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

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QUESTION	
Should tailored screening with digital breast tomosynthesis in addition to digital mammography vs. digital mammography alone be used for early detection of breast cancer in asymptomatic women with high mammographic breast density in organised screening programmes?	
POPULATION:	asymptomatic women with high mammographic breast density
INTERVENTION:	tailored screening with digital breast tomosynthesis (DBT) in addition to digital mammography
COMPARISON:	digital mammography alone
MAIN OUTCOMES:	Breast cancer mortality, breast cancer stage, interval breast cancer, breast cancer detection, recall for assessment, mastectomy, provision of chemotherapy, 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:	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) (1). Screening programmes play a crucial role in early breast cancer detection; they can increase the chance of survival as well as reduce disease specific mortality. Mammography remains the best method to detect breast cancer in an early stage. However, mammography has a lower sensitivity and specificity in women with radiologically dense breasts (2). The use of different screening strategies including other imaging modalities, in addition to mammography, might improve early detection of breast cancer in women with higher mammographic breast density. Digital breast tomosynthesis (DBT) is a pseudo-3D imaging technique based on a series of low dose images of the breast from different angles and therefore has the potential to overcome the tissue superposition issue thus improving detection of breast lesions ((3), (4)). 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, tomosynthesis has been proposed to be used in addition to a 2D image (either done with DBT or mammography). This allows the comparison with previous mammographies that usually are available only in 2D and speeds up the process of interpreting images. 2D images can be obtained either through additional exposures, thus obtaining a regular DM, or through a software that allows the construction of synthesised 2D images. In this question, we compare DBT in addition to DM, regardless if synthetic 2D is available, with DM alone.

	Dense breast tissue is made up mostly of ductal structures and connective tissue, while non-dense breast tissue is mostly fatty. Breast density is seen only on mammograms. Due to lack of evidence using the breast density BIRADS (Breast Imaging Report and Database System) classification edition 5, the GDG decided to base the recommendation on the previous breast density BIRADS classification assuming that the results are comparable for the two versions. Therefore, for the purpose of this clinical guideline, one of the following criteria classifies as dense breast: (1) BIRADS category scale: III-IV score. (2) For studies reporting quantitative percent density, a dense area of 50% as roughly equivalent to BIRADS III-IV (BIRADS III would be 50-75% and BI-RADS IV would be greater than 75%). (3) For those studies reporting the old Wolfe categories: BIRADS III would be P2 and BIRADS IV corresponding DY. **This recommendation was updated in January 2020. Previous versions of the recommendation are available on the ECIBC website.**
CONFLICT OF INTEREST:	Management of Conflicts of Interest (CoI): CoIs for all Guidelines Development Group (GDG) members were assessed and managed by the European Commission Joint Research Centre (JRC) following an established procedure in line with the institutional rules. GDG member participation in the development of the recommendations was restricted, according to CoI disclosure. Consequently, for this particular question, the following GDG member was recused from voting: Axel Gräwingholt. Miranda Langendam, as external expert, was also not allowed to vote, according to the ECIBC rules of procedure. For more information please visit https://healthcare-quality.jrc.ec.europa.eu/discover-ecibc/governance/ecibc-working-groups

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	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) (1). Breast cancer screening with additional screening modalities might improve the early detection of breast cancer in women with mammographically dense breast tissue. Although digital mammography (DM) has become an accepted standard of care in screening and diagnosis of breast cancer, up to 30% of breast cancers are not detected by standard screening (2). This percentage is even higher in women with dense breasts and in women under 50 years of age (2). In women with dense breasts, risk of breast	The GDG prioritised this question for the ECIBC.

cancer is increased (5), and cancers may be masked and missed on mammography due to superposition of tissue; as a result, there might be an excess of late stage disease (stages II and III) (6).

