**UNIVERSIDADE DE SÃO PAULO**
**FACULDADE DE MEDICINA DE RIBEIRÃO PRETO**

**JULIE FRANCIS SPRAKEL**

# A systematic review of the research gaps in breast cancer in the Gulf region

**RIBEIRÃO PRETO**
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Tese apresentada à Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo para obtenção do Título de Doutor em Ciências.

**Área de Concentração:** Ginecologia e Obstetrícia.

**Orientador: Prof. Dr. Hélio Humberto Angotti Carrara**

**RIBEIRÃO PRETO**

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# *Dedication*

*The unwavering belief from my friends, family and colleagues. The drive from my patients and the community. To Prof. Fedorowicz, you have supported me further than I could have ever imagined in my professional career, I am immensely grateful. To Prof. Carrara, your belief in my journey, your guidance, support and friendship- I am indebted to you and the School of Medicine at USP. To each of the respective multidisciplinary teams and patients, your trust and willingness to support will only further support current and future healthcare professionals with evidence based clinical decisions. This PhD was a chance to prove to myself what others already knew, but overall this thesis is for my daughter Yasmine- a future mother, wife and leader.*

# *Dedicatória*

*À crença inabalável de meus amigos, familiares e colegas. À motivação dos meus pacientes e da comunidade. Para o professor Fedorowicz, você me apoiou mais do que eu jamais poderia imaginar em minha carreira profissional, sou imensamente grato. Para o professor Carrara, sua crença em minha jornada, sua orientação, apoio e amizade - estou em débito com você e a Faculdade de Medicina da USP. Para cada uma das equipes multidisciplinares e respectivas pacientes, sua confiança e vontade de apoiar apenas sustentarão ainda mais os profissionais de saúde atuais e futuros, com decisões clínicas baseadas em evidências. Esse doutorado foi uma chance de provar para mim mesmo o que os outros já sabiam, mas no geral essa tese é para minha filha Yasmine - uma futura mãe, esposa e líder.*

## *Declaration*

This PhD thesis was supervised by Prof. Helio Carrara (Department of Gynecology and Obstetrics, Riberão Preto Medical School, University of Sao Paulo, Brazil) and represents an original contribution in research, innovation, aiming at an academic development according to breast cancer guidelines in Bahrain.

## *Declaração*

Esta tese de doutorado foi supervisionada pelo Prof. Helio Carrara (Departamento de Ginecologia e Obstetrícia da Faculdade de Medicina de Riberão Preto, Universidade de São Paulo, Brasil) e representa uma contribuição original em pesquisa, inovação, visando o desenvolvimento acadêmico de acordo com as diretrizes do câncer de mama em Bahrain**.**

***This is the first version of the breast cancer screening, diagnosis and treatment guideline for the Kingdom of Bahrain which was developed using the RAPADAPTE approach to guideline development. This guideline project was presented to the Supreme Council of Health as a national project, with full endorsement. It will be disseminated across Bahrain by the Charity and updated periodically as and when additional evidence is made available or when driven by changes in epidemiological data.***

## *Apoio Financeiro*

Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - CAPES

# *Resumo*

Sprakel JF. **Revisão sistemática das lacunas em pesquisa do câncer de mama na região do Golfo.** Tese (Doutorado) - Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo. Ribeirão Preto. 2020.

Fornecer um recurso de alta qualidade, atualizado e baseado em evidências, com recomendações baseadas na abordagem GRADE e algoritmos clínicos para permitir decisões clínicas compartilhadas. Com base nas diretrizes de prática clínica existentes, o trabalho concluído fornece uma visão local por meio do concurso estratégico de uma equipe multidisciplinar, principalmente local, e que inclui a representação de pacientes. O esforço geral mudou a percepção do papel de uma organização não governamental (ONG) e destacou que uma parceria governamental/não governamental poderia preencher as lacunas e apoiar melhor a comunidade. Esse recurso abrangente e contemporâneo pode ser utilizado em toda a continuidade do tratamento do câncer de mama, tanto para os profissionais de saúde quanto para as pacientes, para navegar melhor pelas vias clínicas e fornecer recomendações de melhores práticas para a tomada de decisões compartilhada e informada. O método RAPADAPTE forneceu rápida adaptação de diretrizes e recursos de evidências e minimizou repetições desnecessárias, em vez de desenvolver a diretriz “de novo”. O RAPADAPTE baseia-se no método ADAPTE bem estabelecido e foi usado para desenvolver uma diretriz semelhante para o câncer de mama na Costa Rica. Esse método inclusivo e inovador envolveu um processo de revisão por pares usando ferramentas como o AGREE II, os Red Flags de Lenzer e os critérios do Institute of Medicine (IOM). Isso deu credibilidade internacional e melhores práticas atualizadas aos profissionais de primeira linha nos centros de saúde de todo o Reino, em relação ao diagnóstico, rastreamento e tratamento do câncer de mama. Também foi projetado para ser facilmente acessível à comunidade no formato de caminhos e algoritmos do paciente. O estabelecimento da primeira abordagem interativa e multidisciplinar, centrada no paciente, para o desenvolvimento de diretrizes para o tratamento, rastreamento e diagnóstico do câncer de mama no Bahrein. Essa diretriz baseada em evidências e com característica local não apenas usou o compartilhamento de recursos, mas foi desenvolvida com pouco custo direto. Durante 18 meses, a equipe multidisciplinar apoiou o desenvolvimento de 35 cenários clínicos relevantes para a gama de apoiadores, juntamente com algoritmos de tratamento. Ter um processo inclusivo e metodologia clara significava que a equipe multidisciplinar defendia o processo e os resultados, reduzindo alguns dos desafios. Embora as diretrizes forneçam base para a futura formulação de políticas e gestão do câncer de mama no Bahrein, a inovação é a identificação de oito cenários clínicos nos quais a tomada de decisão compartilhada é recomendada, capacitando assim o usuário final. Essa iniciativa prática em nível de base abordou questões pertinentes relacionadas a uma equipe multidisciplinar, quando é fundamental apoiar um paciente em seu caminho de tratamento. Todos falarem a mesma língua é vital para melhor apoiar, otimizar e melhorar os resultados em saúde. Reduzir a confusão sobre o que é a melhor prática baseada em evidências, enquanto produz um documento com a característica local, mostrou que as ONGs podem ser usadas como recurso em relação às Parcerias Público-Privadas (PPP). Esta diretriz internacional, revisada por pares para o Bahrein, garantirá a existência de uma relação mais estreita entre médico e paciente, embora reconheça que as chaves para o sucesso, como a

adoção, implementação e sustentabilidade estão no próprio governo. No futuro, a ONG estará apoiando o desenvolvimento de três das oito decisões compartilhadas que auxiliam o apoio de editores internacionais de referências clínicas baseadas em evidências (EBSCO).

**Palavras-chave**: Câncer de mama. Diretrizes clínicas. Base de evidências. Bahrain. Parcerias público-privadas.

# *Abstract*

Sprakel, JF. **A systematic review of the research gaps in breast cancer in the gulf region.** Thesis (Doctoral) - Ribeirão Preto Medical School, University of São Paulo. Ribeirão Preto. 2020.

To provide a high-quality, up-to-date, evidence-based resource with recommendations based on the GRADE approach and clinical algorithms to enable shared clinical decisions. Building on existing clinical practice guidelines the completed work provides a local voice via the strategic championship of a mostly local multidisciplinary team- which includes consumer advocates and patients. The overall effort changed the perception of a role of a Non-Governmental Organization (NGO) and highlighted a governmental/non-governmental partnership could fill the gaps and better support the community. This comprehensive and contemporary resource can be used across the continuum of breast cancer care for both healthcare providers and patients, to better navigate the clinical pathways and provide best practice recommendations for informed and shared decision making. The RAPADAPTE method provided rapid adaptation of guidelines and evidence resources and minimized unnecessary repetition, rather than developing the guideline de novo. RAPADAPTE builds on the well-established ADAPTE method and had been used to develop a similar breast cancer guideline for Costa Rica. This inclusive and innovative method involved a peer review process using tools such as AGREE II, Lenzer's Red Flags and the Institute of Medicine (IOM) criteria. This gave international credibility and up-to-date best practices to the first line professionals in health centres across the Kingdom, in relation to breast cancer diagnosis, screening and treatment. It was also designed to be readily accessible to the community in the format of patient pathways and algorithms. The establishment of the first interactive patient-centered, multidisciplinary approach to guideline development for breast cancer treatment, screening and diagnosis in Bahrain. This locally flavoured, evidenced based guideline not only used sharing of resources but was developed with little direct cost. Over 18 months the multidisciplinary team supported the development of 35 clinical scenarios relevant to the gamut of supporters along with treatment algorithms. Having an inclusive process and clear methodology meant that the multidisciplinary team championed the process and results, reducing some of the challenges. Whilst the guidelines provide an underpinning for future policy making and management of breast cancer in Bahrain the innovation is the identification of eight clinical scenarios in which shared decision making is recommended, thus empowering the end-user. This hands-on initiative at grass roots level addressed pertinent issues related across a multidisciplinary team, when supporting a patient through their treatment pathway is key. Singing all from the same "hymn sheet**"** is vital to better support and optimise and improve health outcomes. Reducing the confusion of what evidence based best practice is, whilst producing a locally flavoured document, showed that NGOs can be used as a resource in relation to Public Private Partnerships (PPP). This international peer reviewed guideline for Bahrain will ensure that there will be a joint clinician and patient focus, whilst recognising that the keys to success, adoption, implementation and sustainability lies with the government itself. Moving forward, the NGO is supporting the development of three of the eight shared decision-making aids the backing of international publishers of evidence- based clinical references (EBSCO).

**Keywords:** Breast cancer, Clinical guidelines, Evidence base, Bahrain, Public-private partnerships.

# *List of Figures*

# *List of Abbreviations*

**ACOG-** American College of Obstetricians and Gynecologists

**ACS-** American Cancer Society

**AGREE-** Appraisal of Guidelines for Research and Evaluation

**ASR-** Age Standardised incidence Rate

**BSE-** Breast Self-Examination

**CBE-** Clinical Breast Examination

**CI5C-X-** Cancer Incidence in 5 Continents

**CTFPHC-** Canadian Task Force on Preventive Health Care

**DCIS-** Ductal Carcinoma In Situ

**ECIBC-** European Commission Initiative on Breast Cancer

**EMR-** Eastern Mediterranean Region

**EMRO-** Eastern Mediterranean Regional Office

**ESMO-** European Society of Medical Oncology

**EUSOMA-** European Society of Breast cancer Specialists

**GCC-** Gulf Cooperation Council

**GCO-** Global Cancer Observatory

**GDG-** Guideline Development Group

**GHO-** Global Health Observatory

**GRADE-** Grading of Recommendations Assessment, Development and Evaluation

**HRT-** Hormone replacement therapy

**IAB-** International Advisory Board

**IACR-** International Association of Cancer Registries

**IARC-** International Agency for Research on Cancer

**IOM-** Institute of Medicine

**IT-** Information technology

**MEG-** Multidisciplinary Expert Group

**MENA-** Middle East and North Africa region

**NCCN-** National Comprehensive Cancer Network

**NGO-** Non-Governmental Organization

**NHSBSP-** NHS Breast Screening Programme

**NHRA-** National Health Regulatory Authority

**PPP-** Public Private Partnerships

**RCT-** Randomised controlled trial

**SCH-** Supreme Council of Health

**SDM-** Shared decision making

**SIGN-** Scottish Intercollegiate Guidelines Network

**TTS-** Triple Test Score

**USPSTF-** United States Preventive Services Task Force

**WHO-** World Health Organization

# SUMARY

# *1- Introduction*

## 1.1 Burden of disease: the need for a Breast Cancer guideline for the Kingdom of Bahrain

"Breast cancer is the most commonly diagnosed cancer in women and the most common cause of cancer death in women worldwide". Estimates at the global level indicate that there were 1.68 million new diagnoses and 0.52 million deaths due to breast cancer in 2012. [1]

Breast Cancer is the leading type of cancer for women in the Eastern Mediterranean Region (EMR) and the commonest in the six Gulf Cooperation Council (GCC) countries. [2] Moreover, several recent reports have indicated that the incidence of breast cancer and the mortality rates in these countries appear to be higher than the world average. [3,4] Many global resources and agencies collect, track and report these data in online databases developed and hosted by highly reputable organizations such as the International Agency for Research on Cancer (IARC) [5] which is the specialized cancer agency of the World Health Organization (WHO), and the International Association of Cancer Registries (IACR). [6] IARC is a global reference center for cancer information which provides reports on cancer incidence for all the countries around the world for which high-quality data have been made available through population-based cancer registries.

The IARC Global Cancer Observatory (GCO) is an interactive web-based platform which provides free access to comprehensive global cancer statistics. [7] This resource also includes the GLOBOCAN database with data which are complete up to 2010 (as of 2018). [8] In addition, GLOBOCAN provides contemporary estimates of incidence, mortality and prevalence for all the major types of cancer for the year 2012, covering 184 countries including Bahrain. Further information is available in the publication, Cancer Incidence in 5 Continents (CI5C-X), [9] which compiles data from more than 400 cancer registries including the Bahrain Cancer Registry. Although the CI5C-X report was published in 2014 it includes mainly data for the years 2003-2007. In general, these resources report data for the incidence of breast cancer as the Age Standardised incidence Rate (ASR) per 100,000 based on the world population. The ASR is a summary measure of the rate that a population would have if it had a standard age structure. The ASR is a weighted mean of the age-specific rates; the weights are taken from population distribution of the *standard*

*population*. The most frequently used standard population is the *World Standard Population.*

The CI5C-X publication, which covers Bahrain, reports an ASR (world) incidence of breast cancer of 56/100,000 and Crude Rate of 40.5/100,000 for the Bahraini national population over the 2003-2007 time period. This value ranked Bahrain, over that time period, 301 among the 423 datasets in the CI5C-X for all age groups. Selecting women aged 20-44yrs the ASR was 33.2 and ranked Bahrain as 262/423, and for the age range 20-49 the ASR was 50.3 and ranked 275/423.

The WHO Global Health Observatory (GHO) [10] has also quantified the burden of disease in 2012 for all cancers in Bahrain but indicates that these did not outrank cardiovascular diseases and diabetes and "other NCDs". However, whilst setting these all in context, the leading cause of death in Bahrain according to the WHO (GHO) in 2012, was and remains ischaemic heart disease followed closely by diabetes mellitus and stroke.

### 1.2 Previous Breast Cancer Guideline for the Kingdom of Bahrain

The Health Promotion Council at the Ministry of Health of Bahrain developed and published a "Guideline for Management of Periodic Screening in Primary Care Settings and Outpatient Clinics in the Kingdom of Bahrain" in 2010. The guideline was adapted extensively from several international resources and provided broad recommendations based on the best synthesized evidence available at that time.

### 1.3 Remit of the new guideline: Purpose, Format, Scope and Target Users

The scope, content and format of breast cancer clinical guidelines varies quite markedly around the world and have been shown to reflect the specialty related interests of the developers and their specific preferences. Research has shown that these factors, coupled with potential conflicts of interest, can contribute to conflicting guidelines. [11] At the outset the Guideline Development Group on this new Bahrain Breast Cancer guideline sought to obviate these challenges by ensuring a balance in composition and interests of the contributors to this guideline, which would be likely

to limit any possible over-influence of participating individuals that might occur through either reputation or demeanor.

This new guideline builds on the previous guideline by absorbing a broader spread of clinical expert opinion, expanding the scope and combining this with current best evidence and incorporating patients preferences and values in accordance with the concept of evidence-based medicine.

The purpose of this new guideline was to provide a robustly developed, high-quality, up to date, evidence-based resource which incorporates recommendations based on the GRADE approach and which can be used to facilitate shared clinical decisions at the point of care.

