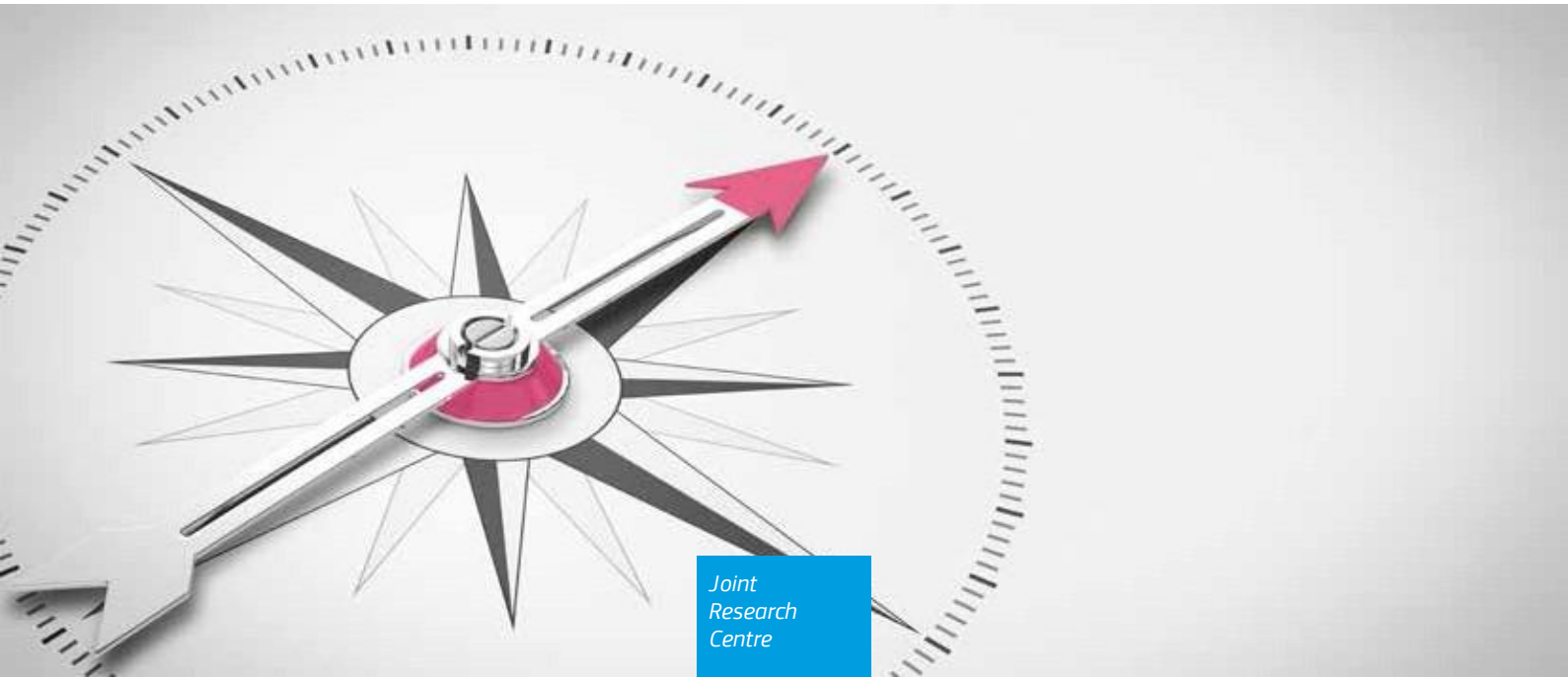
European Commission

# Methods of the European guidelines for breast cancer screening and diagnosis



Joint Research Centre

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The European guidelines for breast cancer screening and diagnosis (in short, *European Breast Guidelines*) include evidence-based recommendations for screening and diagnosis of breast cancer.

The *European Breast Guidelines* are part of the European Commission Initiative on Breast Cancer (ECIBC). They are developed under the supervision of the Joint Research Centre (JRC) with the support of the Guidelines Development Group (GDG). The GDG was nominated via a transparent and open procedure with clearly stated rules (open call for expression of interest).