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT

- ○ Trivial
- ○ Small
- ● Moderate
- ○ Large
- ○ Varies
- ○ Don't know

RESEARCH EVIDENCE

Date of last search: January 2020

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects[*] (95% CI)	
				Risk with digital mammography alone	**Risk difference with tailored screening with digital breast tomosynthesis (DBT) in addition to digital mammography**
Breast cancer detection	414286 (8 observational studies)[1,2,3,4,5,6,7,8,9,a,b]	⨁◯◯◯ VERY LOW[c,d]	**RR 1.36** (1.25 to 1.48)[e]	Study population	
				434 per 100,000[b]	**156 more per 100,000** (109 more to 208 more)
Breast cancer detection (invasive lesions)	8545 (2 observational studies)[7,9,a]	⨁◯◯◯ VERY LOW[f,g]	**RR 1.48** (1.28 to 1.70)	Study population	
				344 per 100,000	**165 more per 100,000** (96 more to 241 more)
Adverse effects (false positive)	30502 (4 observational studies)[1,10,11,2,5,a,h]	⨁⨁◯◯ LOW[d,i,j]	**RR 1.07** (0.86 to 1.34)[k]	Study population	
				8,688 per 100,000	**608 more per 100,000** (1,216 fewer to

ADDITIONAL CONSIDERATIONS

Update 012020

The GDG made the same considerations as for women without high mammographic breast density.

In this update the panel decided to include unpaired studies for all outcomes. The 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 additional to 2D mammography versus 2D mammography), reported data for all outcomes. Results from both types of design were consistent across outcomes, and data was therefore pooled.

The GDG considered all breast cancers detected a desirable effect and overdiagnosis was considered a harm. However, it is unclear how much overdiagnosis there is.

In the case of women with high mammographic breast density, the baseline risk of breast cancer is higher. The higher the lifetime risk is, the lower the concern for overdiagnosis. Therefore, in this population there is a higher proportion of women who have cancer that matters, and a lower proportion with women who are overdiagnosed. Therefore, the GDG agreed that, proportionately, the benefits would be moderate.

					2,954 more)
Recall for assessment	30844 (4 observational studies)[1,12,3,4,5,a,l]	⊕⊕◯◯ LOW[d,i,m]	**RR 1.11** (0.89 to 1.39)[n]	Study population	
				9,486 per 100,000	**1,044 more per 100,000** (1,044 fewer to 3,700 more)
Interval breast cancer	38825 (1 observational study)[8,a]	⊕◯◯◯ VERY LOW[f,o]	**RR 1.58** (0.75 to 3.31)	Study population	
				76 per 100,000	**44 more per 100,000** (19 fewer to 175 more)
Breast cancer mortality - not reported	-	-	-		
Breast cancer stage - not reported	-	-	-		
Rate of mastectomies - not reported	-	-	-		
Provision of chemotherapy - not reported	-	-	-		
Adverse effects - not reported	-	-	-		

