The investigation of a new breast symptom: a guide for General Practitioners 2017

Summary of the development process and methodology

The investigation of a new breast symptom: a guide for General Practitioners 2017, Summary of the development process and methodology was prepared and produced by:

Cancer Australia
Locked Bag 3 Strawberry Hills NSW 2012 Australia
Tel: +61 2 9357 9400 Fax: +61 2 9357 9477
canceraustralia.gov.au

ISBN Online: 978-1-74127-322-9

Recommended citation
Cancer Australia, 2017. The investigation of a new breast symptom: a guide for General Practitioners 2017, Summary of the development process and methodology, Cancer Australia, Surry Hills, NSW.

The investigation of a new breast symptom: a guide for General Practitioners 2017, Summary of the development process and methodology can be downloaded from the Cancer Australia website: canceraustralia.gov.au or ordered by
telephone: 1800 624 973.

Copyright statements

Paper-based publications

Internet sites

Disclaimer

Contents

Background and summary of approach

More than half of the 17,600 breast cancers diagnosed each year[1] are as a result of the investigation of a new breast symptom. Cancer Australia developed *The investigation of a new breast symptom: a guide for General Practitioners* (the INBS guide) in 1997 to support the timely diagnosis of breast cancer through an evidence-based systematic approach to the assessment of a new breast symptom. A second edition of the INBS guide was published in 2006, incorporating evidence published to 2004. In 2016-17 Cancer Australia has undertaken an update of the INBS guide to ensure currency with contemporary practice and latest evidence.

Establishment of a multidisciplinary Working Group

A multidisciplinary Working Group, chaired by Dr Julie Thompson, General Practitioner, was convened to provide Cancer Australia with expert input into the development of an updated evidence-based resource to support health professionals in the investigation of breast symptoms.

The members of the Working Group are listed in Table 1 below. All Working Group members were asked to declare any conflicts of interest at the time of joining the Working Group and at each of the Working Group meetings. No conflicts were declared at any time.

Table 1 Working group membership, 2016–2017

Name	Area of expertise	Role
Dr Julie Thompson	General Practitioner VIC	Chair
Dr Ben Green	Representative, Breast Surgeons of Australia and New Zealand St Andrews War Memorial Hospital, QLD	Member
Ms Alysia Kepert	Consumer Representative, Breast Cancer Network Australia WA	Member
Ms Christine Mitchell	Consumer Representative, Breast Cancer Network Australia NSW	Member
Dr Jenny O'Sullivan	Representative, Australasian Society of Breast Physicians Northern Breast Care, NSW	Member
Dr Dagmara Poprawski	Representative, Australian College of Rural and Remote Medicine Lyell McEwin Hospital, SA	Member
Associate Professor Wendy Raymond	Representative, Royal College of Pathologists of Australasia Flinders Medical Centre, SA	Member
Associate Professor Liz Wylie	Representative, Royal Australian and New Zealand College of Radiologists Royal Perth Hospital, WA	Member

[1] https://breast-cancer.canceraustralia.gov.au/statistics; Accessed 10 October 2017.

Review of comparable current national and international resources

Cancer Australia undertook an assessment of the INBS guide to compare the content of the 2006 edition of the INBS guide to the content of other current national and international guidelines/guides for the investigation of breast symptoms. The results of the assessment are outlined in the following sections.

High level evidence searches were conducted to identify national and international guidelines/guides for the investigation of breast symptoms. The searches covered guides published from 2004 to June 2016, and included a search of the electronic literature database Pubmed, searches of international guideline clearinghouses and general internet searches. The identified guidelines were reviewed and compared with the INBS guide to determine whether the more recent guidelines were consistent and/or provided new evidence. Full details of the methodology and results are provided in the following sections.

Development of updated content

The Working Group attended two face-to-face meetings to consider the results of the review of national and international guidelines and to agree on any changes to the content of the Guide. For each section of the Guide, the Working Group reviewed the information and evidence included in the identified national and international guidelines and considered this in the context of current Australian clinical practice. All changes to the Guide were decided through a consensus process and the final content of the updated Guide was approved by all members of the Working Group. Following agreement on the final content the algorithms for the investigation of a new breast symptom and a new nipple discharge were updated to reflect the new INBS guide content.

Expert review and endorsement

The updated INBS guide was reviewed and endorsed by:

- The Australian College of Rural and Remote Medicine
- Breast Cancer Network Australia
- Breast Surgeons of Australia and New Zealand
- The Royal Australian and New Zealand College of Radiologists
- The Royal College of Pathologists of Australasia

The updated INBS Guide was also reviewed and approved as an Accepted Clinical Resource by the Royal Australian College of General Practitioners.

Methodology

Literature database review

Three searches were undertaken using the electronic literature database Pubmed. The first focused on identifying evidence on the use of the triple test, the second on nipple discharge and the third focused on identifying guidelines for investigating breast symptoms. Details of the searches are provided in Table 2, Table 3 and Table 4 below.

Table 2 PubMed Search 1

Subject	Terms
Breast cancer	Breast AND (neoplasm OR cancer)
Triple test	Clinical exam* OR mammograph* OR mammogram OR ultrasound OR ultrasonography OR sonography OR MRI OR magnetic resonance imaging OR fine needle aspiration OR FNA OR core biopsy OR non-excisional biopsy OR triple test
Diagnostic	Diagnosis OR diagnostic
Publications	Systematic review OR meta-analysis OR guideline OR HTA

Table 3 PubMed search 2

Subject	Terms
Breast cancer	Breast AND (neoplasm OR cancer)
Nipple discharge	(Nipple OR breast) AND discharge
Publications	Systematic review OR meta-analysis OR guideline OR HTA

Table 4 PubMed Search 3

Subject	Terms
Breast symptoms	breast[ti] and (symptom or symptoms or suspected)
Diagnosis	diagnosis or investigation
Publications	guideline

Website searches

In addition, the following websites were searched for relevant guidelines:

- Cochrane reviews
- Google and Google Scholar
- NHMRC Guideline Portal, Australia
- International guidelines library (GIN)
- National Guideline Clearinghouse (AHRQ), US
- AHRQ Effective Health Care Program, US
- Centre for Reviews and Dissemination (CRD), UK
- American Society of Clinical Oncology (ASCO)

- Cancer Care Ontario (CCO), Canada
- European Society of Medical Oncology (ESMO)
- National Comprehensive Cancer Network (NCCN), US
- National Institute for Health and Care Excellence (NICE), UK
- New Zealand Guidelines Group (NZGG) via New Zealand Ministry of Health
- Scottish Intercollegiate Guidelines Network (SIGN).

An overview of the terms used and numbers of records identified by the website searches are provided in Appendix 1.

Search results

Using the methodology above, 31 guides/guidelines were identified as potentially relevant and were sourced for review. Following second round assessment, four guides/guidelines were excluded as not relevant (see Appendix 2). The content of the remaining 27 guides/guidelines was compared with the INBS guide to determine consistencies/inconsistencies and identify more recent evidence referenced in the later guidelines.

The identified guidelines covered a range of topic areas and varied in focus, audience and level of detail:

- Eleven are breast cancer specific,[1-11] of which:
    - six refer to the whole breast cancer management spectrum[5-8, 10, 11]
    - four focus on screening/diagnosis of breast cancer[1-3, 9]
    - one is about GP referral to breast clinics[4]
- Eleven cover investigation of breast symptoms/disease/conditions,[12-22] of which four are specifically on one type of symptom[13-15, 22]
- One guideline covers diagnosis of breast disease and cancer,[23] and one is specifically for benign breast tumours[21]
- One guideline covers referral for suspected cancer in general[24]
- Five are technique-specific, of which four are on imaging,[9, 22, 25, 26] (one is specifically on MRI,[26] and one is on ductoscopy[22]) and one is on biopsy[27]
- Two are specifically targeted to GPs/primary care providers(PCPs).[1, 4]

A large proportion of the guidelines are US-based (12 out of 26). While many are national guidelines, some are regional and others do not have a particular affiliation with an organisation but are published as journal articles.

Brief descriptions of the identified guidelines, including relevant topics covered and included algorithms, are provided in Appendix 3.

Comparison of guidelines to INBS guide

The guidelines were reviewed and compared with the INBS guide to determine whether the more recent guidelines were consistent and/or provided new evidence, in comparison to the INBS guide. An overview of the topics covered in the different guidelines is provided in Table 5. Note the table represents certain areas that are discussed in the guideline, not necessarily recommendations.

The assessment of the INBS guide includes the following components:

a) The triple test approach to diagnosis

b) Accuracy of the triple test
c) Relative frequencies of presenting symptoms of breast cancer
d) Patient history and clinical examination
e) Nipple discharge
f) Algorithm for the investigation of a new breast symptom
g) Diagnostic imaging
h) Non-excisional biopsy
i) Surgical referral
j) Additional areas in other guidelines.

This report does not include risk assessment or screening for asymptomatic women.

Table 5 Content comparison between guidelines

Guideline	Algorithm (s)	Frq	ND	Triple test	Patient history	CBE	*MM*	*US*	*MRI*	*Oth Img*	*FNA*	*CB*	*Oth Bio*	Surgical referral	*Men*	*Preg*	*Aug*	Other
CA INBS guide 2006[28]	✓	✓	✓	✓	✓	✓	✓	✓			✓	✓		✓		✓		
USA																		
ACR – Palpable masses 2012[13]	×						✓	✓	✓ NR	✓ NR	✓	✓ Pref				✓		
ACR – Breast pain 2014[14]	×						✓	✓	✓ NR	✓ NR								
ACR – Male breast 2014[15]	×						✓	✓	✓ NR						✓			
AHRQ biopsy update 2014[27]	×											✓	✓					
California DPH algorithms 2011[1]	✓	✓	✓	✓	✓	✓	✓	✓			✓	✓ Pref	✓	✓†				✓
CRICO algorithm 2014[16]	✓		✓				✓	✓			✓	✓	✓	✓†				✓
ICSI 2012[17]	✓		✓		✓	✓	✓	✓			✓	✓ Rec		✓				
NCCN 2015[2]	✓		✓		✓	✓	✓	✓	✓		✓	✓	✓					
Salzman 2012[18]	✓		✓		✓	✓	✓	✓			✓	✓ Pref	✓	✓†				
University of Michigan 2013[19]	✓	✓	✓			✓	✓	✓	✓		✓	✓	✓	✓†	✓	✓	✓	
Up-to-Date 2016[3]	✓						✓	✓	✓ NR		✓ Biopsy not defined			✓†				
Washington State DoH algorithm 2014[20]	✓				✓	✓	✓	✓			✓	✓		✓†				
Canada																		
British Columbia guidelines 2013[23]	✓		✓	implied	✓	✓	✓	✓				✓				✓		
CAR 2012[25]	×		✓				✓	✓	✓	✓						✓		
UK/Ireland																		
Irish GP guide 2009[4]	✓		✓		✓	✓								✓ Referral to clinic				

