



**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**

<b>QUESTION</b>	
<b>Should tailored screening with magnetic resonance imaging (MRI) based on high mammographic breast density, in addition to mammography, vs. mammography alone be used for early detection of breast cancer in asymptomatic women?</b>	
<b>POPULATION:</b>	Asymptomatic women with high mammographic density and a negative mammography
<b>INTERVENTION:</b>	tailored screening with magnetic resonance imaging (MRI) based on high mammographic breast density, in addition to mammography,
<b>COMPARISON:</b>	mammography alone
<b>MAIN OUTCOMES:</b>	Breast cancer mortality, stage of breast cancer, interval cancer rate, breast cancer detection rate, recall rate, rate of mastectomies, provision of chemotherapy, and adverse effects (including radiation exposure, radiation induced cancers-related to radiation dose, overdiagnosis related adverse effects, false positive related adverse effects).
<b>SETTING:</b>	European Union
<b>PERSPECTIVE:</b>	Population (National Health System)
<b>BACKGROUND:</b>	<p>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).</p> <p>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.</p> <p>Due to lack of evidence using the breast density BIRADS (Breast Imaging Report and Database System) classification edition 5, the ECIBC's Guidelines Development Group (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:</p> <p>(1) BIRADS category scale: III-IV score.</p>

	<p>(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%).</p> <p>(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 are hand-held ultrasound, automated whole breast ultrasound, digital breast tomosynthesis, and breast magnetic resonance imaging.</p>
<b>CONFLICT OF INTEREST:</b>	<p><u>Management of Conflicts of Interest (Col)</u>: Cols for all 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 Col disclosure. Consequently, for this particular question, the following GDG members were recused from voting: Roberto d'Amico, Chris de Wolf, Axel Gräwingholt. Cary van Landsveld-Verhoeven was restricted from voting, as a preventive measure, as the Col information was not provided, but after its provision it was assessed and no Col were found. Miranda Langendam, as external expert, was also not allowed to vote, according to the ECIBC rules of procedure.</p>

## ASSESSMENT

### Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <li>○ No</li> <li>○ Probably no</li> <li>○ Probably yes</li> <li>● Yes</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	<p>Breast cancer 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)</p> <p>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 (3). In women with dense breasts, risk of breast cancer is increased (4), 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) (5) .</p>	<p>The GDG prioritised this question for the ECIBC.</p>

### Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE					ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <li>○ Trivial</li> <li>○ Small</li> <li>● Moderate</li> <li>○ Large</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	<p>The included studies did not assess the following outcomes: breast cancer mortality, stage of breast cancer, interval cancer rate, rate of mastectomies, and 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).</p> <p>The GDG recognised that the evidence is not directly comparable because it incorporates study data that looked at a high risk population (BRCA1/2), where the baseline risk is different than for women with high mammographic breast density. It was assumed, with a potentially four-fold baseline risk, that there would be 1-4/1000 additional breast cancers detected per woman screened. As agreement within the GDG for the desirable effects could not be reached, voting among the members without CoI resulted in the following: 18 members voted in favour of 'moderate desirable anticipated effects', and there were no abstentions.</p>
	Breast cancer detection rate (incremental cancer detection rate per exam)	811 (2 observational studies) <sup>1,2</sup>	⊕○○○ VERY LOW <sup>a</sup>	-	<div>Risk with Mammography alone</div> <div>Risk difference with tailored screening with magnetic resonance imaging (MRI) based on high mammographic breast density, in addition to mammography,</div>	
					400 cancers more per 100,000 exams (from 130 more to 680 more) <sup>b</sup>	