## Overview of transparency and independence in the *European Breast Guidelines* (and ECIBC) context

Identifying and managing conflict of interest (CoI) of contributors is a key attribute and requirement for trustworthy guidelines and reduces the risk of bias in the development of recommendations (1). Preventive actions were taken to ensure independence of the GDG: (i) GDG members and contributors are nominated through a transparent and open process; (ii) GDG members and contributors act upon their personal capacity and do not represent any entity or affiliation; (iii) GDG members and contributors, have to sign a confidentiality and a commitment form, implying that the content of the meetings' discussions and decisions taken in the context of the ECIBC cannot be disclosed during the mandate and in the future – this helps protecting them from possible pressures from external groups of interest; (iv) the systematic reviews were outsourced to an external contractor, the Iberoamerican Cochrane Centre (CCIb - GRADE center, Barcelona, Spain), thus minimising the possible experts bias in the selection and evaluation of the available literature.

As corrective measures, CoI of all GDG members and other contributors are assessed and managed by the JRC following an established procedure in line with the EC rules and their participation in the development of the recommendations limited accordingly.

# Overview of the GRADE approach in the *European Breast Guidelines*

The *European Breast Guidelines* are developed with GRADE (*Grading of Recommendations Assessment, Development and Evaluation*).

Increasingly being adopted by organisations worldwide, GRADE provides a system for rating quality of evidence and strength of recommendations that is structured and explicit (1).

GRADEpro Guideline Development Tool (GRADEpro GDT), is the web solution of the GRADE working group, will allow the management of the whole guideline development process (2) and the GDG indeed uses GRADEpro GDT to select the questions to be answered with recommendations.

***For more information on the use of GRADE Evidence to decision frameworks please see document prepared by the Methodologist Co-Chair of the GDG:***

http://europa.eu/!vu39yX

***For more information on how to apply the GRADE methodology framework:***

http://www.gradeworkinggroup.org/publications/JCE_series.htm.

## 1. Prioritisation of the *European Breast Guidelines* questions

The JRC compiles an extensive list of potential questions, which is completed by the GDG.

The potential questions to be included in the *European Breast Guidelines* are submitted for public consultation, together with the guidelines' scope, and new questions are added to the list.

Finally, the GDG agrees on a final list of potential questions based on an initial maximum overall number of 90 for inclusion in the *European Breast Guidelines*.

The JRC incorporates the list of potential questions into the GRADEpro GDT platform.

Each GDG member rates the relevance of each question and the questions are then ranked according to the aggregated ratings of the GDG members.

The GDG agrees on the final list of prioritised questions at a physical meeting.

## 2. Framing the questions

The GDG formulates the questions of the *European Breast Guidelines* according to a standard structured format, generally called PICO format.

**For management questions** (questions about the effects of interventions), the PICO framework stands for: **P**opulation under study; **I**ntervention; **C**omparator: other main options; and **O**utcomes that are important to consumers and relevant stakeholders.

**For diagnostic questions**, there are four components: Target condition to be diagnosed; Health problem; Index test; Comparator test; and Outcomes.

The GDG defines the components of each question. In the case of the outcomes, a dedicated prioritisation exercise is run and only those marked by the GDG as 'critical' or 'important' for decision making are included.

## 3. Quality of the evidence related to each question

The JRC has outsourced the systematic review to an external team selected according to the usual tendering procedures of the Commission[1]. It is a multidisciplinary group of methodologists, information specialists, health economists, and qualitative researchers based at the CCIb (GRADE center, Barcelona, Spain).

Each guideline recommendation is based on the best available body of evidence obtained through systematic reviews (3-5). For each question, the systematic review team seeks evidence related to all patient-important outcomes and for the value patients place on these outcomes. In order to do so, the systematic review team can identify and use already existing high quality systematic reviews or conduct *de novo* systematic reviews (3). These systematic reviews are based on exhaustive search strategies allowing the identification of relevant evidence related to each critical or important outcome (6).

In the context of guidelines, quality reflects "our confidence that the effect estimates are adequate to support a particular recommendation". GRADE proposes four levels of quality of the evidence: high; moderate; low; or very low. The systematic review team follows a two-step process for rating the quality of evidence (7).

### 1st step: rate the overall quality of evidence for each outcome across studies

The rating of the quality of evidence for each outcome begins with the study design (trials or observational studies). For questions about the effects of healthcare interventions, the study design of choice is the randomised controlled trial (8).