Guideline	Algorithm (s)	Frq	ND	Triple test	Patient history	CBE	*MM*	*US*	*MRI*	*Oth Img*	*FNA*	*CB*	*Oth Bio*	Surgical referral	*Men*	*Preg*	*Aug*	Other
Irish BC CPGs 2015[5]	×			✓		✓	✓	✓			✓	✓						✓
NICE BC CPGs 2009[6]	×			✓		✓	✓	✓			✓	✓						
NICE SC CPGs 2015[24]	×													✓ Referral to cancer service				
UK DoH CPGs 2010[12]	✓		✓	✓	✓	✓	✓	✓	✓ NR		✓	✓ Pref	✓	✓ Referral to clinic	✓	✓	✓	✓
Europe																		
KCE Belgium BC CPGs 2013[7]	×			✓		✓	✓	✓	✓ NR	✓ NR	✓	✓						
ESMO BC CPGs 2015[8]	×			implied	✓	✓	✓	✓	✓ NR		✓	✓ Pref					✓	
EUSOMA MRI PS 2010[26]	×								✓						✓		✓	
French CPGs 2016[21]	×		✓				✓	✓		✓		✓	✓					
IKNL NABON Dutch BC CPGs 2012[11]	×		✓		✓	✓	✓	✓	✓				✓	✓ Referral to clinic	✓	✓	✓	
Waaijer 2016[22]	×		✓							✓								
Asia																		
JBCS CPGs 2015[9]	×						✓	✓	✓	✓								
MoH Malaysia 2010[10]	×			✓			✓	✓			✓	✓					✓	

†Surgical/specialist referral indicated within algorithms. ACR=American College of Radiology; AHRQ=Agency for Healthcare Research and Quality; Aug=augmented breasts; BC=breast cancer; CA=Cancer Australia; CAR=Canadian Association of Radiologists; CB=core biopsy; CBE=clinical breast examination; CPG=clinical practice guideline; DoH=Department of Health; DPH=Department of Public Health; FNA=fine needle aspiration; Frq=frequency; GP=general practitioner; ICSI=Institute for Clinical Systems Improvement; NCCN=National Comprehensive Cancer Network; MoH=Ministry of Health; MM=mammography; MRI=magnetic resonance imaging; ND=nipple discharge; NR=not recommended; Oth=other; Oth Bio=other biopsy; Oth Img=other imaging; Pref=preferred; Preg=pregnant/lactating; PS=position statement; Rec=recommended; SC=suspicious cancer; UK=United Kingdom; US=ultrasound; USA=United States of America.

The triple test approach to diagnosis

The INBS guide[28] recommends the triple test approach to diagnosis and refers to three diagnostic components: i) medical history and clinical breast examination (CBE); ii) imaging – mammography and/or ultrasound; and iii) non-excision biopsy – fine needle aspiration (FNA) cytology and/or core biopsy. The triple test is positive if any component is indeterminate, suspicious or malignant.

Six other guidelines explicitly mention the use of the triple test/assessment for diagnosis of breast cancer.[1, 5-7, 10, 12] Another two guides imply using the triple test, describing the use of all components together.[8, 23]

Most of the remaining guides/guidelines, while not explicitly mentioning 'triple test/assessment' do recommend each of the components of patient history and/or clinical exam, diagnostic imaging and biopsy.[2, 11, 17-20]

One of these guidelines suggests that while the triple test is needed to diagnose malignancy, there is some indication that the full triple test may not be necessary for palpable abnormalities where malignancy is not suspected (with high negative predictive value of a negative mammogram and a negative ultrasound).[11]

Additional information

Two guidelines (from the UK and Ireland) suggest that all assessments should be performed during one visit.[5, 12] Statements from these guidelines are provided in Table 6. No primary references were provided for any of the statements.

Table 6 Guideline statements regarding 'one stop' triple test assessments

Guideline	Statement
Irish BC guidelines 2015[5]	Good practice point: "When breast cancer is suspected, diagnosis in the breast clinic is made by triple assessment (clinical assessment, mammography and/or ultrasound imaging with core biopsy and/or fine needle aspiration cytology). It is best practice to perform these assessments during the same visit.
UK DoH 2010[12]	"One Stop Assessment • At one-stop assessment all the required elements of triple assessment are performed during a single visit. This provides: - a basis for definitive diagnosis in the majority of patients - reassurance with no need for further attendance in most patients with non-malignant conditions - information for multidisciplinary meeting treatment planning prior to review of those diagnosed to have cancer • Some patients do not require all the elements of triple assessment, as outlined below and defined in the Algorithms. This includes those with: - resolved symptoms and no clinical abnormality - clearly identified benign conditions with no other suspicious features found on clinical and imaging assessment such as: o areas of benign breast change and diffuse nodularity without a dominant mass o simple cysts whether aspirated or not o breast pain o non-bloody nipple discharge o gynaecomastia • One-stop breast assessments are generally more favourable for people without cancer as they go home without further waiting, knowing they do not have cancer. • Generally, a same-day core biopsy reporting service is not practical.

Guideline	Statement
	Expected turnaround time for pathology reporting of diagnostic needle core biopsy samples should be specified locally. • Time is required during one-stop assessment for patients to raise questions and concerns (regardless of diagnostic outcome), and for these to be addressed promptly."

BC=breast cancer; DoH=Department of Health.

Accuracy of the triple test

The INBS guide[28] includes details on the accuracy (sensitivity, specificity) of the triple test and each of its components which is based on information published pre-1995.[29]

The Malaysian Breast Cancer guidelines,[10] referenced a small cross-sectional study (N=50), published in 2008,[30] regarding the accuracy of the triple test score (physical examination, mammography and fine needle aspirate cytology) in the diagnosis of a palpable breast lump on women above 35 years old. The triple test components examined differ slightly between the two guides therefore while direct comparison cannot be made, it is noted that the sensitivity reported was similar to that reported in the INBS guide (100% versus >99.6% respectively), however specificity was higher (95.2% versus >62% respectively) and false positive rate was lower (3.3% versus <38% respectively).

The Californian Department of Public Health guideline[1] notes that with regards to the triple test, when findings from CBE, breast imaging and biopsy are concordant, diagnostic accuracy approaches 100% (with reference to a paper by Vetto et al published in 1995[31]).

The diagnostic accuracy of some other combinations of diagnostic tests is provided in Table 7.

Individual components

Some of the guidelines provide information on sensitivity/specificity for individual diagnostic techniques[3, 7, 10, 11, 13-15, 19, 22, 27] (most often mammography and/or ultrasound), with a range of references cited (see Table 7). Some other guidelines make general comments regarding varying sensitivities for different techniques, but do not provide direct percentages.[12, 18, 21]

Table 7 Accuracy reported for individual diagnostic techniques

Guideline	Diagnostic accuracy	Reference(s)
ACR – Palpable masses 2012[13]	MM + US: NPV 97.4-100% MM preoperatively in pregnant patients: sensitivity 90% MM for palpable masses: sensitivity 86-91% MM for women age 30-39 with focal breast symptoms: sensitivity 60.9%, specificity 94.4% US for women age 30-39 with focal breast symptoms: sensitivity 95.7%, specificity 89.2%	Dennis 2001,[32] Moy 2002,[33] Shetty 2002,[34] Soo 2001[35] Yang 2006[36] Murphy 2007,[37] Shetty 2003[38] Lehman 2012[39] Lehman 2012[39]
ACR – Breast pain 2014[14]	MM + US for focal breast pain without palpable mass: NPV 100% US in younger women: sensitivity 100%, NPV 100%	Tumyan 2005[40] Loving 2010[41]
ACR – Male breast 2014[15]	MM in men: sensitivity 92-100%, specificity 90-95%, NPV 99-100% US in men: sensitivity 89-100%, specificity 74-95%	Evans 2001,[42] Patterson 2006,[43] Munoz Carrasco 2010[44] Munoz Carrasco 2010,[44] Patterson 2006[43]
AHRQ biopsy update 2014[27]	CNB freehand: sensitivity 91%, specificity 98% CNB ultrasound, automated: sensitivity 99%, specificity 97% CNB ultrasound, vacuum-assisted: sensitivity 97%, specificity 98% CNB stereotactically guided, automated: sensitivity 97%, specificity 97% CNB stereotactically guided, vacuum-assisted: sensitivity 99%, specificity 92% CNB MRI-guided, automated: sensitivity 90%, specificity 99% CNB MRI-guided, vacuum-assisted: sensitivity 100%, specificity 91%	Meta-analysis – a total of 160 studies, published between 1990 and 2013, contributed information to analysis of test performance of core needle biopsy methods (details not provided in summary report regarding which studies contributed to each CNB method)
University of Michigan 2013[19]	CBE: sensitivity 88%, specificity 71% CBE + MM in agreement: PPV 96.4%, NPV 96.3% MM + US: FNR 1-3% MM: sensitivity 82-94%, specificity 55-84% FNA: false negatives 1-35% for palpable lesions, up	No specific references cited

Guideline	Diagnostic accuracy	Reference(s)
	to 68% for nonpalpable lesions	
Up-to-Date 2016[3]	US: sensitivity 98.4%, NPV 99.5%	Stavros 1995[45] (similar findings noted in studies: Harvey 2009, Flobbe 2003,[46] Soo 2001[35])
	CBE + MM + US: sensitivity 96.9%, specificity 94.8%, PPV 39.2%, NPV 99.9%	Flobbe 2003[46]
	CBE + MM: sensitivity 96.9%, specificity 94.8%, PPV 39.2%, NPV 99.9%	Flobbe 2003[46]
	MRI: sensitivity 88-100%, pooled specificity 72%	Bluemke 2004,[47] Esserman 1999a[48]/b,[49] Peters 2008[50]
KCE Belgium BC CPGs 2013[7]	MRI: pooled sensitivity 90-92%, pooled specificity 72%	Peters 2008,[50] AHRQ 2006[51]
	SMM: sensitivity 58-93%, specificity 71-91%, pooled data - sensitivity 84%, specificity 81%, PPV 84%, NPV 76%	Bagni 2003,[52] Howarth 2005,[53] Bekis 2004,[54] Chen 2003,[55] Fondrinier 2004,[56] Krishnaiah 2003,[57] Sampalis 2003,[58] Tiling 2005,[59] Medical Advisory Secretariat of Ontario Ministry of Health and Long-Term Care 2007[60] (pooled data)
	PET: sensitivity 76-82%, specificity 73-78%	AHRQ 2006,[51] Facey 2007[61]
	US: sensitivity 86%, specificity 66%	AHRQ 2006[51]
IKNL NABON Dutch BC CPGs 2012[11]	MM: sensitivity 85.5%, specificity 87.7%	Barlow 2002[62]
	Normal/negative MM and US: NPV 97.3-100%	Kerlikowske 2003,[63] Dennis 2001,[32] Moy 2002,[33] Shetty 2002,[34] Soo 2001[35]
	MRI: sensitivity 90%, specificity 72%, diagnostic accuracy 69-89%	AHRQ 2006,[51] Peters 2008,[50] Bluemke 2004,[47] Hrung 1999,[64] Nunes 2001,[65] Gibbs 2004,[66] Liberman 2002[67]
Waaijer 2016[22]	Ductoscopy any (all visualized ductoscopic abnormalities classified as positive): pooled sensitivity 94%, specificity 47%	Twelve studies, including 1994 patients, were eligible for meta-analysis, studies published between 2002 and 2015. Studies contributing to ductoscopy any analysis: Bender 2009,[68] Denewer 2008,[69] Deshmane 2010,[70] Dietz 2002,[71] Fackler 2009,[72] Fisher 2011,[73] Kamali 2014,[74] Khan 2011,[75] Liu 2008,[76] Moncrief 2005,[77] Simpson 2009,[78] Waaijer 2015.[79] Studies contributing to ductoscopy suspicious analysis: Bender 2009,[68] Denewer 2008,[69] Dietz 2002,[71] Fisher 2011,[73] Kamali 2014,[74] Moncrief 2005,[77] Simpson 2009,[78] Waaijer 2015[79]
	Ductoscopy suspicious (only suspicious findings were considered positive): pooled sensitivity 50%, specificity 83%	
MoH Malaysia 2010[10]	MM: sensitivity 56.6%, specificity 99.4%	McCavert 2009[80]
	Adjunct US: sensitivity 80.8%, specificity 99.1%	