	Breast cancer detection rate (incremental cancer detection rate per women)	0 (2 observational studies) <sup>3,4</sup>	⊕○○○ VERY LOW <sup>c</sup>	-	3250 cancers more per 100,000 women (from 1810 more to 4690 more) <sup>b</sup>	
	Recall rate	0 (1 observational study) <sup>5</sup>	⊕○○○ VERY LOW <sup>d</sup>	-	12,670 women recalled per 100,000 exams (from 11,240 more to 14,100 more). <sup>e</sup>	
	Breast cancer mortality - not measured	-	-	-		
	Stage of breast cancer - not measured	-	-	-		
	Interval cancer rate - not measured	-	-	-		
	Rate of mastectomies - not measured	-	-	-		
	Provision of chemotherapy - not measured	-	-	-		
	Adverse effects - not reported	-	-	-	-	-
1. Berg WA, Zhang Z,Lehrer D,Jong RA,Pisano ED,Barr RG,et al. Detection of breast cancer with addition of annual screening ultrasound or a single screening MRI to mammography in women with elevated breast cancer						

	<p>risk. JAMA ; 2012.</p> <ol style="list-style-type: none"> <li>Kriege M, Brekelmans CT, Boetes C, et al.. Efficacy of MRI and mammography for breast cancer screening in women with a familial or genetic predisposition. N Engl J Med; 2004.</li> <li>Kuhl CK, Schrading S, Strobil K, Schild HH, Hilgers RD, Bieling HB. Abbreviated Breast Magnetic Resonance Imaging (MRI): First Postcontrast Subtracted Images and Maximum-Intensity Projection-A Novel Approach to Breast Cancer Screening With MRI. J Clin Oncol; 2014.</li> <li>Chen SQ, Huang M, Shen YY, Liu CL, Xu CX. Application of Abbreviated Protocol of Magnetic Resonance Imaging for Breast Cancer Screening in Dense Breast Tissue. Acad Radiol; 2017.</li> <li>Kuhl CK, Strobil K, Bieling H, Leutner C, Schild HH, Schradingb S. Supplemental Breast MR Imaging Screening of Women with Average Risk of Breast Cancer. Radiology; 2017.</li> </ol> <ol style="list-style-type: none"> <li>Unexplained but unimportant inconsistency with high statistical heterogeneity (<math>I^2 = 95\%</math>, <math>P=0.00</math>).</li> <li>Incremental recall rate.</li> <li>Kuhl study 2014 included women with at least one risk factor for breast cancer.</li> <li>Unexplained but unimportant inconsistency with high statistical heterogeneity (<math>I^2 = 96\%</math>, <math>P=0.0000</math>).</li> <li>Incremental recall rate.</li> </ol> <p>* tailored screening with tomosynthesis based on breast density.</p> <p>No research evidence was identified on the undesirable effects.</p>	
--	--	--

## Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE						ADDITIONAL CONSIDERATIONS
<div>● Large</div> <div>○ Moderate</div> <div>○ Small</div> <div>○ Trivial</div> <div>○ Varies</div> <div>○ Don't know</div>	Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)		MRI does not employ ionising radiation but uses radiofrequency and magnetic fields. There are no papers on the radiation dose from ionising radiation with MRI because there is no radiation dose. MRI is generally considered to have less detrimental health effects compared to imaging which uses ionising radiation.
					Risk with Mammography alone	Risk difference with tailored screening with magnetic resonance imaging (MRI) based on high mammographic breast density, in addition to mammography,	Although no evidence was incorporated on the undesirable effects, the GDG discussed the importance of especially false positives and also possible side effects of contrast enhancement, including allergic reaction or intravenous procedure complications, that are higher with MRI-based screening for women with high mammographic breast density. The GDG agreed that the false positives could be calculated by subtracting the detection rate from the recall rate. Therefore, subtracting 4

	Breast cancer detection rate (incremental cancer detection rate per exam)	811 (2 observational studies) <sup>1,2</sup>	⊕○○○ VERY LOW <sup>a</sup>	-	400 cancers more per 100,000 exams (from 130 more to 680 more) <sup>b</sup>	
	Breast cancer detection rate (incremental cancer detection rate per women)	0 (2 observational studies) <sup>3,4</sup>	⊕○○○ VERY LOW <sup>c</sup>	-	3250 cancers more per 100,000 women (from 1810 more to 4690 more) <sup>b</sup>	
	Recall rate	0 (1 observational study) <sup>5</sup>	⊕○○○ VERY LOW <sup>d</sup>	-	12,670 women recalled per 100,000 exams (from 11,240 more to 14,100 more). <sup>e</sup>	
	Breast cancer mortality - not measured	-	-	-		
	Stage of breast cancer - not measured	-	-	-		
	Interval cancer rate - not measured	-	-	-		
	Rate of mastectomies - not measured	-	-	-		
	Provision of chemotherapy - not measured	-	-	-		
	Adverse effects - not reported	-	-	-	-	-