The developers sought to ensure that the guidance was based on current best-evidence which would enhance the quality of care, improve patient outcomes, ensure patient safety, increase patient satisfaction, and optimize the use of resources across the continuum of breast cancer care. This guideline contains several clinical algorithms which have been adapted from two of the foundational guidelines, from Catalonia and Costa Rica, which were used in the development process. [12,13] The content also includes check lists which can be used by clinicians to ensure provision of best practice and consistency of care. Links are provided to key clinical resources and the guideline is supported by an extensive bibliography. An important additional component of this Bahrain guideline is the comprehensive section on screening which provides key WHO supported recommendations for policymaking on screening programmes. This was not covered by either of the foundational guidelines and, therefore, the scope of this new guideline was enhanced further by examining and evaluation other relevant regional and international clinical resources which covered the detection of breast cancer. Their recommendations were taken into consideration in the development of the screening section of this guideline.

Current trends in clinical guideline format at global level and across healthcare specialties show a distinct and progressive shift away from the all-encompassing guideline format which covers all aspects of diagnosis and management. The trend is towards developing guidance which is focused on answering a set of specific and highly relevant clinical questions and scenarios that have been defined *a priori*, by a multidisciplinary team of clinicians and other intended users. Consequently, the

format of this breast cancer guideline for Bahrain follows the style of several recent Gulf Region and many international clinical guidelines in adopting this contemporary approach of prioritizing those clinical questions of most relevance to users.

The scope of this guideline encompasses; screening, diagnosis and staging, and treatment involving surgery, chemotherapy / hormone therapy and radiotherapy. To ensure that the guideline covered specific topics which target aspects of management which can lead to improvement in the quality of life of patients, the development process involved patients and their carer's and relevant advocacy groups at all key stages.

The target 'audience' and intended users of this guideline include all who are involved in the overall care pathway for women being assessed or treated for breast cancer; clinicians, support staff, patients and their carer's as well as policymakers. Fundamental to the development process was the early involvement of the potential users who were actively encouraged to provide additional and continuing input and to review drafts at key stages of the guideline development. Participation by the intended users in the consensus process was considered pivotal to ensuring ownership of the clinical guideline and ultimately to its successful implementation.

### 1.4 Key clinical questions and scenarios

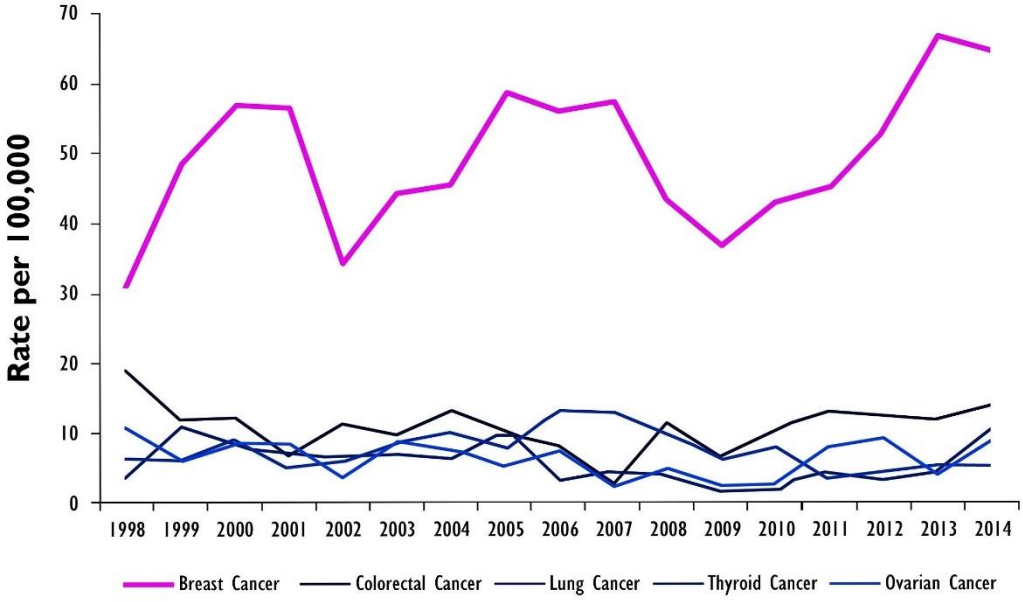
The initiators for developing key questions for this guideline were 9 fundamental clinical questions which had been used in the Costa Rican guideline (Appendix One). These questions had been previously formulated by the Costa Rican team, which consisted of a broad range of experts in clinical medicine and research, and were considered to be a satisfactory baseline for the Bahrain Breast Cancer guideline. An additional question was added to underpin the periodic mammography screening of age-appropriate asymptomatic women aspect of this guideline. These 10 clinical questions were shared widely with multidisciplinary experts and were discussed, clarified and agreed upon during extensive face-to-face weekly consultation meetings with the Guideline Development Group (GDG). (Appendix Two) Further expansion of these fundamental clinical questions into

clinical scenarios, deemed relevant to the management of breast cancer in Bahrain, was based on the approach used in the Costa Rican guideline.

## 1.5 Incidence of Breast Cancer based on Cancer Registry data for the Kingdom of Bahrain

Current breast cancer incidence and mortality data for Bahrain were obtained from epidemiologists based at the Bahrain Cancer Registry at the Ministry of Health and collated with data available from researchers at the College of Medicine and Medical Sciences at the Arabian Gulf University in Bahrain. This included recently published data by the Bahrain Cancer Registry on cancer incidence covering the period 2008-2014. Data reported by the Bahrain Cancer Registry showed that "in 2014 breast cancer was the most common cancer among Bahrainis, accounting for 40% of all new cases of cancer in females and 23.9% of all new cancer cases overall". The report also stated that the world ASR for breast cancer in Bahraini women was 65.6 per 100,000 females (Figure 1).

**Figure 1 -** Age-standardized incidence rates of most common cancers among Bahraini females, 1998-2014



Experts from the IARC at the WHO and the European Commission Initiative on Breast Cancer (ECIBC) were consulted to facilitate further evaluation of these local data and to enable fair assessments and rational comparisons of the Bahrain data with global figures on breast cancer incidence and mortality.

# 2. Objective

To map gaps and local data, through systematic literature review, to develop a guideline for breast cancer care in Bahrain.

# *3. Material and Methods: Overview*

### 3.1 Participants and membership

This guideline was developed under the auspices and guidance of the Steering Committee and included a broad group of members tasked with roles and functions based on their expertise as clinicians, methodologists and patient advocates (Appendix Three).

### 3.2 Steering Committee

The Steering Committee consisted of the President of the Supreme Council of Health, together with the leadership of the major healthcare service providers in the Kingdom of Bahrain. The Director of the Royal Medical Services- Maj. Gen. (Prof) Khalid Al-Khalifa, the CEO of King Hamad University Hospital- Major General. (Dr.) Salman bin Ateyatalla Abdulrahman Al Khalifa, the CEO of NHRA(National Health Regulatory Authority) - Dr. Mariam Al Jalahma, the Chairwoman of Think Pink Bahrain Breast Cancer Society- Mrs. Julie Sprakel. The Steering Committee provided broad oversight of the guideline development process, recommending and designating additional experts to the GDG as required, and providing balance and a focal point for arbitration where consensus with any aspect of the development process was not attainable. Subject to satisfactory peer review both internally and via external experts the Steering Committee will ratify the publication of the completed guideline and authorize its further dissemination.

### 3.3 Guideline Development Group (GDG)

Participants in this core group were selected based on their clinical expertise related to breast cancer and/or experience as patients who had experienced breast cancer. The clinical specialties included all those directly relevant to aspects of diagnosis and management of breast cancer. There was an expectation that the members of this group had at least some knowledge of the concept of evidence-based medicine and critical appraisal of clinical research. Patients were co-opted through key advocacy groups such as Think Pink and the Bahrain Breast Cancer

Society. Additional members with experience in health economics and quality management were added to the group to provide a perspective on the challenges that would be encountered with implementation and audit of the guideline.

### 3.4 Multidisciplinary Expert Group (MEG) and Stakeholders

These were recruited locally based on their clinical skills in oncology, radiotherapy, surgery and plastic surgery, pathology and radiology and nuclear medicine. Input was sought as to whether the (9+1) key questions covered the topic generically and comprehensively for the respective clinical discipline and if any additional questions were appropriate. This group of stakeholders were involved directly in reviewing and selecting the clinical scenarios from the Costa Rican guideline which would underpin the scope of this clinical guideline for Bahrain. The members of the GDG and MEG have overlapping roles and thus their expertise and involvement was shared across both groups. The two authors Julie Sprakel and Prof Zbys Fedorowicz provided the lead to ensure overall cohesion and integration of the two groups within the guideline development process.

### 3.5 Guideline International Advisory Board & Review Panel

The International Advisory Board (IAB) was assembled from a wide-ranging group of global experts with experience as guideline developers, clinical content expertise relevant to breast cancer, methodologists and systematic reviewers with knowledge and skills in evidence-synthesis and the subsequent grading of the quality of the evidence to the making of recommendations. Ex-officio members from several leading international healthcare organisations were co-opted and consulted on an *ad hoc* basis.

## 3.6 Process and Methodology: RAPADAPTE based

### 3.6.1 Identification of foundational guidelines

Developing clinical guidelines can be costly and time and resource intensive and therefore for clinical topics such as breast cancer, for which there are a plethora of existing guidelines, the process of adaptation is widely considered to be the preferred option, over *de novo* guideline development. In view of the current availability of so many guidelines, and to minimize unnecessary duplication of effort, the developers followed a recently tested process of rapid adaptation, RAPADAPTE. (Appendix Four) [14] The RAPADAPTE methodological process builds on the well-established ADAPTE method [15] and was used to develop the breast cancer guideline for Costa Rica. The Costa Rican guideline had been developed following searches of three comprehensive databases (International Guideline Library [from Guidelines International Network], MEDLINE and National Guideline Clearinghouse). Key factors in the selection process of the foundational guidelines for Costa Rica were their scope and currency (publication in or after 2005). Five guidelines matched the selection criteria and were subjected to further assessment with the Appraisal of Guidelines for Research and Evaluation (AGREE II) instrument to rate the quality of guidelines. [16] Two guidelines received ratings of 80% or higher in each domain and were selected as the guidelines suitable for adaptation: the Scottish Intercollegiate Guidelines Network (SIGN) [17] guideline on management of breast cancer in women (published in 2005, minor update in 2007) and the Health Department of Catalonia guideline on breast cancer (published in 2008). [12]

In turn, the Bahrain Breast cancer guideline development group selected two foundational guidelines which had underpinned the Costa Rican guideline development. The Clinical Practice Guidelines in Cancer in Catalonia (Breast Cancer OncoGuia: Update 2008) [12] which had been used in the development of the Costa Rican guideline (Guia de Practica Clinica papa el Tratamiento del Cancer de Mama Costa Rica) as well as the completed guideline itself. [13] However as neither of these two foundational guidelines covered periodic mammography screening, the GDG examined a number of regional and international screening guidelines to

provide the foundation for the screening component of the Bahrain guideline. Further details on the process of selection of the foundational guideline on screening are provided in the section; **Screening: Mammography, clinical Breast Examination and Breast Self-Examination.**

### 3.6.2 Overview of the consultation and review process with multidisciplinary stakeholders

The wide dispersion of the team throughout the healthcare services of Bahrain and consequent differing availability were recognised as potential limitations to continuous enagagement but every effort was made by the members of the GDG to ensure as broad a participation as possible. Consequently, the process of development, primarily for logistic reasons, relied very heavily on personal interaction and regular weekly group meetings with the multidisciplinary team members. Minutes were taken at the meetings and these were dispersed via email and followed up if further clarification was required. All comments, suggestions and disagreements were discussed, addressed and responded to within 2 clear working days by either of the two principal editors of the guideline. Although there was very limited opportunity to provide comprehensive methodologic training, in most instances any disagreements were resolved, for example, by identifying the source of a recommendation and illustrating the supporting evidence.

### 3.6.3 Formulating of the clinical scenarios based on the foundation guidelines

The GDG in collaboration with the multidisciplinary experts comprehensively reviewed the list of clinical scenarios used in the Costa Rican guideline to ratify how close a match they were for the clinical scenarios relevant to the population and health care services of the Kingdom of Bahrain. Consequently the two foundational guidelines that were selected were used to confirm and provide a basic framework of clinical scenarios which could underpin the development process of the Bahrain guideline. To achieve this the GDG engaged with a broad set of representatives from the relevant clinical disciplines in addition to individuals and advocacy groups with a specific interest in breast cancer. Communication was either in face-to-face meetings

individually or in small groups and followed up via electronic mail to expedite the process and to facilitate broad participation.

The multidisciplinary team were also requested to suggest additional topics with a broader scope which could be used in the future to shape updated versions of the guideline. These were consolidated into a simple matrix which highlighted key considerations which could be utilised by policymakers to guide future enhancements to the current breast cancer care services in Bahrain. (Appendix Five)

### 3.6.4 Formulating of the recommendations

The two foundation guidelines had used the GRADE approach (see below) to formulate recommendations across the clinical scenarios covered by each guideline. The GDG considered that this process did not require replicating *de novo* in view of the relative consistency across the foundation guidelines. However, for each clinical scenario the individual recommendations and their strengths were reviewed comprehensively by MEG panel members with the relevant clinical expertise. The panel were assisted in comprehending and evaluating the corresponding evidence base supporting the recommendations in collaboration with the lead methodologist on the GDG. Although no formal voting took place in these working group sessions, disagreements were discussed comprehensively, referred to external experts for clarification if required and with agreement reached ultimately through consensus.

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach had been used in the Costa Rican guideline to formulate recommendations for the clinical scenarios and these were reviewed and confirmed by the Bahrain GDG

The GRADE working group has suggested adopting the following terminology.

| | |
|---|---|
| **For STRONG RECOMMENDATIONS:** | **"we recommend," or "clinicians should", "clinicians should not" or "Do", "Don't".** |
| **For WEAK RECOMMENDATIONS:** | **"we suggest," or "clinicians might" or "We conditionally recommend" or "We make a qualified recommendation that".** |

**Implications Of Strong And Weak Recommendations For Different Guideline Users**

| | **Strong Recommendation** | **Conditional (weak) Recommendation** |
|---|---|---|
| **For patients** | **Most individuals in this situation would want the recommended course of action and only a small proportion would not.** | **Majority of individuals in this situation would want the suggested course of action, but many would not.** |
| **For clinicians** | **Most individuals should receive the recommended course of action.** | **Recognize that different choices will be appropriate for different patients, and that you must help each patient arrive at a management decision consistent with her or his values and preferences.** |
| **For policy makers** | **The recommendation can be adapted as policy in most situations** | **Policy making will require substantial debates and involvement of many stakeholders.** |

Adapted from the GRADE Handbook 6.1 [updated October 2013].

## 3.7 External Peer Review

The final draft of the guideline was submitted to a panel of experts, with no relationship to industry, who were requested to comment on sections of the draft which were relevant to their expertise ie the methodology, clinical content, consumer advocacy style and layout.

Dr Brian Alper contributed to the organizational framework of the guideline, provided extensive input on the breast screening and mammography section as well as guidance to ensure overall transparency of the reporting methodology. Dr Susan Troyan reviewed the clinical scenarios and corresponding recommendations and provided comments which were incorporated into the clinical content in line with current best practice in breast cancer care. Dr Esther van Zuuren reviewed the guideline to ensure compliance with the grading of recommendations based on the

GRADE approach. Professor Mike Clarke reviewed the draft comprehensively and provided edits and recommendations to improve overall consistency in style, layout and reporting. Two external peer reviewers, Dr Amy Price and Mr Bernd Arents, with patient and public involvement expertise reviewed the draft and provided commentary to ensure the guideline had the appropriate balance in content for all stakeholders. Dr Yasser Sami Amer from King Saud University Saudi Arabia, who has extensive clinical guideline adaptation experience both regionally and internationally, reviewed the guideline and provided valuable commentary on both methodological quality, implementation and regional appropriateness. Additionl clinical content and oversight was provided by Prof Helio Carrara, both a Breast Surgeon and Academic from the University of Sao Paulo Brazil.