BC=breast cancer; CBE=clinical breast examination; CNB=core needle biopsy; CPG=clinical practice guideline; FNA=fine needle aspiration; FNR=false negative rate; MoH=Ministry of Health; MM=mammography; MRI=magnetic resonance imaging; NPV=negative predictive value; PET=positron emission tomography; PPV=positive predictive value; SMM=scintimammography; US=ultrasound.

Relative frequencies of presenting symptoms of breast cancer

The INBS guide[28] presents relative frequencies of presenting symptoms of breast cancer in a table, based on observational Australian data from a single centre.

None of the other guidelines included relative frequencies of presenting symptoms of breast cancer. Two US guidelines referred to the most common breast complaints (usually pain as most common followed by palpable mass then nipple discharge).[1, 19] It is noted that in the majority of cases risk of breast cancer is not indicated.

Patient history and clinical examination

The INBS guide[28] provides detailed information on what should be included in patient history, history of presenting symptom and clinical breast examination.

Overall, the other guidelines were consistent in the need to undertake a patient history and CBE.[1, 2, 4, 8, 11, 12, 17, 18, 20, 23] Some guidelines discuss CBE but do not explicitly state taking a detailed patient history.[5-7, 19]

Patient history

Guidelines which provided information on details to discuss regarding history were consistent with that provided in the INBS guide (such as risk factors, family history, reproductive history).[1, 11, 12, 18, 23] Some of the guidelines state to take patient history but do not give the components to discuss.[2, 4, 8, 20]

The Californian guidelines include a template form to document patient information regarding breast cancer history and risk assessment.[1] The UK Department of Health (DoH) guidelines include examples of pre-clinic patient questionnaire questions.[12]

Clinical breast examination (CBE)

Almost all guidelines included the use of clinical breast examination to investigate breast symptoms. [1, 2, 4-8, 11, 12, 17-20, 23] Overall the guidelines were consistent with the INBS guide[28] in the description of how to perform CBE, although various levels of details were provided.

The Californian guidelines provide detailed information on how to perform CBE including visual aids and covers the same areas as the INBS guide including inspection, palpation and recording.[1] These guidelines also include a detailed template form to document CBE results.

Nipple discharge

The INBS guide[28] includes a separate algorithm for the investigation of a new nipple discharge as well as information on the probability of cancer by age and nature of discharge and brief mention of discharge cytology and galactography.

Algorithms

A number of guidelines included separate algorithms for investigating nipple discharge. [1, 2, 4, 16-19] Two of the guidelines' algorithms specifically refer to spontaneous nipple discharge.[1, 16]

Overall, the content of the algorithms are consistent with that presented in the INBS guide.[4, 17-19] Spontaneous, unilateral, single duct, bloody or serous discharge were all indications for surgeon/specialist referral and diagnostic imaging.

The NCCN algorithm for nipple discharge[2] provides further guidance by age (<40 years and ≥40 years for non-spontaneous or multi-duct; <30 years and ≥30 years for pathologic discharge) and includes more details on diagnostic follow-up than the INBS guide.[28]

Probability of cancer by age and nature of discharge

None of the guidelines included evidence on the *probability* (%) of cancer by age and nature of discharge, however the Californian guidelines note that 5-15% of causes of pathologic nipple discharge are due to an underlying malignancy (cited UpToDate 2010) and that the risk of cancer is greater for women >40 years.[1] ICSI guidelines note that pathologic discharge is more worrisome in patients > 50 years old.[17] NCCN guidelines recommend that women ≥40 years should undergo diagnostic imaging even for non-spontaneous or multi-duct discharge.[2] The UK DoH guidelines consider women under 50 years who have nipple discharge that is from multiple ducts or is intermittent and is neither blood stained nor troublesome can be managed at least initially by the GP.[12]

Some guidelines discuss pathological versus physiologic discharge[17-19] and some algorithms consider age to determine pathways.[2, 4, 16, 19] Two of the guidelines notes to perform mammography and ultrasound for those ≥30 years with spontaneous nipple discharge, and ultrasound for those <30 years. [2, 19] One guideline note to perform bilateral diagnostic mammogram for those ≥30 years with spontaneous nipple discharge from multiple ducts.[16] One guideline notes to refer anyone with nipple discharge ≥50 years to a specialist breast clinic.[4] The INBS guide nipple discharge algorithm notes to refer anyone with nipple discharge >60 to a surgeon.[28]

Discharge cytology

The INBS guide notes under implications for practice that positive discharge cytology result is indicative of cancer, but a negative result cannot be used to rule out the disease.[28]

Cytology is not included in any of the nipple discharge algorithms in the other guidelines. The UK DoH guidelines note that nipple cytology is rarely of any value and must be treated with great caution after recent lactation.[12] Salzman et al reports that cytology of nipple discharge is not recommended, because the absence of malignant cells does not exclude cancer.[18] The Californian guidelines note that cytologic examination of nipple discharge is considered useful in some cases; however, as with imaging, a negative result should not stop further evaluation.[1]

Galactography

The INBS guide briefly mentions that the use of galactography should be based on the availability of expertise, preferably after consultation with a surgeon.[28]

A recently published systematic review and meta-analysis[22] evaluated the diagnostic accuracy of ductoscopy in pathological nipple discharge (PND). Twenty studies were included, of which 12 studies, including 1994 patients, were eligible for meta-analysis. The authors concluded that ductoscopy detects about 94 per cent of all underlying malignancies in patients with PND, but does not permit reliable discrimination between malignant and benign findings.

Washington State guidelines note that persistent spontaneous unilateral nipple discharge can be worked up by the addition of a ductogram in addition to the usual imaging workup.[20]

The Canadian Association of Radiologists (CAR) note that for investigation of spontaneous bloody or clear nipple discharge, ductography (galactography) is indicated if mammography and ultrasound are inconclusive.[25]

Additional information

Three guidelines include an additional step in their nipple discharge algorithm to perform hormonal evaluation/pregnancy tests for those with bilateral or milky discharge.[17-19]

Three guidelines include information on medications which can cause nipple discharge.[2, 18, 23]

Additional techniques

A few of the guidelines include the potential use of ductography and/or MRI following mammography/ultrasound in their algorithms, particularly for BI-RADS category 1-3.[2, 17, 18] Note tissue biopsy is recommended for BI-RADS 4-5.[2, 18]

The University of Michigan notes that MRI may be indicated for women with significant nipple discharge when diagnosis remains unclear after mammography, ultrasound and breast specialist evaluation.[19] Similarly, the CAR guidelines state that for investigation of spontaneous bloody or clear nipple discharge, MRI is indicated only in specific circumstances, if all other tests are inconclusive.[25]

Algorithm for the investigation of a new breast symptom

The INBS guide provides a one page algorithm for the investigation of a new breast symptom (other than nipple discharge).[28]

Eleven guides/guidelines provided algorithms for investigating new breast symptoms.[1-4, 12, 16-20, 23] Overall, the content within the algorithms was consistent with the INBS guide, however in many cases, different algorithms were presented for individual symptoms. Most commonly, different algorithms were presented for investigating:

- Palpable breast lumps*[1-4, 12, 16-19]
    - Two US guidelines separated algorithms for palpable breast lumps into two groups: <30 years, ≥30 years.[2, 3]
- Nipple discharge[1, 2, 4, 16-19]
- Breast pain[1, 4, 12, 16-19]
- Skin changes[1, 2]
- Asymmetric thickening/nodularity*[2, 19]

* Note the University of Michigan combined breast lumps and asymmetric thickening/nodularity into one algorithm[19]

In addition, three guidelines provided a separate algorithm for biopsy,[1, 3, 17] (see Section 0).

Variations in content within the algorithms reflect variations discussed in each of the sections in this assessment. The Californian and NCCN guidelines provided the most detailed algorithms.[1, 2]

Diagnostic imaging

The INBS guide includes recommendations for the use of mammography and/or ultrasound for the following groups: under age 25, 25-34 years, 35-50 years, over 50 years, and in pregnancy or lactation.[28]

The guidelines were consistent with recommending the use of mammography and/or ultrasound for diagnostic imaging.[1-3, 5-8, 10-21, 23] However there were some differences with regards to age groups and the use of additional diagnostic techniques such as MRI.

Age

A number of guidelines also recommended different modalities by age, however age groups differed to the INBS guide.[28] Most of these guidelines provided recommendations to two groups <30 and ≥30, with ultrasound recommended as the initial imaging investigation for those aged <30 years.[2, 3, 11, 13, 17-20, 23, 25] One guideline recommended ultrasound as the initial imaging modality for women <35 years[10] and one guideline recommended ultrasound for those aged <40 years.[12] ACR recommends that for women with a palpable mass age 30-39, either ultrasound or diagnostic mammography may be used for initial evaluation.[13] Mammography ± ultrasound was recommended for those aged ≥30 years.[2, 3, 11, 13, 17-20, 23, 25] The Malaysian guidelines recommend that adjunctive ultrasound assessment improves breast

cancer detection in women of all ages and where possible should be offered to all symptomatic breast patients.[10]

A number of guidelines were consistent with the INBS guide[28] that mammography should be performed in all age groups if the clinical or ultrasound findings are suspicious or malignant.[2, 11-13, 23] However, one Japanese guideline recommends that while diagnostic mammography performed with meticulous care may be considered, there are as yet no sufficient scientific grounds for application of diagnostic mammography in young women.[9] This guideline cites a 2007 reference by Osako et al.[81]

Pregnancy/lactation

Six other guidelines included recommendations on diagnostic imaging for pregnant/lactating women.[11-13, 19, 23, 25]

Guidance on diagnostic imaging in pregnancy or lactation was consistent between the INBS guide[28] and the other guidelines, with ultrasound recommended as the initial modality of choice, and mammography following suspicious or inconsistent findings. The Dutch guideline provides more detail regarding diagnostic investigations as well as pathology for pregnancy associated breast cancer.[11]

Details regarding specific recommendations regarding pregnant/lactating women are provided in Table 12 (see Section 0).