per 1000 from 120 per 1000 we would get a false positive rate of 116 per 1000 women screened. As agreement within the GDG for the undesirable anticipated effects could not be reached, voting among the members without Col resulted in the following: 7 members voted in favour of 'moderate undesirable anticipated effects', 11 members voted in favour of 'large undesirable anticipated effects'. The GDG discussed the (Kuhl CK, 2017) paper and the (Chen SQ, 2017) paper that presented direct evidence for MRI-tailored screening in average risk population. The GDG expressed concern on the findings of the paper, notably with respect to the way the diagnosis of breast cancer by mammography was carried out. Nevertheless, both papers demonstrated a significantly increased detection rate by MRI, and the concern expressed by the GDG was that there may be a high increase of overdiagnosis by MRI-tailored screening in comparison to mammography screening.

	<ol style="list-style-type: none"> <li>1. Berg WA, Zhang Z,Lehrer D,Jong RA,Pisano ED,Barr RG,et al. Detection of breast cancer with addition of annual screening ultrasound or a single screening MRI to mammography in women with elevated breast cancer risk. JAMA ; 2012.</li> <li>2. Kriege M, Brekelmans CT,Boetes C,et al.. Efficacy of MRI and mammography for breastcancer screening in women with a familial or genetic predisposition. N Engl J Med; 2004.</li> <li>3. Kuhl CK, Schrading S,Strobel K,Schild HH,Hilgers RD,Bieling HB. Abbreviated Breast Magnetic Resonance Imaging (MRI): First Postcontrast Subtracted Images and Maximum- Intensity Projection-A Novel Approach to Breast Cancer Screening With MRI. J Clin Oncol; 2014.</li> <li>4. Chen SQ, Huang M,Shen YY,Liu CL,Xu CX. Application of Abbreviated Protocol of Magnetic Resonance Imaging for Breast Cancer Screening in Dense Breast Tissue. Acad Radiol; 2017.</li> <li>5. Kuhl CK, Strobel K,Bieling H,Leutner C,Schild HH,Schradingb S. Supplemental Breast MR Imaging Screening of Women with Average Risk of Breast Cancer. Radiology; 2017.</li> </ol> <ol style="list-style-type: none"> <li>a. Unexplained but unimportant inconsistency with high statistical heterogeneity (<math>I^2 = 95\%</math>, <math>P=0.00</math>).</li> <li>b. Incremental recall rate.</li> <li>c. Kuhl study 2014 included women with at least one risk factor for breast cancer.</li> <li>d. Unexplained but unimportant inconsistency with high statistical heterogeneity (<math>I^2 = 96\%</math>, <math>P=0.0000</math>).</li> <li>e. Incremental recall rate.</li> </ol> <p>* tailored screening with tomosynthesis based on breast density.</p> <p>No research evidence was identified on the undesirable effects.</p>	
--	--	--

## Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <li>● Very low</li> <li>○ Low</li> <li>○ Moderate</li> <li>○ High</li> <li>○ No included studies</li> </ul>		<p>The GDG agreed the overall certainty is very low as this was the lowest certainty of the critical outcomes (breast cancer detection rate and recall rate) for tailored screening for high mammographic breast density. The research incorporated screening of high-risk women of a range of ages. Age of screening was identified as a concern by the GDG because younger women have higher breast density and this would impact the false positive rates.</p>



