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

European Commission, Via Enrico Fermi 2749, I-21027 Ispra (Varese) - Italy. Telephone: (39)0332-78-9111. E-mail: JRC-CANCER-POLICY-SUPPORT@ec.europa.eu

QUESTION	
Should tailored screening with digital breast tomosynthesis (DBT) based on high mammographic breast density, in addition to mammography, vs. mammography alone be used for early detection of breast cancer in asymptomatic women?	
POPULATION:	asymptomatic women with high mammographic breast density and negative mammography in screening
INTERVENTION:	tailored screening with digital breast tomosynthesis (DBT) based on high mammographic breast density, in addition to mammography,
COMPARISON:	mammography alone
MAIN OUTCOMES:	breast cancer mortality, stage of breast cancer, interval cancer rate, breast cancer detection rate, recall rate, rate of mastectomies, provision of chemotherapy, adverse effects.
SETTING:	Standard screening program
PERSPECTIVE:	Population (National Health System)
BACKGROUND:	Breast cancer is the second most commonly diagnosed cancer in the world (1.67 million cases diagnosed in 2012) and ranks as the fifth cause of death from cancer overall (522 000 deaths in 2012) (Ferlay 2012). 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 (Gilbert 2015). 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. 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. The most commonly considered supplemental screening modalities to digital mammography (DM) are hand-held ultrasound (HHUS), automated whole breast ultrasound (ABUS), digital breast tomosynthesis (DBT), and breast magnetic resonance imaging.
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 members were recused from voting: Bettina Borisch, Roberto d'Amico, Chris de Wolf, and Axel Gräwingholt. Solveig Hofvind, Peter Rabe, Holger Schünemann, Alberto Torresin, Ruben van Engen, and Cary van Landsveld-Verhoeven were restricted from voting, as a preventive measure, as the CoI information was not provided, but after its provision it was assessed and no CoI were found. Miranda Langendam was not allowed to vote due to the established rules for external experts.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Breast cancer ranks as the fifth cause of death from cancer overall (522 000 deaths in 2012) and while it is the most frequent cause of cancer death in women in less developed regions (324 000 deaths), it is now the second cause of cancer death in more developed regions (198 000 deaths) after lung cancer (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 (Gilbert 2015). In women with dense breasts, risk of breast cancer is increased (3) , 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) (4) .	The GDG prioritised this question for the ECIBC.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	See table below	The included studies did not assess the outcomes of: breast cancer mortality, stage of breast cancer, interval cancer rate, rate of mastectomies, provision of chemotherapy or adverse effects (including radiation exposure, radiation induced cancers-related to radiation dose, overdiagnosis related adverse effects, false positive related adverse effects). The GDG agreed that digital breast tomosynthesis (DBT) has a large effect on cancer detection rate, particularly in women with high mammographic breast density where more cancers are missed with DM. The anticipated effects on mortality, cancer stage and interval cancer detection rate are not known as the studies included did not examine these outcomes. The studies cover a single round of screening and the findings at this round only. Therefore, the GDG agreed that overall desirable anticipated effects were not known.

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with mammography alone	Risk difference with tailored screening with digital breast tomosynthesis (DBT) based on high mammographic breast density, in addition to mammography,
Breast cancer detection rate	8814 (3 observational studies)[1,2,3,4,a]	⨁⨁◯◯ LOW	**OR 1.76** (1.38 to 2.24)[b,c]	Study population	
				635 per 100,000[a]	**477 more per 100,000** (239 more to 777 more)

False positive recall	3762 (2 observational studies)[1,2,5,6]	⨁⨁◯◯ LOW	**OR 1.41** (1.12 to 1.77)[b]	Low	
				10,700 per 100,000[d]	**3,753 more per 100,000** (1,132 more to 6,797 more)
				High	
				41,500 per 100,000	**8,506 more per 100,000** (2,775 more to 14,167 more)
Breast cancer mortality - not reported	-	-	-		
Stage of breast cancer - not reported	-	-	-		
Interval cancer rate - not reported	-	-	-		
Rate of mastectomies - not reported	-	-	-		
Provision of chemotherapy - 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.
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5. 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.
6. 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.

a. Median or mean of the control group of the included studies as appropriate unless otherwise specified.
b. Relative effect was adjusted for paired design.
c. Incremental cancer detection rate 540 more per 100.000 (from 200 more to 1020 more)
d. Baseline risk from the control group of Roman 2014 (PMID 24972452).