1. Ciatto S, Houssami N,Bernardi D,Caumo F,Pellegrini M,Brunelli S,et al. Integration of 3D digital mammography with tomosynthesis for population breast-cancer screening (STORM): a prospective comparison study. The Lancet Oncology; 2013.
2. Bernardi D, Macaskill P,Pellegrini M,Valentini M,Fantò C,Ostillio 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. 3. Lång K, Nergården M,Andersson I,Rosso A,Zackrisson S. False positives in breast cancer screening with one-view breast tomosynthesis: An analysis of findings leading to recall, work-up and biopsy rates in the Malmö Breast Tomosynthesis Screening Trial. Eur Radiol; 2016. 4. Lång K, Andersson I,Rosso A,Tingberg A,Timberg P,Zackrisson S. Performance of one-view breast tomosynthesis as a stand-alone breast cancer screening modality: results from the Malmo Breast Tomosynthesis Screening Trial, a population-based study. Eur Radiol; 2016 . 5. Osteräs BH, Martinsen ACT,Gulien R,Skaane P. Digital mammography versus breast tomosynthesis: impact of breast density on diagnostic performance in population-based screening. Radiology; 2019. 6. Alsheik NH, Dabbous F,Pohlman SK,Troeger KM,Gliklich RE,Donadio GM,Su Z,Menon V,Conant EF.. 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. 7. McCarthy AM, Kontos D,Synnestvedt M,Tan KS,Heitjan DF,Schnall M,Conant EF.. Screening outcomes following implementation of digital breast tomosynthesis in a general-population screening program.. J Natl Cancer Inst.; 2014. 8. Conant EF, Barlow WE,Herschorn SD,Weaver DL,Beaber EF,Tosteson ANA,Haas JS,Lowry KP,Stout NK,Trentham-Dietz A,diFlorio-Alexander RM,Li CI,Schnall MD,Onega T,Sprague BL, , . Association of Digital Breast Tomosynthesis vs Digital Mammography With Cancer Detection and Recall Rates by Age and Breast Density.. JAMA Oncol.; 2019. 9. Rafferty E, Durand M,Conant E,Copit DS,Friedewald S,Plecha D,Miller D. Breast cancer screening using tomosynthesis and digital mammography in dense and nondense breasts. JAMA; 2016. 10. Skaane P, Bandos AI,Eben EB,Jebsen IN,Krager M,Haakenaasen U,et al.. Two-view digital breast tomosynthesis screening with synthetically reconstructed projection images: comparison with digital breast tomosynthesis with full-field digital mammographic images. Radiology ; 2014. 11. Skaane P, Bandos AI,Gullien R,et al.. Prospective trial comparing full-field digital mammography (FFDM) vs. combined FFDM and tomosynthesis in a population-based screening programme using independent double reading with arbitration.. Eur Radiol; 2013. 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. a. Cohort studies provided partial diagnostic information from paired analysis. The risk of bias was assessed using an ad-hoc modified QUADAS-2 tool. b. Median or mean of the control group of the included studies as appropriate	

	unless otherwise specified. c. The results shows imprecise estimates going from relevant decrease to increase on the breast cancer detection rate. d. There was variability in the number of readings, readers' experience and number of readers (i.e. single or double) across studies. e. STORM-2 additionally reports cancer detection rate of DBT + synthetic mammography, RR: 1.80 (95%CI: 1.04 to 3.10). f. Imprecise estimates due to low number of events in both arms. g. The included study used an unpaired design. Participants might differ by relevant non-measured characteristics. The reader experience for DBT was not clearly reported. h. A pooled analysis of the unpaired diagnostic studies (Alsheik 2018, Conant 2019, McCarthy 2014) showed an inconsistent result (RR 0.76; 95% CI 0.79 to 1.00). We presented here only the estimates from the lower RoB studies (paired design). i. There was important remaining heterogeneity on the effect size across studies among the paired studies. j. The results shows imprecise estimates going from relevant decrease to increase on the false positive rate. k. STORM-2 additionally reports false positive rate of DBT + synthetic mammography, RR: 1.53 (95%CI: 1.20 to 1.96). l. A pooled analysis of the unpaired diagnostic studies (Alsheik 2018, Conant 2019, McCarthy 2014) showed an inconsistent result (RR 0.78; 95% CI 0.72 to 0.85). We presented here only the estimates from the lower RoB studies (paired design). m. The results shows imprecise estimates going from relevant decrease to increase on the recall rate. n. STORM-2 additionally reports recall rate of DBT + synthetic mammography, RR: 1.50 (95%CI: 1.20 to 1.87). o. The included study used an unpaired design. Participants might differ by relevant non-measured characteristics. The minimum reader experience for DBT might be insufficient (50 previous screening exam).	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	**Date of last search: January 2020**	Additional radiation in the intervention (combined DBT with mammography) that is at least double compared to mammography alone. The undesirable effects are overdiagnosis in these women that is proportionally lower than in women without high breast density. Additionally, there is a greater number of false positives (608 more per 100 000). The GDG agreed, therefore, that the undesirable effects would be moderate.