Additional information

Other diagnostic imaging modalities, particularly MRI, are discussed in a number of guidelines, however the routine use of these is not recommended for diagnostic purposes.

MRI

Thirteen guidelines discuss the potential use of MRI as part of imaging (which is not discussed in the INBS guide).[2, 3, 7-9, 11-15, 19, 25, 26] Overall the guidelines do not recommend MRI for routine diagnostic imaging of the breast, although MRI may be indicated in special circumstances.

In particular, EUSOMA issued a position statement in 2010 (including evidence to 2008) regarding MRI of the breast.[26] Indications relevant for the INBS guide included:

- Patients with breast augmentation or reconstruction
- The use of MRI for investigation of nipple discharge
- To characterise equivocal findings at conventional imaging
- To image the male breast.

Relevant EUSOMA recommendations are provided in Table 8.

Table 8 EUSOMA recommendations regarding use of MRI to investigate breast symptoms[26]

Topic	Relevant EUSOMA recommendations
Patients with breast augmentation or reconstruction	Cosmetic breast augmentation:* • In patients with implants and signs/symptoms of parenchymal disease (e.g. breast lump), when conventional imaging is not diagnostic, non-contrast MRI and dynamic contrast-enhanced MRI is indicated to exclude implant rupture and to evaluate the breast gland parenchyma. • In symptomatic patients that have undergone breast augmentation with direct polyacrylamide gel injection, non-contrast MRI and dynamic contrast-enhanced MRI are indicated. Breast augmentation for oncoplastic reconstruction:* • In symptomatic women, when conventional imaging is negative or equivocal, non-contrast MRI and dynamic contrast-enhanced MRI are indicated
The use of MRI for	• There is insufficient evidence of benefit to recommend the routine

Topic	Relevant EUSOMA recommendations
investigation of nipple discharge	use of MRI in the clinical context of suspicious nipple discharge. • In countries where ductography is considered the routine test for suspicious nipple discharge, non-contrast T2-weighted and contrast-enhanced MRI can be considered if ductography fails for technical reasons or the patient refuses the procedure.
To characterise equivocal findings at conventional imaging	• MRI should not be used as an alternative to needle biopsy when needle biopsy can be performed. • MRI should be considered for cases with abnormal imaging but inconclusive findings on conventional imaging where it is not possible to perform or define a site for needle biopsy.
To image the male breast	• MRI should not be used for routine diagnosis of breast cancer in men.

*These sections include additional recommendations, however only those relating to use of MRI for symptomatic women are included here. MRI=magnetic resonance imaging.

Other imaging modalities

A few of the guidelines discuss other imaging modalities, however none of these were recommended for routine diagnostic use. Other imaging modalities discussed include:

- FDG-positron emission mammography (PEM)[13, 14]
- Breast-specific gamma imaging (BSGI)[13, 14]
- 99mTc-MIBI scintimammography (SMM)[7]
- Positron emission tomography (PET)[7]
- Computed tomography (CT).[9]

Other populations

Some guidelines provide diagnostic imaging recommendations for different populations such as for men, or for women with augmented breasts, see Section 0).

Non-excisional biopsy

The INBS guide[28] notes that both FNA cytology and core biopsy can be performed, with no absolute rules on which is the more appropriate investigation.

Overall, the other identified guidelines are consistent in the recommended use of core biopsy and/or FNA cytology.[1, 2, 5-8, 10, 12, 13, 16, 17, 19, 20]

However, some guidelines indicate a preference for core biopsy over FNA cytology, which differs from the INBS guide.[1, 8, 12, 13, 17, 18] One guideline only recommends core biopsy.[23] The guidelines note various reasons for superiority of core biopsy compared with fine needle aspiration, such as improved sensitivity/specificity, however references for these statements are not always provided, see Table 9.

Additional information

Three guidelines have specific algorithms for biopsy.[1, 3, 17] The algorithms provide some information on how to manage non-malignant conditions (such as lobular neoplasia) and when excisional biopsy may be used.

Some guidelines provide information on the techniques to perform core biopsy, such as use of stereotactic or ultrasound-guided breast biopsy.[1, 8, 12, 13, 17, 18] A literature review comparing core needle biopsy with open/surgical biopsy[27] concluded that ultrasound- and stereotactically-guided core needle biopsy procedures have sensitivity and specificity close to that of open biopsy procedures, and are associated with fewer adverse events. The review did not include FNA cytology.

The INBS guide explicitly discusses non-excisional biopsy,[28] however the following additional biopsy methods (which are not included in the INBS guide) were discussed in a few guidelines:

- Open/surgical biopsy[1, 2, 19, 27] – usually for when unable to perform core needle biopsy
- Punch biopsy[1, 12, 19, 23] – usually to diagnose inflammatory breast cancer or Paget's disease.

Table 9 Guideline statements regarding preference for core biopsy compared with fine needle aspiration

Guideline	Statement/Recommendation	References
American College of Radiology 2012 – Palpable breast masses[13]	In text: "larger series demonstrate that core biopsy is superior to FNAB in terms of sensitivity, specificity, and correct histological grading of palpable masses"	Garg 2007,[82] Homesh 2005,[83] Pisano 2001[84]
California DPH 2011[1]	In text: "Core needle biopsy (CNB) is the method of choice for obtaining diagnostic tissue for patients with breast lesions where the differential diagnosis includes cancer. Fine needle aspiration biopsy (FNAB) is another technique but due to significant limitations, FNAB is not recommended when CNB is available." "FNAB uses a thin, hollow needle to obtain a small sample of cellular tissue from the area of concern. Accuracy relies upon the specialized training and experience of the pathologist as well as the clinician obtaining the sample." "CNB is similar to FNAB but uses a wider needle to remove larger, multiple samples of tissue. CNB is generally considered more accurate than FNAB and is the preferred method of biopsy for determining whether a breast abnormality is breast cancer."	No references provided
ICSI 2012[17]	In text: "Large core imaging-guided breast biopsy is now the technique of choice in most institutions in the United States for biopsy of non-palpable breast masses and abnormal calcifications based on decreased cost and less invasiveness."	No references provided
Salzman 2012[18]	Clinical recommendation: "Ultrasound-guided core needle biopsy is the preferred method of tissue sampling for suspicious palpable breast masses." In text: "Fine-needle aspiration combined with clinical examination and imaging (the "triple test") confers more than 99 percent certainty that a mass is benign if all three tests suggest a benign process. Ultrasound-guided core needle biopsy is the preferred method of tissue sampling for suspicious palpable breast masses. The sensitivity and specificity of ultrasound-guided core needle biopsy have been shown to be as high as 100 percent in diagnosing malignant palpable lesions, comparable to the sensitivity and specificity of surgical biopsy."	American College of Radiology 2011,[85] Pearlman 2010,[86] Yeow 2001,[87] Steinberg 1996[88]
British Columbia guidelines 2013[23]	Recommendation: "Core biopsy is the standard of care to establish a histological diagnosis"	No references provided
UK DoH 2010[12]	In text :"Needle core biopsy is preferred rather than FNAC for most solid lesions and for lesions suspicious for cancer because of the higher sensitivity and specificity achieved in most centres and because of the importance of oncological information including tumour type, grade and receptor status obtained with histology. In units where appropriate expertise exists, FNAC is an acceptable alternative to needle core biopsy in the initial evaluation of symptomatic breast lesions and in patients presenting with a lump in the axilla alone with no known clinical abnormality of the breast. Centres using cytology should demonstrate appropriate sensitivity and specificity."	No references provided

Guideline	Statement/Recommendation	References
ESMO 2015[8]	In text: "Pathological diagnosis should be based on a core needle biopsy, obtained preferably by ultrasound or stereotactic guidance. A core needle biopsy (if this is not possible, at least a fine needle aspiration indicating carcinoma) must be obtained before any type of treatment is initiated. If preoperative systemic therapy is planned, a core needle biopsy is mandatory to ensure a diagnosis of invasive disease and assess biomarkers"	No references provided

CNB=core needle biopsy; DoH=Department of Health; DPH=Department of Public Health; FNAB=fine needle aspiration biopsy; FNAC=fine needle aspiration cytology.

Surgical referral

The INBS guide notes in the algorithms when to refer to surgeon, however also incorporates a separate section including situations where surgical referral is recommended.[28]

Within the algorithms provided in the other guidelines, there is reference of when to refer to surgeon/specialists, however separate sections on surgical referral are often not included.[1, 3, 16-20, 23] Situations of when to refer to surgeon/specialists are presented in Table 10. Overall, the situations where surgical/specialist referral is indicated are consistent with the INBS guide,[1, 16-18, 20] although the level of detail provided varies.[28]

The ICSI breast disease guide includes a section on referral to a surgeon but does not have any associated recommendations or references.[17] This section notes that patients may be referred following detection of an abnormality via mammography or physical findings and that it is the role of the surgeon to evaluate each and every abnormality in the patient. This guide also notes the importance of communication between the surgical consultant and the primary care clinician.

