CI: 0.73, 0.84)</p> <p><u>1600–2000 studies</u>: OR = 0.81 (95% CI: 0.75, 0.88)</p>		No impact of reading volume on the recall rate	⊗⊗○○ LOW <sup>g,h</sup>

DBT: Digital Breast Tomosynthesis. €: Euros. \$: US Dollar. QALY: Quality adjusted life years.

#### Explanations

a. There are concerns with regards to indirectness due to the study was conducted in Norway and its results may not be applicable to other European countries. There are not concerns regarding risk of bias, imprecision or inconsistency.

b. The cost per screened woman was not reported. However, it was reported that 16% of the increase was due to the



	<p>additional cost of the DBT equipment, 37% to storage requirements, 12% to connectivity, 19% to additional examination time and 16% to additional reading times.</p> <p>c. Serious indirectness since one of the studies was performed in the USA and the other is from Norway.</p> <p>d. Serious imprecision since numerical data and confidence interval were not shown in the study performed in the USA, and the difference was not statistically significant in the study from Norway.</p> <p>e. Serious indirectness. Study performed in Australia. The results might not be directly applicable to European countries.</p> <p>f. Not concerns regarding imprecision. Data was obtained from more than 20,000 screen readings performed in one year.</p> <p>g. Large prospective study including 106,126 DBT and 221,248 DM examinations in 271,362 women (mean age, 57.5 years) from 2010 to 2017 that were interpreted by 104 radiologists from 53 facilities in the Breast Cancer Surveillance Consortium.</p> <p>h. Very serious indirectness. One single study performed in the USA. The results might not be applicable to European countries.</p> <p><b>References</b></p> <ol style="list-style-type: none"> <li>1. Moger TA, et al. Cost differences between digital tomosynthesis and standard digital mammography in a breast cancer screening programme: results from the To-Be trial in Norway. The European journal of health economics: HEPAC: health economics in prevention and care. 2019.</li> <li>2. Alsheik N, et al. Comparison of Resource Utilization and Clinical Outcomes Following Screening with Digital Breast Tomosynthesis Versus Digital Mammography: Findings From a Learning Health System. Acad Radiol. 2019; 26(5): 597-605.</li> <li>3. Houssami N, et al. Pilot trial of digital breast tomosynthesis (3D mammography) for population-based screening in BreastScreen Victoria. The Medical journal of Australia. 2019.</li> <li>4. Miglioretti DL, et al. Digital Breast Tomosynthesis: Radiologist Learning Curve. Radiology. 2019; 291(1): 34-42.</li> </ol>	
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## Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <li>○ Very low</li> <li>● Low</li> <li>○ Moderate</li> <li>○ High</li> <li>○ No included studies</li> </ul>	<p>The certainty of the evidence is <b>moderate</b> regarding <b>cost per screened women, use of additional DBT, ultrasound, and biopsy in recalled women, reading time per mammogram, reading time of double reading, and time of consensus</b> since there are not concerns regarding risk of bias, imprecision or inconsistency. There are concerns with regards to indirectness due to the studies were conducted in Norway, Australia, or the USA and its results may not be directly applicable to all European countries.</p> <p>The certainty of the evidence is <b>low</b> regarding the <b>use of additional diagnostic mammography</b> due to indirectness since one of the studies was performed in the USA and the other in Norway. There is also serious imprecision since numerical data and confidence interval were not shown in the study performed in the USA, and the difference was not statistically significant in the study from Norway.</p> <p>The certainty of the evidence is <b>low</b> regarding <b>the impact of reading volume on the recall rate</b> due to serious indirectness since the evidence is from one single study performed in the USA.</p>	

## Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <li>○ Favors the comparison</li> <li>● Probably favors the comparison</li> <li>○ Does not favor either the intervention or the comparison</li> <li>○ Probably favors the intervention</li> <li>○ Favors the intervention</li> <li>○ Varies</li> <li>○ No included studies</li> </ul>	<p>One cost-effectiveness study performed in the US (Lowry2019) reported an ICER of \$195,026 to \$270,135 per QALY.</p>	<p>One cost-effectiveness study was performed to project the long-term impact of DBT compared to DM for breast cancer screening in the USA. Three Cancer Intervention and Surveillance Modelling Network (CISNET) model simulated women aged ≥40 years undergoing breast cancer screening with either DBT or DM. The time horizon was from 2011 to lifetime. Analyses simulate a 4% increase in sensitivity, which is similar to the results observed in the evidence of effects. However, these results were not obtained from European data since they were from Medicare tariffs. Costs and utilities were discounted at 3% annually.</p> <p>ICERs ranged from USD 195 026- USD 270 135/QALY for DBT relative to DM. When assuming 4% higher DBT sensitivity, ICERs decreased to USD 130 533-USD 156 624/QALY. ICERs were sensitive to DBT costs, decreasing to USD 78 731-USD 168 883 and USD 52 918-USD 118 048 when the additional cost of DBT was reduced to USD 36 and USD 26 (from baseline of USD 56), respectively.</p>

Study	Incremental cost per 1000 women	Incremental effect per 1000 women	ICER	Quality
ICER per QALY				
1 cost-effectiveness CISNET model study	400,000 to 450,000 \$ (Lifetime horizon)	1.97 to 3.27 QALY (Lifetime horizon)	\$195,026 to \$270,135 / QALY	⊕⊕⊕ LOW <sup>a 1-3</sup>

ICER: Incremental cost-effectiveness ratio.  
QALY: Quality adjusted life years.  
\$: US Dollar.

