



**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 tomosynthesis (including synthesised 2D images) in addition to digital mammography** vs. **digital mammography** be used for **early detection of breast cancer in asymptomatic women**?

<b>POPULATION:</b>	early detection of breast cancer in asymptomatic women	<b>BACKGROUND:</b> Breast cancer is the second most common cancer in the world and, by far, the most frequent cancer among women, with an estimated 1.67 million new cancer cases diagnosed in 2012 (25% of all cancers) (Ferlay 2012). Breast cancer ranks as the fifth cause of death from cancer overall (522 000 deaths), the most frequent cause of cancer death in women in less developed regions (324 000 deaths, 14.3% of total), and it is now the second cause of cancer death in more developed regions (198 000 deaths, 15.4%) after lung cancer (Ferlay 2012). 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 the rate of death from breast cancer. Mammography remains the best method to detect breast cancer in an early stage. Mammography 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. Digital breast tomosynthesis 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 (Rafferty 2013; Gur 2009). The series of projections is then processed by a reconstruction algorithm to estimate the 3D radiographic appearance of the breast which can be viewed in successive slices. Additional software can also allow
<b>INTERVENTION:</b>	screening using tomosynthesis (including synthesised 2D images) in addition to digital mammography	
<b>COMPARISON:</b>	digital mammography	
<b>MAIN OUTCOMES:</b>	Breast cancer mortality, stage of breast cancer, breast cancer detection rate, interval cancer rate, recall rate, adverse effects, radiation induced cancers related to radiation dose, quality of life, other cause mortality	
<b>SETTING:</b>	European Union	
<b>PERSPECTIVE:</b>  <b>Management of Conflicts of Interest (Col):</b>	Population (National Health System)  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:	

	Edoardo Colzani, Roberto d'Amico, Jan Danes, Solveig Hofvind, Miranda Langendam, Elsa Pérez, and Kenneth Young.		the construction of synthesised 2D images.
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## Assessment