## 3.8 Screening: Mammography, Clinical Breast Examination (CBE) and Breast Self-Examination (BSE)

### 3.8.1 Mammography screening for asymptomatic women of average risk: age-specific recommendations

"*Screening for breast cancer aims to reduce mortality from this cancer, as well as the morbidity associated with advanced stages of the disease, through early detection in asymptomatic women*" [18]

Effective screening of asymptomatic women of appropriate age and average risk would enable adequate treatment to be provided before the cancer poses a more serious threat to the individual woman. However, physicians, advocacy groups, lawmakers, and scientists continue to debate the effectiveness and balance of benefits and harms of breast cancer screening. Opinions vary widely from the extreme; that "mammography screening is harmful and should be abandoned" [19] to a wider endorsement of age-specific recommendations by a globally distributed number of cancer prevention advocates and professional societies. These include the WHO, American Cancer Society, American College of Radiology, the Canadian Task Force on Preventative Health Care, European Society of Medical Oncology (ESMO), ECIBC, the National Comprehensive Cancer Network (NCCN), the Saudi

Center for Evidence Based Health Care, NHS Breast Screening Programme (NHSBSP) and the US Preventive Services Task Force (USPSTF).

The WHO reported in its position paper on mammography screening that “so far the only breast cancer screening method that has proved to be effective in organized population-based programmes is mammography screening”. [20] This report also referred to some of the uncertainties in the age-specific recommendations and concurred with the report from the IARC Working Group that the evidence for effectiveness of mammography screening in women aged 40-49 years is limited. [18,21,22] Both reports including the IARC Breast Cancer Screening Handbook [1], refer to the lack of consensus about the exact effect of mammography screening on breast cancer mortality reduction, and that there is a demonstrable association between screening and overdiagnosis albeit the magnitude remains unclear specifically in the younger age-groups. These uncertainties were also considered by the Independent UK Panel on Breast Cancer Screening which stressed the importance of taking into account the risk of over-diagnosis and over-treatment, as well as false-positive screening, when balancing the benefits and harms of screening. [23] Some of these views and concerns were further reiterated in the guidelines developed by the ESMO [24], by the American College of Radiology [25], the USPSTF [26], the American Cancer Society [27], and several other organizations. However, overall these organisations judged mammography to be a valuable tool to reduce breast cancer mortality, and concluded that the benefits of mammography increase with age.

### 3.8.2 Mammography screening approaches: organized population based versus opportunistic programmes

Screening entails repeated interactions between ‘healthy’ individuals and healthcare providers. Screening of asymptomatic women involves mammography screening at specified intervals followed by referral of women with positive screening results for additional investigations and possible treatment. Screening programmes can be either organized or unorganized (opportunistic) programmes. [20,28] These two approaches differ somewhat in terms of their structure, implementation and

availability at global level, the details of which are reported concisely in the IARC Handbook. [1]

Organized screening programmes are characterized by centralized screening, invitations to a well-defined target population, systematic call and recall, delivery of test results, investigations, treatment and follow-up care, centralized quality assurance, and a programme database with linkages to cancer registration systems which can be used for monitoring and evaluation purposes. Opportunistic programmes are less well-structured, tend to be more ad hoc, dependent on encouraging women individually to attend for breast cancer screening within the scope of routine health services and are likely to access a more limited number of women compared to organized programmes.

Organized screening programmes have a well-established history across Europe and Canada whereas in the USA the tendency is towards opportunistic screening. In Latin America, as with many parts of Africa, very few countries provide organized programmes. In the Middle East region, several countries have implemented national screening programmes over recent years with some mixed results. However, the age-specific recommendations for screening as well as the frequency of screening appear to vary somewhat across this region and it has also been reported that participation by women in screening programmes is generally low. [29] The WHO Eastern Mediterranean Regional Office (EMRO) held a consultative meeting on early detection of priority cancers in 2016 at which some of these issues were highlighted and further discussed. There was agreement that the feasibility of mammography screening across the countries of the EMR was likely to be resource dependent, and a strong recommendation “that all existing screening programmes in the Region be reviewed”. [30]

The key criteria and requirements of an organized, population-based breast cancer screening programme have been concisely delineated by the WHO. Implementation of such organized screening programmes, as was stated in the WHO mammography screening monograph, would be particularly relevant to high-income and upper-middle-income countries. [1]

### 3.9 Purpose and scope

This section of the guideline provides evidence-based recommendations on the screening of asymptomatic women who are at average risk for breast cancer in different age groups. It is anticipated that following acceptance of the recommendations these can be implemented and used to guide shared clinical decision making and provide guidance for developing future policy and systems which can optimize the delivery of breast cancer care and improve relevant health outcomes in the Kingdom of Bahrain. The scope of the screening section of this guideline has a focus on mammography in women at average risk but also covers clinical breast examination and breast self-examination.

1. Women at average-risk

   The GDG considered average risk to comprise women without any of the following; a personal history of breast cancer, a confirmed or suspected genetic mutation known to increase the risk of breast cancer (such as a *BRCA1* or *BRCA2* gene mutation or other familial breast cancer syndrome) or a history of previous radiotherapy to the chest at an early age.

2. Target audience

   The variability and relative inconsistency in recommendations between guidelines on age specificity and frequency of mammography screening continues to present challenges to clinical decision making and policy making. (Appendix Six) Nonetheless it is increasingly recognised that women should receive appropriate and timely information on both the benefits and potential harms of mammography screening, and that shared decision making between women and healthcare providers is essential to the process. Therefore, the target audience for the screening recommendations in this guideline comprise a broad range of stakeholders including clinicians from diverse specialties, patients and their carers and consumer advocacy groups as well as other stakeholders with a potential role in policy making, and the design and delivery of healthcare services.

3. Key questions

   What are the age-specific and interval recommendations for mammography screening in asymptomatic women of average risk in the Kingdom of Bahrain, taking into consideration the balance of benefits and harms?

### 3.10 Development process and foundation guideline

The screening section of the guideline was developed by the GDG following a comprehensive search and evaluation of recent clinical guidelines which covered screening. These searches covered all databases and clinical resources which were likely to be consulted by clinicians at local regional and international level. For further details see (Appendix Seven).

Extensive consultations were also undertaken in several face-to-face meetings with members of the GDG and international experts in the field such as the Special Advisor on Cancer Control IARC WHO, contributors to the Cancer Incidence in Five Continents IARC project [9] and members of the Coordination Team at the ECIBC. [31] These key interactions involved broad discussion of the most recently reported Breast Cancer epidemiological data for Bahraini nationals, made available from the Bahrain Cancer Registry, and how best to set the widely and internationally accepted age-specific screening recommendations within the context of these data. Additional factors which were taken into consideration were the current absence of a fully operable and comprehensive organized population-based screening programme covering the total population of Bahrain both Bahraini and non-Bahraini. The age-specific recommendations provided in this guideline are structured around such a programme and while it is recognised that these recommendations may not be an exact fit currently, they constitute a starting point. Updates of these screening recommendations will necessitate periodic review of Bahrain Cancer Registry data which may result in further amendment to the recommendations, subject to the availability of comprehensive total-population breast cancer incidence data.

The WHO position paper on mammography screening presents succinct recommendations which are stratified by age group as well as by resource settings.

[20] These comprise; well-resourced settings (most high-income countries), limited resource settings with relatively strong health systems (some upper-middle income countries), and limited resource settings with weak health systems (low-income and lower-middle income countries). The screening recommendations outlined in the WHO position paper also strongly emphasise the importance of shared decision-making strategies thereby ensuring women's decisions are consistent with their values and preferences. In addition, these recommendations refer to and suggest that an organized population-based mammography screening programme is an integral component of any national implementation strategy.

Well-resourced settings were categorised in the position paper as "settings with very strong health systems that, in general have an existing capacity that allows them to develop and sustain organized population-based mammography screening programmes (e.g. most high-income countries)". The Kingdom of Bahrain is classified as a 'high income economy' country by the World Bank and thus fits into the "well-resourced settings" category defined in the WHO position paper. The WHO age-specific mammography screening recommendations were evaluated by the GDG as potential foundations for adaptation as part of the development of the screening component of the Breast Cancer Clinical Guideline for Bahrain.

### 3.11 Assessment of reporting quality and overall trustworthiness of the WHO foundational guideline

The WHO position paper on mammography was independently evaluated by two members of the GDG for its reporting quality, using the AGREE II Reporting Checklist 2016 [32], and for trustworthiness using the Institute of Medicine (IOM) [33] standards for guideline development. Additional assessment of the integrity of the WHO position paper was undertaken based on Lenzer's "Red Flags". [34]

The assessments of the foundational WHO position paper on mammography screening by the two members realised maximum scores for twenty out of the 23 items on the AGREE II Reporting Checklist. For the remaining three items (Target population preferences and views, Facilitators & barriers to application, Monitoring/auditing criteria) it was unclear how these had been addressed by the developers of the WHO position paper and thus they were given a mid-level score.

No Red Flags were identified, and the position paper broadly matched the IOM criteria for trustworthiness. The results of the assessments by the two members of the GDG are available in the Supplementary documents. (**See** Supplementary Files).

### 3.12 Grading of recommendations

This screening guideline was developed to include recommendations for different age groups and placed in the context of the resource settings considered appropriate for the Kingdom of Bahrain. The foundational reference WHO position paper on mammography screening followed GRADE methodology to rate the overall quality of evidence and subsequent recommendations, which required no further replication. The recommendations we provide are adapted directly from that resource and have been reviewed in conjunction with the recommendations provided by other key guidelines and clinical resources (Appendix Six). The process of development of the foundational WHO position paper was underpinned by the GRADE methodology and therefore matched the requirements of the Bahrain GDG. [35]

### 3.13 Recommendations on mammography screening of women of average-risk by age group in well-resourced settings, appropriate for the Kingdom of Bahrain

*Acknowledgement*

The mammography screening recommendations provided in this guideline are adapted directly from the WHO position paper on Mammography Screening. [Permission to reproduce and adapt these screening recommendations was obtained from the Manager Copyright, Licensing and External Publications WHO Press. (3rd June 2017)]

**Women aged 70-75 years (Average-Risk)**

**In well-resourced settings, such as the Kingdom of Bahrain, we suggest an organized, population-based screening programme for women aged 70−75 years only if such programme is conducted in the context of rigorous research and monitoring and evaluation, if the conditions for implementing an organized programme are met by the health-care system, and shared decision-making strategies are implemented so that women's decisions are consistent with their values and preferences.**
**(Conditional recommendation based on low quality evidence)**

**Women aged 50-69 years (Average-Risk)**

**In well-resourced settings, such as the Kingdom of Bahrain, we recommend an organized, population based mammography screening programmes for women aged 50−69 years if the conditions for implementing an organized programme are met by the health-care system, and if shared decision-making strategies are implemented so that women's decisions are consistent with their values and preferences.**
**(Strong recommendation based on moderate quality evidence)**
**We suggest a screening interval of two years.**
**(Conditional recommendation based on low quality evidence)**

**Women aged 40-49 years (Average-Risk)**

**In well-resourced settings, such as the Kingdom of Bahrain, we suggest an organized, population-based screening programme for women aged 40−49 years only if such programme is conducted in the context of rigorous research and monitoring and evaluation, if the conditions for implementing an organized programme are met and if shared decision-making strategies are implemented so that women's decisions are consistent with their values and preferences.**
**(Conditional recommendation based on moderate quality evidence)**

The WHO position paper only provided a recommendation on the screen interval, of two years, for women of average risk in the 50-69-years group. The report indicated that there was "uncertainty about the magnitude of harms - particularly overdiagnosis and overtreatment" and that "the best trade off seems to be provided by screening every two years". The position paper stated "there is uncertainty as to the balance between benefits and harms of mammography screening programmes in women aged 40-49 years" and that "there is also uncertainty about the optimal screening interval". These statements are also reported in the paper as justifications for women aged 70-75 years because of "the limited and low level of evidence available".

## 3.14 Clinical Breast Examination (CBE) and Breast Self-Examination (BSE)

### 3.14.1 Overview

A CBE is a physical exam of the breasts and the underarm area by a trained healthcare professional. BSE consists of examination of one's own breasts and underarm area by an individual in a consistent and systematic way at regular intervals. The earlier Bahrain guideline made recommendations to start CBE and BSE for women from the age of 20, based on "the high prevalence of Breast Cancer in Bahrain especially in a young age", but recommendations around the world have largely questioned the value and utility of CBE and BSE.

### 3.14.2 Recommendations across guidelines

Leading specialty groups that have been strong advocates for breast cancer screening do not currently promote CBE or BSE as major components of screening. The American Cancer Society (ACS), in its recent "Breast Cancer Screening for women at average risk" guideline update (2015), does not recommend CBE and indicates "the evidence does not support routine clinical breast examination as a screening method for women at average risk". [27] The ACS does not provide any recommendations for routine BSE due to lack of evidence of improved outcomes. The American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin (2017, # 179) states CBE "may be offered every 1-3 years for women aged 25-39 years and annually for women 40 years and older". [36] However, it qualifies this recommendation with an explicit statement to "offer in the context of a shared, informed decision-making approach that recognizes the uncertainty of additional benefits and harms of clinical breast examination beyond screening mammography". Regarding BSE the ACOG Practice Bulletin states "breast self-examination is not recommended in average-risk women because there is a risk of harm from false-positive test results and a lack of evidence of benefit." The Bulletin also states that, although no studies in the US have examined the effectiveness of breast self-awareness, women at average-risk should be "counseled about breast self-

awareness" and "be aware of changes in their bodies and discuss these changes with their clinicians". ACOG supports this shift with evidence stating "Although breast self-examination is no longer recommended, evidence on the frequency of self-detection of breast cancer provides a strong rationale for breast self-awareness in the detection of breast cancer. Approximately 50% of cases of breast cancer in women 50 years and older and 71% of cases of breast cancer in women younger than 50 years are detected by women themselves". [36]

Other leading public health groups have recommended against CBE or BSE. The Canadian Task Force on Preventive Health Care (CTFPHC, 2011) makes a weak recommendation against advising women to routinely practice BSE, given that there is no evidence to show reduction in mortality, and a weak recommendation against CBE, either alone or in conjunction with mammography, based on low quality of evidence. [37] The USPSTF (2016) did not update its 2009 recommendation against teaching BSE though the USPSTF "supports all patients being aware of changes in their bodies and discussing these changes with clinicians". The USPSTF also did not update CBE recommendations for which they found insufficient evidence to assess additional benefits or harms of CBE when added to screening mammography. [38]

The IARC Breast Cancer Screening Handbook covers the range of screening techniques with an emphasis on mammography screening but also considers both CBE and BSE. The Handbook reported that CBE had a moderate sensitivity (range 50-60%) and a specificity in excess of 85%. BSE had a sensitivity of 58.3%, specificity of 87.4% and a positive predictive value (PPV) of 29.2%. No specific recommendations are provided for either technique, only the following statements:

- There is inadequate evidence that screening by clinical breast examination alone reduces breast-cancer mortality.
- There is inadequate evidence that breast self-examination reduces breast cancer mortality in women who practice it competently and regularly.

Recommendations across organisations that have issued guidelines on screening range from recommending against CBE and BSE to considering offering the option of CBE with shared decision making and counseling women about breast self-awareness but not routine BSE. For early detection in women at average-risk

there is now a broader agreement on the lack of evidence of benefit for CBE and BSE. Moreover, the value of CBE for women in the average-risk category has also been questioned as it has been shown to be associated with a high false-positive rate. [39]

However, whilst general international consensus does not appear to support routine, systematic BSE, breast awareness is still considered important by both clinicians and patients in this regional population. Increased awareness in recognising breast changes and seeking timely professional healthcare support coupled with timely shared decision making are felt to be the key steps forward.