Outcomes	№ of participants (studies)	Certainty of the evidence	Relative effect	Anticipated absolute effects* (95% CI)

	Follow up	(GRADE)	(95% CI)	Risk with digital mammography alone	Risk difference with tailored screening with digital breast tomosynthesis (DBT) in addition to digital mammography
Breast cancer detection	414286 (8 observational studies)[1,2,3,4,5,6,7,8,9,a,b]	⊕◯◯◯ VERY LOW[c,d]	**RR 1.36** (1.25 to 1.48)[e]	Study population 434 per 100,000[b]	 **156 more per 100,000** (109 more to 208 more)
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Recall for assessment	30844 (4 observational studies)[1,12,3,4,5,a,l]	⊕⊕◯◯ LOW[d,i,m]	**RR 1.11** (0.89 to 1.39)[n]	Study population 9,486 per 100,000	 **1,044 more per 100,000** (1,044 fewer to 3,700 more)
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Breast cancer mortality - not reported	-	-	-		
Breast cancer stage - not reported	-	-	-		
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Provision of chemotherapy - not reported	-	-	-		
Adverse effects - not reported	-	-	-		

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	Z,Menon V,Conant EF.. 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. 7. McCarthy AM, Kontos D,Synnestvedt M,Tan KS,Heitjan DF,Schnall M,Conant EF.. Screening outcomes following implementation of digital breast tomosynthesis in a general-population screening program.. J Natl Cancer Inst.; 2014. 8. Conant EF, Barlow WE,Herschorn SD,Weaver DL,Beaber EF,Tosteson ANA,Haas JS,Lowry KP,Stout NK,Trentham-Dietz A,diFlorio-Alexander RM,Li CI,Schnall MD,Onega T,Sprague BL, , . Association of Digital Breast Tomosynthesis vs Digital Mammography With Cancer Detection and Recall Rates by Age and Breast Density.. JAMA Oncol.; 2019. 9. Rafferty E, Durand M,Conant E,Copit DS,Friedewald S,Plecha D,Miller D. Breast cancer screening using tomosynthesis and digital mammography in dense and nondense breasts. JAMA; 2016. 10. Skaane P, Bandos AI,Eben EB,Jebsen IN,Krager M,Haakenaasen U,et al.. Two-view digital breast tomosynthesis screening with synthetically reconstructed projection images: comparison with digital breast tomosynthesis with full-field digital mammographic images. Radiology ; 2014. 11. Skaane P, Bandos AI,Gullien R,et al.. Prospective trial comparing full-field digital mammography (FFDM) vs. combined FFDM and tomosynthesis in a population-based screening programme using independent double reading with arbitration.. Eur Radiol; 2013. 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. a. Cohort studies provided partial diagnostic information from paired analysis. The risk of bias was assessed using an ad-hoc modified QUADAS-2 tool. b. Median or mean of the control group of the included studies as appropriate unless otherwise specified. c. The results shows imprecise estimates going from relevant decrease to increase on the breast cancer detection rate. d. There was variability in the number of readings, readers' experience and number of readers (i.e. single or double) across studies. e. STORM-2 additionally reports cancer detection rate of DBT + synthetic mammography, RR: 1.80 (95%CI: 1.04 to 3.10). f. Imprecise estimates due to low number of events in both arms. g. The included study used an unpaired design. Participants might differ by relevant non-measured characteristics. The reader experience for DBT was not clearly reported. h. A pooled analysis of the unpaired diagnostic studies (Alsheik 2018, Conant 2019, McCarthy 2014) showed an inconsistent result (RR 0.76; 95% CI 0.79 to 1.00). We presented here only the estimates from the lower RoB studies (paired design). i. There was important remaining heterogeneity on the effect size across	

	studies among the paired studies. j. The results shows imprecise estimates going from relevant decrease to increase on the false positive rate. k. STORM-2 additionally reports false positive rate of DBT + synthetic mammography, RR: 1.53 (95%CI: 1.20 to 1.96). l. A pooled analysis of the unpaired diagnostic studies (Alsheik 2018, Conant 2019, McCarthy 2014) showed an inconsistent result (RR 0.78; 95% CI 0.72 to 0.85). We presented here only the estimates from the lower RoB studies (paired design). m. The results shows imprecise estimates going from relevant decrease to increase on the recall rate. n. STORM-2 additionally reports recall rate of DBT + synthetic mammography, RR: 1.50 (95%CI: 1.20 to 1.87). o. The included study used an unpaired design. Participants might differ by relevant non-measured characteristics. The minimum reader experience for DBT might be insufficient (50 previous screening exam).	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies		The GDG members agreed the overall certainty of evidence was very low.