	JUDGEMENT	RESEARCH EVIDENCE					ADDITIONAL CONSIDERATIONS																						
PROBLEM	<p><b>Is the problem a priority?</b></p> <p><input type="radio"/> No</p> <p><input type="radio"/> Probably no</p> <p><input type="radio"/> Probably yes</p> <p><input checked="" type="radio"/> Yes</p> <p><input type="radio"/> Varies</p> <p><input type="radio"/> Don't know</p>	Breast cancer ranks as the fifth cause of death from cancer overall (522 000 deaths), the most frequent cause of cancer death in women in less developed regions (324 000 deaths, 14.3% of total), and it is now the second cause of cancer death in more developed regions (198 000 deaths, 15.4%) after lung cancer (Ferlay 2012). Breast cancer is the fourth cancer with the highest disease burden (Tsilidis 2016). Digital mammography (DM) is widely used in screening and diagnosis of breast cancer. However, some aspects such as superposition of breast tissue reduce the sensitivity of mammography and increase false-positives and false negatives. Digital Breast Tomosynthesis (DBT) might provide better imaging and discriminative capacity in these cases.																											
DESIRABLE EFFECTS	<p><b>How substantial are the desirable anticipated effects?</b></p> <p><input type="radio"/> Trivial</p> <p><input type="radio"/> Small</p> <p><input type="radio"/> Moderate</p> <p><input type="radio"/> Large</p> <p><input type="radio"/> Varies</p> <p><input checked="" type="radio"/> Don't know</p>	<table><tr><th>Outcomes</th><th>Nº of participants (studies) Follow up</th><th>Quality of the evidence (GRADE)</th><th>Relative effect (95% CI)</th><th colspan="2">Anticipated absolute effects* (95% CI)</th></tr><tr><td></td><td></td><td></td><td></td><th>Risk with digital mammography</th><th>Risk difference with UPDATE screening using tomosynthesis (including synthesised 2D images) in addition to digital mammography</th></tr><tr><td>Breast cancer detection rate (double reading)</td><td>59180 (3 observational studies)<sup>a</sup></td><td>⊕⊕○○ LOW<sup>b</sup></td><td>OR 1.36 (1.26 to 1.46)<sup>c d</sup></td><td colspan="2">Study population</td></tr><tr><td></td><td></td><td></td><td></td><td>598 per 100.000<sup>a</sup></td><td><b>214 more per 100.000</b> (154 more to 273 more)</td></tr></table>	Outcomes	Nº of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)						Risk with digital mammography	Risk difference with UPDATE screening using tomosynthesis (including synthesised 2D images) in addition to digital mammography	Breast cancer detection rate (double reading)	59180 (3 observational studies) <sup>a</sup>	⊕⊕○○ LOW <sup>b</sup>	OR 1.36 (1.26 to 1.46) <sup>c d</sup>	Study population						598 per 100.000 <sup>a</sup>	<b>214 more per 100.000</b> (154 more to 273 more)	<p>The currently included studies only present data from first round DBT plus DM screening.</p> <p>The included studies did not assess the outcomes of breast cancer mortality, quality of life, and other causes of mortality.</p> <p>The anticipated desirable effects were examined individually by the GDG:</p> <p>Cancer detection rate: <b>large</b>, based on the results of the 3 studies included.</p>		
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UNDESIRABLE EFFECTS		Recall rate	19914 (2 observational studies) <sup>e</sup>	⊕⊕○○ LOW <sup>b f</sup>	OR 1.26 (1.22 to 1.30)	Low		Mortality: <b>don't know</b> as no studies were available that examined mortality.
						2.200 per 100.000 <sup>e</sup>	556 more per 100.000 (471 more to 641 more)	Cancer stage: <b>don't know</b> , in that there were no studies reporting the effect on incidence of cancer by stage. However, given the relative increase of 46% in invasive cancer's detected, the technology is likely to confer a substantial reduction in late stage disease.
					High			
					15.600 per 100.000 <sup>e</sup>	3.290 more per 100.000 (2.800 more to 3.773 more)		
		False positive recall	73646 (4 observational studies)	⊕⊕○○ LOW <sup>b</sup>	OR 1.22 (1.16 to 1.27)	Low		Interval cancer rate: <b>don't know</b> based on included studies reporting only data from a first DBT plus DM screening round. However, the GDG took the view that a decrease in interval cancer rates can be expected as the sensitivity of the intervention proved to be higher.
					10.700 per 100.000 <sup>g</sup>	2.054 more per 100.000 (1.503 more to 2.507 more)		
					High			
					41.500 per 100.000 <sup>g</sup>	4.894 more per 100.000 (3.643 more to 5.894 more)		
	Invasive stage cancer	39826 (2 observational studies) <sup>a</sup>	⊕○○○ VERY LOW <sup>b h</sup>	OR 1.46 (1.30 to 1.64)	Study population			
						457 per 100.000 <sup>a</sup>	209 more per 100.000 (136 more to 290 more)	
	Radiation exposure	0 (3 observational studies)	⊕○○○ VERY LOW <sup>i j</sup>	-	Radiation doses for digital mammography plus tomosynthesis were approximately twice that reported for digital mammography alone. <sup>k</sup>			
	<div>How substantial are the undesirable anticipated effects?</div> <div>○ Large ○ Moderate ○ Small ○ Trivial  ● Varies ○ Don't know</div>							<div>The anticipated undesirable effects were examined individually by the GDG:</div> <div>Recall rate: the GDG notes that the recall rate may <b>vary</b> based on the baseline recall rate in the screening population (Hofvind 2012, Roman 2014).</div> <div>False positive rate: <b>varies</b>. The GDG agreed the effect would vary depending, once again, on the baseline rate (Bernardi 2016).</div>
	<div>a. Median or mean of the control group of the included studies as appropriate unless otherwise specified.</div> <div>b. Although only women with suggestive findings of malignancy were followed-up, it was agreed that there was not an important risk of information bias, as the same strategy was implemented in both arms of the included studies, and the effects were consistent across them.</div> <div>c. Relative effect was adjusted for paired design.</div> <div>d. Incremental cancer detection was 215 cancers per 100 000 (from 162 more to 267 more).</div>							