## Values

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <li>○ Important uncertainty or variability</li> <li>● Possibly important uncertainty or variability</li> <li>○ Probably no important uncertainty or variability</li> <li>○ No important uncertainty or variability</li> <li>○ No known undesirable outcomes</li> </ul>	<p>No specific studies focusing in MRI were identified. The findings, all from mammography studies, however, are likely to be generalisable to MRI, as both screening tests are associated with similar desirable and undesirable effects (e.g. false positive findings or overdiagnosis).</p> <p>A systematic review (JRC Technical Report PICO 10-11, contract FWC443094012015; available upon request) shows that participants in mammography screening programmes place a low value on the psychosocial and physical effects of false positive results and overdiagnosis. However, participants generally consider these undesirable effects acceptable (<i>low confidence</i>). These findings are of limited value mainly given the significant concerns regarding the adequacy of the information provided to the participants, in order to take an informed decision. Also, acceptability of false positive results is based on studies of participants who have already received a false positive result, whose preferences may differ from the general population. Another finding is that breast cancer screening represents a significant burden for some participants due to the associated psychological distress and inconvenience.</p> <p>Regarding breast cancer diagnosis, there is very limited data available on patients' views. One of the main themes identified in the literature is that patients 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, women have a higher overall preference towards more comfortable, brief diagnostic procedures (<i>low confidence</i>).</p>	<p>The GDG agreed that there is possibly important uncertainty in the way the women would value the increased detection, in the context of the undesirable effects discussed (use of contrast and intravenous injection in a screening population).</p>

## Balance of effects

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <li>○ Favors the comparison</li> <li>● Probably favors the comparison</li> <li>○ Does not favor either the intervention or the comparison</li> <li>○ Probably favors the intervention</li> <li>○ Favors the intervention</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>		<p>The GDG felt that the evidence incorporated was indirect because it is from a high risk population (have BRCA 1/2 mutations) that may be a different age and have different mammographic breast densities. The GDG felt that there is a concern about allergic reactions due to the use of contrast in MRI, and the additional procedure of requiring IV administration of contrast. Age of screening was identified as a concern by the GDG as most studies included a population ranging between 25 and 73 years of age. These are younger women than the normal screening age population (and younger women have higher mammographic density) and this question addresses women with high breast density in the screening age.</p> <p>The GDG agreed that the general population would probably have more false positives in MRI than the high risk population evaluated here, so the comparison (digital mammography) would be favoured even more.</p>

		<p>The GDG felt there is possible uncertainty and variation about the values and preferences of people.</p> <p>As agreement within the GDG for the balance between desirable and undesirable effects could not be reached, voting among the members without Col resulted in the following: 3 members voted in favour of 'favors the comparison', 9 members voted in favour of 'probably favors the comparison' 5 members voted in favour of 'does not favor either the intervention or the comparison', and 1 member abstained. It was noted that the patient representatives on the GDG felt that the balance 'probably favors the comparison', due to the assumed increased risk of false positives with MRI-tailored screening, a significant concern for women.</p>
--	--	---

## Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<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>	<p>No relevant economic evaluations were identified.</p>	<p>Costs associated with breast MRI screening include:</p> <ul style="list-style-type: none"> <li>- Costs of the technology, capital costs of the machines and the lifetime of the machine.</li> <li>- Time to acquire and read the images, storage of several hundred images.</li> <li>- Training for radiographers and radiologists.</li> <li>- Costs associated with the increased recall rate.</li> </ul> <p>The GDG noted that the cost considerations must also include the increased costs that result from the increased recall rate including repetition of exams and biopsies. The GDG noted that the MRI equipment is about four times as expensive, and the examination costs of MRI could be estimated to be ten times higher than those for digital mammography.</p>