The concept of shared decision making (SDM) has gathered increasing momentum and acceptance by health care providers with evidence showing that participation by patients in decision-making improved their knowledge satisfaction and ultimately their outcomes. The evidence for SDM also shows patient decision aids can identify patient values to frame and interpret choices in ways that matter to patients, increase accuracy of risk perceptions, increase preparedness for discussions with physicians, decrease proportions of undecided patients, increase congruency between informed values and care choices, align decisions with patient preferences, increase decision certainty (reduce decisional conflict), and increase breast patient engagement. [40]

There is insufficient evidence to make a recommendation to healthcare professionals for or against either conducting CBE or counseling for BSE, but absence of a recommendation is not an adequate answer for healthcare professionals seeking guidance. With the considerations above, we recommend informing women about the potential benefits and harms (and the uncertainty around them) for CBE and BSE and supporting women making informed decisions whether or not they desire to proceed with routine screening using CBE or BSE techniques, or both. Patient decision aids that provide accurate information on the benefits and harms and are easy to understand for most women should be created to facilitate this dialog. Regardless of decisions whether or not to use CBE and BSE, it would be prudent to advise women to be aware of their own breasts and discuss changes with clinicians.

## 3.15 Breast cancer management in women

### 3.15.1 Clinical Evaluation, Testing, Diagnosis and Staging for suspected Breast Cancer: [Clinical Algorithms and Patient Care Pathways]

#### 3.15.1.1 Clinical presentation and history [Elevated Risk for Breast Cancer]

Breast abnormalities may be detected during screening and may not always be accompanied by other clinical signs or symptoms. The most frequently observed signs and symptoms include; palpable breast mass, nipple discharge, changes in the skin of breast or nipple, asymmetric thickening or nodular changes and pain located in the breast. History taking should be comprehensive and systematic and include past medical history and family history, and should cover the following.

| **Past Medical History** | **Family History** |
|---|---|
| | See: Elevated Risk for Breast Cancer |
| Prior history of breast cancer, cancer of uterus or ovary | BRCA1 or BRCA2 |
| Prior breast carcinoma in situ | cancer incidence in first or second-degree relatives, age at presentation, especially if breast or ovarian cancer |
| Previous breast biopsies | |
| Atypical hyperplasia in a breast biopsy | |
| Prior thoracic radiation | |
| Postmenopausal hormone replacement therapy (HRT) | |
| Age at first live birth | |
| Age at menarche | |

**Elevated Risk for Breast Cancer**

**Increased risk:**

Prior history of breast cancer

5-year risk of invasive breast cancer ≥1.7% in women ≥35yr (per Gail Model)

Women who have a lifetime risk >20% based on history of LCIS or ADH/ALH

Women who have a lifetime risk >20% as defined by models that are largely dependent on family history

Prior thoracic radiotherapy for patients younger than 30yr (e.g. mantle irradiation)

Pedigree suggestive of known genetic predisposition - Referral to genetic counselor if not already done

**NCCN guidelines 2016: Breast Cancer Screening and Diagnosis version**

The history taking should also include the following:

Enquire about the duration and change in size of any mass or any skin changes such as asymmetric thickening or nodularity and if any of the changes are related to the menstrual cycle. Ask about nipple discharge its duration and colour if any and whether it occurs spontaneously. Record details of any pain in the breast; the type, its location duration and severity and whether it is associated with the menstrual cycle or physical activity. See Evaluation of Palpable Breast Masses (Appendix Eight).

### 3.15.1.2 Physical evaluation [Guidelines for Referral to Breast Center]

CBE: should be undertaken in the upright and supine position and involve inspection for skin changes e.g., peau d'orange, skin thickening, edema, and erythema, nipple excoriation, scaling or eczema, or ulcers and include palpation to detect any mass, asymmetric thickening, or nodularity.

Chest: palpation of lymph draining regions of axillae, supraclavicular, and infraclavicular fossae for adenopathy recommended as part of clinical breast exam.

## Guidelines For Referral To Breast Center

**Lump, lumpiness, change in texture**
Discrete lump in any woman 30 years and older that persists after next period or presents after menopause

**At any age:**
- Discrete hard lump with fixation +/- skin tethering/dimpling/altered contour
- A lump that enlarges
- A persistent focal area of lumpiness or focal change in breast texture
- Progressive change in breast size with signs of oedema
- Skin distortion
- Previous history of breast cancer with a new lump or suspicious symptoms

**Nipple symptoms**
- Spontaneous unilateral blood stained nipple discharge
- Unilateral nipple eczema or nipple change that does not respond to topical treatment
- Recent nipple retraction or distortion
- ***(Women who can be managed at least initially by GP:*** Women under 50 years who have nipple discharge that is from multiple ducts or is intermittent and is neither blood stained nor troublesome)

**Breast Pain**
Patient with minor/moderate degree of breast pain with no discrete palpable abnormality, when initial treatment fails and/or with unexplained persistent symptoms

**Axillary lump**
- Persistent unexplained axillary swelling

**Male patients:**
Over 50 years with unilateral firm subareolar mass +/- nipple discharge or associated skin changes

**Abnormal Radiology**
Recommend patients with abnormal radiology requiring further imaging or biopsy (BIRAD III - V) to oncology center.

Adapted from **Association of Breast Clinicians**. *Best practice diagnostic guidelines for patients presenting with breast symptoms* Editors Alexis M Willett, Michael J Michell, Martin J R Lee 2010

### 3.16 Initial testing: Triple Test

Diagnosis is based on the clinical breast exam including lymph node assessment in conjunction with imaging and with diagnosis confirmed by biopsy and pathological assessment. The combination of the results of these three tests can be used to generate a Triple Test Score (TTS). [41]

The TTS can be used to assist clinicians with the resolution of discordant results from the three test components i.e. CBE, imaging, and tissue sampling. When the three assessments are completed satisfactorily with concordant results, diagnostic accuracy of the test approaches 100 percent. While discordant results or results that cannot be evaluated may indicate the necessity of a more invasive biopsy. The TTS is based on the use of a three-point scale for each component of the triple test (1 = benign, 2 = suspicious, 3 = malignant). A TTS of 3 or 4 is consistent with a benign lesion; a TTS of 6 or more indicates possible malignancy that may require surgical intervention. Excisional biopsy is recommended in patients with a TTS of 5 to obtain a definitive diagnosis. The test score has been validated and designated accurate for diagnosing breast cancer if the score ≥6 and in ruling out breast cancer if the score is 3-4. [42]

### 3.17 Clinical algorithms [Symptomatic Patients] [Asymptomatic Patients]

The relevant pathways for symptomatic and asymptomatic women differ and are summarized as algorithms (Figures 2 and 3). These algorithms were based on those in the two foundational guidelines (Catalan and Costa Rican); were further refined in several face-to-face meetings with members of the MEG and checked for consistency with the NCCN flow diagrams by Dr Nuha Birido (the NCCN MENA - Middle East and North Africa region contributor) (Figure 4).

**Figure 2 -** Pathways for symptomatic women

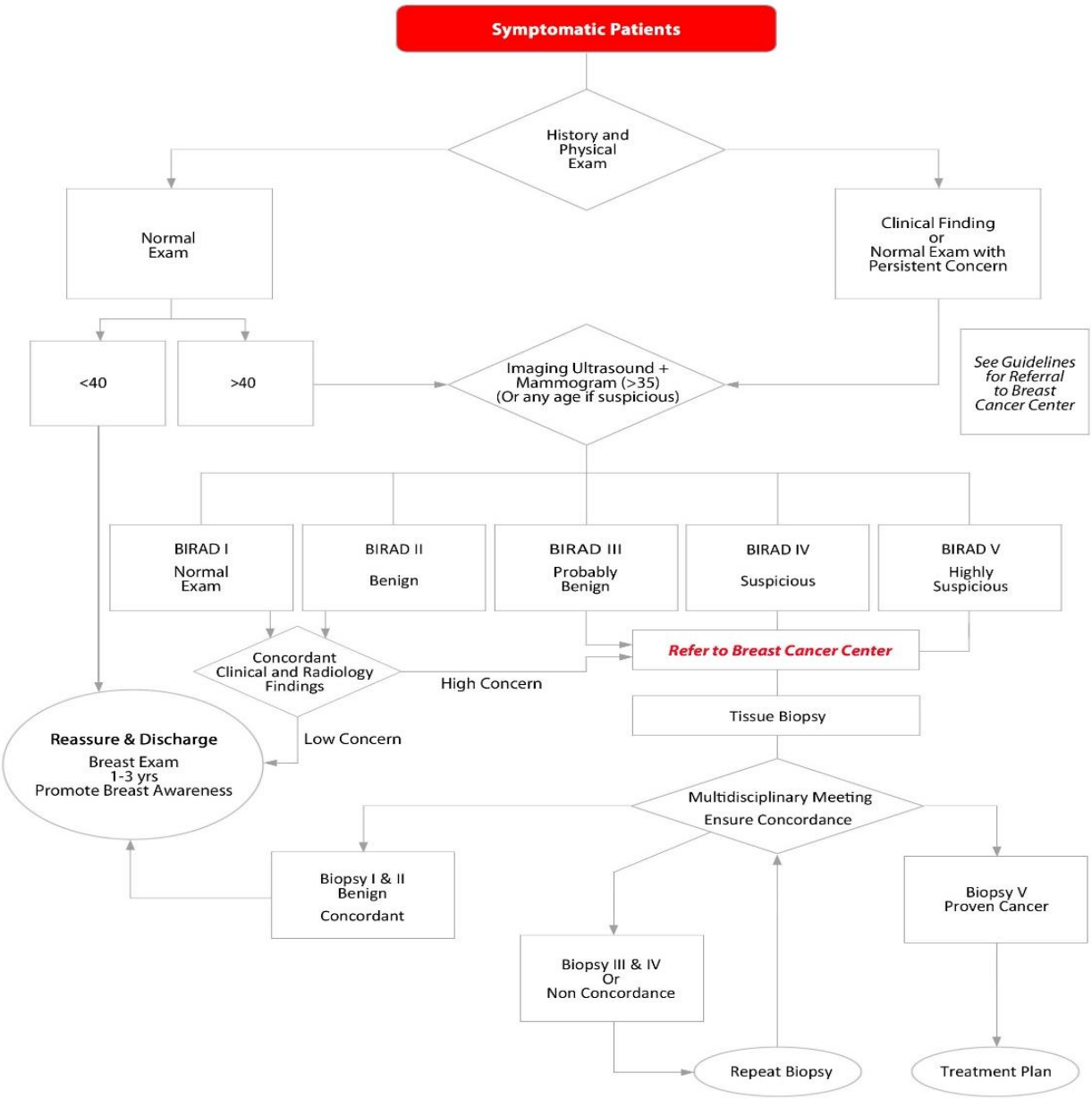


**Figure 3 -** Pathways for asymptomatic women

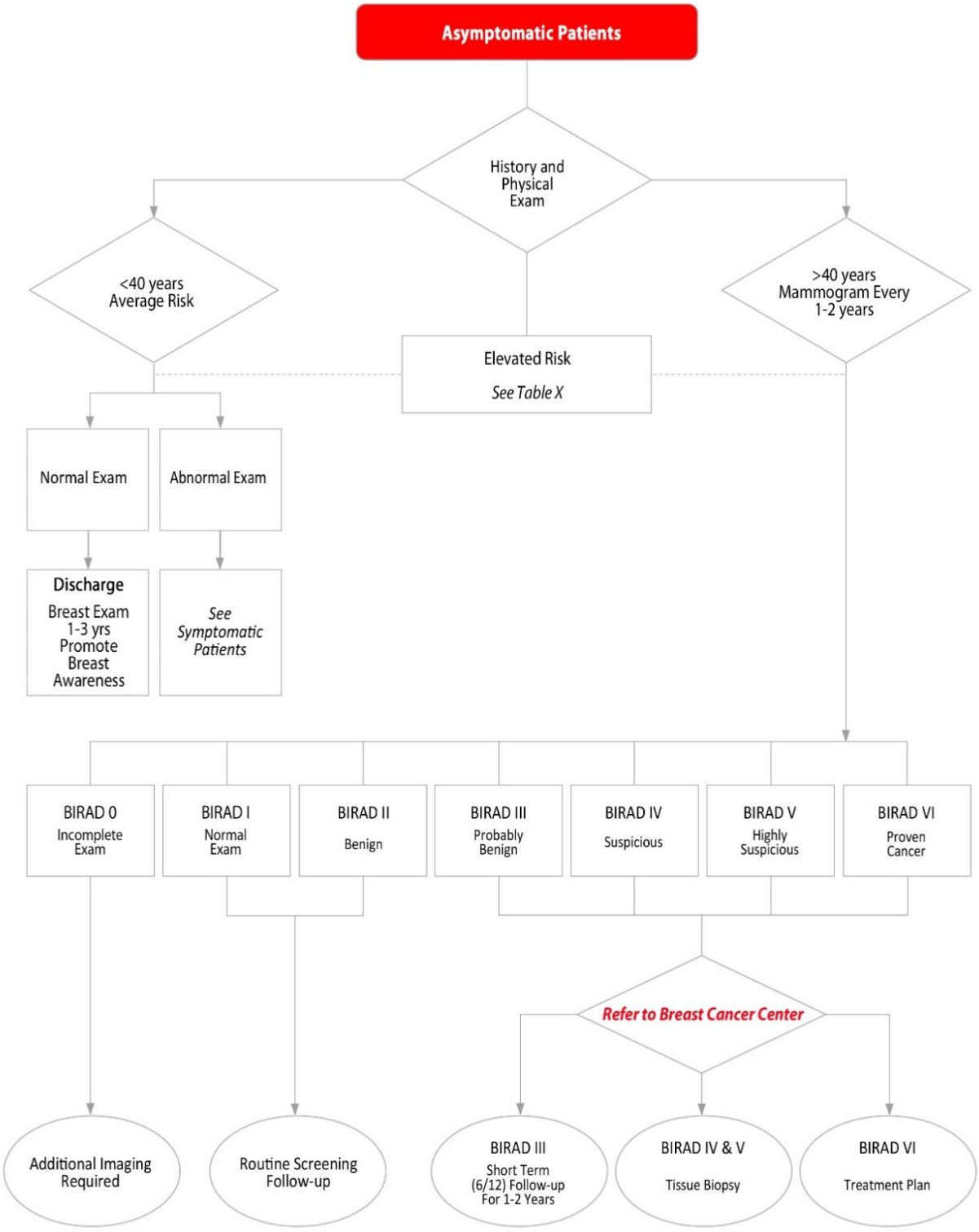
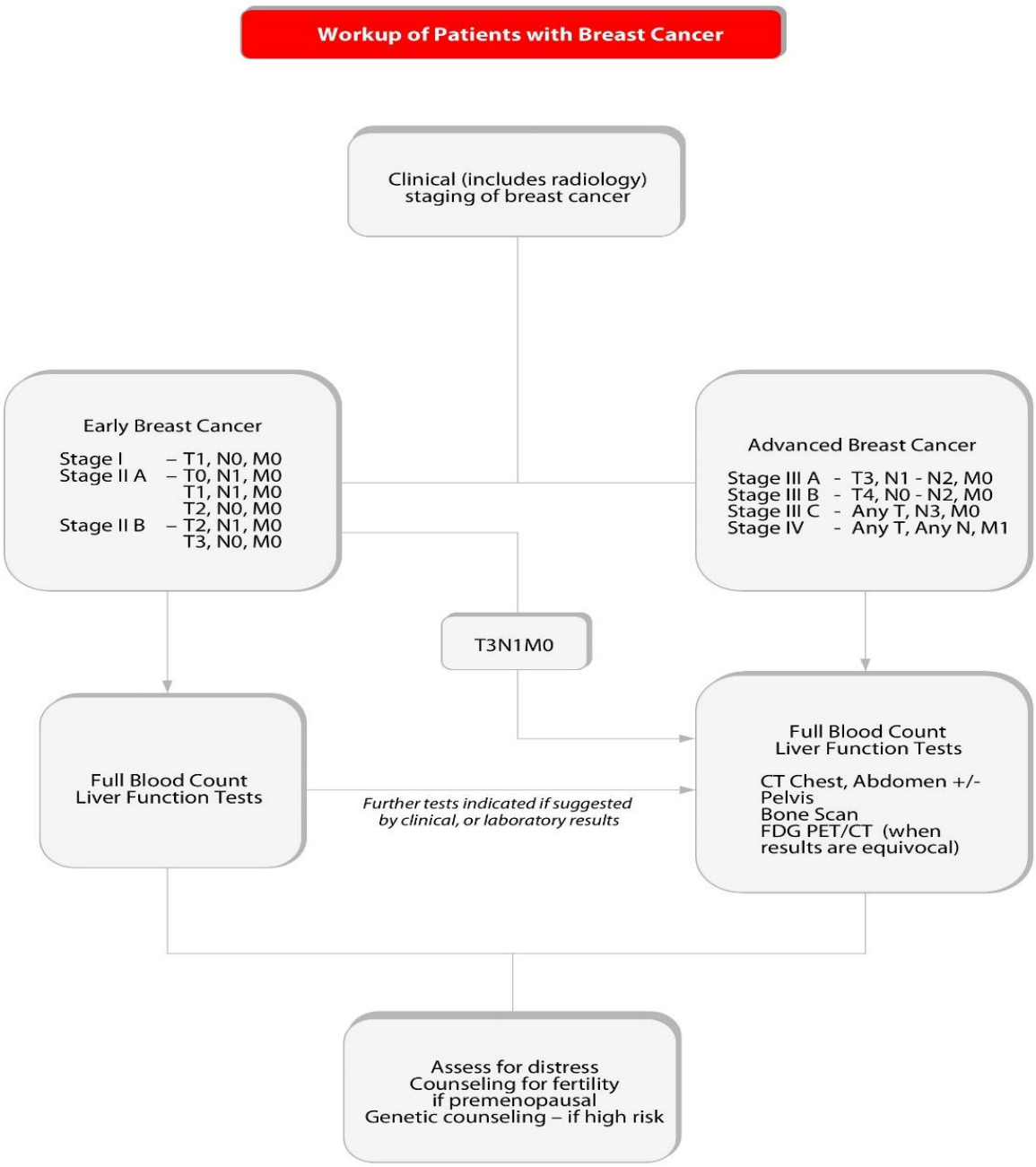