1. No serious risk of bias. Markov model study with low risk of bias.
2. Serious indirectness. One single study performed in the USA<sup>a</sup>. The results might not be directly applicable to European countries.
3. Serious imprecision. ICERs ranged from \$195,026-\$270,135/QALY for DBT relative to DM. This variation was driven by differences in the sensitivity of the test, which varies according to age and breast density. For instance, DBT Sensitivity in 40-49 years women with dense breast was 75% to 84%. When assuming 4% higher DBT sensitivity, ICERs decreased to \$130,533-\$156,624/QALY. ICERs were sensitive to DBT costs, decreasing to \$78,731-\$168,883 and \$52,918-\$118,048 when the additional cost of DBT was reduced to \$36 and \$26 (from baseline of \$56), respectively.

**Reference**

a) Lowry KP, et al. Long-term Outcomes and Cost-effectiveness of Breast Cancer Screening with Digital Breast Tomosynthesis in the United States. J Natl Cancer Inst. 2019 Sep 10.

## Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <li>○ Reduced</li> <li>○ Probably reduced</li> <li>○ Probably no impact</li> <li>○ Probably increased</li> <li>○ Increased</li> <li>● Varies</li> <li>○ Don't know</li> </ul>	<p><b>Date of last search: April 2016</b></p>	<p>The GDG felt that within screening programmes there may be policy decisions to restrict the programme if there are increased costs and the screening programme is unable to fund universal participation. This could have an influence on equity in either direction.</p>

## Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <li>○ No</li> <li>○ Probably no</li> <li>○ Probably yes</li> <li>○ Yes</li> <li>● Varies</li> <li>○ Don't know</li> </ul>	<p><b>Date of last search: April 2016</b></p> <p>No specific studies focusing on DBT were identified. The findings, all from DM studies, however, are likely to be generalisable to DBT, as both (DBT and DM) are associated with similar desirable and undesirable effects.</p> <p>However, a systematic review (JRC Technical Report PICO 16-17, contract FWC443094032016; available upon request) found the following barriers associated with breast cancer screening with DM: (a) lack of knowledge and misperceptions regarding preventive medicine and breast health (high certainty of evidence), (b) poor communication skills of healthcare providers (high certainty of evidence), (c) poor accessibility to breast screening, especially among women with disabilities (high certainty of evidence), (d) fear and stress related to the procedure and the possibility of cancer diagnosis (high certainty of evidence), (e) pain and discomfort during the procedure (moderate certainty of evidence), (f) embarrassment and shyness during the procedure (moderate certainty of evidence), (g) lack of support and encouragement from family members, caregivers and social network (moderate certainty of evidence), (h) lack of information regarding the available resources (low certainty of evidence) and (i) low prioritisation of breast cancer screening (low certainty of evidence). Women and relevant stakeholders expressed similar opinions.</p>	<p><u>Participants:</u> There is likely variability in acceptability for women. If there is a higher radiation dose, women may be more concerned. Additional compression time for the test and/or additional compressions might be necessary depending on the manufacturer of the device. Women who come for screening may be concerned that if they only have DM, and are not offered DBT, they are not getting the screening technology with the highest detection rate. Women may appreciate the increased confidence in the screening result if there is higher detection of cancers with DBT compared to DM. Participation rates in the trials reviewed are high, which may indicate their general acceptability of DBT.</p> <p><u>Radiologists:</u> DBT may be preferred by radiologists reading screening tests because their certainty in the diagnosis may be higher when using DBT than when using DM.</p> <p><u>Policymakers:</u> In settings with universal healthcare coverage, for directors of hospitals and screening programmes, it may not be an acceptable intervention, despite the increased detection capability, because there will likely be increased costs.</p>

## Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <li>○ No</li> <li>○ Probably no</li> <li>○ Probably yes</li> <li>○ Yes</li> <li>● Varies</li> <li>○ Don't know</li> </ul>	<p><b>Date of last search: April 2016</b></p>	<p>The GDG felt that in contexts where there are the resources to support this and where there is access to new technologies that are capable of DBT, it is feasible. For other countries without the technology and resources to support this, it may not be feasible. In addition, although DBT requires some extra training for radiologists, this was not seen by GDG as a major barrier to implementation.</p> <p>The need to establish quality standards for synthesised 2D imaging for implementation was mentioned by the GDG.</p>

