EUROPEAN COMMISSION
JOINT RESEARCH CENTRE

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

European Commission Initiative on Breast Cancer (ECIBC):

European guidelines on breast cancer screening and diagnosis

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QUESTION	
Should tailored screening with automated breast ultrasound system (ABUS) 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 density and a negative mammography
INTERVENTION:	tailored screening with automated breast ultrasound system (ABUS) 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, and adverse effects (including radiation exposure, radiation induced cancers-related to radiation dose, overdiagnosis related adverse effects, false positive related adverse effects).
SETTING:	European Union
PERSPECTIVE:	Population (National Health System)
BACKGROUND:	Breast cancer is the second most 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 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: (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 (MRI).
CONFLICT OF INTEREST:	Management of Conflicts of Interest (CoI): CoIs 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 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

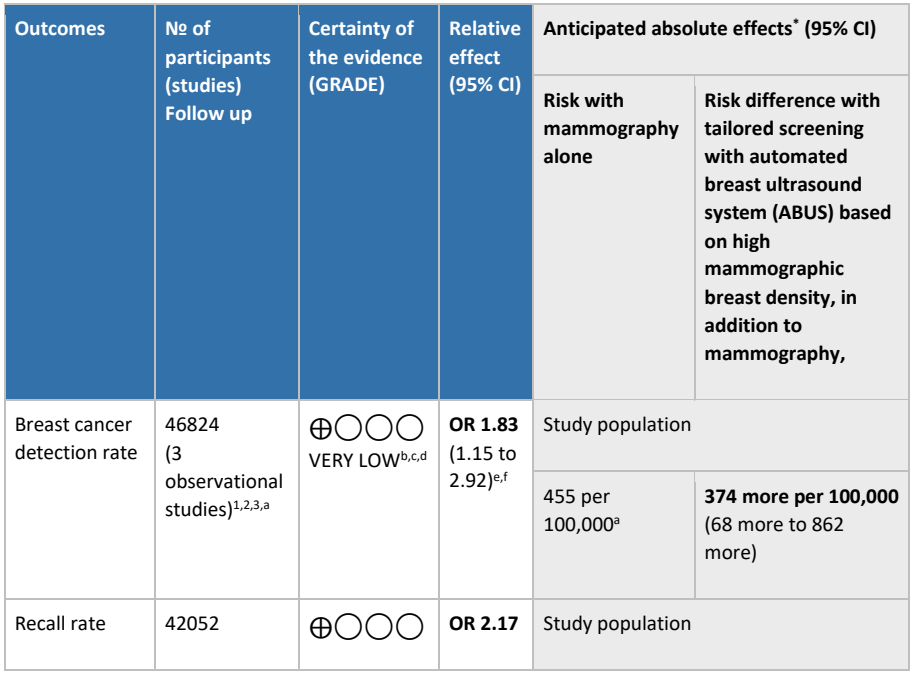
Problem

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 (2). 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		The included studies did not assess the following outcomes: 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). Increases in cancer detection rates were 119-238 additional cases of cancer detected per 100,000 women screened. The GDG members noted that the sensitivity in the Giuliano study appeared to be very low for the mammography screening that was conducted (5) . Detection rate for absolute effects in high risk vs. low risk populations cannot be compared. However, relative effects should not differ. GDG members pointed out that there is an interaction between risk factors (other than breast density) and detection rate, and therefore absolute or relative effects may not be comparable. As agreement was not reached, voting was conducted among GDG members: 8 members voted "moderate" effects; 7 members voted they "don´t know".

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 automated breast ultrasound system (ABUS) based on high mammographic breast density, in addition to mammography,
Breast cancer detection rate	46824 (3 observational studies)[1,2,3,a]	⨁◯◯◯ VERY LOW[b,c,d]	**OR 1.83** (1.15 to 2.92)[e,f]	Study population	
				455 per 100,000[a]	**374 more per 100,000** (68 more to 862 more)
Recall rate	42052	⨁◯◯◯	**OR 2.17**	Study population	

	(2 observational studies)[2,3,g]	VERY LOW[b,c,h,i]	(0.75 to 6.25)[e]	11,517 per 100,000[g]	**10,507 more per 100,000** (2,623 fewer to 33,341 more)
Interval cancer rate (one-year)	6425 (1 observational study)[2]	⨁⨁◯◯ LOW[j]	-	Interval cancer rate of 1.7 per 1,000 exams (11/6425 exams)	
Breast cancer Mortality - not reported	-	-	-	-	-
Stage of breast cancer - not reported	-	-	-	-	-
Rate of mastectomies - not measured	-	-	-	-	-