**Figure 4 -** Workup and Staging [Workup of Patients with Breast Cancer]. See Breast Cancer Staging Form AJCC (Appendix Nine)



# *4. Results and Discussion*

## 4.1 Management of Specific Clinical Scenarios

The following clinical scenarios were developed as part of a comprehensive iterative process which expanded the 9 clinical questions used to develop one of the foundational guidelines and considered additional aspects from the broad scope of topics provided by the multidisciplinary team in Bahrain (Appendix 6). Multiple meetings were held with a cross-section of clinicians, patients and senior level policymakers to ensure that every voice was heard and that the clinical scenarios selected from the foundational guideline best reflected the clinical questions of the participants and contributors. Although only a proportion were selected it was evident with a reasonable degree of certainty that the clinical scenarios in the foundation guidelines mirrored the types of clinical questions and scenarios appropriate for the Bahrain setting.

The recommendations in the 30 selected clinical scenarios were agreed upon following extensive consultation and open discussion jointly involving the GDG and the MEG. Every effort was made to ensure that these recommendations correlated with the existing content in the foundational guidelines as well as with other current clinical resources e.g. NCCN, NICE and SIGN. In particular the guideline developers sought to ensure that the GRADE approach or an equally robust methodology had been used to grade the strength of recommendations and to ensure the overall consistency and agreement with those recommendations across resources.

Five additional questions were submitted by patients and advocacy groups. These were added to the 30 to help the healthcare system and future policy making be more cogniscent of the individual care requirements of women with breast cancer. The level of evidence in two specific scenarios is based on randomised controlled trials (Level 1) and two relevant Cochrane Reviews which indicate low to moderate quality of evidence for the outcomes specified in the Cochrane reviews. The remaining two scenarios were evaluated by NCCN and received 2A categories of evidence.

The recommendations are based on the date when the foundational guidelines and other resources were accessed (February 2018) and may be subject to alteration based on availability of further updates to the research. The GDG will make every

effort to ensure the currency of this information and that it is updated periodically to take account of new evidence. Notifications of these updates will be posted on websites hosting the electronic versions of this guideline.

| **RECOMMENDATIONS FOR SPECIFIC CLINICAL SCENARIOS**<br><br>A strong recommendation is one for which guideline panel is confident that the desirable effects of an intervention outweigh its undesirable effects (strong recommendation for an intervention) or that the undesirable effects of an intervention outweigh its desirable effects (strong recommendation against an intervention).<br>A weak recommendation is one for which the desirable effects probably outweigh the undesirable effects (weak recommendation for an intervention) or undesirable effects probably outweigh the desirable effects (weak recommendation against an intervention) but appreciable uncertainty exists. [GRADE Handbook Section 6.1] | | |
|---|---|---|
| **1** | **For women with lobular carcinoma in situ, we recommend observation together with offering (based on individualized shared decision-making) risk reduction strategies** | **Strong recommendation** |
| **2** | **For women having bilateral mastectomy for risk reduction such as for hereditary breast cancer, we suggest offering (based on individualized shared decision-making) breast reconstruction** | **Weak Recommendation** |
| **3** | **For women having a mastectomy for extensive ductal carcinoma in situ we suggest sentinel lymph node biopsy** | **Weak Recommendation** |
| **4** | **For women with ductal carcinoma in situ, we recommend surgical resection with breast conserving surgery (but consideration of total mastectomy if unable to achieve disease-free margins with lumpectomy)** | **Strong Recommendation** |
| **5** | **For women with ductal carcinoma in situ who have breast conserving surgery and are not at low risk for recurrence, we recommend adjuvant whole breast radiation therapy** | **Strong Recommendation** |
| **6** | **For women with estrogen receptor-positive ductal carcinoma in situ treated with lumpectomy without radiation therapy, we suggest offering, based on shared decision-making, tamoxifen (premenopausal or postmenopausal) or an aromatase inhibitor (postmenopausal)** | **Weak Recommendation** |
| **7** | **For women with infiltrating carcinoma of the breast, we recommend surgical resection with individualized shared decision-making to choose between the options of conservative surgery (breast-conserving surgery followed by radiation therapy to the breast) or mastectomy** | **Strong Recommendation** |
| **8** | **For women having mastectomy, we recommend offering (based on individualized shared decision-making) options of immediate or delayed reconstructive surgery** | **Strong Recommendation** |
| **9** | **For women with early breast cancer, we recommend offering (based on individualized shared decision-making, interdisciplinary discussion, and individualized risk assessment) adjuvant chemotherapy** | **Strong Recommendation** |
| **10** | **For women with early breast cancer, who are going to be treated with chemotherapy, we recommend chemotherapy regimens containing anthracyclines and/or taxanes** | **Strong Recommendation** |
| **11** | **For women with early breast cancer with negative hormone receptors and positive HER2-receptor** | |

| | | |
|---|---|---|
| **a** | **we suggest offering chemotherapy and trastuzumab for cancers that are <10mm in size with or without nodal micrometastasis** | **Weak Recommendation** |
| **b** | **we recommend offering chemotherapy for cancers that are >10 mm or node positive (more than micrometastasis)** | **Strong Recommendation** |
| **12** | **For women with early breast cancer with negative hormone receptors and negative HER2 receptor:** | |
| **a** | **we suggest offering chemotherapy for cancers <10mm in size with or without micrometastasis** | **Weak Recommendation** |
| **b** | **we recommend offering chemotherapy for cancers > 10mm in size or with positive lymph nodes (more than micrometastasis)** | **Strong Recommendation** |
| **13** | **For women with large operable early breast cancer, we recommend offering (based on individualized shared decision-making) neoadjuvant (preoperative) chemotherapy** | **Strong Recommendation** |
| **14** | **For women who have had breast conserving surgery for breast cancer, we recommend adjuvant radiotherapy** | **Strong Recommendation** |
| **15** | **For women < 60 yrs with early breast cancer and tumor resections with margins <1mm or extensive intraductal component, and already receiving whole breast radiotherapy, we recommend additional radiation (16 Gy) boost to the tumor bed** | **Strong Recommendation** |
| **16** | **For hormone receptor positive premenopausal women, we suggest offering Tamoxifen** | **Weak Recommendation** |
| **17** | **For postmenopausal women with hormone receptor-positive early breast cancer (after treatment with chemotherapy if chemotherapy given), we recommend hormonal therapy with aromatase inhibitor for 5 years (with consideration for an additional 5 years) or tamoxifen for 2-3 years followed by an aromatase inhibitor for a total period of at least 5 years** | **Strong Recommendation** |
| **18** | **For women with local recurrence after breast-preserving treatment for breast cancer, we suggest mastectomy** | **Weak Recommendation** |
| **19** | **For women with local recurrence following a modified radical mastectomy and no prior radiotherapy, we suggest complete surgical excision if possible and radiation** | **Weak Recommendation** |
| **20** | **For women with HER 2 positive locally advanced breast cancer, we recommend chemotherapy and trastuzumab** | **Strong Recommendation** |
| **21** | **For women with locally advanced breast cancer with negative hormone receptors and negative HER2 receptor, we recommend chemotherapy** | **Strong Recommendation** |
| **22** | **For women with advanced breast cancer and with severe bone metastasis symptoms, or symptomatic organ metastasis or rapidly developing metastases, we recommend offering chemotherapy** | **Strong Recommendation** |
| **23** | **For women with hormone receptor negative advanced breast cancer or hormone receptor positive advanced breast cancer refractory to hormone therapy, we recommend offering chemotherapy** | **Strong Recommendation** |
| **24** | **For women with metastatic HER2 positive, breast cancer we recommend offering trastuzumab with pertuzumab and chemotherapy** | **Strong Recommendation** |
| **25** | **For postmenopausal women with metastatic cancer and disease progression on hormonal therapy, we recommend offering second-line hormone therapy** | **Strong Recommendation** |

| | | |
|---|---|---|
| **26** | **For premenopausal women with hormone positive metastatic breast cancer, we recommend offering ovarian ablation or suppression together with hormone therapy** | **Strong Recommendation** |
| **27** | **For premenopausal women with low-volume, low-aggressive metastatic breast cancer whose estrogen receptors and / or progesterone receptors are strongly positive, we recommend offering tamoxifen or toremefine without ovarian suppression/ablation** | **Strong Recommendation** |
| **28** | **For women with symptomatic metastatic disease in the bone, we recommend bisphosphonates (especially zoledronic acid), radiotherapy or both** | **Strong Recommendation** |
| **29** | **For women with breast cancer and a resectable oligometastatic brain lesion, we recommend offering resection followed by radiation therapy** | **Strong Recommendation** |
| **30** | **For women who survive breast cancer (stages I, II or III), we do not recommend routine follow-up chest X-ray, bone studies, liver ultrasound, CT scan and tumor markers (CA 15-3, CEA)** | **Strong Recommendation AGAINST** |

**For links to the evidence See Supplementary File**

**DELIVERY OF CARE-SYSTEM LEVEL RECOMMENDATIONS**
**PATIENT INDIVIDUAL CARE RECOMMENDATIONS**

| | | | |
|---|---|---|---|
| **1** | **For women with a potential diagnosis or confirmed diagnosis of breast cancer, we suggest they have access to a breast care nurse specialist for information and support at each stage of diagnosis and treatment** | **Weak Recommendation** | **https://www.ncbi.nlm.nih.gov/pubmed/?term=18254086**<br>**Cochrane Review: Limited evidence** |
| **2** | **For women with breast cancer, we suggest access to psychosocial interventions provided by nurse specialists or psychologist in breast care** | **Weak Recommendation** | **https://www.ncbi.nlm.nih.gov/pubmed/?term=18490891**<br>**Randomised controlled trial (RCT) Level 1** |
| **3** | **For women with breast cancer, we recommend offering group education interventions for stress and physical activity developed by nurse practitioners specialist in breast care** | **Strong Recommendation** | **https://www.ncbi.nlm.nih.gov/pubmed/?term=18490891**<br>**RCT Level 1**<br>**https://www.ncbi.nlm.nih.gov/pubmed/29376559**<br>**Cochrane Review: Low to moderate evidence** |
| **4** | **For women with breast cancer, both during and after treatment, we recommend regular physical exercise which should include moderate- intensity physical activity (and include those patients undergoing adjuvant therapies** | **Strong Recommendation** | **https://www.dynamed.com/topics/dmp~AN~T113654#Activity**<br>(NCCN Category 2A) based on lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate |
| **5** | **For women undergoing treatment for breast cancer, we recommend walking as a part of physical rehabilitation therapy** | **Strong Recommendation** | **https://www.dynamed.com/topics/dmp~AN~T113654#Exercise-during-treatment**<br>(NCCN Category 2A) based on lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate |

## 4.2 Grading of Recommendations

Recommendations are graded as either strong or weak according to the Grades of Recommendation Assessment, Development and Evaluation system (GRADE).

GRADE offers two strengths of recommendation: strong and weak. The strength of recommendations is based on the quality of supporting evidence, the degree of uncertainty about the balance between desirable and undesirable effects, the degree of uncertainty or variability in values and preferences, and the degree of uncertainty about whether the intervention represents a wise use of resources.

- Strong recommendations are those for which the task force is confident that the desirable effects of an intervention outweigh its undesirable effects (strong recommendation for an intervention) or that the undesirable effects of an intervention outweigh its desirable effects (strong recommendation against an intervention).

A strong recommendation implies that most people will be best served by the recommended course of action.

- Weak recommendations are those for which the desirable effects probably outweigh the undesirable effects (weak recommendation for an intervention) or undesirable effects probably outweigh the desirable effects (weak recommendation against an intervention) but appreciable uncertainty exists.

A weak recommendation implies that most women would want the recommended course of action, but many would not.

For clinicians, this means they must recognize that different choices will be appropriate for individual women, and they must help each woman arrive at a management decision consistent with her own values and preferences. Weak recommendations result when the balance between desirable and undesirable effects is small, the quality of evidence is lower, and there is more variability in the values and preferences of patients.

## 4.3 Suggestions for future work

### 1. Organised population-based breast cancer screening programmes

Emphasis has been placed by the WHO on the most optimal way of reducing inequality of access and ensuring the quality of care in national breast cancer screening programmes.[20] The key criteria for successful implementation of organized population-based screening programmes have been defined by the WHO and provide a road map for the future development of the current Breast Cancer guideline for the Kingdom of Bahrain.

**Organized, population-based breast cancer screening programmes**
**Key criteria for successful programme implementation**

- Demonstrated feasibility, cost-effectiveness and affordability of the screening process in the respective setting through pilot studies and modelling.
- Coordination of all activities, including planning, feasibility testing, piloting and gradual rollout of the programme across a country or region, by an autonomous management team responsible for service delivery, quality assurance, and evaluation.
- A well-developed, equitable, health system with cancer control planning integrated into the national noncommuncable disease (NCD) prevention and control strategy and with balanced, objective information of women about the benefits and harms of mammography screening.
- Validated protocols for all steps in the screening process, including identification and individual invitation of all eligible women to attend screening, performing the screening test, diagnosis, treatment and palliative care.
- Adherence to comprehensive, evidence-based guidelines for quality assurance of the entire screening process, including standards and protocols for professional and technical quality assurance; and that are regularly updated based on current evidence.
- Quality assurance and information systems covering the entire screening process, including call and recall of participants for follow-up of abnormalities detected in screening, and for monitoring and evaluating programme performance at each step in the screening process.