<b>Certainty of evidence of required resources</b> What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <li>○ Very low</li> <li>○ Low</li> <li>○ Moderate</li> <li>○ High</li> <li>● No included studies</li> </ul>	No relevant economic evaluations were identified.	
<b>Cost effectiveness</b> Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <li>○ Favors the comparison</li> <li>○ Probably favors the comparison</li> <li>○ Does not favor either the intervention or the comparison</li> <li>○ Probably favors the intervention</li> <li>○ Favors the intervention</li> <li>○ Varies</li> <li>● No included studies</li> </ul>	No relevant economic evaluations were identified.	
<b>Equity</b> What would be the impact on health equity?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <li>○ Reduced</li> <li>○ Probably reduced</li> <li>○ Probably no impact</li> <li>○ Probably increased</li> <li>○ Increased</li> <li>● Varies</li> <li>○ Don't know</li> </ul>	A systematic review was not conducted.	<p>The utilisation of breast cancer screening services may largely depend on the availability of national public screening programmes. There are findings in Europe highlighting that inequalities are larger in countries without population-based screening programmes (Palència L, 2010) . This is indirect evidence as it does not refer to MRI screening.</p> <p>The GDG felt that the impacts on health equity may vary. The GDG felt that the intervention would have different impacts on health equity within countries and between countries. Within countries, there may be different access for persons who have private insurance or easier access to MRI. Across countries, the GDG felt that there would be different access to MRI depending on the country's ability to fund tailored MRI for high mammographic breast density.</p>

## Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <li><input type="radio"/> No</li> <li><input checked="" type="radio"/> Probably no</li> <li><input type="radio"/> Probably yes</li> <li><input type="radio"/> Yes</li> <li><input type="radio"/> Varies</li> <li><input type="radio"/> Don't know</li> </ul>	No specific studies on acceptability of MRI screening were identified.	<p>The GDG discussed acceptability among different stakeholders:</p> <p>For policymakers, increased costs would be a strong concern for acceptability.</p> <p>For radiologists acceptability varies depending on their professional opinion on MRI tailored-screening. Those professionals concerned about contrast medium may not consider it to be at all acceptable.</p> <p>Women would probably not find MRI acceptable due to increased risk of false positives and risk of adverse events.</p>

## Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <li><input type="radio"/> No</li> <li><input checked="" type="radio"/> Probably no</li> <li><input type="radio"/> Probably yes</li> <li><input type="radio"/> Yes</li> <li><input type="radio"/> Varies</li> <li><input type="radio"/> Don't know</li> </ul>	A systematic review was not conducted.	The GDG felt that it would probably not be feasible to implement due to high costs, too few MRI facilities, longer radiologist examination and reading times, increased inequity, and lack of direct evidence on the balance of effects for MRI-tailored screening would make it difficult to convince stakeholders to implement it.

## SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	<b>Moderate</b>	Large		Varies	Don't know
UNDESIRABLE EFFECTS	<b>Large</b>	Moderate	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	<b>Very low</b>	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	<b>Possibly important uncertainty or variability</b>	Probably no important uncertainty or variability	No important uncertainty or variability			No known undesirable outcomes
BALANCE OF EFFECTS	Favors the comparison	<b>Probably favors the comparison</b>	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	<b>Large costs</b>	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			<b>No included studies</b>
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	<b>No included studies</b>
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	<b>Varies</b>	Don't know
ACCEPTABILITY	No	<b>Probably no</b>	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	<b>Probably no</b>	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 a negative mammography, in the context of an organised screening programme, the ECIBC's Guidelines Development Group (GDG) suggests not implementing tailored screening with magnetic resonance imaging (MRI) over mammography screening alone (conditional recommendation, very low certainty of the evidence).

### Justification

#### Overall justification

As agreement within the GDG for the strength of this recommendation could not be reached, voting among the members without CoI resulted in the following: 9 members voted in favour of 'strong recommendation against the intervention', 9 members voted in favour of 'conditional recommendation against the intervention', and there were no abstentions. GDG voting rules indicate that a strong recommendation cannot be made without an 80% qualified majority.

#### Detailed justification

##### *Desirable Effects*

The GDG felt there would be moderate desirable effects through the increased identification of approximately 1-4 cancers per 1000 women screened through the use of MRI-tailored screening for high mammographic breast density.

##### *Undesirable Effects*

The GDG felt there would be large undesirable effects due to the increased recall rate and false positive rate. Additionally there would be increased adverse events due to the use of intravenous administered contrast enhancement for MRI-tailored screening.