Next, GRADE addresses five reasons to possibly rate down and three to possibly rate up the quality of evidence (3).

| **Factors that can reduce the quality of evidence** | **Factors that can increase the quality of evidence** |
|---|---|
| 1. Limitations in study design or execution (risk of bias)<br>2. Inconsistency of results<br>3. Indirectness of evidence<br>4. Imprecision<br>5. Publication bias | 1. Large magnitude of effect<br>2. All plausible confounding would reduce the demonstrated effect or increase the effect if no effect was observed<br>3. Dose-response gradient |

1 Tender: http://ted.europa.eu/udl?uri=TED:NOTICE:248695-2014:TEXT:EN:HTML&tabId=1

### 2nd step: rate the overall quality of evidence for each recommendation across all outcomes

The quality of evidence may differ across the outcomes of the same question. Therefore, the overall quality of evidence for a recommendation is a combined rating of the quality of evidence across all outcomes considered critical for answering that question (9). In this line, the systematic review team proposes an overall quality of evidence across all the critical outcomes essential for each recommendation.

This overall quality of evidence is then discussed and agreed with the GDG.

The systematic review team produces 'evidence tables' summarising the body of evidence for each recommendation (9).

This to facilitate a transparent discussion during the GDG meetings. In particular, two tables per question are shared and discussed with the GDG (3):

a. **«GRADE evidence profile»**, which presents the quality of evidence, the judgments that bear on the quality rating, and the effects of alternative management strategies on the outcomes of interest.

b. **«Summary of findings (SoF)» table**, which provides a summary of findings for each of the included outcomes and the quality of evidence for each outcome in a quick and accessible format, without details of the judgements.

In cases where there is:

- no readily available direct evidence
- the GDG has high confidence that indirect evidence supports a net benefit, but retrieving and reviewing this evidence would be onerous and very time consuming;

The GDG will decide whether to proceed with a formal GRADE appraisal or check if the good practice statement checklist criteria are met (11, 12). In brief, the GDG must agree that:

- the statement is clear and actionable
- the message is really necessary
- there is a large and unequivocal net benefit
- specific issues are considered (eg. equity)
- the rationale is explicitly made.

Only when all these criteria are met will the GDG issue a good practice statement instead of carrying out a full evidence assessment. The specific workflow followed is outlined in Annex I.

## 4. Going from the evidence to the recommendation

The systematic review team provides frameworks to help the GDG making recommendations.

The systematic review team populates the Evidence to Decision (EtD) frameworks which provide a systematic and transparent approach for going from the evidence to the healthcare decision. EtDs include criteria and judgements based on these criteria that are informed by research evidence and additional considerations. The EtDs criteria examine: a.) Magnitude of the problem. b.) Magnitude of desirable anticipated effects. c) Magnitude of undesirable anticipated effects. d.) Certainty of the evidence of effects. e.) Confidence in people's values and preferences of main outcomes. f.) Balance between desirable and undesirable effects. g.) Magnitude of resource requirements (costs). h.) Certainty of evidence of required resources. i.) Cost-effectiveness of the intervention. j.) Impact on health equity. k.) Acceptability of intervention

to key stakeholders. l.) Feasibility of implementation of intervention.

The EtD frameworks prepared by the systematic review team are used to vote or achieve consensus within the GDG meetings on the criteria that influence a recommendation or decision.

The systematic review team proposes a neutral draft recommendation. Based on this draft (and on the final EtD framework) the GDG agrees on the direction of each recommendation (for or against an option) and its strength (strong or weak- conditional).GRADE defines the strength of a recommendation as "the extent to which one can be confident that the desirable effects of an intervention outweigh its undesirable effects" (10).

## 5. Approval and publication of the *European Breast Guidelines* recommendations

All the recommendations and good practice statements, and underpinning work, once approved, will be made publicly available on the *ECIBC web hub*. The approval process foresees several steps:

The GDG approves the recommendation.

The JRC agrees with the GDG and with the European Commission Directorate General for Health and Food Safety (DG SANTE) the publication strategy (how and when recommendations are issued on the *ECIBC web hub*) and the dissemination strategy.