(Adapted from the WHO (2014)).

In addition, several international organisation such as, ECIBC have developed quality audit processes and indicators that can be utilised to monitor screening services and to provide feedback geared towards continuous quality improvement. [43]

**2.Specialist Breast Cancer Centre Services**

Centralised breast cancer services are increasingly recognised at global level as the best way of providing high quality and cost effective care. [44] The conceptual framework behind a breast cancer specific centre takes into account how patient-centred, evidence based, high quality care can be delivered. Six components are considered by the IOM (Committee on Improving the Quality of Cancer Care) to be essential prerequisites to the establishment of a centre: [45]

1. Engaged patients
2. An adequately trained staff and coordinated workforce
3. Evidence-based cancer care: A system that uses scientific research, such as clinical trials and comparative effectiveness research (CER), to inform medical decisions
4. A learning healthcare information technology (IT) system for cancer
5. Translation of evidence into clinical practice which is quality measured and performance approved
6. Accessible and affordable cancer care

Breast cancer centres can foster a standardised quality of service provision and health care delivery for breast cancer patients. There is a consensus on the minimum requirements for a breast cancer specific unit as per the EUSOMA (European Society of Breast cancer Specialists, 2013). [44] The overview is that the centre provides:

- Sufficient cases that allow effective work and therefore continuing expertise
- Dedicated specialists within the multidisciplinary team and throughout the pathway

- Data collection
- Audit
- Multidisciplinary competencies
- High quality palliative services
- Comprehensive support
- Referral

The principal aim of these specific summary recommendations is to provide reliable evidence-based guidance to underpin future policy making for the management of breast cancer in the Kingdom of Bahrain. Moreover it is to ensure that this has a joint clinician and patient focus, whilst recognising that the key to success, adoption, implementation and sustainability lies with the governance of the Supreme Council of Health (SCH) and the NHRA.

# *5. Conclusion*

The establishment of the first interactive patient-centered, multidisciplinary approach to guideline development for breast cancer treatment, screening and diagnosis in Bahrain. This locally flavoured, evidenced based guideline not only used sharing of resources but was developed with little direct cost. Over 18 months the multidisciplinary team lead by the researchers, supported the development of 35 clinical scenarios relevant to the gamut of supporters along with treatment algorithms. Having an inclusive process and clear methodology meant that the multidisciplinary team championed the process and results, reducing some of the challenges. Whilst the guidelines provide an underpinning for future policy making and management of breast cancer in Bahrain the innovation is the identification of eight clinical scenarios in which shared decision making is recommended, thus empowering the end-user. This hands-on initiative at grass roots level addressed pertinent issues related across a multidisciplinary team, when supporting a patient through their treatment pathway is key. Singing all from the same “hymn sheet” is vital to better support and optimise and improve health outcomes. Reducing the confusion of what evidence based best practice is, whilst producing a locally flavoured document, showed that Non-Governmental Organization (NGOs) can be used as a resource in relation to Public Private Partnerships (PPP). This international peer reviewed guideline for Bahrain will ensure that there will be a joint clinician and patient focus, whilst recognising that the keys to success, adoption, implementation and sustainability lies with the government itself. Moving forward, the researcher will lead the development of three of the eight shared decision-making aids the backing of international publishers of evidence-based clinical references (EBSCO).

# *6. References*[1]

[1]Elaboradas de acordo com as Diretrizes para Apresentação de Dissertações e Teses da USP: Documento Eletrônico e Impresso - Parte IV (Vancouver) 3ª ed. São Paulo: SIBi/USP, 2016.

1. International Agency for Research of Cancer World Health Organization. Handbook of Prevention: Breast Cancer Screening. Vol 7. IARC Press. 2002. 236p. Available at: https://publications.iarc.fr/Book-And-Report-Series/Iarc-Handbooks-Of-Cancer-Prevention/Breast-Cancer-Screening-2002. Access in: 18 abr. 2018.

2. Hamadeh RR et al. Epidemiology of breast cancer among Bahraini women: Data from the Bahrain Cancer Registry. Sultan Qaboos Univ Med J. 2014;14(2):e176-82.

3. Al-Othman S et al. Tackling cancer control in the Gulf Cooperation Council Countries. Lancet Oncol. 2015;16(5):e246-57.

4. Najjar H, Easson A. Age at diagnosis of breast cancer in Arab nation. Int J Surg. 2010;8(6):448-52.

5. International Agency for Research on Cancer (IARC). Available at: Website http://www.iarc.fr/. Access in: 18 abr. 2018.

6. International Association of Cancer Registries (IACR). Available at: Website http://www.iacr.com.fr/. Access in: 18 abr. 2018.

7. IARC Global Cancer Observatory (GCO). Available at: Website http://gco.iarc.fr/. Access in: 18 abr. 2018.

8. GLOBOCAN 2012. Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012. Available at: http://globocan.iarc.fr/Default.aspx. Access in: 18 abr. 2018.

9. Cancer Incidence in Five Continents (CI5). Website and monographs available at: http://ci5.iarc.fr/Default.aspx. Access in: 18 abr. 2018.

10. WHO Global Health Observatory (GHO). Website and data available at: http://www.who.int/gho/mortality_burden_disease/en. Access in: 18 abr. 2018.

11. Norris SL et al. Author's specialty and conflicts of interest contribute to conflicting guidelines for screening mammography. J Clin Epidemiol. 2012;65(7):725-33.

12. Clinical Practice Guidelines in cancer in Catalonia. Breast cancer OncoGuia Update 2008. 91p. Available at: https://portal.guiasalud.es/wp-content/uploads/2019/01/GPC_497_oncog_mama_2008_ing.pdf. Access in: 18 abr. 2018.

13. Ramírez-Morera A et al. Guia de Practica Clinica para el tratamiento del cancer de mama. San José: Costa Rica, Organisación Panamericana de La Salud, 2012. 165p.

14. Alper BS et al. RAPADAPTE for rapid guideline development: high-quality clinical guidelines can be rapidly developed with limited resources. Int J Qual Health Care. 2016;28(3):268-74.

15. Guidelines International Networks. ADAPTE Resource Toolkit for Guideline Adaptation Version 2.0. 2010. 95p. Available at: http://www.g-i-n.net/document-store/working-groups-documents/adaptation/adapte-resource-toolkit-guideline-adaptation-2-0.pdf/view. Access in: 18 abr. 2018.

16. AGREE Advancing the Science of Practice Guidelines. AGREE II Instrument. Available at: https://www.agreetrust.org/agree-ii/. Access in: 18 abr. 2018.

17. Scottish Intercollegiate Guidelines Network (SIGN). Available at: http://www.sign.ac.uk/. Access in: 18 abr. 2018.

18. Lauby-Secretan B et al. Breast-cancer screening--viewpoint of the IARC Working Group. N Engl J Med. 2015;372(24):2353-8.

19. Gøtzsche PC. Mammography screening is harmful and should be abandoned. J R Soc Med. 2015;108(9):341-5.

20. World Health Organization (WHO). WHO position paper on mammography screening. Geneva: Suiça. World Health Organization. 2014. 85p. Available at: http://www.who.int/cancer/publications/mammography_screening/en/. Access in: 18 abr. 2018.

21. Gøtzsche PC, Jørgensen KJ. Screening for breast cancer with mammography. Cochrane Database Syst Rev. 2013;2013(6):CD001877.

22. Lauby-Secretan B, Loomis D, Straif K. Breast-Cancer Screening--Viewpoint of the IARC Working Group. N Engl J Med. 2015;373(15):1479.

23. Marmot MG et al. The benefits and harms of breast cancer screening: an independent review: Independent UK Panel on Breast Cancer Screening. Lancet. 2012;380(9855):1778-86.

24. Senkus E et al. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26(Suppl 5):v8-30.

25. Lee CH et al. Breast cancer screening with imaging: recommendations from the Society of Breast Imaging and the ACR on the use of mammography, breast MRI, breast ultrasound, and other technologies for the detection of clinically occult breast cancer. J Am Coll Radiol. 2010;7(1):18-27.

26. Siu AL et al. Convergence and Divergence Around Breast Cancer Screening. Ann Intern Med. 2016;164(4):301-2.

27. Oeffinger KC et al. Breast cancer screening for women at average risk: 2015 Guideline Update From the American Cancer Society. JAMA. 2015;314(15):1599-614.

28. Stewart BW, Wild CP (eds). World Cancer Report 2014. Lyon: France. IARC Publications. 2014. 632p.

29. Elobaid YE et al. Breast cancer screening awareness, knowledge, and practice among arab women in the United Arab Emirates: a cross-sectional survey. PLoS One. 2014;9(9):e105783.

30. World Health Organization (WHO). Detection and screening of priority cancers in the Eastern Mediterranean Region. EMHJ. 2016;22(9):707-8.

31. European Commission Initiative on Breast Cancer. Available at: http://ecibc.jrc.ec.europa.eu/home. Access in: 18 abr. 2018.

32. AGREE Advancing the science of practice guidelines. AGREE II Reporting Checklist. Available at: https://www.agreetrust.org/resource-centre/agree-reporting-checklist/. Access in: 18 abr. 2018.

33. Institute of Medicine (US) Committee on Standards for Developing Trustworthy Clinical Practice Guidelines. Graham R et al. (eds). Clinical Practice Guidelines We Can Trust. Washington: USA. National Academies Press (US); 2011. Available at: https://www.ncbi.nlm.nih.gov/books/NBK209539/. Access in: 18 abr. 2018.

34. Lenzer J et al. Ensuring the integrity of clinical practice guidelines: a tool for protecting patients. BMJ. 2013;347:f5535.

35. Schünemann H et al. (eds). Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach. Updated October 2013. Available at: https://gdt.gradepro.org/app/handbook/handbook.html. Access in: 18 abr. 2018.

36. Committee on Practice Bulletins—Gynecology. Practice Bulletin Number 179: Breast Cancer Risk Assessment and Screening in Average-Risk Women. Obstet Gynecol. 2017;130(1):e1-e16.

37. Tonelli M et al. Recommendations on screening for breast cancer in average-risk women aged 40-74 years. CMAJ. 2011;183(17):1991-2001.

38. Preventive Services Task Force U.S. Final Recommendation Statement: Screening for Breast Cancer. January 2016. Available at https://www.uspreventiveservicestaskforce.org/uspstf/announcements/final-recommendation-statement-screening-breast-cancer. Access in: 18 abr. 2018.

39. Chiarelli AM et al. The contribution of clinical breast examination to the accuracy of breast screening. J Natl Cancer Inst. 2009;101(18):1236-43.

40. Stacey D et al. Decision aids for people facing health treatment or screening decisions. Cochrane Database Syst Rev. 2017;4(4):CD001431.

41. Klein S. Evaluation of palpable breast masses. Am Fam Physician. 2005;1(9):1731-8.

42. Morris KT et al. Usefulness of the triple test score for palpable breast masses; discussion 1012-3. Arch Surg. 2001;136(9):1008-12.

43. European Commission Initiative on Breast Cancer Methodology for selecting requirements and indicators. Available at: http://ecibc.jrc.ec.europa.eu/qa-methodology. Access in: 18 abr. 2018.

44. Wilson AR et al. The requirements of a specialist Breast Centre. Eur J Cancer. 2013;49(17):3579-87.

45. Committee on Improving the Quality of Cancer Care: Addressing the Challenges of an Aging Population; Board on Health Care Services; Institute of Medicine; Levit L et al. (eds). Delivering High-Quality Cancer Care: Charting a New Course for a System in Crisis. Washington (DC): USA. National Academies Press (US); 2013 Dec 27. Available at: https://www.ncbi.nlm.nih.gov/books/NBK202150/. Access in: 18 abr. 2018.

# *7. Appendices*

## APPENDIX ONE - Key Questions Used in Developing the Costa Rican Guideline

1. What is the best therapeutic option for women with stage I-III breast cancer?
2. What is the best therapeutic option for women with metastatic disease in stage IV breast cancer?
3. What is the best therapeutic option for women with local, regional or generalized breast cancer recurrence?
4. What is the best follow-up method for women with breast cancer?
5. What is the best evidence for treatment of pregnant women with breast cancer?
6. What is the best evidence for treatment of postmenopausal women with breast cancer who use hormone replacement therapy?
7. What is the best evidence on psychological support for women with breast cancer?
8. What is the best evidence on nutritional counseling in women with breast cancer?
9. What is the best evidence on physical activity in women with breast cancer?

**NB This guideline did not include breast cancer screening**

## APPENDIX TWO: Key Initial Questions Used in This Guideline for the Kingdom of Bahrain

1. What is the best therapeutic option for women with stage I-III breast cancer?
2. What is the best therapeutic option for women with metastatic disease in stage IV breast cancer?
3. What is the best therapeutic option for women with local, regional or generalized breast cancer recurrence?
4. What is the best follow-up method for women with breast cancer?
5. What is the best evidence for treatment of pregnant women with breast cancer?
6. What is the best evidence for treatment of postmenopausal women with breast cancer who use hormone replacement therapy?
7. What is the best evidence on psychological support for women with breast cancer?
8. What is the best evidence on nutritional counseling in women with breast cancer?
9. What is the best evidence on physical activity in women with breast cancer?
10. What is the best evidence for screening with mammography; age based and risk based?

## APPENDIX THREE - The Bahrain Breast Cancer Society (TPB) Clinical Guideline Terms of Reference (TOR) - Contributors and their role in the guideline development process

- The Steering Committee (SC)
- The Guideline Development Group (GDG)
- Multidisciplinary Experts Group (MEG)
- The International Advisory Board (IAB)/ the external review group

**Purpose / role of the group:**

**The Steering Committee (SC):**

The Steering Committee consists of senior leaders (8-10) from the healthcare services in Bahrain. Their principal role is to provide overall administrative support and 'local' oversight of the guideline development process which will include reviewing the draft scope of the guideline and the key clinical questions. They are helped with identifying additional members for the Guideline Development Group (GDG) and in recommending clinical experts for the Multidisciplinary Experts Group (MEG). In collaboration with the GDG, they will evaluate the disclosures of interest of participants involved with development of the guideline and monitor any potential conflicts or disagreements. After authorization, the SC will submit the final guideline to the relevant authorities and oversee its publication and dissemination.

**The Guideline Development Group (GDG):**

The GDG comprises of individuals with key areas of methodological expertise relevant to clinical guideline development. These include broad ranging experience in assessing and grading evidence and developing of subsequent recommendations informed by the evidence. Other technical experts e.g. health economics, quality assurance/management and equity, among others, were co-opted to provide balance to the group. Specific tasks include evidence retrieval, its assessment and synthesis; drafting of the recommendations for the final guideline, overseeing peer review, responding to reviewers' comments and revising of the draft guideline as appropriate. On completion of the guideline, their representative will submit the guideline iy to the Steering Committee for final approval before dissemination.

**Multidisciplinary Experts Group (MEG):**

The MEG is multidisciplinary and composed essentially of individuals who are likely to use the guideline. The group also includes individuals from groups who are also

likely to be most affected by the recommendations in the guideline, such as service users in addition to representatives of patient advocacy groups. Thus, its membership should be balanced between clinical expertise and laypersons. The aim is to have a diverse group of contributors that include clinical topic experts and end-users, such as programme managers and health professionals, who will ultimately adapt, adopt, and facilitate with implementation of the guideline.
Breast cancer specific expertise and experience encompasses; Surgery, Nutrition, Pathology, Radiography, Oncology, Plastics/Reconstruction, Epidemiology, Nursing, Physiotherapy, Counselling and Consumer Advocacy.