## SUMMARY OF JUDGEMENTS

CRITERIA	PREVIOUS VERSION JUNE 2018	UPDATE JANUARY 2020
PROBLEM	Yes	The same as original
DESIRABLE EFFECTS	Don't know	Moderate
UNDESIRABLE EFFECTS	Varies	Small
CERTAINTY OF EVIDENCE	Very low	The same as original
VALUES	Important uncertainty or variability	The same as original
BALANCE OF EFFECTS	Don't know	Probably favors the intervention
RESOURCES REQUIRED	Moderate costs	Moderate costs
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	No included studies	Low
COST EFFECTIVENESS	No included studies	Probably favors the comparison
EQUITY	Varies	The same as original
ACCEPTABILITY	Varies	The same as original
FEASIBILITY	Varies	The same as original

## TYPE OF RECOMMENDATION

Strong recommendation against the intervention ○	Conditional recommendation against the intervention ○	Conditional recommendation for either the intervention or the comparison ●	Conditional recommendation for the intervention ○	Strong recommendation for the intervention ○
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# CONCLUSIONS

## Recommendation

For asymptomatic women with an average risk of breast cancer the ECIBC's Guidelines Development Group (GDG) suggests using either digital breast tomosynthesis (DBT) or digital mammography (DM) in the context of an organised screening programme (conditional recommendation, very low certainty of the evidence).

## Justification

### Overall justification

The GDG agreed that the balance of benefits and harms is probably in favour of DBT but the certainty of the evidence is very low.

New studies reporting data on resource use and cost effectiveness seem to favour DM in several settings.

There is important uncertainty and variability in how much people will value the main outcomes.

### Detailed justification

#### *Desirable Effects*

The desirable effects considered for this recommendation are breast cancer detection and false positive recall for assessment reduction. The GDG agrees that DBT has higher cancer detection rate. The detected cancers are not all desirable, but are not more than 206/100,000. A proportion of the increased detection, not known conclusively, will probably lead to overdiagnosis, which is considered an undesirable effect. The inconsistency of the results of interval cancer (not fitting with the expected direction of the results) suggests that a large proportion of detected cancers may be indeed overdiagnosis. Some members of the panel questioned if the observation of increased interval cancers is indeed creating an inconsistency because of the biology being possibly different. The GDG also emphasizes that research on the direct outcomes on breast cancer stage at diagnosis and breast cancer mortality are not yet available.

#### *Undesirable Effects*

The undesirable effects considered for this recommendation are: interval breast cancer, overdiagnosis, radiation exposure. The GDG judged that they are small.

#### *Balance of effects*

Considering the desirable and undesirable effects, the certainty of the evidence available and the values of the main outcome, the GDG judged that the balance probably favours DBT.

#### *Resources required*

Considering a new study for this updating, the GDG judged that there are additional moderate costs required with DBT compared to DM. The certainty of the evidence for this study is LOW.

#### *Cost effectiveness*

One new study from the US was included for cost-effectiveness. The results of the incremental cost-effectiveness ratio per QALY value (ICER of \$195,026 to \$270,135 per QALY) is above common willingness to pay thresholds. Despite the indirectness of this study, being US data, the GDG judged that the cost-effectiveness probably favours DM.

## Subgroup considerations

Women with high mammographic breast density are likely to benefit most from the increased detection capability of DBT. The GDG developed a specific recommendation for this subgroup on the use of DBT vs DM in the context of an organised screening programme.

## Implementation considerations

- Evidence will be emerging from ongoing and newly starting screening trials on tomosynthesis that may influence the current recommendations.
- The GDG identified variability in the quality of DBT machines currently available and their methods of capturing images. The Malmö study used a machine that has a wide-angle form of DBT image capture and may result in different breast cancer detection rates and also used a single view DBT format.
- The GDG notes that new quality assurance standards of technologies and screening programmes must be considered in choosing DBT over DM. The GDG emphasised that specific standards for synthesised 2D imaging, and their use in comparison to previously captured DM screening images will be necessary in order to implement this recommendation.
- There will be significantly increased data storage needs for screening programmes using DBT as compared to DM.
- The GDG noted that health equity in access to screening should be considered for countries choosing DBT-based screening programmes, due to different resource settings and the capacity for different countries to be able to pay for DBT over DM which may lead to increased health inequities.

## Monitoring and evaluation

- Quality control/standardisation of the technology for better image storage should be undertaken.
- Standards should be developed for the image quality of tomosynthesis.
- Screening monitoring and evaluation programs should be able to distinguish test done with DBT and with DM, stratified standard indicators should be computed.

## Research priorities

- Evidence will be emerging from ongoing and newly starting screening trials on tomosynthesis that may influence the current recommendations.
- Collecting evidence relevant to implementation challenges of DBT-based screening programmes. To do that, screening programs should be able to produce stratified indicators (see monitoring and evaluation considerations)
- Research regarding distribution of tumour grade/biology/prognostic measures in the additionally detected cancers might help in clarifying the amount of possible overdiagnosis.
- Further research is needed to build the evidence on benefits and harms of DBT vs DM through comparison of direct outcomes, including impacts of interval cancer incidence, stage of breast cancer at detection and mortality reduction.
- Research investigating the cost-effectiveness of a breast cancer screening programme using DBT is needed to inform decision-making on breast cancer screening.
- Research is needed to define the quality parameters that need to be fulfilled for DBT-based breast cancer screening programmes to be implemented.