Values

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes	No specific studies focusing in DM+DBT were identified. The findings are all from mammography studies (JRC Technical Report PICO 10-11, contract FWC443094012015; available upon request). However, the findings are likely to be generalisable DBT, as both screening tests are associated with similar desirable and undesirable effects (e.g. false positive findings or overdiagnosis). 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 confidence*). **Date of last search: April 2016**	The GDG members discussed that, there is also evidence of psychological adverse effects of screening and false positive recall. These effects, however, would apply to both the intervention and comparison in this case. There is no clear evidence on how these psychological effects might differ with the imaging technology. The GDG members agreed that "important uncertainty or variability" exists.

Balance of effects

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		In this update the benefits were considered less promising or smaller than anticipated. The detection rate, with information from the additional studies considered, was worse than in the original question and overdiagnosis was considered less probable. Therefore, the GDG agreed that, considering also the very low certainty of the evidence and the important uncertainty or variability in how people value the main outcomes, the balance does not favour either the intervention or the comparison.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Date of last search: January 2020** No new evidence was included.	As no new evidence was included, the GDG members used the same judgement made in the previous version of this criterion, using previous considerations: Indirect evidence from one cost-effectiveness study performed in the USA in women with dense breasts was considered: For a cohort of 1 000 women in the US, the lifetime costs (3% discounted) would be USD 4 440 for the combined screening, and it would be USD 4 091 for mammography screening alone. In this study, the cost of adjunct tomosynthesis was USD 50 (all costs were in 2013 in value (Lee CI, 2015). This modelling study assumed a reduction in false positive rates with DBT in contrast to some of the results reported for undesirable effects above. The GDG members agreed that costs would be moderate. These costs may include costs of this new technology, capital costs of the machines and the lifetime of the machine, capacity for data storage, and additional time for radiologists to read tomosynthesis images, amongst other factors. Staff cost may vary depending on the country context and these costs are not transferable from one country to another. Despite the savings that may occur with DBT due to a reduced recall rate, the extra costs mentioned above (equipment, additional radiologists time, etc) would probably not be outweighed. However, since the intervention would only apply to a minority with dense breast tissue, the absolute addition in staff costs might be modest. The additional cost will vary according to the proportion of women with sufficiently dense breast tissue to qualify for the intervention. Local and regional level economic analyses are required to

		estimate the cost for the implementation of tomosynthesis.

Certainty of evidence of required resources

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	No new evidence was included	The certainty of the evidence of resource requirements is very low since the included study was based on observational data and it was conducted in the USA. The costs, and resources used may not be applicable to European settings.