		<p>e. Baseline risk calculated from Roman 2014 (PMID 24972452) and Hofvind (PMID 22972811)</p> <p>f. Although the STORM study (2013/2014) and OTST study (2013) evaluated women recalled in a different way (radiologist vs. radiologist plus meeting arbitration) the results were consistent.</p> <p>g. Baseline risk calculated from Roman 2014 (PMID 24972452).</p> <p>h. Invasive cancer stage is a surrogate outcome of cumulative incidence of advance breast cancer.</p> <p>i. Radiation exposure is a surrogate outcome of "other cancer related to radiation".</p> <p>j. Results were consistent independently of the technology used (Hologic Selenia Dimension or Senographe Dimension).</p> <p>k. Doses levels are known to vary (diagnostic reference levels are typically country/region and system specific).</p> <p>* with screening using tomosynthesis (including synthesised 2D images) in addition to digital mammography .</p>	<p>Increase in other cancers due to radiation dose: <b>small</b>. Although the dose would be increased by using DBT plus DM, the absolute increase in radiation induced cancers is likely to be small.</p> <p>Overall the GDG felt that the undesirable anticipated effects vary.</p>
CERTAINTY OF EVIDENCE	<p><b>What is the overall certainty of the evidence of effects?</b></p> <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>Due to varied undesirable effects and uncertain effects of DBT plus DM on breast cancer mortality the GDG agreed that there is very low certainty of the evidence of effects. However, the GDG agreed that DBT in addition to DM has substantially greater detection capability than DM alone.</p>
VALUES	<p><b>Is there important uncertainty about or variability in how much people value the main outcomes?</b></p> <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>No specific studies focusing in tomosynthesis 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 tomosynthesis, 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 (<i>low confidence</i>). 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>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 rate (although there is uncertainty about how this affects breast cancer mortality), as well as the variation in recall rate, and the increase in radiation exposure are likely to be valued very differently by</p>

		Regarding breast cancer diagnosis, there is very limited data available on people's 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 confidence). Also, people have a higher overall preference towards more comfortable, brief diagnostic procedures (moderate confidence).	women.
BALANCE OF EFFECTS	<p><b>Does the balance between desirable and undesirable effects favor the intervention or the comparison?</b></p> <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>Given the lack of research and the uncertainty of the effects of DBT plus DM screening on mortality, the GDG could not reach consensus on whether the balance of desirable and undesirable effects favours the intervention or the comparison.</p> <p>As agreement was not reached, voting was conducted among GDG members: One member voted that the balance "does not favour either the intervention or the comparison"; 11 members voted that it "probably favours the intervention"; one member voted that it "varies"; six members voted they "don't know"; two members abstained.</p>
RESOURCES REQUIRED	<p><b>How large are the resource requirements (costs)?</b></p> <ul style="list-style-type: none"> <li>○ Large costs</li> <li>● Moderate costs</li> <li>○ Negligible costs and savings</li> <li>○ Moderate savings</li> <li>○ Large savings</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	No relevant economic evaluations were identified.	The GDG agreed that resources required for moving from digital mammography alone to tomosynthesis combined with digital mammography could be moderate. These resources may include, amongst other factors: costs of the technology, capital costs of the machines and

			<p>the lifetime of the machine, data transport and capacity for data storage, and additional time for radiologists to read tomosynthesis images, and increased time for the DBT plus DM examination compared to 2D mammography only examination.</p> <p>Based on the information from three observational studies identified from the systematic review of Gilbert et al. (Gilbert 2016) radiologists' reading time would have an increase of between 100% and 200% for the combination of tomosynthesis with digital mammography compared with digital mammography alone (Skaane 2013, Bernardi 2012a, Wallis 2012). This corresponds to absolute times of 33-67 seconds for digital mammography alone and 77-191 seconds for tomosynthesis plus digital mammography.</p> <p>Staff cost may vary depending on the country context and they are not transferable from one country to another.</p> <p>As there is a variation in recall rates expected and reported, a variation in savings or additional expenses should be</p>
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			<p>expected. Nevertheless, the GDG members took the view that even if these variations were in favour of screening with DBT plus DM, they would probably not outweigh the extra costs mentioned above (equipment, reading time, etc.). As agreement was not reached, voting was conducted among GDG members: two members voted "large costs"; 12 voted "moderate costs"; one member voted "varies"; two members voted "don't know"; two members abstained.</p>
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	<p><b>What is the certainty of the evidence of resource requirements (costs)?</b></p> <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>	No relevant economic evaluations were identified.	
COST EFFECTIVENESS	<p><b>Does the cost-effectiveness of the intervention favor the intervention or the comparison?</b></p> <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>	No relevant economic evaluations were identified.	