* tailored screening with digital breast tomosynthesis based on breast density.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial ● Varies ○ Don't know		Only data on false positive recall rate was available, but none for recall rate. Nevertheless, comparison of recall rates between DBT and DM is difficult to interpret, because the surveillance protocol may imply that first a DM is performed and then a DBT in the case of dense tissue. Thus if the latter is counted as recall, there is a higher recall rate due to the second screening test conducted in the intervention arm (DBT). The GDG members considered that the increase in other cancers due to radiation dose is small**.** Although the dose would be increased by using DBT plus DM, the absolute increase in radiation induced cancers is likely to be small. The GDG members could not reach consensus regarding how substantial the

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Breast cancer	8814	⨁⨁◯◯	**OR 1.76**	Study population	

detection rate	(3 observational studies)[1,2,3,4,a]	LOW	(1.38 to 2.24)[b,c]	635 per 100,000[a]	**477 more per 100,000** (239 more to 777 more)	
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Stage of breast cancer - not reported	-	-	-			
Interval cancer rate - not reported	-	-	-			
Rate of mastectomies - not reported	-	-	-			
Provision of chemotherapy - not reported	-	-	-			

undesirable anticipated effects were, so voting was conducted:

1 member considered the undesirable anticipated effects as "moderate",

1 member as "small",

12 members agreed the effects "vary" (recall rates or false positive recall -FPR- may vary depending on the baseline recall rate in the screening population. Published results suggest an increased recall with DBT in programmes with pre-existing low recall rates and a reduced recall rate in programmes with high rates),

1 voting member abstained.

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.
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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 that there is low certainty in the evidence of effects, as this was the lowest quality evidence among the critical outcomes - namely, breast cancer detection rate and false positive recall rate.

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*).	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		The GDG members agreed that the balance probably favours the intervention in women with higher mammographic breast density as more cancers are detected with digital breast tomosynthesis, and there was no indication that this is outweighed by undesirable effects. However, research evidence on undesirable effects is sparse, so there remains significant uncertainty.

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	No relevant economic evaluations were identified.	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 (5). 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 relevant economic evaluations were identified.	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	No relevant economic evaluations were identified.	Substantial differences could be observed across European countries according to their willingness to pay threshold. Based on the evidence provided by (5), 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 (5) 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		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	*Participants* There is likely variability in acceptability for women. If 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

	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 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.	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 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		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

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	**Don't know**
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		**Varies**	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	**Important uncertainty or variability**	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			No known undesirable outcomes
BALANCE OF EFFECTS	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
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**Very low**	Low	Moderate	High			No included studies
COST EFFECTIVENESS	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**
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know

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 and negative mammography, in the context of an organised screening programme, the ECIBC's Guidelines Development Group (GDG) suggests screening with digital breast tomosynthesis or mammography screening alone (conditional recommendation, low certainty of the evidence).

Justification

Overall justification

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

The GDG recommendation reflects the state of research that only presents outcomes on cancer detection rate and false positive recall rate, and not on other important outcomes. There are additional factors of increased costs for DBT plus DM over DM alone that must be considered on a country-by-country basis, depending on resources available, for breast cancer screening programmes.

Detailed justification

Desirable Effects

The STORM, STORM-2, MALMO studies demonstrated increases in the incremental cancer detection rates using mammography with tomosynthesis in addition to 2D mammography compared to mammography alone. There is no research assessing mortality or cancer stage at diagnosis using tomosynthesis. Increased cancer detection rates with tomosynthesis may be more important to women with higher breast density due to a greater number of cancers that are missed using mammography alone in this population.

Undesirable Effects

There is data suggestive of a higher false positive rate after doing both a mammography and tomosynthesis test versus mammography alone, although this is not universally observed. Recall rates cannot be compared between the interventions in this question because mammography is used to determine whether tomosynthesis is conducted and therefore recall rates are falsely elevated, due to two screening procedures being performed in the intervention arm.

Certainty of evidence

The GDG members felt there was low certainty due to the lack of direct outcome measures.

Balance of effects

In women with higher breast density the GDG members agreed that it would be reasonable to offer the addition of DBT after a negative mammography over DM alone as the addition of DBT confers a higher detection rate of breast cancers. However, evidence was not sufficiently strong to make a positive recommendation in favour of the intervention, so both additional DBT and standard care are acceptable.

Resources required

The GDG members felt that there would be increased costs associated with tailored screening with tomosynthesis based on breast density. Local and regional level economic analyses are required to estimate the cost for the implementation of tomosynthesis.