Cost effectiveness

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	**Date of last search: January 2020** No new evidence was included.	As no new evidence was included, the GDG members used the same judgement made in the previous version of this criterion, using previous considerations: Substantial differences could be observed across European countries according to their willingness to pay threshold. Based on the evidence provided by (Lee CI, 2015), the incremental cost-effectiveness ratio (ICER) per Quality-Adjusted Life Year (QALY) gained by adding tomosynthesis to digital mammography screening was USD 53 893 (using a 3% discount rate). At a willingness to pay of USD 100 000 per QALY gained, the authors concluded that the biennial combined digital mammography and tomosynthesis screening for US women aged 50 to 74 was cost-effective. However, the GDG members considered that the costs and effects observed in that study (Lee CI, 2015) may not be transferable to European settings.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	No new evidence was included	As no new evidence was included, the GDG members used the same judgement made in the previous version of this criterion, using previous considerations: The GDG felt that within programmes there may be policy decisions to restrict them, if there are increased costs and the programme is unable to fund universal participation.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	No specific studies focusing on tomosynthesis (including synthetic 2D images) were identified. The findings, all from mammography studies, however, are likely to be generalisable to tomosynthesis (including synthetic 2D images) in addition to digital mammography, as both screening tests are associated with similar desirable and undesirable effects (e.g. false positive findings or overdiagnosis). 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 mammography: (*a*) lack of knowledge and misperceptions regarding preventive medicine and breast health (high confidence in evidence), (*b*) poor communication skills of healthcare providers (high confidence in evidence), (*c*) poor accessibility to breast screening, especially among women with disabilities (high confidence in evidence), (*d*) fear and stress related to the procedure and the possibility of cancer diagnosis (high confidence in evidence), (*e*) pain and discomfort during the procedure (moderate confidence in evidence), (*f*) embarrassment and shyness during the procedure (moderate confidence in	*Participants*: There is likely variability in acceptability for women. As there is a higher radiation dose, women may be more concerned. There is additionally a second examination that will take additional time and involve an additional compression for women experiencing the test. However, this may be countered by the knowledge that they are at higher risk due to density, which may render the intervention more acceptable. Women who come for screening may be concerned that if they only have 2D mammography 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 and DM vs DM alone. Participation

	evidence), (*g*) lack of support and encouragement from family members, caregivers and social network (moderate confidence in evidence), (*h*) lack of information regarding the available resources (low confidence in evidence) and (*i*) low prioritisation of breast cancer screening (low confidence in evidence). Women and relevant stakeholders expressed similar opinions. **Date of last search: April 2016**	rates in the trials reviewed are high which may indicate their general acceptability of DBT plus DM vs DM alone. *Radiologists*: DBT may be preferred by radiologists reading screening tests because their certainty in the diagnosis may be higher when using DBT and DM than when using DM alone. *Policy makers*: In settings with universal healthcare coverage, for managers of hospitals and screening programmes, carrying out DBT as well as DM is probably not acceptable because there will likely be increased costs.
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	No new evidence was included.	As no new evidence was included, the GDG members used the same judgement made in the previous version of this criterion, using previous considerations: The GDG members felt that in contexts where the resources are available and where there is access to new technologies that are capable of DBT tailored screening based on breast density, it is feasible. For other countries without the technology and resources, 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. The need to define the quality parameters that need to be fulfilled for implementation of breast cancer screening programmes using DBT was mentioned by the GDG.

SUMMARY OF JUDGEMENTS

CRITERIA	PREVIOUS VERSION APRIL 2016	UPDATE JANUARY 2020
PROBLEM	Yes	Yes
DESIRABLE EFFECTS	Don't know	Moderate
UNDESIRABLE EFFECTS	Varies	Moderate
CERTAINTY OF EVIDENCE	Low	Very low

CRITERIA	PREVIOUS VERSION APRIL 2016	UPDATE JANUARY 2020
VALUES	Important uncertainty or variability	The same as original
BALANCE OF EFFECTS	Probably favors the intervention	Does not favor either the intervention or the comparison
RESOURCES REQUIRED	Moderate costs	Moderate costs
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Very low
COST EFFECTIVENESS	No included studies	No included studies
EQUITY	Varies	The same as original
ACCEPTABILITY	Varies	Varies
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
○	●	○	○	○

CONCLUSIONS

Recommendation

For asymptomatic women, with high mammographic breast density, in the context of an organised screening programme, the ECIBC's Guidelines Development Group (GDG) suggests not implementing tailored screening with both digital breast tomosynthesis (DBT) and digital mammography (DM) (conditional recommendation, very low certainty of the evidence).

Justification

This recommendation was agreed upon by consensus within the GDG with no need for voting.

With the additional studies included in this update, the results show a slightly lower breast cancer detection, so the expected desirable effects are lower now.