**The International Advisory Board (IAB):**

The members of the IAB are a cross-section of internationally recognized experts with broad experience in either clinical guideline development or as clinicians in the field of breast cancer. Their key role is to provide oversight of the process of development and to provide *ad hoc* support and guidance to ensure the robustness of the guideline and its compliance with best practice. The members came from organizations such as Guidelines International Network (G-I-N), GRADE, Cochrane and the WHO. Additional members are invited as required to provide input on specific task areas. The geographical spread of the IAB precludes frequent virtual meetings or teleconferencing of all members but efforts are made to ensure these meetings are organized at times and dates to maximize possible availability. These meetings may also be conducted on a one to-one-basis if necessary. Routine communication is via email with regular teleconferencing.

**Responsibilities**

The contributors to the development of this breast cancer clinical guideline are expected to share their professional expertise and knowledge, around relevant best practices and policies and contribute to the process in a collaborative and collegial fashion. Any diversity in expert opinion or individual personal experience related to the clinical topic is resolved through discussion and a consensus process which may involve the SC or IAB if appropriate. Members of the GDG and MEG work on the specific tasks allocated to them effectively and efficiently either in working groups or individually, with the clear objectives of improving clinical processes and coordinating quality improvement in the management of breast cancer.

**Communication and meetings**

Meetings are arranged by the coordinator of the GDG. These meetings provide opportunities for participants to review evidence related to their expertise and to enable them to reach agreement on proposed guideline recommendations. Training

is be provided, as necessary, to assist members with evaluating the quality of evidence underpinning the existing recommendations in the foundational guidelines. Open access information is distributed via electronic mail and non-confidential documents will be shared via DROPBOX or similar on line resources. Members of the group are expected to understand and abide by standard regulations related to the confidentiality of data and information.

**Accountability**

The coordinator of the GDG is an international expert that has been appointed by the Bahrain Breast Cancer Society based on current experience with breast cancer guideline development. Regular reports and updates on the activities of the supporting groups, including the minutes of any meetings, are provided to the Supreme Council of Health and CEO National Health Regulatory Authority (NHRA), following each meeting.

## APPENDIX FOUR - RAPADAPTE Method

1 Identify and select team and schedule resources.

2 Train team members as needed in content domain and evidence-based methodology.

3 Define clinical questions.

4 Identify candidate guidelines for adaptation.

5 Select most useful guidelines for adaptation, with iterative evaluation until adequate set of foundational guidelines is established. (Contacting guideline developers is suggested to facilitate collaboration which can improve both guidelines.)

6 Identify existing summarized evidence for each clinical question from foundational guidelines and from clinical references with systematic processes for evidence selection, critical appraisal, summarization, and synthesis. (Contacting clinical reference developers is suggested to facilitate collaboration which can improve both resources.)

7 Search for evidence for clinical questions where existing summarized evidence is inconsistent or lacking.

8 Grade the quality of the body of evidence for each question, with evaluation of original articles for evidence with appraisals that are inconsistent or lacking, and to confirm high-quality evidence.

9 Create draft recommendations considering the body of evidence for benefits and harms, values, preferences, and costs.

10 Share draft recommendations and supporting evidence with expert review panel using a process to identify convergence and divergence of opinion, and facilitate iterative dialog.

11 Adjust recommendations as determined by informed expert review. Repeat expert review process as needed.

12 Share the resulting Clinical Practice Guideline for external review

## APPENDIX FIVE - Broad scope of suggested topics from the multidisciplinary team (Bahrain)

1. What is the recommended screening protocol for breast cancer for women of average risk?
2. Where should breast cancer patients be treated?
3. How should breast cancer patients be assessed?
4. What are the therapeutic options for women with:
    i. Early (Stage I and II) breast cancer
    ii. Locally advanced (Stage III) breast cancer
    iii. Locoregional recurrence of breast cancer
    iv. Metastatic (Stage IV) breast cancer
5. What is the recommended follow up for women with breast cancer?
6. Supportive care:
    i. What fertility consultations are useful for breast cancer patients? When should women be referred for a fertility consultation?
    ii. What psychological support is needed for women with breast cancer?
    iii. What ancillary care (i.e. breast care nurses, social workers) should be provided for women with breast cancer?
    iv. When should reconstructive surgery be offered?
    v. When should the palliative care team be involved?
    vi. What is the role of physiotherapy in the management of women with breast cancer?

# APPENDIX SIX - Comparison of global guidelines on screening recommendations. Accessed April 2018

| Organization | Methods used | Age specific recommendations | | | |
|---|---|---|---|---|---|
| American Cancer Society (2015) | GRADE | SDM 40-44 "opportunity to begin" **annual** | 45-54 **annual/ biennial** | >55 **annual/ biennial** | Continue based on comorbidity, life expectancy 10years |
| American College of Radiology/Society of Breast Imaging (2010) | N/S (consensus based) | 40 **annual** | Continue based on comorbidity, life expectancy <5 to 7years | | No upper age limit |
| American Society of Breast Surgeons (2015) | N/S | SDM 40-44 **annual** | 45-54 **annual/ biennial** | >55 **annual/ biennial** | >75 **biennial** |
| American College of Ob-Gyn (2017) | N/S Review of CPGs | SDM >40 **annual** | --- | --- | >75 Continue based on comorbidity, life expectancy |
| MD Anderson Cancer Center (2017) | N/S | 40 **annual** | Continue based on comorbidity, life expectancy 10years | | |
| USPSTF (2016) | A/B/C/D/I. Levels of certainty of net benefit | SDM 40-49 **biennial** | 50-74 **biennial** | | No recommendation |
| British Columbia Breast Ca Agency (2014) | N/S | SDM 40-49 **biennial** | 50-74 **biennial** | | >75 SDM **(2-3yearly)** based on comorbidity, life expectancy |
| Canadian Task Force on Preventive Health (2011) | GRADE (strong/weak) | 40-49 Not recommend. Routinely | 50-69 **every 2-3yrs** | | 70-74 **every 2-3yrs** |
| NCCN (2017) | Categories of evidence +NCCN consensus | 40-49 **annual** | 50-74 **annual** | | >75 based on life expectancy |
| European Society for Medical Oncology (2015) | Grades of recommendation (A-E) | 40-49 no consensus | SDM 50-69 **biennial** | | |
| European Commission (ECIBC) (2016) | GRADE Recommendations: [*context of organized screening programme*] [*No interval indicated*] | 40-44 Not recommend Conditional | 45-49 Recommend Conditional | 50-69 Recommend Strong | 70-74 Recommend Conditional |
| IARC (WHO) Handbook of Cancer Prevention (2014) | Only degree of evidence for reduction in mortality | 40-45 limited evidence | 45-49 limited evidence | 50-69 sufficient evidence | 70-74 sufficient evidence |
| WHO mammography screening (2014)<br>a) Well-resourced settings<br>---<br>b) Limited resource settings | GRADE<br>Recommendations:<br>[*context of organized/population based screening programme*] | 40-49<br>Recommend Conditional **No interval**<br>---<br>Not Recommend Strong | 50-69<br>Recommend Conditional **biennial**<br>---<br>Recommend Conditional **biennial** | | 70-75<br>Recommend Conditional **No interval**<br>---<br>Not Recommend Strong |
| SCEBHC. MOH Saudi Arabia | GRADE | 40-49 | 50-69 | | 70-74 |

| | | | | | |
|---|---|---|---|---|---|
| (2014) | | Recommend Conditional<br>**Every 1-2yrs** | Recommend Conditional<br>**Every 1-2yrs** | | Not Recommend Conditional<br>But maybe every **2-3 yrs** |
| Lebanon Breast Cancer National Task Force (2009) | N/S | >40 **annual** | --- | --- | --- |
| Royal Australian College of GPs (2016) | Grades of recommendation (A-D) | 40-49<br>Based on SDM<br>**No interval** | 50-74<br>**biennial** | >75 Continue based on comorbidity, life expectancy 10years | |

**N/S Not Specified**

## APPENDIX SEVEN - Searches of screening guidelines. Accessed April 2018

| Organization | Website |
|---|---|
| American Cancer Society (2015) | https://jamanetwork.com/journals/jama/fullarticle/2463262 |
| American College of Radiology/Society of Breast Imaging (2010) | http://chrmschicago.org/images/meeting/092509/acrguideline_mammo_guidelines.pdf |
| American Society of Breast Surgeons (2015) | https://www.breastsurgeons.org/new_layout/about/statements/PDF_Statements/Screening_Mammography.pdf |
| American College of Ob-Gyn (2017) | https://www.acog.org/-/media/Practice-Bulletins/Committee-on-Practice-Bulletins----Gynecology/Public/pb179.pdf?dmc=1&ts=20171021T0813202898 |
| MD Anderson Cancer Center (2017) | https://www.mdanderson.org/documents/for-physicians/algorithms/screening/screening-breast-web-algorithm.pdf |
| USPSTF (2016) | https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/breast-cancer-screening1 |
| British Columbia Breast Ca Agency (2014) | http://www.bccancer.bc.ca/screening/Documents/SMP_GuidelinesManual-PhysicianProtocolForScreeningMammograms.pdf |
| Canadian Task Force on Preventive Health (2011) | http://www.cmaj.ca/content/183/17/1991.long |
| NCCN (2017) | https://www.nccn.org/professionals/physician_gls/f_guidelines.asp |
| European Society for Medical Oncology (2015) | https://academic.oup.com/annonc/article-lookup/doi/10.1093/annonc/mdv298 |
| European Commission (ECIBC) (2016) | http://ecibc.jrc.ec.europa.eu/recommendations/ |
| IARC (WHO) Handbook of Cancer Prevention (2014) | https://www.iarc.fr/en/meetings/handbooks/index.php |
| WHO mammography screening (2014) | http://www.who.int/cancer/publications/mammography_screening/en/ |
| SCEBHC. MOH Saudi Arabia (2014) | https://faculty.psau.edu.sa/m.alghadier/page/5315 |
| Lebanon Breast Cancer National Task Force (2009) | http://lebanesemedicaljournal.org/articles/57-2/doc2.pdf |
| Royal Australian College of GPs (2016) | https://www.racgp.org.au/your-practice/guidelines/redbook/ |

## APPENDIX EIGHT - Evaluation of Palpable Breast Masses

| Relevant History in Women with Palpable Breast Masses |
|---|
| **Breast lump characteristics** |
| Changes in size over time |
| Change relative to menstrual cycle |
| Duration of mass |
| Pain or swelling |
| Redness, fever, or discharge |
| **Diet and medications** |
| Current medications |
| History of hormone therapy |
| **Family history** |
| History of breast disease |
| Relationship to patient |
| Relative's age at onset |
| **Medical and surgical history** |
| Personal history of breast cancer |
| Previous breast masses and biopsies |
| Recent breast trauma or surgery |
| Recent radiation therapy or chemotherapy |
| Other exposure to radiation |
| **Personal characteristics** |
| Age at first childbearing |
| Age at menarche |
| Age at menopause |
| Current age |
| Current lactation status |
| History of breastfeeding |
| Number of children |
| **Social history** |
| Radiation and chemical exposure |
| Smoking |

## APPENDIX NINE - Breast Cancer Staging Form AJCC

Breast cancer is staged using the American Joint Committee on Cancer (AJCC) **TNM** system, which is based on:

- The size of the breast tumor (**T**) and if it has grown into nearby areas
- Whether the cancer has reached nearby lymph nodes (**N**)
- Whether the cancer has metastasized (spread to other parts of the body) (**M**)

Once the T, N, and M categories for your cancer have been determined, your doctor will combine the information to find the stage of the cancer. This process is called *stage grouping*. Cancers with similar stages tend to have a similar outlook and are often treated in a similar way.

| | | |
|---|---|---|
| **Stage 0** | **Tis, N0, M0** | This is *ductal carcinoma in situ (DCIS)*, a pre-cancer of the breast. Many consider DCIS the earliest form of breast cancer. In DCIS, cancer cells are still within a duct and have not invaded deeper into the surrounding fatty breast tissue.<br>*Lobular carcinoma in situ (LCIS)* sometimes also is classified as stage 0 breast cancer, but most oncologists believe it is not a true cancer or pre-cancer.<br>Paget disease of the nipple (without an underlying tumor mass) is also stage 0.<br>In all cases the cancer has not spread to lymph nodes or distant sites. |
| **Stage IA** | **T1, N0, M0** | The tumor is 2 cm (about 3/4 of an inch) or less across (T1) and has not spread to lymph nodes (N0) or distant sites (M0). |
| **Stage IB** | **T0 or T1, N1mi, M0** | The tumor is 2 cm or less across (or is not found) (T0 or T1) with micrometastases in 1 to 3 axillary lymph nodes (the cancer in the underarm lymph nodes is greater than 0.2mm across and/or more than 200 cells but is not larger than 2 mm)(N1mi). The cancer has not spread to distant sites (M0). |
| **Stage IIA** | **T0 or T1, N1 (but not N1mi), M0:** | The tumor is 2 cm or less across (or is not found) (T1 or T0) and either:<br>It has spread to 1 to 3 axillary (underarm) lymph nodes, with the cancer in the lymph nodes larger than 2 mm across (N1a),<br>OR<br>Tiny amounts of cancer are found in internal mammary lymph nodes (nodes near the breast bone) on sentinel lymph node biopsy (N1b),<br>OR<br>It has spread to 1 to 3 axillary lymph nodes and to internal mammary lymph nodes (found on sentinel lymph node biopsy) (N1c).<br>The cancer has not spread to distant sites (M0). |
| | **OR** | |
| | **T2, N0, M0** | The tumor is larger than 2 cm but less than 5 cm (about 2 inches) across (T2) but hasn't spread to the lymph nodes (N0). The cancer has not spread to distant sites (M0). |
| **Stage IIB** | **T2, N1, M0** | The tumor is larger than 2 cm but less than 5 cm across (T2). It has spread to 1 to 3 axillary lymph nodes and/or tiny amounts of cancer are found in internal mammary lymph nodes on sentinel lymph node biopsy (N1). The cancer hasn't spread to distant sites (M0). |
| | **OR** | |
| | **T3, N0, M0** | The tumor is larger than 5 cm across but does not grow into the chest wall or skin (T3). The cancer has not spread to the lymph nodes (N0) or to distant sites (M0). |

| | | |
|---|---|---|
| **Stage IIIA** | **T0 to T2, N2, M0** | The tumor is not more than 5 cm across (or cannot be found) (T0 to T2). It has spread to 4 to 9 axillary lymph nodes, or it has enlarged the internal mammary lymph nodes (N2). The cancer hasn't spread to distant sites (M0). |
| | **OR** | |
| | **T3, N1 or N2, M0** | The tumor is larger than 5 cm across but does not grow into the chest wall or skin (T3). It has spread to 1 to 9 axillary nodes, or to internal mammary nodes (N1 or N2). The cancer hasn't spread to distant sites (M0). |
| **Stage IIIB** | **T4, N0 to N2, M0** | The tumor has grown into the chest wall or skin (T4), and one of the following applies:<br>• It has not spread to the lymph nodes (N0).<br>• It has spread to 1 to 3 axillary lymph nodes and/or tiny amounts of cancer are found in internal mammary lymph nodes on sentinel lymph node biopsy (N1).<br>• It has spread to 4 to 9 axillary lymph nodes, or it has enlarged the internal mammary lymph nodes (N2).<br>The cancer hasn't spread to distant sites (M0).<br>**Inflammatory breast cancer** is classified as T4d and is at least stage IIIB. If it has spread to many nearby lymph nodes (N3) it could be stage IIIC, and if it has spread to distant lymph nodes or organs (M1) it would be stage IV. |
| **Stage IIIC** | **any T, N3, M0** | The tumor is any size (or can't be found), and one of the following applies:<br>• Cancer has spread to 10 or more axillary lymph nodes (N3).<br>• Cancer has spread to the lymph nodes under the collar bone (infraclavicular nodes) (N3).<br>• Cancer has spread to the lymph nodes above the collar bone (supraclavicular nodes) (N3).<br>• Cancer involves axillary lymph nodes and has enlarged the internal mammary lymph nodes (N3).<br>• Cancer has spread to 4 or more axillary lymph nodes, and tiny amounts of cancer are found in internal mammary lymph nodes on sentinel lymph node biopsy (N3).<br>The cancer hasn't spread to distant sites (M0). |
| **Stage IV** | **any T, any N, M1** | The cancer can be any size (any T) and may or may not have spread to nearby lymph nodes (any N). It has spread to distant organs or to lymph nodes far from the breast (M1). The most common sites of spread are the bones, liver, brain, or lungs. |

## Supplementary Files: three checklists (AGREE II, IOM criteria, Lenzers RED FLAGS) used to assess the WHO position paper on mammography

*AGREE II Reporting Checklist:*

[Each item scored on a scale of one to seven; where 1 is strongly disagree and 7 is strongly agree.
Please refer to the AGREE II Manual for guidance.]