##### *Acceptability*

The GDG agreed that MRI-tailored screening would probably not be acceptable to key stakeholders including women and policy makers; the GDG felt there would be variable acceptance among radiologists.

##### *Feasibility*

The GDG felt that it would probably not be feasible to implement due to high costs, too few MRI facilities, longer radiologist examination and reading times, increased inequity, and lack of direct evidence on the balance of effects for MRI-tailored screening.

## Subgroup considerations

The GDG used indirect evidence from women in whom MRI is recommended. This recommendation is for the women specified in the question. In very high risk women (with BRCA gene mutations) the balance of desirable and undesirable health effects is different.

## Implementation considerations

The GDG did not feel that there is a current trend towards women receiving MRI-tailored screening for dense breast in practice, and therefore no considerations required for this conditional recommendation against using MRI-tailored screening.

## Monitoring and evaluation

The GDG did not feel that there were any monitoring and evaluation considerations as MRI-tailored screening for women with high mammographic breast density was not felt to be currently conducted in practice.

## Research priorities

Not all GDG members felt that there is a need for further research. GDG members acknowledged that there are clinical trials ongoing regarding MRI-tailored screening for women with high breast density. Research priorities included:

1. Research into the balance of effects, including the potential risk of adverse events due to contrast reaction or intravenous procedures is required for MRI.
2. Research to improve the specificity of MRI-tailored screening.

## REFERENCES SUMMARY

1. Ferlay, J, Soerjomataram, I , Ervik, M, Dikshit, R , Eser, S , Mathers, C, Rebelo, M, Parkin, DM, Forman, D, Bray, F. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide. 2013.
2. Gilbert, F. J., Tucker, L., Gillan, M. G., Willsher, P., Cooke, J., Duncan, K. A., Michell, M. J., Dobson, H. M., Lim, Y. Y., Suaris, T., Astley, S. M., Morrish, O., Young, K. C., Duffy, S. W.. Accuracy of Digital Breast Tomosynthesis for Depicting Breast Cancer Subgroups in a UK Retrospective Reading Study (TOMMY Trial). Radiology; Dec 2015.
3. Gilbert FJ, Tucker L,Gillan MG,Willsher P,Cooke J,Duncan KA,Michell MJ,Dobson HM,Lim YY,Purushothaman H,Strudley C,Astley SM,Morrish O,Young KC,Duffy SW.. The TOMMY trial: a comparison of TOMosynthesis with digital MammographY in the UK NHS Breast Screening Programme--a multicentre retrospective reading study comparing the diagnostic performance of digital breast tomosynthesis and digital mammography with digital mammography alone.. Health Technol Assess; 2015.
4. McCormack VA, dos Santos Silva I. Breast Density and Parenchymal Patterns as Markers of Breast Cancer Risk: A Meta-analysis. Cancer Epidemiol Biomarkers Prev; 2006.
5. Gierach GL, Ichikawa L,Kerlikowske K,Brinton LA,Farhat GN,Vacek PM,et al. Relationship between mammographic density and breast cancer death in the Breast Cancer Surveillance Consortium. J Natl Cancer Inst; 2012.



# Evidence profile

<b>Healthcare question</b>	Should tailored screening with magnetic resonance imaging (MRI) 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?
<b>Date</b>	April 2016
<b>Authors</b>	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
<b>Abbreviations</b>	<b>CI:</b> Confidence interval <b>RR:</b> Risk ratio <b>MD:</b> Mean difference

Certainty assessment							N° of patients		Effect		Certainty	Importance
N° of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tailored screening with MRI based on high demographic breast density, in addition to mammography	Mammography alone	Relative (95% CI)	Absolute (95% CI)		
Breast cancer detection rate (incremental cancer detection rate per exam)												
2 (1,2)	observational studies	not serious	serious (a)	not serious	not serious	none	400 cancers more per 100 000 exams (from 130 more to 680 more) (b)				⊕○○○ VERY LOW	CRITICAL
Breast cancer detection rate (incremental cancer detection rate per women)												
2 (3,4)	observational studies	not serious	not serious	serious (c)	not serious	none	3 250 cancers more per 100 000 women (from 1810 more to 4690 more) (b)				⊕○○○ VERY LOW	CRITICAL
Recall rate												
1 (5)	observational studies	not serious	serious (d)	not serious	not serious	none	12 670 women recalled per 100 000 exams (from 11 240 more to 14 100 more) (e)				⊕○○○ VERY LOW	CRITICAL
Breast cancer mortality - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Stage of breast cancer - not measured												