Table 10 Referral to surgeon/specialist(s)

Guide	Refer to surgeon/specialist

CA INBS guide 2006[28]	• Where any one component of the triple test is positive i.e:
	  o Clinical examination (suspicious or malignant)
	  o Imaging (indeterminate, suspicious or malignant – classification category 3, 4, or 5)
	  o FNA cytology or core biopsy (indeterminate, suspicious or malignant – classification 3, 4, or 5)
	• Where a cyst aspiration is incomplete, results in bloody aspirate (not traumatic) or lump remains post-aspiration
	• Spontaneous unilateral discharge from a single duct especially in women 60 years and over
	• If any test result is inconsistent and requires additional investigation

California DPH 2011 guidelines[1] Referral to specialist Note biopsy indicating malignancy or DCIS leads to 'definitive treatment' rather than referral	• Persistent palpable mass • Discordant findings on CBE and imaging and/or pathology • Spontaneous unilateral nipple discharge • Biopsy indicates not malignant but concerning (atypical ductal hyperplasia, atypical lobular hyperplasia, flat epithelial atypia, lobular carcinoma in situ, lobular neoplasia, mucocele lesion, papillary lesion, phyllodes tumour, radial scar • Persistent breast pain, imaging indicates probably benign, however patients considered at increased risk for breast cancer, or patient concerned about results
CRICO 2014[16] Referral to surgeon	• Spontaneous nipple discharge, single duct • Spontaneous nipple discharge, multiple ducts, any evidence of blood, positive guaiac • Post-menopause with palpable mass • Pre-menopause with persistent palpable mass after two cycles • Complicated cyst with bloody fluid • Image-guided core needle biopsy is not available • Biopsy results malignant • Radiology/pathology discordance following biopsy • Benign biopsy - atypical lesions, papillomas, radial scars
ICSI 2012[17] Referral to surgeon	• Dominant mass, even if negative imaging • Discharge is single duct or bloody/clear or mass present • Abnormal pathologic findings from image-directed biopsy • Lobular neoplasia (atypical lobular hyperplasia, lobular carcinoma in situ) atypical ductal hyperplasia, phyllodes tumor, papillary lesions
Salzman 2012[18]	• Palpable mass

Guide	Refer to surgeon/specialist
Referral to surgeon	• Imaging results BIRADS 4,5 • Pathologic discharge (spontaneous, unilateral, single duct, clear, serous, or bloody) • Physiologic discharge with symptoms bothersome to patient
University of Michigan 2013[19] Referral to breast specialist	• Any suspicious mass • Any woman at very high risk for breast cancer with palpable mass or asymmetric thickening/nodularity on physical exam • Imaging results BIRADS 4,5 • Cellulitic breast skin changes which do not completely resolve after antibiotics • Cellulitic breast skin changes which are associated with a fluctuant, painful mass • Eczematoid changes of the nipple-areolar skin which persist >1-2 weeks or do not respond to topical treatment • Persistent or localized pain not responsive after 2-3 months of conservative treatment • Discharge is spontaneous or watery/serous or if other risk factors are present (persistent, serosanguinous, single duct) • Discharge is non-spontaneous, from multiple ducts and gray to green in colour, only refer if patient requests for symptomatic relief
UpToDate 2016[3] Referral to surgeon Note in other algorithms where malignancy is indicated states 'treat as appropriate' rather than to refer to surgeon	• Imaging results BIRADS 4,5
Washington State algorithm 2014[20] Referral to breast specialist (experienced clinician able to dependably obtain a valid tissue diagnosis. This includes radiologists, surgeons, and adequately trained primary care providers)	• Imaging results BIRADS 4,5 • Palpable mass • Imaging results simple cyst and symptomatic • Cancer or atypia following biopsy • Non-cyclic pain where no hormonal cause can be found • Unilateral skin changes that do not resolve following antibiotics or topical treatment • Bloody or heme-occult positive discharge • Non-bloody discharge that is spontaneous and persists over two months
British Columbia guidelines 2013[23] Referral to surgeon	• Malignant findings following imaging and biopsy

BIRADS= breast imaging reporting and data system; CBE=clinical breast examination; DPH=Department of Public Health; FNA=fine needle aspiration.

Referral to specialist clinics

Some European guides focus on symptoms which present in the primary care setting and warrant referral to specialist breast clinics.[4, 11, 12, 24] Two guides include information on primary care referral of symptomatic patients to specialist breast clinics as well as information on assessment of the symptoms.[11, 12] While the surgeon is part of the multidisciplinary team in the clinic, details are not provided specifically regarding surgical referral. Two other UK guides/guidelines are specifically on referral of symptomatic patients to specialist breast clinics[4, 24] and focus on what symptoms to be aware of, but do not include information on diagnostic tests or investigation. This may reflect different health care systems/roles of primary care providers in the UK.

Additional areas in other guidelines

Specific populations

Specific populations covered in some of the other guides/guidelines include:

- Men[11, 12, 15, 19, 26]
- Pregnant/lactating women[11-13, 19, 23, 25]
- Women with augmented breasts.[8, 10-12, 17, 19, 26]

Men and women with augmented breasts are not explicitly included in the INBS guide.[28]

The INBS guide[28] includes guidance on diagnostic imaging in pregnancy or lactation, with content consistent with the other guidelines (see Section 0). The Dutch guideline provides more detail regarding diagnostic investigations and pathology for pregnancy associated breast cancer.[11]

Recommendations for these populations are summarised in the tables below. Most of the recommendations refer to diagnostic imaging, however some guidelines provide additional detail on history, clinical exam and/or biopsy.

Table 11 Statements/Recommendations for men

Guideline	Statements/Recommendations
ACR – Male breast 2014[15]	Men with typical symptoms of gynecomastia or pseudogynecomastia do not usually need imaging For men with an indeterminate palpable mass, begin with US if the patient is <25 years of age, as breast cancer is highly unlikely. Mammography should be performed if US is suspicious For men ≥25 years of age, or men with a highly concerning physical examination, begin with mammography. US is useful if mammography is inconclusive or suspicious.
University of Michigan 2013[19]	Men – Diagnose and treat enlargement or pain. Breast mass is rare, but suspicious for cancer
UK DoH 2010[12]	History & clinical assessment to be performed (note testicles also to be examined) Imaging: "Mammography and/or ultrasound should be performed in men with unexplained or suspicious unilateral breast enlargement" Biopsy: "Needle core biopsy should be performed following imaging in those patients with uncertain or suspicious clinical or radiological findings … Fine needle aspiration is not to be recommended"
EUSOMA 2010[26]	MRI should not be used for routine diagnosis of breast cancer in men
IKNL NABON Dutch BC guidelines 2012[11]	Imaging in men may be conducted in the same manner as with women: • younger than 30 years: ultrasound, clinical signs of gynaecomastia are no indication for imaging • over 30 years of age: mammography, supplemented by ultrasound and punction if the findings are inconclusive Consultation of a clinical geneticist is indicated in male breast cancer, because the chance of a BRCA1/2 mutation is at least 10%.

ACR=American College of Radiology; DoH=Department of Health; MoH=Ministry of Health; MRI=magnetic resonance imaging; US=ultrasound.

Table 12 Statements/Recommendations for pregnant or lactating women

Guideline	Statements/Recommendations
ACR – Palpable masses 2014[13]	"Due to its lack of ionizing radiation, US is the modality of choice for evaluating a palpable mass in pregnant women … US is also the modality of choice for evaluating palpable masses in lactating women … However, mammography is not contraindicated during pregnancy or lactation and should be performed if malignancy is suspected, because it is particularly effective in detecting microcalcifications and subtle architectural distortion, features often not as well seen on US"
University of Michigan 2013[19]	Pregnant women – If concerning indications, imaging is relatively safe and should be done
British Columbia 2013[23]	Pregnant and lactating women with lumps or breast complaints and/or symptoms should be investigated promptly. A diagnostic ultrasound is recommended as the initial investigation.
Canadian Association of Radiologists 2012[25]	Ultrasound is the initial imaging technique to evaluate palpable masses in lactating and pregnant women
UK DoH 2010[12]	Imaging assessment: "Ultrasound is the imaging method of choice for the majority of women aged < 40 years and during pregnancy and lactation." Investigation of nipple symptoms: "Nipple cytology is rarely of any value and must be treated with great caution after recent lactation."

Guideline	Statements/Recommendations
IKNL NABON Dutch BC guidelines 2012[11]	The following radiological and nuclear medicine diagnostic methods are possible during pregnancy without a notable risk of damage to the foetus: mammography, chest X-ray, an ultrasound of the breast, axilla and liver, skeletal scintigraphy, SN procedure The feasibility of MRI with gadolinium contrast in pregnant or lactating women is (still) unclear Diagnosis and treatment of pregnancy associated breast cancer is most certainly multidisciplinary; aside from the breast care team, a perinatologist and neonatologist must also be involved Radiological diagnostic procedures are possible, taking the ALARA principle into account – Mammography and ultrasound for locoregional diagnosis – Conventional staging (chest X-ray, liver ultrasound and skeletal scintigraphy) only in the case of locally advanced disease or suspected metastasis (complaints) – As a standard, MRI (with intravenous gadolinium) and FDG-PET-CT are not recommended Cytology and histology are possible. The pathologist must be informed about the pregnant or lactating status

ACR=American College of Radiology; ALARA= as low as reasonably achievable; DoH=Department of Health; FDG-PET-CT=^{18}F-fluorodeoxyglucose positron emission tomography–computed tomography; MoH=Ministry of Health; MRI=magnetic resonance imaging; SN=sentinel node; US=ultrasound.

Table 13 Statements/Recommendations for women with augmented breasts

Guideline	Statements/Recommendations
ICSI 2012[17]	In certain circumstances where diagnosis is difficult, a functional exam, either breast MRI or nuclear (molecular) imaging may be suggested by the radiologist or surgeon to sort out inconclusive cases. These cases may include… the presence of silicone injections/implants or other problematic issues
University of Michigan 2013[19]	Augmented breasts – Evaluation/management of above conditions [common breast problems] is similar, but imaging issues
UK DoH 2010[12]	History: "in women with breast implants symptoms may be incidental or related to the implant, including changes in texture, size or shape; following reconstructive surgery for previous breast cancer there may be concern about recurrence. Record the original reason for the implant (augmentation or reconstruction); the site, i.e. submuscular or subglandular; the nature of any associated reconstructive procedure e.g. latissimus dorsi flap; the date of surgery and type of implant used. If there are symptoms of pain or lump record details as under above protocols." Clinical examination: "note any breast lump, swelling or distortion, and examine nodes. Assess the state of the implant: size, position, shape, and capsular contracture" Imaging: "include ultrasound and mammography as indicated. Performing needle biopsy of any breast lesion under ultrasound guidance is advisable to reduce risk of damage to the implant. Mammography can be performed by compressing the breast in front of the implant, though it is not possible to achieve full imaging of the breast tissue."
ESMO 2015[8]	Imaging: An MRI of the breast is not routinely recommended, but should be considered in cases of: … breast implants
EUSOMA 2010[26]	Cosmetic breast augmentation: - In patients with implants and signs/symptoms of parenchymal disease (e.g. breast lump), when conventional imaging is not diagnostic, non-contrast MRI and dynamic contrast-enhanced MRI is indicated to exclude implant rupture and to evaluate the breast gland parenchyma - In symptomatic patients that have undergone breast augmentation with direct polyacrylamide gel injection, non-contrast MRI and dynamic contrast-enhanced MRI are indicated Breast augmentation for oncoplastic reconstruction:

Guideline	Statements/Recommendations
	- In symptomatic women, when conventional imaging is negative or equivocal, non-contrast MRI and dynamic contrast-enhanced MRI are indicated
IKNL NABON Dutch BC guidelines 2012[11]	There is no standard procedure available for women with silicone prostheses. The guideline development group is of the opinion that the radiologist, together with the laboratory technician, must determine the choice and sequence of clinical imaging on the basis of consistency, relative size and localisation of the prosthesis. Mammography and ultrasound are performed if there are symptoms. If mammography does not work, ultrasound is the procedure of choice
MoH Malaysia 2010[10]	MRI may be considered in clinical situations where other imaging modalities are unreliable or inconclusive which include: … Patients with breast implants/foreign bodies

ACR=American College of Radiology; DoH=Department of Health; MoH=Ministry of Health; MRI=magnetic resonance imaging; US=ultrasound.