Therefore, taking also into consideration the recommendation made for DBT vs. DM, the GDG judged that the additional harm and cost is higher using both tests together than for the comparison of the single technique alone (either DM or DBT) with no known added benefits.

Subgroup considerations

The only subgroup assessed in this recommendation was women with high mammographic breast density.

Implementation considerations

The GDG members felt that information and education for women about dense breasts iscritical. This includes information about limitations or uncertainty about effects of tomosynthesis. For the population here, those with dense breast tissue, it is important that the context of increased risk and lesser accuracy of 2D mammography be explained. The opinion of women on tomosynthesis depends on the quality and impartiality of the education provided to them on the evidence behind this modality for tailored screening, including the limitations of tomosynthesis. Inappropriate worry about radiation dose should be dealt with in case programmes are using the DBT plus DM combination. In general, the GDG believed it is important to educate women and health professionals on the risk of radiation in the context of possible benefits of screening. The GDG members considered that this regimen would involve establishing a baseline, based on breast density, after the first examination, and a cut-off point which determines which women should be offered DBT.

There are currently ongoing trials exploring the automation of breast density measurement. There is a need for improvement in data management and storage for screening organisations. Women will have to attend a breast screening centre that has DBT technology available.

Monitoring and evaluation

Feasibility and acceptability could be assessed in monitoring of programmes. Quality control procedures and quality standards should be further developed. Standards should be developed in particular for the image quality of synthesised 2D images from the tomosynthesis technology.

Research priorities

There is a need for research examining the classification of mammographic breast density and standardization of the classification systems used for breast density, including technology for the automation of the determination of breast density. Research should also aim at establishing the appropriate density threshold for additional imaging.

An optimal combination of screening modalities in women with high breast density should be conducted in the research setting.

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Evidence profile

Healthcare question	Should tailored screening with digital breast tomosynthesis in addition to digital mammography vs. digital mammography alone be used for early detection of breast cancer in asymptomatic women with high mammographic breast density in organised screening programmes?
Date	January 2020
Authors	Guideline Development Group (GDG): Mariangela Autelitano, Bettina Borisch, Mireille Broeders, Xavier Castells, Edoardo Colzani, Jan Daneš, Stephen Duffy, Patricia Fitzpatrick, Markus Follmann, Livia Giordano, Paolo Giorgi Rossi, Axel Gräwingholt, Solveig Hofvind, Lydia Ioannidou-Mouzaka, Susan Knox, Miranda Langendam, Annette Lebeau, Helen Mcgarrigle, Lennarth Nyström, Elsa Pérez Gómez, Cecily Quinn, Holger Schünemann, Alberto Torresin, Ruben Van Engen, Cary Van Landsveld-Verhoeven, Sue Warman, Kenneth Young. Systematic Review team: Carlos Canelo-Aybar, Jessica Beltran, Ingrid Arévalo-Rodríguez, Ignacio Ricci, Ivan Solá, Nieves Plana, Margarita Posso, David Rigau, Pablo Alonso-Coello. JRC Healthcare Quality team: Zuleika Saz-Parkinson, Elena Parmelli
Abbreviations	**CI:** Confidence interval **RR:** Risk ratio