1. Giuliano V, Giuliano C. Improved breast cancer detection in asymptomatic women using 3D-automated breast ultrasound in mammographically dense breasts. Clin Imaging ; 2013.
2. Kelly KM, Dean J,Comulada WS,Lee SJ. Breast cancer detection using automated whole breast ultrasound and mammography in radiographically dense breasts. Eur Radiol; 2010.
3. Brem RF, Tabár L,Duffy SW,Inciardi MF,Guingrich JA,Hashimoto BE,et al. Assessing improvement in detection of breast cancer with three dimensional automated breast US in women with dense breast tissue: the SomoInsight Study. Radiology; 2015.

a. Median or mean of the control group of the included studies as appropriate unless otherwise specified.
b. Potential aspects related with risk of bias (selection and misclassification bias) were considered not important given the consistency of results across studies.
c. Two studies included women with personal or family history of breast cancer (Brem 2015, Kelly 2010).
d. High statistical heterogeneity (I^2= 86%, P= 0,001) were considered not important given the consistency of results across studies.
e. Relative effect was adjusted for paired design.
f. Incremental cancer detection rate was 174 cancers per 100,000 (from 119

more to 238 more) (Brem 2015, Kelly 2010). Incremental cancer detection rate was 1053 more cancers per 100,000 (from 738 more to 1455 more) (Giuliano 2013)

g. Median or mean of the control group of the included studies may vary based on baseline risk in a population.
h. High statistical heterogeneity (I^2= 100%, P= 0,000) were considered not important given the consistency of results across studies.
i. 95% CI includes both benefits and harms.
j. One study included women with personal or family history of breast cancer (Kelly 2010).

* tailored screening automated breast ultrasound system (ABUS) based on breast density

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT

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

RESEARCH EVIDENCE

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 automated breast ultrasound system (ABUS) based on high mammographic breast density, in addition to mammography,
Breast cancer detection rate	46824 (3 observational studies)[1,2,3,a]	⨁◯◯◯ VERY LOW[b,c,d]	**OR 1.83** (1.15 to 2.92)[e,f]	Study population	
				455 per 100,000[a]	**374 more per 100,000** (68 more to 862 more)
Recall rate	42052 (2 observational studies)[2,3,g]	⨁◯◯◯ VERY LOW[b,c,h,i]	**OR 2.17** (0.75 to 6.25)[e]	Study population	
				11,517 per 100,000[g]	**10,507 more per 100,000** (2,623 fewer to 33,341 more)

ADDITIONAL CONSIDERATIONS

Recall rate definitions vary cross included studies: In Kelly's study, it is defined as women needing additional imaging or other investigation after imaging (6). In Brem's study it is defined as all women with potential malignancies needing other evaluations (7). Giuliano's study provides no definition (5).

GDG members disagreed on whether the same recall rate can be used for different risk groups.

Interval cancer rate (one-year)	6425 (1 observational study)[2]	⨁⨁◯◯ LOW[j]	-	Interval cancer rate of 1.7 per 1,000 exams (11/6425 exams)	
Breast cancer Mortality - not reported	-	-	-	-	-
Stage of breast cancer - not reported	-	-	-	-	-
Rate of mastectomies - not measured	-	-	-	-	-

1. Giuliano V, Giuliano C. Improved breast cancer detection in asymptomatic women using 3D-automated breast ultrasound in mammographically dense breasts. Clin Imaging ; 2013.
2. Kelly KM, Dean J,Comulada WS,Lee SJ. Breast cancer detection using automated whole breast ultrasound and mammography in radiographically dense breasts. Eur Radiol; 2010.
3. Brem RF, Tabár L,Duffy SW,Inciardi MF,Guingrich JA,Hashimoto BE,et al. Assessing improvement in detection of breast cancer with three dimensional automated breast US in women with dense breast tissue: the SomoInsight Study. Radiology; 2015.

a. Median or mean of the control group of the included studies as appropriate unless otherwise specified.
b. Potential aspects related with risk of bias (selection and misclassification bias) were considered not important given the consistency of results across studies.
c. Two studies included women with personal or family history of breast cancer (Brem 2015, Kelly 2010).
d. High statistical heterogeneity (I^2= 86%, P= 0,001) were considered not important given the consistency of results across studies.
e. Relative effect was adjusted for paired design.
f. Incremental cancer detection rate was 174 cancers per 100,000 (from 119 more to 238 more) (Brem 2015, Kelly 2010). Incremental cancer detection rate was 1053 more cancers per 100,000 (from 738 more to 1455 more) (Giuliano 2013)
g. Median or mean of the control group of the included studies may vary based on baseline risk in a population.
h. High statistical heterogeneity (I^2= 100%, P= 0,000) were considered not

	important given the consistency of results across studies. i. 95% CI includes both benefits and harms. j. One study included women with personal or family history of breast cancer (Kelly 2010). * tailored screening automated breast ultrasound system (ABUS) based on breast density	

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		This was the lowest certainty of the critical outcomes (breast cancer detection rate and recall rate) for tailored screening for high mammographic breast density.