Communication

There are no specific references to communication in the INBS guide, other than within the main algorithm to reassure patients with normal results following imaging ± biopsy.[28]

Consistent with the INBS guide,[28] some of the other guidelines also include notes in the algorithms to reassure the patient following negative findings where breast cancer is not indicated.[4, 17]

The UK Department of Health guidelines include large sections on communication in two areas: Referral and Assessment.[12] Recommendations refer to communication between health professionals and the patient and between different health professionals involved with the patients care.[12]

The CRICO guidelines also include information regarding physician-patient discussion including points on communication, test results and when patients are unsatisfied with negative findings.[16]

Statements/recommendations regarding communication are presented in Table 14.

Table 14 Statements/Recommendations regarding communication

Guideline	Topic	Statements/Recommendations
UK DoH guidelines 2010[12]	Role of the GP	• The general practitioner plays a fundamental role in supporting the management of symptomatic breast patients. They are supported in their decision to refer (and to re-refer where necessary) by the existence of national guidelines. General practitioners are well placed to support the patient through the referral process, by providing choice and information, and also through any subsequent treatment phases by providing ongoing holistic support. They are often seen as the first port of call by the patient.
	Presentation of the patient with new breast symptoms	• In the initial consultation the GP should assess the patient with a view to referral to a symptomatic breast clinic. The GP may find that the patient has normal or benign changes that do not require referral and, at this point, they should give reassurance supported with the appropriate literature. • All patients should be aware of present breast screening processes and informed not to await their next screening appointment if they develop symptoms.
	Referral to clinic	• Once the patient is referred to the breast clinic, clear communication between professionals is vital at this point to ensure that all relevant information regarding the patient is relayed to the clinic prior to the patient's clinic attendance. • The patient should receive written and/or verbal information regarding the symptomatic breast clinic. This information should include waiting times for an appointment and the likely process that will occur during the clinic. This information may be sent out with the appointment letter and should ideally also include information on length of visit. • The patient should also be provided with guidance for obtaining further information. • Patients should be reminded of the importance of keeping their appointment.
	Assessment	• All staff should possess appropriate communication skills for both communicating with patients and ensuring consistent communication with all health professionals involved in the patient's care. • Healthcare professionals should assess women during the diagnostic process (i.e. ascertain the patient's understanding of the situation and expectations) to intervene accordingly as patients' own appraisals of their illnesses will affect their understanding of their situation and the diagnostic process, and their psychological well-being. • The patient should be given clear information, that meets their individual needs, at each stage of the diagnostic process and made aware of the availability of, and contact details for, their breast care nurse. • For patients who undergo needle biopsy, both written and verbal information should be provided, for those who wish, regarding the likely diagnosis and outcome of the biopsy. • All patients who undergo needle biopsy should be provided with a definite appointment or other agreed arrangement for communication of the biopsy result, within five working days. • A discussion between the patient and a clinician who has been involved with the assessment of the patient should occur prior to leaving clinic. This is to inform the patient of the likely outcome of the biopsy result in light of the clinical examination and imaging findings. If these are felt likely to be malignant a breast care nurse should be present at that consultation where possible. • Patients should be advised of when they may receive their diagnosis – i.e. know at what point they will receive their diagnosis, so they can arrange to be accompanied by family/friend if they wish.

Guideline	Topic	Statements/Recommendations
		• Patients who perceive themselves to have a high risk of breast cancer may continue to feel distressed following a benign diagnosis so it is important to accurately address these (mis)perceptions at the initial consultation. • The results of Triple Assessment should be discussed at a multidisciplinary meeting for all women who undergo needle biopsy. The results of each element of the Triple Assessment should be considered in order to ensure a correct diagnosis and appropriate further management. If there is discordance between the results, further assessment, if necessary including repeat biopsy, should be considered.
CRICO 2014[16]*	Patient unsatisfied with a negative finding	• Engage the patient in a discussion about her breast care management subsequent to negative test/imaging results. Develop a clear and effective plan, and ensure the patient's understanding and agreement of that plan. • Document all interactions as they occur to support future care and to clarify any disputes that may arise later.
	Communication	• Communicate all abnormal findings to the patient and document that act. • Avoid sending the wrong message to a patient by just telling her that a palpable lump is probably benign. Stress that additional studies may be needed to rule out malignancy. • Share any uncertainty on your part in a way that helps your patient appreciate the importance of adherence to follow-up. • Confirm and document with other providers which of you will be the clinician of record and responsible for ordering tests and following up with the patient.
	Test results	• Explain to the patient how test results will be communicated to her and (if appropriate) other clinicians. • Document any telephone conversations with patients regarding the reported results. • To ensure notification of test results, employ a system to track ordered tests through the receipt and communication to the patient.

*Additional points are included in this guide, however those most relevant to communication are reported here.

Appendix 1: Additional website and internet searches

Searches originally conducted to 7 April 2016.

Site	Search terms	Results
AHRQ Effective Health Care Program	'breast cancer'	• 69 records retrieved • 1 record relevant
American Society of Clinical Oncology (ASCO)	All current practice guidelines under the heading 'breast cancer'	• None relevant
Cancer Care Ontario (CCO)	All current Evidence-Based Guidelines and Non-PEBC Guidelines	• None relevant
Centre for Reviews and Dissemination (CRD)	Title: 'breast' AND 'cancer' AND 'diagnosis' Date: 2004–2016	• 63 records retrieved • 1 record relevant
Cochrane library	cancer diagnosis	• None relevant
European Society for Medical Oncology (ESMO)	Breast cancer guidelines	• 1 relevant guideline, already identified
Google	'breast cancer diagnosis guide' 'breast symptom algorithm' 'breast symptom diagnosis' 'breast symptom diagnosis primary care'	• 8 records relevant
Google	'investigation breast symptom'	• No relevant records identified
International Guidelines Library (GIN)	'breast'	• 168 records retrieved • Reviewed by title only • 8 records relevant (1 in German)
International Guidelines Library (GIN)	cancer diagnosis	• No relevant records identified
National Comprehensive Cancer Network (NCCN)	Guidelines for detection, prevention, & risk reduction	• 1 relevant guideline, already identified
National Guideline Clearinghouse (AHRQ)	'breast' AND 'cancer' AND 'diagnosis'	• 161 records retrieved • 2 records relevant
National Guideline Clearinghouse (AHRQ)	'investigation' AND 'breast' AND 'symptoms'	• 100 records retrieved 1 additional relevant record identified
National Institute for Health and Care Excellence (NICE)	'Breast cancer' and 'Cancer: general and other' guidelines	• 1 already identified, 1 additional relevant guideline
New Zealand Guidelines Group via New Zealand Ministry of Health	'breast'	• 37 records retrieved • None relevant
New Zealand Guidelines Group via New Zealand Ministry of Health	cancer diagnosis	• 1 relevant record identified
NHMRC Guideline Portal	'breast'	• 15 records retrieved • None relevant
NHMRC Guideline Portal	cancer and/or diagnosis	• No relevant records identified
Scottish Intercollegiate Guidelines Network (SIGN)	all current guidelines under the heading cancer	• No relevant records identified

Appendix 2: Excluded guidelines

Organisation Year Country Title	**Relevant topics covered**	**Reason(s) for exclusion**
Klein S 2005 USA Evaluation of Palpable Breast Masses	History & CBE Imaging Biopsy Triple test Algorithm	Not an official guideline (American Family Physician article).
NHSBSP 2010 UK Clinical Guidelines for Breast Cancer Screening Assessment	Triple test assessment	This guideline covers the context of assessment of abnormalities detected during screening rather than presentation of symptoms.
NZGG 2009 New Zealand Suspected cancer in primary care	Some general information regarding referral/investigations for BC symptoms	Limited information provided, similar to NICE 2015 guideline. NZGG is no longer in existence, not a current guideline.
Ärztliches Zentrum für Qualität in der Medizin 2011 Synopse evidenzbasierter Leitlinien-Empfehlungen zur Diagnostik, Therapie und Nachsorge des Mammakarzinoms.		In German language

BC=breast cancer; CBE=clinical breast examination

Appendix 3: Summary of included guidelines

Organisation Year Title	Relevant topics covered	Algorithms included	Summary/comments*
USA			
Agency for Healthcare Research and Quality (AHRQ) 2014[27] USA Core Needle and Open Surgical Biopsy for Diagnosis of Breast Lesions: An Update to the 2009 Report	Biopsy (core needle, open surgical)	No	Technique-specific (biopsy) Summary of a literature review comparing core needle and open surgical biopsy (total of 316 included studies) Includes evidence up to 2013
American College of Radiology 2012[13] ACR Appropriateness Criteria – Palpable breast masses	Investigation of palpable breast mass variations; Imaging (mammography, ultrasound, MRI, FDG-PEM, BSGI); Biopsy (FNA, core biopsy)	No	Symptom-specific (mass) Includes evidence up to 2012
American College of Radiology 2014[14] ACR Appropriateness Criteria – Breast pain	Investigation of breast pain variations; Imaging (mammography, ultrasound, MRI, FDG-PEM, BSGI)	No	Symptom-specific (pain) Includes evidence up to 2013
American College of Radiology 2014[15] ACR Appropriateness Criteria – Evaluation of the Symptomatic Male Breast	Investigation of various symptomatic male breast; Imaging (mammography, US, MRI)	No	Symptom-specific (symptoms in men) Includes evidence up to 2013
California Department of Public Health 2011[1] USA Breast Cancer Diagnostic Algorithms for Primary Care Providers	Risk assessment; Investigation of various symptoms (palpable mass, nipple discharge, breast skin changes/nipple retraction, breast pain); CBE; Imaging (mammogram, ultrasound); Biopsy (CNB preferred, FNAB, skin punch biopsy, surgical biopsy)	1) New palpable mass; 2) Abnormal screening mammogram with normal CBE; 3) Spontaneous unilateral nipple discharge; 4) Breast skin changes/nipple retraction; 5) Breast pain; 6) Breast biopsy	BC screening/diagnosis Guidance for PCPs Includes evidence up to 2010
CRICO 2014[16] USA CRICO Breast Care Management Algorithm: A Decision support tool	Imaging (mammogram, ultrasound); Investigation of various symptoms (nipple discharge, palpable mass, pain)	1) Spontaneous nipple discharge with no palpable mass (non-lactating); 2) Palpable mass detected or confirmed by clinician; 3) Breast pain	Investigation of breast symptoms Limited references provided, refers to 2013 NCCN guidelines
Institute for Clinical Systems	Investigation of various symptoms (including	1) Evaluation of breast mass; 2)	Investigation of breast disease