EQUITY	<p><b>What would be the impact on health equity?</b></p> <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>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 influences on equity in either direction.</p>
ACCEPTABILITY	<p><b>Is the intervention acceptable to key stakeholders?</b></p> <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>No specific studies focusing on tomosynthesis (including synthesised 2D images) in addition to digital mammography were identified. The findings, all from mammography studies, however, are likely to be generalisable to tomosynthesis (including synthesised 2D images) in addition to digital mammography, 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 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 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.</p>	<p><u>Participants:</u></p> <p>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 2-D-mammography, 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 when screening with DBT in addition to 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.</p>

			<p><u>Radiologists:</u></p> <p>DBT may be preferred by radiologists reading screening tests because their certainty in the diagnosis may be higher when using DBT plus DM compared to using DM alone.</p> <p><u>Policy makers:</u></p> <p>In settings with universal healthcare coverage, for directors of hospitals and screening programmes, carrying out DBT as well as DM may not be acceptable because there will likely be increased costs.</p>
FEASIBILITY	<p><b>Is the intervention feasible to implement?</b></p> <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>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

	JUDGEMENT							IMPLICATIONS
<b>PROBLEM</b>	No	Probably no	Probably yes	<b>Yes</b>		Varies	Don't know	
<b>DESIRABLE EFFECTS</b>	Trivial	Small	Moderate	Large		Varies	<b>Don't know</b>	
<b>UNDESIRABLE EFFECTS</b>	Large	Moderate	Small	Trivial		<b>Varies</b>	Don't know	
<b>CERTAINTY OF EVIDENCE</b>	<b>Very low</b>	Low	Moderate	High			No included studies	
<b>VALUES</b>	<b>Important uncertainty or variability</b>	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			No known undesirable outcomes	
<b>BALANCE OF EFFECTS</b>	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	<b>Probably favors the intervention</b>	Favors the intervention	Varies	Don't know	
<b>RESOURCES REQUIRED</b>	Large costs	<b>Moderate costs</b>	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
<b>CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES</b>	Very low	Low	Moderate	High			<b>No included studies</b>	
<b>COST EFFECTIVENESS</b>	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or	Probably favors the intervention	Favors the intervention	Varies	<b>No included studies</b>	

	JUDGEMENT							IMPLICATIONS
			the comparison					
<b>EQUITY</b>	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	<b>Varies</b>	Don't know	
<b>ACCEPTABILITY</b>	No	Probably no	Probably yes	Yes		<b>Varies</b>	Don't know	
<b>FEASIBILITY</b>	No	Probably no	Probably yes	Yes		<b>Varies</b>	Don't know	

## Conclusions

**Should screening using tomosynthesis (including synthesised 2D images) in addition to digital mammography vs. digital mammography be used for early detection of breast cancer in asymptomatic women?**

<b>TYPE OF RECOMMENDATION</b>	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  ○
<b>RECOMMENDATION</b>	For asymptomatic women with an average risk of breast cancer, the ECIBC's Guidelines Development Group (GDG) suggests screening with either DBT in addition to DM or DM alone, in the context of an organised screening programme (conditional recommendation, very low certainty in the evidence).				
<b>JUSTIFICATION</b>	<b>Overall justification</b>				

The GDG agreed that there is high certainty for test accuracy of DBT in addition to DM over DM alone. However, it has to be taken into account that at present the included studies only present data from first round DBT plus DM screenings and there is still a lack of studies on subsequent screening rounds. In addition, the GDG agrees that there is uncertainty in the link between test accuracy and impact on outcomes due to the use of indirect measures such as cancer detection rates instead of mortality due to breast cancer. There are additional factors like 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. Evidence will be emerging from ongoing and newly starting screening trials on tomosynthesis that may influence the current recommendation. As there was not agreement within the GDG for the direction of this recommendation, voting among members took place, the results of which were: 17 for 'conditional recommendation for either the intervention or the comparison'; 1 for 'conditional recommendation against the intervention'.