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tailored screening with digital breast tomosynthesis (DBT) in addition to digital mammography	Digital mammography alone	Relative (95% CI)	Absolute (95% CI)		
Breast cancer detection												
8 [1,2,3,4,5,6,7,8,9]	observational studies [a]	serious [b]	not serious	not serious	very serious [c]	none	1071/191834 (0.6%)	966/222452 (0.4%) [d]	**RR 1.36** (1.25 to 1.48) [e]	**156 more per 100,000** (from 109 more to 208 more)	⨁◯◯◯ VERY LOW	CRITICAL
Breast cancer detection (invasive lesions)												
2 [7,9]	observational studies [a]	very serious [f]	not serious	not serious	serious [g]	none	24/5056 (0.5%)	12/3489 (0.3%)	**RR 1.48** (1.28 to 1.70)	**165 more per 100,000** (from 96 more to 241 more)	⨁◯◯◯ VERY LOW	CRITICAL
Adverse effects (false positive)												
4 [1,2,5,10,11]	observational studies [a,h]	serious [b]	serious [i]	not serious	not serious [j]	none	1287/15251 (8.4%)	1325/15251 (8.7%)	**RR 1.07** (0.86 to 1.34) [k]	**608 more per 100,000** (from 1,216 fewer to 2,954 more)	⨁⨁◯◯ LOW	CRITICAL
Recall for assessment												
4 [1,3,4,5,12]	observational studies [a,l]	serious [b]	serious [i]	not serious	not serious [m]	none	1478/15422 (9.6%)	1463/15422 (9.5%)	**RR 1.11** (0.89 to 1.39) [n]	**1,044 more per 100,000** (from 1,044 fewer to 3,700 more)	⨁⨁◯◯ LOW	CRITICAL
Interval breast cancer												
1 [8]	observational studies [a]	very serious [o]	not serious	not serious	very serious [g]	none	10/8393 (0.1%)	23/30432 (0.1%)	**RR 1.58** (0.75 to 3.31)	**44 more per 100,000** (from 19 fewer to	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tailored screening with digital breast tomosynthesis (DBT) in addition to digital mammography	Digital mammography alone	Relative (95% CI)	Absolute (95% CI)		
										175 more)		
Breast cancer mortality - not reported												
-	-	-	-	-	-	-					-	CRITICAL
Breast cancer stage - not reported												
-	-	-	-	-	-	-					-	CRITICAL
Rate of mastectomies - not reported												
-	-	-	-	-	-	-					-	CRITICAL
Provision of chemotherapy - not reported												
-	-	-	-	-	-	-					-	CRITICAL
Adverse effects - not reported												
-	-	-	-	-	-	-					-	CRITICAL

Explanations

a. Cohort studies provided partial diagnostic information from paired analysis. The risk of bias was assessed using an ad-hoc modified QUADAS-2 tool.
b. There was variability in the number of readings, readers' experience and number of readers (i.e. single or double) across studies.
c. The results shows imprecise estimates going from relevant decrease to increase on the breast cancer detection rate.
d. Median or mean of the control group of the included studies as appropriate unless otherwise specified.
e. STORM-2 additionally reports cancer detection rate of DBT + synthetic mammography, RR: 1.80 (95%CI: 1.04 to 3.10).
f. The included study used an unpaired design. Participants might differ by relevant non-measured characteristics. The reader experience for DBT was not clearly reported.
g. Imprecise estimates due to low number of events in both arms.
h. A pooled analysis of the unpaired diagnostic studies (Alsheik 2018, Conant 2019, McCarthy 2014) showed an inconsistent result (RR 0.76; 95% CI 0.79 to 1.00). We presented here only the estimates from the lower RoB studies (paired design).
i. There was important remaining heterogeneity on the effect size across studies among the paired studies.
j. The results shows imprecise estimates going from relevant decrease to increase on the false positive rate.
k. STORM-2 additionally reports false positive rate of DBT + synthetic mammography, RR: 1.53 (95%CI: 1.20 to 1.96).
l. A pooled analysis of the unpaired diagnostic studies (Alsheik 2018, Conant 2019, McCarthy 2014) showed an inconsistent result (RR 0.78; 95% CI 0.72 to 0.85). We presented here only the estimates from the lower RoB studies (paired design).
m. The results shows imprecise estimates going from relevant decrease to increase on the recall rate.
n. STORM-2 additionally reports recall rate of DBT + synthetic mammography, RR: 1.50 (95%CI: 1.20 to 1.87).
o. The included study used an unpaired design. Participants might differ by relevant non-measured characteristics. The minimum reader experience for DBT might be insufficient (50 previous screening exam).

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Values and preferences

JRC Technical Report PICO 10-11, contract FWC443094012015; available upon request.

Acceptability

JRC Technical Report PICO 16-17, contract FWC443094032016; available upon request.