Organisation Year Title	Relevant topics covered	Algorithms included	Summary/comments*
Improvement (ICSI) 2012[17] USA Health Care Guideline: Diagnosis of Breast Disease	nipple discharge); Imaging (mammogram, ultrasound); Biopsy (CNB)	Evaluation of the breast for nipple discharge; 3) Evaluation of breast pain; 4) Radiologic evaluation of the breast; 5) Image-directed core needle biopsy	Includes evidence up to 2009
National Comprehensive Cancer Network (NCCN) 2015[2] USA Breast Cancer Screening and Diagnosis	Investigation of various symptoms (palpable mass; nipple discharge; asymmetric thickening/nodularity; skin changes); History & CBE; Imaging (mammogram, ultrasound, MRI mentioned); Biopsy (FNA and core (needle or vacuum-assisted) both considered valuable, excisional biopsy also mentioned)	Investigating various presenting signs/symptoms (including palpable mass (<30, ≥30); nipple discharge, no palpable mass; asymmetric thickening/nodularity; skin changes: peau d'orange, erythema, nipple excoriatrion, scaling/eczema, skin ulcers) with detailed diagnostic follow-up	BC screening/diagnosis Relevant evidence up to 2012 (NB discussion is currently being updated therefore there may be more recent references to be included)
Salzman et al 2012[18] USA Common Breast Problems	Investigation of various symptoms (palpable breast mass, mastalgia, nipple discharge); Imaging (mammography, ultrasound); Biopsy (US guided CNB)	1) Approach to the patient with a Palpable breast mass; 2) Approach to the patient with Breast pain; 3) Approach to the patient with Nipple discharge	Investigation of breast disease Journal article, no organisational affiliation however does provide some clinical recommendations Relevant evidence up to 2010
University of Michigan 2013[19] USA Common breast problems	Investigation of various symptoms (including nipple discharge); CBE; Imaging (mammography, ultrasound, MRI); Biopsy (FNA, core biopsy, punch biopsy, open (surgical) biopsy); Special populations (pregnant women, men, augmented breasts)	1) Palpable breast mass or asymmetric thickening/nodularity: diagnosis and treatment; 2) Breast pain diagnosis and treatment; 3) Nipple discharge diagnosis and treatment	Investigation of breast disease Individual statements not referenced, other than 2012 NCCN guidelines, most recent evidence to 2007
Up-to-Date 2016[3] USA Diagnostic evaluation of women with suspected breast cancer	Imaging (mammography, ultrasound, MRI); Biopsy	1) Management algorithm for patients with abnormal mammograms; 2) Diagnostic algorithm for palpable breast abnormalities in women less than 30 years of age; 3) Breast biopsy algorithm for solid lesions, indeterminate or suspicious; 4) Diagnostic algorithm for palpable breast abnormalities in women aged 30 years or over	BC diagnosis Peer-reviewed publication, no organisational affiliation however does provide some clinical recommendations Includes evidence up to 2013 (most recent MRI)
Washington State Department of Health 2014[20]	Investigation of various symptoms (palpable mass; breast pain; skin changes involving	BCCHP Breast care algorithm	Investigation of breast symptoms Algorithm and notes only

Organisation Year Title	Relevant topics covered	Algorithms included	Summary/comments*
USA Breast, Cervical and Colon Health Program (BCCHP) Breast Care Algorithm	nipple-areolar complex or other sites on the breast; discharge)		No references provided
Canada			
British Columbia Guidelines 2013[23] Canada Breast Disease and Cancer: Diagnosis	History and physical examination; Imaging (mammography, ultrasound); Biopsy (core biopsy); Abnormality characteristics (such as nipple discharge) and management	Algorithms of breast cancer and disease guidelines 1) Symptomatic women; 2) Asymptomatic women	Breast disease and cancer Limited references provided, evidence up to 2013
Canadian Association of Radiologists (CAR) 2012[25] Canada 2012 CAR Diagnostic Imaging Referral Guidelines	Imaging (mammography, ultrasound, MRI, ductography (galactography)); Nipple discharge	No	Technique-specific (imaging) Top-line diagnostic recommendations for symptomatic patients: clinical suspicion of carcinoma; suspected Paget's disease; spontaneous bloody or clear nipple discharge No references provided
UK/Ireland			
Health Service Executive/National Cancer Control Programme 2009[4] Ireland National Breast Cancer GP Referral Guidelines	Assessment of various symptoms (breast pain, breast lumps, nipple discharge)	1) Algorithm for referral of patients with breast pain; 2) Algorithm for referral of patients with breast lumps; 3) algorithm for referral of patients with nipple discharge	Assessment of breast symptoms GP guide Does not cover investigation, only identification of symptoms to be referred to specialist breast clinic No references provided
Health Service Executive/National Cancer Control Programme/Department of Health 2015[5] Ireland Diagnosis, staging and treatment of patients with breast cancer. National Clinical Guideline No. 7	Triple assessment (clinical assessment, mammography and/or ultrasound imaging with core biopsy and/or fine needle aspiration cytology) - good practice point (GPP) rather than recommendation	No	BC – complete management No references provided regarding diagnosis GPP
National Institute for Health and Care Excellence (NICE) 2009[6] UK Early and locally advanced breast cancer: diagnosis and treatment	Briefly mentions triple assessment (clinical assessment, mammography and/or ultrasound, and core biopsy and/or FNA cytology)	No	BC – complete management Limited relevant recommendations regarding INBS No references provided
National Institute for Health and	Briefly discusses symptoms for referral, not	No	Suspected cancer – referral only

Organisation Year Title	Relevant topics covered	Algorithms included	Summary/comments*
Care Excellence (NICE) 2015[24] UK Suspected cancer: recognition and referral	diagnostic tests		Limited relevant recommendations No references provided
UK Department of Health 2010[12] Best practice diagnostic guidelines for patients presenting with breast symptoms	Referral for various symptoms (lump, lumpiness, change in texture; nipple symptoms; breast pain; axillary lump (in absence of clinical breast abnormality)); Triple assessment recommended; Detailed information on CE, Imaging (mammography, ultrasound, MRI) & Biopsy (CNB, FNA (though CNB usually preferred)); Additional information on communication, one-stop assessments, men, and women with breast implants	1) Assessment: Lump/lumpiness; 2) Assessment: Breast pain	Investigation of breast symptoms Detailed diagnostic document Overall references provided, however individual points not specifically referenced, relevant evidence up to 2010
Europe			
Belgian Health Care Knowledge Centre (KCE) 2013[7] Breast cancer in women: diagnosis, treatment and follow-up	Diagnosis of breast cancer; Triple assessment (clinical examination, imaging (comprising mammography and/or ultrasonography) and sampling of the lesion with a needle for histological/cytological assessment); Imaging (mammography, ultrasound, MRI, SMM, PET); Biopsy (Core biopsy, FNAC)	No	BC – complete management Relevant evidence up to 2009
ESMO 2015[8] Europe Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up	CE; Imaging (mammography, ultrasound, MRI); Biopsy/pathology (CNB preferred, by ultrasound or stereotactic guidance; FNA may be performed if CNB not possible)	No	BC – complete management Limited references provided for diagnosis statements, latest relevant reference up to 2010 (regarding MRI)
EUSOMA 2010[26] Europe Magnetic resonance imaging of the breast: Recommendations from the EUSOMA working group	Relevant sections: Use of MRI for investigation of nipple discharge; characterise equivocal findings at conventional imaging; male breast	No	Technique-specific (MRI) Relevant evidence up to 2008
French College of Gynecologists and Obstetricians (CNGOF) 2016[21] Clinical practice guidelines from the French College of	Imaging (mammography, ultrasound, galactography); Biopsy (percutaneous biopsy, CNB); Investigation/ management of various symptoms (including nipple discharge, nipple	No	Benign breast tumours Does not provide references to primary studies, rather 2015 recommendations (in French)

Organisation Year Title	Relevant topics covered	Algorithms included	Summary/comments*
Gynecologists and Obstetricians (CNGOF): benign breast tumors - short text.	lesions, breast pain, breast cysts)		
IKNL (Comprehensive Cancer Centre the Netherlands) NABON 2012[11] The Netherlands Breast Cancer Dutch Guideline, version 2.0	History & CBE; Investigation of various symptoms (local complaints or abnormalities, diffuse complains or abnormalities, nipple discharge); Imaging (mammography, ultrasound, MRI); Some limited information on punction (biopsy)	No	BC – complete management Relevant evidence up to 2010 (most recent evidence relates to MRI)
Waaijer L et al 2016[22] The Netherlands Systematic review and meta-analysis of the diagnostic accuracy of ductoscopy in patients with pathological nipple discharge	Ductoscopy	No	Symptom-specific (nipple discharge)/technique-specific (ductoscopy) Journal article rather than guideline Includes 20 studies (12 in meta-analysis) Includes evidence up to 2015
Asia			
Japanese Breast Cancer Society 2015[9] The Japanese Breast Cancer Society Clinical Practice Guideline for screening and imaging diagnosis of breast cancer	Imaging (mammography, ultrasound, MRI)	No	Technique-specific (imaging) Relevant evidence up to 2009
Ministry of Health Malaysia 2010[10] Clinical Practice Guidelines: Management of Breast Cancer	Triple assessment (including accuracy); Imaging (mammography, ultrasound); Biopsy (FNA and/or core biopsy)	No	BC – complete management Relevant evidence up to 2009

*evidence date refers to latest publication date of included/cited relevant references. BC=breast cancer; CBE=clinical breast examination; CE=clinical examination; CNB=core needle biopsy; FNA=fine needle aspiration; GP=general practitioner; GPP=good practice point; INBS=investigation of a new breast symptom; MRI=magnetic resonance imaging