Two independent assessments (JS ZF) December 2017

| DOMAIN | THEME | | SCORE |
|---|---|---|---|
| 1. Objectives | Health Intent (e.g. diagnosis, therapy)<br>Expected benefits<br>Target population (e.g. outpatients) | √ Addressed in full (score 7)<br>☐ Partially addressed<br>☐ Unclear if or how addressed<br>☐ Not addressed (score 1)<br>☐ Not relevant (score N/A) | 7 ZF<br>7 JS |
| 2. Questions | Target population - disease(s) included<br>Intervention(s)<br>Comparisons<br>Outcome(s)<br>Health care setting or context | √ Addressed in full<br>☐ Partially addressed<br>☐ Unclear if or how addressed<br>☐ Not addressed<br>☐ Not relevant | 7 ZF<br>7 JS |
| 3. Population | Target population sex & age<br>Clinical condition<br>Severity of disease<br>Comorbidities<br>Excluded populations | √ Addressed in full<br>☐ Partially addressed<br>☐ Unclear if or how addressed<br>☐ Not addressed<br>☐ Not relevant | 7 ZF<br>7 JS |
| 4. Group membership | Names of participant<br>Disciplines/content expertise<br>Institutions<br>Locations<br>Member's role in development process | √ Addressed in full<br>☐ Partially addressed<br>☐ Unclear if or how addressed<br>☐ Not addressed<br>☐ Not relevant | 7 ZF<br>7 JS |
| 5. Target population preferences and views | Statement of type of strategy used to capture patients views/preferences<br>Methods by which sought<br>Outcomes/information gathered<br>How used to inform process and/or recommendations | ☐ Addressed in full<br>☐ Partially addressed<br>X Unclear if or how addressed<br>☐ Not addressed<br>☐ Not relevant | 4 ZF<br>4 JS |
| 6. Target users | Intended guideline audience<br>How may be used by them | √ Addressed in full<br>☐ Partially addressed<br>☐ Unclear if or how addressed<br>☐ Not addressed<br>☐ Not relevant | 7 ZF<br>7 JS |
| 7. Search methods | Named databases or evidence sources<br>Time period searched<br>Search terms<br>Full search strategy included | √ Addressed in full<br>☐ Partially addressed<br>☐ Unclear if or how addressed<br>☐ Not addressed<br>☐ Not relevant | 7 ZF<br>7 JS |
| 8. Evidence selection criteria | Target population<br>Study design<br>Comparisons<br>Outcomes<br>Language<br>Context (e.g. settings where used) | √ Addressed in full<br>☐ Partially addressed<br>☐ Unclear if or how addressed<br>☐ Not addressed<br>☐ Not relevant | 7 ZF<br>7 JS |
| 9. Strengths & limitations of the evidence | Study design(s) included in the body of evidence<br>Study methodology limitations<br>Appropriateness of $1^{o}$ and $2^{o}$ outcomes<br>Consistency of result across studies<br>Direction of result across studies | √ Addressed in full<br>☐ Partially addressed<br>☐ Unclear if or how addressed<br>☐ Not addressed<br>☐ Not relevant | 7 ZF<br>7 JS |

| | | | |
|---|---|---|---|
| | Magnitude of benefit vs magnitude of harm<br>Applicability to practice context | | |
| 10. Formulation of recommendations | Development process<br>Outcomes of the process<br>How the process influenced the recommendations | √ Addressed in full<br>☐ Partially addressed<br>☐ Unclear if or how addressed<br>☐ Not addressed<br>☐ Not relevant | 7 ZF<br>7 JS |
| 11. Consideration of benefits & harms | Supporting date & report of benefits<br>Supporting data & report of harms<br>Reporting of the balance between benefits & harms<br>Recommendations reflect consideration of both benefits & harms | √ Addressed in full<br>☐ Partially addressed<br>☐ Unclear if or how addressed<br>☐ Not addressed<br>☐ Not relevant | 7 ZF<br>7 JS |
| 12. Link between recommendations & evidence | How the GDG linked & used the evidence to inform recommendations<br>Link between each recommendation and key evidence<br>Link between recommendations and evidence summaries or evidence tables in the results section | √ Addressed in full<br>☐ Partially addressed<br>☐ Unclear if or how addressed<br>☐ Not addressed<br>☐ Not relevant | 7 ZF<br>7 JS |
| 13. External review | Purpose & intent of review<br>Methods to undertake review<br>Description of the reviewers<br>Information gathered<br>How used | √ Addressed in full<br>☐ Partially addressed<br>☐ Unclear if or how addressed<br>☐ Not addressed<br>☐ Not relevant | 7 ZF<br>7 JS |
| 14. Updating procedure | Statement that the guideline will be updated<br>Explicit time interval and/or criteria to guide decision<br>Methodology for updating | √ Addressed in full<br>☐ Partially addressed<br>☐ Unclear if or how addressed<br>☐ Not addressed<br>☐ Not relevant | 7 ZF<br>7 JS |
| 15. Specific & unambiguous recommendations | Statement of the recommended action<br>Intent/purpose of the action<br>Relevant population<br>Caveats or qualifying statements<br>Uncertainty about best care option | √ Addressed in full<br>☐ Partially addressed<br>☐ Unclear if or how addressed<br>☐ Not addressed<br>☐ Not relevant | 7 ZF<br>7 JS |
| 16. Management options | Description of management options<br>Population or clinical situation most appropriate to each option | √ Addressed in full<br>☐ Partially addressed<br>☐ Unclear if or how addressed<br>☐ Not addressed<br>☐ Not relevant | 7 ZF<br>7 JS |
| 17. Identifiable key recommendations | Recommendations in a summarized box or presented as flow charts or algorithms<br>Specific recommendations grouped together in one section | √ Addressed in full<br>☐ Partially addressed<br>☐ Unclear if or how addressed<br>☐ Not addressed<br>☐ Not relevant | 7 ZF<br>7 JS |
| 18. Facilitators & barriers to application | Types of facilitators & barriers considered<br>Methods by which they were sought<br>Description of the facilitators & barriers that emerged.<br>How the information influenced the guideline | ☐ Addressed in full<br>☐ Partially addressed<br>X Unclear if or how addressed<br>☐ Not addressed<br>☐ Not relevant | 4 ZF<br>4 JS |
| 19. Implementation advice/tools | Additional materials to support implementation of the guideline in practice e.g.<br>Guideline summary<br>Checklists, algorithms<br>How-to manual<br>Solutions linked to barrier analysis<br>Tools to capitalize on guideline facilitators<br>Outcome of pilot tests & lessons learned | √ Addressed in full<br>☐ Partially addressed<br>☐ Unclear if or how addressed<br>☐ Not addressed<br>☐ Not relevant | 7 ZF<br>7 JS |
| 20. Resource implications | Types of cost information considered | √ Addressed in full | 7 ZF |

| | | | |
|---|---|---|---|
| | Methods by which cost information was sought<br>Description of the cost information that emerged<br>How the information influenced the guideline | ☐ Partially addressed<br>☐ Unclear if or how addressed<br>☐ Not addressed<br>☐ Not relevant | 7 JS |
| 21. Monitoring/auditing criteria | Criteria to assess guideline implementation or adherence<br>Criteria to assess impact of implementing the recommendations<br>Advice on the frequency/interval of measurement<br>Operational definitions of how the criteria should be measured | ☐ Addressed in full<br>☐ Partially addressed<br>X Unclear if or how addressed<br>☐ Not addressed<br>☐ Not relevant | 4 ZF<br>4 JS |
| 22. Funding body | Name of funding source<br>Statement that funder did not influence the content of the guideline | √ Addressed in full<br>☐ Partially addressed<br>☐ Unclear if or how addressed<br>☐ Not addressed<br>☐ Not relevant | 7 ZF<br>7 JS |
| 23. Competing interests | Types considered<br>Methods by which sought<br>Description of competing interests | √ Addressed in full<br>☐ Partially addressed<br>☐ Unclear if or how addressed<br>☐ Not addressed<br>☐ Not relevant | 7 ZF<br>7 JS |

## Institute of Medicine (IOM) criteria

The eight US Institute of Medicine's criteria of guidelines trustworthiness

[Three independent assessments (JS ZF HC) October 2017]

| Number | Criterion | Match |
|---|---|---|
| 1 | Establishing transparency | √ |
| 2 | Management of conflicts of interest | √ |
| 3 | Guideline development group composition | √ |
| 4 | Clinical practice guideline -systematic review intersection | √ |
| 5 | Establishing evidence foundation for and rating strength of recommendations | √ |
| 6 | Articulation of recommendations | √ |
| 7 | External review | √ |
| 8 | Updating | √ |

## Lenzers RED FLAGS

[Two independent assessments (JS ZF) October 2017]

| RED FLAG | RATING |
|---|---|
| Sponsor(s) is a professional society that receives substantial industry funding; | No |
| Sponsor is a proprietary company, or is undeclared or hidden | No |
| Committee chair(s) have any financial conflict* | No |
| Multiple panel members have any financial conflict* | Yes (3), further assessed by WHO legal panel as "no impediment to full participation" |
| Any suggestion of committee stacking that would pre-ordain a recommendation regarding a controversial topic | No |
| No or limited involvement of an expert in methodology in the evaluation of evidence | No |
| No external review | Sent out to External Review Group (7) |
| No inclusion of non-physician experts/patient representative/community stakeholders | Included |

*Includes a panelist with either or both a financial relationship with a proprietary healthcare company and/or whose clinical practice/specialty depends on tests or interventions covered by the guideline.

## Links to the Evidence for the Clinical Scenarios

| Scenario | |
|---|---|
| **1** | https://www.dynamed.com/topics/dmp~AN~T114068/Lobular-carcinoma-in-situ#Treatment-overview |
| **2** | https://www.dynamed.com/topics/dmp~AN~T115902/BRCA-mutation-testing-and-management#sec-Prophylactic-mastectomy<br>https://www.dynamed.com/topics/dmp~AN~T920658/Locoregional-therapy-for-early-and-locally-advanced-breast-cancer#sec-Breast-reconstruction |
| **3** | https://www.dynamed.com/topics/dmp~AN~T115780/Ductal-carcinoma-in-situ#Surgery-and-procedures |
| **4** | https://www.dynamed.com/topics/dmp~AN~T115780/Ductal-carcinoma-in-situ#sec-Surgery-and-procedures |
| **5** | https://www.dynamed.com/topics/dmp~AN~T115780/Ductal-carcinoma-in-situ#sec-Radiation-therapy |
| **6** | https://www.dynamed.com/topics/dmp~AN~T115780/Ductal-carcinoma-in-situ#sec-Medications |
| **7** | https://www.dynamed.com/topics/dmp~AN~T901192#Overview |
| 8 | https://www.dynamed.com/topics/dmp~AN~T901192/Surgery-for-early-and-locally-advanced-breast-cancer#Breast-reconstruction-prosthesis |
| 9 | https://www.dynamed.com/topics/dmp~AN~T114271#Overview |
| 10 | https://www.dynamed.com/topics/dmp~AN~T114271/Chemotherapy-for-early-and-locally-advanced-breast-cancer#Anthracycline-efficacy<br>https://www.dynamed.com/topics/dmp~AN~T114271/Chemotherapy-for-early-and-locally-advanced-breast-cancer#Taxane-Drug-class-efficacy |
| 11a | https://www.dynamed.com/topics/dmp~AN~T901191#Adjuvant-Therapy |
| 11b | https://www.dynamed.com/topics/dmp~AN~T901191#Adjuvant-Therapy |
| 12a | http://www.dynamed.com/topics/dmp~AN~T114271/Chemotherapy-for-early-and-locally-advanced-breast-cancer#Combination-Chemotherapy |
| 12b | http://www.dynamed.com/topics/dmp~AN~T114271/Chemotherapy-for-early-and-locally-advanced-breast-cancer#Combination-Chemotherapy |
| 13 | https://www.dynamed.com/topics/dmp~AN~T114271/Chemotherapy-for-early-and-locally-advanced-breast-cancer#Preoperative-Neoadjuvant-Chemotherapy |
| 14 | https://www.dynamed.com/topics/dmp~AN~T901113/Radiation-therapy-for-breast-cancer#Efficacy-of-adjuvant-radiation-therapy |
| 15 | https://www.dynamed.com/topics/dmp~AN~T901113/Radiation-therapy-for-breast-cancer#Tumor-bed |
| 16 | https://www.dynamed.com/topics/dmp~AN~T114433/Endocrine-therapy-for-early-and-locally-advanced-breast-cancer#sec-Efficacy-in-adjuvant-therapy |
| 17 | https://www.dynamed.com/topics/dmp~AN~T114433/Endocrine-therapy-for-breast-cancer#Aromatase-efficacy |
| 18 | https://www.dynamed.com/topics/dmp~AN~T906063/Management-of-metastatic-or-locally-recurrent-breast-cancer#Surgery |
| 19 | https://www.dynamed.com/topics/dmp~AN~T906063/Management-of-metastatic-or-locally-recurrent-breast-cancer#Surgery<br>https://www.dynamed.com/topics/dmp~AN~T906063/Management-of-metastatic-or-locally-recurrent-breast-cancer#Radiation-therapy |
| 20 | https://www.dynamed.com/topics/dmp~AN~T901191#Neoadjuvant-Therapy<br>https://www.dynamed.com/topics/dmp~AN~T901191#Adjuvant-Therapy |
| 21 | https://www.dynamed.com/topics/dmp~AN~T114271/Chemotherapy-for-early-and-locally-advanced-breast-cancer#Preoperative-Neoadjuvant-Chemotherapy<br>https://www.dynamed.com/topics/dmp~AN~T114271/Chemotherapy-for-early-and-locally-#Combination-Chemotherapy |
| 22 | http://www.dynamed.com/topics/dmp~AN~T900469/Chemotherapy-for-metastatic-breasth-cancer#sec-Overview |
| 23 | https://www.dynamed.com/topics/dmp~AN~T900469/Chemotherapy-for-metastatic-breast-cancer#Overview |
| 24 | https://www.dynamed.com/topics/dmp~AN~T901191#Efficacy-metastatic |
| 25 | https://www.dynamed.com/topics/dmp~AN~T906063/Management-of-metastatic-or-locally-recurrent-breast-cancer#Endocrine-therapy<br>https://www.dynamed.com/topics/dmp~AN~T906063/Management-of-metastatic-or-locally-recurrent-breast-cancer#Chemotherapy |
| 26 | https://www.dynamed.com/topics/dmp~AN~T906063/Management-of-metastatic-or-locally-recurrent-breast-cancer#Endocrine-therapy |
| 27 | https://www.dynamed.com/topics/dmp~AN~T906063/Management-of-metastatic-or-locally-recurrent-breast-cancer#Endocrine-therapy |
| 28 | https://www.dynamed.com/topics/dmp~AN~T901209/Bone-modifying-agents-in-breast-cancer#Treatment-of-painful-bone-metastases |
| 29 | https://www.dynamed.com/topics/dmp~AN~T906063/Management-of-metastatic-or-locally-recurrent-breast-cancer#Brain-metastases |
| 30 | https://www.dynamed.com/topics/dmp~AN~T113654/Breast-cancer-in-women#Other-imaging-studies-for-detection-of-recurrence |