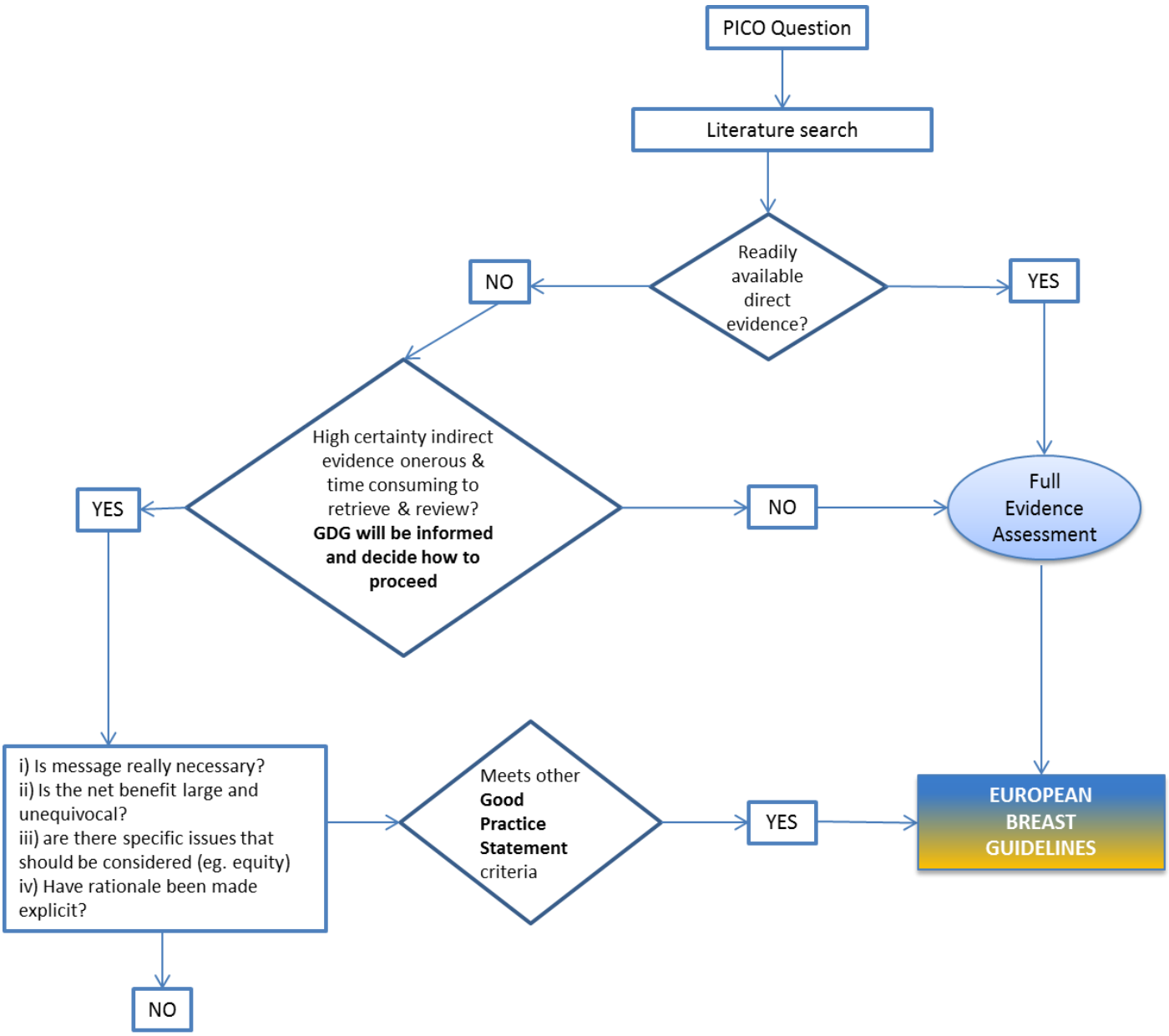
The EC (JRC + DG SANTE) presents the recommendations to the EU Expert Group on Cancer Control (the expert group supporting the EC for cancer-related policies).

The recommendations are published on the ECIBC web hub.

**Only after having posted the recommendations and attached information on the *ECIBC web hub*, publications on peer-reviewed journals can be foreseen.**

Only when updating would be needed, e.g. due to new available evidence, the text and underpinning information of recommendations and good practice statements will be changed and the update date clearly marked.

# 6. Annex I: Good practice statement flowchart



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