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 standardisation 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 the additional imaging. 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. There is also a need for research evidence on repeated DBT examinations, since the current evidence is mainly restricted to a single surveillance episode. Trials in this area are ongoing and their results will influence the revision of this recommendation in the future. Further research should also assess cost-effectiveness implications of tailored DBT screening for high mammographic breast density. Additional research should also assess the comparison between DBT and DM plus ultrasound for dense breast screening. Research is needed to define the quality parameters that need to be fulfilled for DBT-based breast cancer screening programmes to be implemented.

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Evidence profile

Healthcare question	Should tailored screening with digital breast tomosynthesis (DBT) based on high mammographic breast density, in addition to mammography, compared to mammography alone be used for early detection of breast cancer in asymptomatic women?
Date	April 2016
Authors	ECIBC Guideline Development Group (GDG): Mariangela Autelitano, Bettina Borisch, Mireille Broeders, Xavier Castells, Roberto D'Amico, Edoardo Colzani, Jan Daneš, Chris De Wolf, 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, Peter Rabe, Holger Schünemann, Alberto Torresin, Ruben Van Engen, Cary Van Landsveld-Verhoeven, Sue Warman, Kenneth Young Systematic Review team: Mónica Ballesteros, Ivan Solá, Nieves Plana, Margarita Posso, Carlos Canelo, David Rigau, Pablo Alonso-Coello. JRC Healthcare Quality team: Zuleika Saz-Parkinson, Donata Lerda
Abbreviations	**CI:** Confidence interval **OR:** Odds ratio

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tailored screening with digital breast tomosynthesis based on high mammographic breast density, in addition to mammography	Mammography alone	Relative (95% CI)	Absolute (95% CI)		
Breast cancer detection rate												
3 (1,2,3,4)	observational studies	not serious	not serious	not serious	not serious	none	52/4 407 (1.2%)	28/4 407 (0.6%) (a)	**OR 1.76** (1.38 to 2.24) (b,c)	**477 more per 100 000** (from 239 more to 777 more)	⊕⊕◯◯ LOW	CRITICAL
False positive recall												
2 (1,2,5,6)	observational studies	not serious	not serious	not serious	not serious	none	179/3 762 (4.8%)	10.7% (d)	**OR 1.41** (1.12 to 1.77) (b)	**3 753 more per 100 000** (from 1 132 more to 6 797 more)	⊕⊕◯◯ LOW	CRITICAL
								41.5% (d)		**8 506 more per**		

Quality assessment							Nº of patients		Effect		Quality	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tailored screening with digital breast tomosynthesis based on high mammographic breast density, in addition to mammography	Mammography alone	Relative (95% CI)	Absolute (95% CI)		
										100 000 (from 2 775 more to 14 167 more)		
Breast cancer mortality - not reported												
-	-	-	-	-	-	-					-	CRITICAL
Stage of breast cancer - not reported												
-	-	-	-	-	-	-					-	CRITICAL
Interval cancer rate - not reported												
-	-	-	-	-	-	-					-	CRITICAL
Rate of mastectomies - not reported												
-	-	-	-	-	-	-					-	CRITICAL
Provision of chemotherapy - not reported												
-	-	-	-	-	-	-					-	CRITICAL
Adverse effects - not reported												
-	-	-	-	-	-	-					-	CRITICAL

Explanations

a. Median or mean of the control group of the included studies as appropriate unless otherwise specified.
b. Relative effect was adjusted for paired design.
c. Incremental cancer detection rate 540 more per 100.000 (from 200 more to 1 020 more)
d. Baseline risk from the control group of Roman 2014 (PMID 24972452).

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Acceptability

Lee CI, Cevik M, Alagoz O, Sprague BL, Tosteson AN, Miglioretti DL, Kerlikowske K, Stout NK, Jarvik JG, Ramsey SD, Lehman CD. Comparative effectiveness of combined digital mammography and tomosynthesis screening for women with dense breasts. Radiology. 2015; 274(3): 772-80.

Economic evidence

Lee CI, Cevik M, Alagoz O, Sprague BL, Tosteson AN, Miglioretti DL, Kerlikowske K, Stout NK, Jarvik JG, Ramsey SD, Lehman CD. Comparative effectiveness of combined digital mammography and tomosynthesis screening for women with dense breasts. Radiology. 2015; 274(3): 772-80.

Values and preferences

For more details about the results see the full report (Contract: FWC 443094 012015 PICO 10-11).