### **Detailed justification**

#### *Desirable Effects*

The evidence reviewed showed a large effect size in the increase of breast cancer detection rate from 1 to 4 per 1000 women at first round of DBT plus DM screening. The GDG, however, had very low certainty in the evidence of effects of the intervention (DBT plus DM) due to the lack of certainty in how this increased breast cancer detection rate relates to mortality. In addition, there was no evidence on other desirable effects such as decreases in interval breast cancer detection rate, decreases in detection of advanced stage breast cancer or reduction in breast cancer mortality.

#### *Undesirable Effects*

The GDG agreed that the undesirable anticipated effects vary due to evidence on varying recall and false positive rates, and a small increased risk of developing other cancers due to increased radiation dose of DBT plus DM.

#### *Resources required*

No research evidence addressing resource considerations was found. However, the GDG considered that there would be likely an increase in costs for using DBT plus DM compared to using only DM. These must be considered on a country-by-country basis depending on resources available for breast cancer screening programmes. In settings where the additional costs of DBT are a barrier to implementation, the GDG notes the uncertainty of the evidence of cost effectiveness of DBT. These resource considerations will also vary greatly based on the healthcare setting and health system funding for countries with universal healthcare coverage as compared to settings where DBT will be implemented in private healthcare settings. The GDG expressed concern that this may lead to increased health inequities with varied implementation in different countries across Europe.

#### *Acceptability*

Acceptability among stakeholders was found to be variable for different key stakeholders. The GDG felt that for women, there is likely variable acceptability due to higher radiation dose, increased compression time using DBT and in addition to DM vs DM alone; however, women may find a test with a higher detection rate more acceptable and desirable. It is not clear, however, what the effect on false positive results would be in routine screening, and this would be a factor to be taken into account for acceptability. The GDG felt that DBT plus DM would be more acceptable for radiologists who may place more confidence in their

	assessments using the additional information that DBT provides. For policy-makers, the GDG felt that there may be decreased acceptability for countries with universal health coverage due to increased screening programme costs.
<b>SUBGROUP CONSIDERATIONS</b>	Women with high mammographic breast density are likely to benefit most from the increased detection capability of DBT plus DM. However, this group was not specifically considered in this question.
<b>IMPLEMENTATION CONSIDERATIONS</b>	<ul style="list-style-type: none"> <li>- Evidence will be emerging from ongoing and newly starting screening trials on tomosynthesis that may influence the current recommendations.</li> <li>- Inappropriate worry about radiation dose should be dealt with in case programmes that are using the DBT plus DM combination. In general, the GDG believes it is important to educate women and health professionals on the risk of radiation in the context of possible benefits of screening.</li> <li>- GDG indicates that it will be very unlikely to implement DBT plus DM in practice because it means two examinations instead of one, with additional radiation and discomfort for women. However, other GDG members indicate that this is currently already done in certain settings.</li> <li>- There will be significantly increased data storage needs for screening programmes using DBT plus DM as compared to only DM.</li> <li>- 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 plus DM over DM which may lead to increased health inequities.</li> </ul>
<b>MONITORING AND EVALUATION</b>	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.
<b>RESEARCH PRIORITIES</b>	<ul style="list-style-type: none"> <li>- Evidence will be emerging from ongoing and newly starting screening trials on tomosynthesis that may influence the current recommendations.</li> <li>- Collecting evidence relevant to implementation challenges of screening programmes using DBT in addition to DM.</li> <li>- Further research information on harms of DBT used together with DM, including rates of overdiagnosis of breast cancer, are warranted.</li> <li>- The currently included studies only present data from first round DBT plus DM screening studies, thus the effects for several patient important outcomes, which need a longer follow-up period, could not be taken into account. Thus, research on several screening rounds of DBT plus DM are warranted. <ul style="list-style-type: none"> <li>- Further research is needed to build the evidence on benefits and harms of DBT in addition to DM vs DM through comparison of direct outcomes, including impacts of interval cancer detection, stage of breast cancer at detection and mortality reduction.</li> </ul> </li> <li>- Research investigating the cost-effectiveness of a breast cancer screening programme using DBT in addition to DM is needed to inform decision-making on breast cancer screening.</li> <li>- Research is needed to define the quality parameters that need to be fulfilled for breast cancer screening programmes using DBT in addition to DM to be implemented.</li> </ul>