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 on ABUS 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 ABUS, 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*). However, these were not investigated specifically in relation to the potential outcomes from ABUS in addition to mammography. Also, the results do not necessarily apply to this population, of women informed of their enhanced risk due to breast density and offered additional imaging as a result.	The GDG members agreed that there is important uncertainty or variability in the value people place on the main outcomes.

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	Insufficient research evidence was identified.	GDG had smaller concerns with the link between higher detection rate and mortality for this recommendation than for the HHUS one, because the increase in the detection rate in ABUS is substantially higher than in HHUS.

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 research evidence was identified.	ABUS equipment is much more expensive than HHUS, but there are savings with regards to physicians' time as technicians perform the test, unlike HHUS where radiologists perform the test. However, interpretation time by physicians is longer in ABUS, although it is easier to organise. The GDG members felt that interpretation time for ABUS is similar to DBT. Whereas HHUS utilises the same ultrasound machines already used in a hospital, ABUS requires a new machine with significant increased costs. As agreement was not reached, voting was conducted among GDG members: 9 members voted "large costs"; 5members voted "moderate costs".

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 research evidence was identified.	

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 research evidence was identified.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence was identified.	The GDG considered that there may be increased inequity with respect to implementation across Europe. This is due to variation in availability of systems, trained specialists and financial resources. The GDG felt that, within programmes, there may be policy decisions to restrict the programme, 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 about considering the use of ABUS were identified. However, a systematic review (JRC Technical Report PICO 16-17, contract FWC443094032016; available upon request) found a number of barriers associated with breast cancer screening with mammography. See the reviews of mammography screening for details. However, the results of these may not apply specifically to this population of women at enhanced risk and informed as such, due to breast density, and offered additional imaging as a result.	The GDG members acknowledged that the fact that ABUS is being already used in certain settings is evidence that it is, therefore, probably an acceptable intervention. The GDG members felt ABUS would be very acceptable to screening participants, as ABUS-tailored screening has no radiation exposure and the physical discomfort associated with mammography would not be present. Payers may not find it acceptable due to larger costs of ABUS for minor increases in breast cancer detection rates.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know		The cost for purchasing the specialised equipment impacts on feasibility.

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 not implementing tailored screening with automated breast ultrasound system (ABUS) over mammography screening alone (conditional recommendation, very low certainty of the evidence).

Justification

The conditional recommendation (rather than strong) against tailored screening with ABUS in addition to mammography screening over mammography screening alone in women with high mammographic breast density, in the context of an organised screening programme, was the result of a balance of the health effects that does not favour either the intervention nor the comparison, in the context of very low certainty in the evidence about these effects. There were concerns regarding the optimal quality control and workflow necessary for implementing ABUS as well as the large resource (cost) associated.

The GDG noted the scarcity of evidence. There was an improved detection rate of ABUS plus mammography over mammography, however, this improvement was smaller as compared to alternative imaging modalities such as DBT (see recommendation for this intervention), although no direct comparison of ABUS and DBT was made. The GDG members expressed their concern about the quality assurance for ABUS in contexts where training is variable and screening is opportunistic and not organised. The GDG members also noted that for ABUS, the time needed by the physician to interpret the image is increased, although there is a saving with regards to the physician time in carrying out ABUS, as it is a technician who does this. In the future, evidence may answer some of the outstanding questions on resources, clinical endpoints etc., and the the recommendation will be updated.

Subgroup considerations

Women with high mammographic breast density are the subgroup assessed for this recommendation. The GDG members felt that it may be of interest to study the benefit of this technology for women with other risk factors (apart from mammographic breast density).

Implementation considerations

The GDG felt that information and education for women about dense breasts is critical. The opinion of women regarding ABUS depends on the quality of the information provided to them with regards to the evidence behind this modality for tailored screening, including the information concerning the limitations or uncertainty about the effects of ABUS and inter-operator variability. Whereas HHUS utilises the same ultrasound machines already used in a hospital, ABUS requires a new machine with significant increased costs. In addition, special training is required for radiographers delivering the intervention and radiologists interpreting the images.

If ABUS were implemented, either contrary to the recommendation above, or after further evidence, quality assurance and monitoring protocols would need to be developed.

Monitoring and evaluation

None were considered by the GDG.

Research priorities

The absence of evidence on beneficial and adverse effects suggests a need for research to provide this evidence.

Development of quality standards might also flow from this research.

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6. Kelly KM, Dean J,Comulada WS,Lee SJ. Breast cancer detection using automated whole breast ultrasound and mammography in radiographically dense breasts. Eur Radiol; 2010.
7. Brem RF, Tabár L,Duffy SW,Inciardi MF,Guingrich JA,Hashimoto BE,et al. Assessing improvement in detection of breast cancer with three dimensional automated breast US in women with dense breast tissue: the SomoInsight Study. Radiology; 2015.