Certainty assessment							N° of patients		Effect		Certainty	Importance
N° of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tailored screening with MRI based on high demographic breast density, in addition to mammography	Mammography alone	Relative (95% CI)	Absolute (95% CI)		
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Interval cancer rate - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Rate of mastectomies - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Provision of chemotherapy - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Adverse effects - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

## Explanations

- Unexplained but unimportant inconsistency with high statistical heterogeneity ( $I^2 = 95\%$ ,  $P=0.00$ ).
- Incremental recall rate.
- Kuhl study 2014 included women with at least one risk factor for breast cancer.
- Unexplained but unimportant inconsistency with high statistical heterogeneity ( $I^2 = 96\%$ ,  $P=0.0000$ ).
- Incremental recall rate.

## References

- Berg WA, Zhang Z, Lehrer D, Jong RA, Pisano ED, Barr RG, et al. Detection of breast cancer with addition of annual screening ultrasound or a single screening MRI to mammography in women with elevated breast cancer risk. JAMA ; 2012.
- Kriege M, Brekelmans CT, Boetes C, et al.. Efficacy of MRI and mammography for breastcancer screening in women with a familial or genetic predisposition. N Engl J Med; 2004.
- Kuhl CK, Schrading S, Strobel K, Schild HH, Hilgers RD, Bieling HB. Abbreviated Breast Magnetic Resonance Imaging (MRI): First Postcontrast Subtracted Images and Maximum- Intensity Projection-A Novel Approach to Breast Cancer Screening With MRI. J Clin Oncol; 2014.
- Chen SQ, Huang M, Shen YY, Liu CL, Xu CX. Application of Abbreviated Protocol of Magnetic Resonance Imaging for Breast Cancer Screening in Dense Breast Tissue. Acad Radiol; 2017.
- Kuhl CK, Strobel K, Bieling H, Leutner C, Schild HH, Schradingb S. Supplemental Breast MR Imaging Screening of Women with Average Risk of Breast Cancer. Radiology; 2017.

# Bibliography

## Evidence of effects

Berg WA, Zhang Z, Lehrer D, Jong RA, Pisano ED, Barr RG, et al. Detection of breast cancer with addition of annual screening ultrasound or a single screening MRI to mammography in women with elevated breast cancer risk. JAMA 2012;307(13):1394-404.

Chen SQ, Huang M, Shen YY, Liu CL, Xu CX. Application of Abbreviated Protocol of Magnetic Resonance Imaging for Breast Cancer Screening in Dense Breast Tissue. Acad Radiol. 2017 Mar;24(3):316-320..

Kriege M, Brekelmans CT, Obdeijn IM, Boetes C, Zonderland HM, Muller SH, et al. Factors affecting sensitivity and specificity of screening mammography and MRI in women with an inherited risk for breast cancer. Breast Cancer Res Treat. 2006;100(1):109-19.

Kuhl CK, Schrading S, Strobel K, Schild HH, Hilgers RD, Bieling HB. Abbreviated Breast Magnetic Resonance Imaging (MRI): First Postcontrast Subtracted Images and Maximum-Intensity Projection-A Novel Approach to Breast Cancer Screening With MRI. J Clin Oncol. 2014;32(22):2304-10.

Kuhl CK, Strobel K, Bieling H, Leutner C, Schild HH, Schrading S. Supplemental Breast MR Imaging Screening of Women with Average Risk of Breast Cancer. Radiology. 2017 May;283(2):361-370.

## 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

Not available

## Values and preferences

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