# Evidence profile

<b>Healthcare question</b>	Should screening using tomosynthesis (including synthesised 2D images) in addition to digital mammography vs. digital mammography be used for early detection of breast cancer in asymptomatic women?
<b>Date</b>	April 2016
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<b>Abbreviations</b>	<b>CI:</b> Confidence interval <b>OR:</b> Odds Ratio

Quality assessment							Nº of patients		Effect		Quality	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Screening using tomosynthesis (including synthesised 2D images) in addition to digital mammography	Digital mammography	Relative (95% CI)	Absolute (95% CI)		
Breast cancer detection rate (double reading)												
3	observational studies	not serious <sup>a</sup>	not serious	not serious	not serious	none	242/29590 (0.8%)	177/29590 (0.6%) <sup>b</sup>	OR 1.36 (1.26 to 1.46) <sup>c,d</sup>	214 more per 100,000 (from 154 more to 273 more)	⊕⊕○○ LOW	CRITICAL
Recall rate												
2	observational studies	not serious <sup>a</sup>	not serious <sup>e</sup>	not serious	not serious	none	857/19914 (4.3%)	2.2% <sup>f</sup>	OR 1.26 (1.22 to 1.30)	556 more per 100,000 (from 471 more to 641 more)	⊕⊕○○ LOW	CRITICAL
								15.6% <sup>f</sup>		3,290 more per 100,000 (from 2,800 more		

Quality assessment							Nº of patients		Effect		Quality	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Screening using tomosynthesis (including synthesised 2D images) in addition to digital mammography	Digital mammography	Relative (95% CI)	Absolute (95% CI)		
										to 3,773 more)		
False positive recall												
4	observational studies	not serious <sup>a</sup>	not serious	not serious	not serious	none	1929/36823 (5.2%)	10.7% <sup>g</sup>	OR 1.22 (1.16 to 1.27)	2,054 more per 100,000 (from 1,503 more to 2,507 more)	⊕⊕○○ LOW	CRITICAL
								41.5% <sup>g</sup>		4,894 more per 100,000 (from 3,643 more to 5,894 more)		
Invasive stage cancer												
2	observational studies	not serious <sup>a</sup>	not serious	serious <sup>h</sup>	not serious	none	133/19913 (0.7%)	91/19913 (0.5%) <sup>b</sup>	OR 1.46 (1.30 to 1.64)	209 more per 100,000 (from 136 more to 290 more)	⊕○○○ VERY LOW	CRITICAL
Radiation exposure												
3	observational studies	not serious	not serious <sup>i</sup>	serious <sup>j</sup>	not serious	none	Radiation doses for digital mammography plus tomosynthesis were approximately twice that reported for digital mammography alone. <sup>k</sup>				⊕○○○ VERY LOW	CRITICAL
Breast cancer mortality - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Interval cancer rate - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Quality of life - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Radiation induced cancers-related to radiation dose - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Other causes of mortality - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	



## Explanations

- a. Although only women with suggestive findings of malignancy were followed-up, it was agreed that there was not an important risk of information bias, as the same strategy was implemented in both arms of the included studies, and the effects were consistent across them.
- b. Median or mean of the control group of the included studies as appropriate unless otherwise specified.
- c. Relative effect was adjusted for paired design.
- d. Incremental cancer detection was 215 cancers per 100 000 (from 162 more to 267 more).
- e. Although the STORM study (2013/2014) and OTST study (2013) evaluated women recalled in a different way (radiologist vs. radiologist plus meeting arbitration) the results were consistent.
- f. Baseline risk calculated from Roman 2014 (PMID 24972452) and Hofvind 2012 (PMID 22972811)
- g. Baseline risk calculated from Roman 2014 (PMID 24972452).
- h. Invasive cancer stage is a surrogate outcome of cumulative incidence of advance breast cancer.
- i. Results were consistent independently of the technology used (Hologic Selenia Dimension or Senographe Dimension).
- j. Radiation exposure is a surrogate outcome of "other cancer related to radiation".
- a. Doses levels are known to vary (diagnostic reference levels are typically country/region and technology specific).

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## Evidence of effects and background

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