References

1. Cancer Detection Section Breast Expert Workgroup. Breast Cancer Diagnostic Algorithms for Primary Care Providers. California Department of Public Health 2011.
2. NCCN. Breast Cancer Screening and Diagnosis. National Comprehensive Cancer Network, 2015.
3. Esserman LJ and Joe BN. Diagnostic evaluation of women with suspected breast cancer. UpToDate, 2016.
4. Health Service Executive and National Cancer Control Programme. National Breast Cancer GP Referral Guidelines. Ireland 2009.
5. National Clinical Effectiveness Committee. Diagnosis, staging and treatment of patients with breast cancer. National Clinical Guideline No. 7. Department of Health, Ireland, 2015.
6. NICE. Early and locally advanced breast cancer: diagnosis and treatment. National Institute for Health and Care Excellence, 2009.
7. KCE. Breast Cancer in Women: Diagnosis, Treatment and Follow-up. Belgian Health Care Knowledge Centre, 2013.
8. Senkus E, Kyriakides S, Ohno S, et al. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26 Suppl 5:v8-30.
9. Tozaki M, Isomoto I, Kojima Y, et al. The Japanese Breast Cancer Society Clinical Practice Guideline for screening and imaging diagnosis of breast cancer. Breast Cancer. 2015;22(1):28-36.
10. Ministry of Health Malaysia and Academy of Medicine Malaysia. Clinical Practice Guidelines. Management of Breast Cancer. 2010.
11. IKNL and NABON. Breast cancer Dutch Guideline, version 2.0. NABON, The Netherlands, 2012.
12. Willett AM, Michell MJ and Lee MJR. Best practice diagnostic guidelines for patients presenting with breast symptoms. UK Department of Health, 2010.
13. American College of Radiology. ACR Appropriateness Criteria - Palpable Breast Masses. 2012.
14. American College of Radiology. ACR Appropriateness Criteria - Breast Pain. 2014.
15. American College of Radiology. ACR Appropriateness Criteria - Evaluation of the Symptomatic Male Breast. 2014.
16. CRICO. CRICO Breast Care Management Algorithm, A Decision Support Tool. CRICO, Cambridge, MA, 2014.
17. ICSI. Health Care Guideline: Diagnosis of Breast Disease. Institute for Clinical Systems Improvement, 2012.
18. Salzman B, Fleegle S and Tully AS. Common breast problems. Am Fam Physician. 2012;86(4):343-9.
19. University of Michigan and Breast Care Guideline Team. Common Breast Problems. 2013.
20. Washington State Department of Health. BCCHP Breast Care Algorithm. 2014.
21. Lavoue V, Fritel X, Antoine M, et al. Clinical practice guidelines from the French College of Gynecologists and Obstetricians (CNGOF): benign breast tumors - short text. Eur J Obstet Gynecol Reprod Biol. 2016;200:16-23.
22. Waaijer L, Simons JM, Borel Rinkes IH, et al. Systematic review and meta-analysis of the diagnostic accuracy of ductoscopy in patients with pathological nipple discharge. Br J Surg. 2016;103:632-643.
23. BCGuidelines.ca. Breast Disease and Cancer: Diagnosis. British Columbia Minsitry of Health, British Columbia Medical Association, Canada, 2013.
24. NICE. Suspected cancer: recognition and referral. National Institute for Health and Care Excellence, 2015.
25. Canadian Association of Radiologists. 2012 CAR Diagnostic Imaging Referral Guidelines. 2012.

26. Sardanelli F, Boetes C, Borisch B, et al. Magnetic resonance imaging of the breast: recommendations from the EUSOMA working group. Eur J Cancer. 2010;46(8):1296-316.
27. AHRQ. Effective Health Care Program. Core Needle and Open Surgical Biopsy for Diagnosis of Breast Lesions: An Update to the 2009 Report. Executive Summary. 2014.
28. Cancer Australia. The investigation of a new breast symptom, a guide for General Practitioners. 2006.
29. National Breast Cancer Centre. Evidence Relevant to Guidelines for the Investigation of Breast Symptoms. Second Edition. National Breast Cancer Centre, Camperdown, NSW, 2006.
30. Ghimire B, Khan MI, Bibhusal T, et al. Accuracy of triple test score in the diagnosis of palpable breast lump. JNMA J Nepal Med Assoc. 2008;47(172):189-92.
31. Vetto J, Pommier R, Schmidt W, et al. Use of the "triple test" for palpable breast lesions yields high diagnostic accuracy and cost savings. Am J Surg. 1995;169(5):519-22.
32. Dennis MA, Parker SH, Klaus AJ, et al. Breast biopsy avoidance: the value of normal mammograms and normal sonograms in the setting of a palpable lump. Radiology. 2001;219(1):186-91.
33. Moy L, Slanetz PJ, Moore R, et al. Specificity of mammography and US in the evaluation of a palpable abnormality: retrospective review. Radiology. 2002;225(1):176-81.
34. Shetty MK and Shah YP. Prospective evaluation of the value of negative sonographic and mammographic findings in patients with palpable abnormalities of the breast. J Ultrasound Med. 2002;21(11):1211-6; quiz 1217-9.
35. Soo MS, Rosen EL, Baker JA, et al. Negative predictive value of sonography with mammography in patients with palpable breast lesions. AJR Am J Roentgenol. 2001;177(5):1167-70.
36. Yang WT, Dryden MJ, Gwyn K, et al. Imaging of breast cancer diagnosed and treated with chemotherapy during pregnancy. Radiology. 2006;239(1):52-60.
37. Murphy IG, Dillon MF, Doherty AO, et al. Analysis of patients with false negative mammography and symptomatic breast carcinoma. J Surg Oncol. 2007;96(6):457-63.
38. Shetty MK, Shah YP and Sharman RS. Prospective evaluation of the value of combined mammographic and sonographic assessment in patients with palpable abnormalities of the breast. J Ultrasound Med. 2003;22(3):263-8; quiz 269-70.
39. Lehman CD, Lee CI, Loving VA, et al. Accuracy and value of breast ultrasound for primary imaging evaluation of symptomatic women 30-39 years of age. AJR Am J Roentgenol. 2012;199(5):1169-77.
40. Tumyan L, Hoyt AC and Bassett LW. Negative predictive value of sonography and mammography in patients with focal breast pain. Breast J. 2005;11(5):333-7.
41. Loving VA, DeMartini WB, Eby PR, et al. Targeted ultrasound in women younger than 30 years with focal breast signs or symptoms: outcomes analyses and management implications. AJR Am J Roentgenol. 2010;195(6):1472-7.
42. Evans GF, Anthony T, Turnage RH, et al. The diagnostic accuracy of mammography in the evaluation of male breast disease. Am J Surg. 2001;181(2):96-100.
43. Patterson SK, Helvie MA, Aziz K and Nees AV. Outcome of men presenting with clinical breast problems: the role of mammography and ultrasound. Breast J. 2006;12(5):418-23.
44. Munoz Carrasco R, Alvarez Benito M, Munoz Gomariz E, et al. Mammography and ultrasound in the evaluation of male breast disease. Eur Radiol. 2010;20(12):2797-805.
45. Stavros AT, Thickman D, Rapp CL, et al. Solid breast nodules: use of sonography to distinguish between benign and malignant lesions. Radiology. 1995;196(1):123-34.
46. Flobbe K, Bosch AM, Kessels AG, et al. The additional diagnostic value of ultrasonography in the diagnosis of breast cancer. Arch Intern Med. 2003;163(10):1194-9.
47. Bluemke DA, Gatsonis CA, Chen MH, et al. Magnetic resonance imaging of the breast prior to biopsy. JAMA. 2004;292(22):2735-42.

48. Esserman L, Hylton N, Yassa L, et al. Utility of magnetic resonance imaging in the management of breast cancer: evidence for improved preoperative staging. J Clin Oncol. 1999;17(1):110-9.
49. Esserman L, Hylton N, George T and Weidner N. Contrast-Enhanced Magnetic Resonance Imaging to Assess Tumor Histopathology and Angiogenesis in Breast Carcinoma. Breast J. 1999;5(1):13-21.
50. Peters NH, Borel Rinkes IH, Zuithoff NP, et al. Meta-analysis of MR imaging in the diagnosis of breast lesions. Radiology. 2008;246(1):116-24.
51. Agency for Healthcare Research and Quality. Effectiveness of Noninvasive Diagnostic Tests for Breast Abnormalities. AHRQ, Rockville, 2006.
52. Bagni B, Franceschetto A, Casolo A, et al. Scintimammography with 99mTc-MIBI and magnetic resonance imaging in the evaluation of breast cancer. Eur J Nucl Med Mol Imaging. 2003;30(10):1383-8.
53. Howarth D, Slater S, Lau P, et al. Complementary role of adjunctive breast magnetic resonance imaging and scintimammography in patients of all ages undergoing breast cancer surgery. Australas Radiol. 2005;49(4):289-97.
54. Bekis R, Derebek E, Balci P, et al. 99mTc sestamibi scintimammography. Screening mammographic non-palpable suspicious breast lesions: preliminary results. Nuklearmedizin. 2004;43(1):16-20.
55. Chen J, Wu H, Zhou J and Hu J. Using Tc-99m MIBI scintimammography to differentiate nodular lesions in breast and detect axillary lymph node metastases from breast cancer. Chin Med J (Engl). 2003;116(4):620-4.
56. Fondrinier E, Muratet JP, Anglade E, et al. Clinical experience with 99mTc-MIBI scintimammography in patients with breast microcalcifications. Breast. 2004;13(4):316-20.
57. Krishnaiah G, Sher-Ahmed A, Ugwu-Dike M, et al. Technetium-99m sestamibi scintimammography complements mammography in the detection of breast cancer. Breast J. 2003;9(4):288-94.
58. Sampalis FS, Denis R, Picard D, et al. International prospective evaluation of scintimammography with (99m)technetium sestamibi. Am J Surg. 2003;185(6):544-9.
59. Tiling R, Kessler M, Untch M, et al. Initial evaluation of breast cancer using Tc-99m sestamibi scintimammography. Eur J Radiol. 2005;53(2):206-12.
60. Medical Advisory Secretariat of Ontario Ministry of Health and Long-Term Care. Scintimammography as an Adjunctive Breast Imaging Technology - Integrated Health Technology Literature Review. Toronto 2007.
61. Facey K, Bradbury I, Laking G and Payne E. Overview of the clinical effectiveness of positron emission tomography imaging in selected cancers. Health Technol Assess. 2007;11(44):iii-iv, xi-267.
62. Barlow WE, Lehman CD, Zheng Y, et al. Performance of diagnostic mammography for women with signs or symptoms of breast cancer. J Natl Cancer Inst. 2002;94(15):1151-9.
63. Kerlikowske K, Smith-Bindman R, Ljung BM and Grady D. Evaluation of abnormal mammography results and palpable breast abnormalities. Ann Intern Med. 2003;139(4):274-84.
64. Hrung JM, Sonnad SS, Schwartz JS and Langlotz CP. Accuracy of MR imaging in the work-up of suspicious breast lesions: a diagnostic meta-analysis. Acad Radiol. 1999;6(7):387-97.
65. Nunes LW, Schnall MD and Orel SG. Update of breast MR imaging architectural interpretation model. Radiology. 2001;219(2):484-94.
66. Gibbs P, Liney GP, Lowry M, et al. Differentiation of benign and malignant sub-1 cm breast lesions using dynamic contrast enhanced MRI. Breast. 2004;13(2):115-21.
67. Liberman L, Morris EA, Lee MJ, et al. Breast lesions detected on MR imaging: features and positive predictive value. AJR Am J Roentgenol. 2002;179(1):171-8.
68. Bender O, Balci FL, Yuney E and Akbulut H. Scarless endoscopic papillomectomy of the breast. Onkologie. 2009;32(3):94-8.

69. Denewer A, El-Etribi K, Nada N and El-Metwally M. The role and limitations of mammary ductoscope in management of pathologic nipple discharge. Breast J. 2008;14(5):442-9.
70. Deshmane V. Intraductal approach to breast cancer: the role of mammary ductoscopy. Indian J Surg Oncol. 2010;1(3):228-31.
71. Dietz JR, Crowe JP, Grundfest S, et al. Directed duct excision by using mammary ductoscopy in patients with pathologic nipple discharge. Surgery. 2002;132(4):582-7; discussion 587-8.
72. Fackler MJ, Rivers A, Teo WW, et al. Hypermethylated genes as biomarkers of cancer in women with pathologic nipple discharge. Clin Cancer Res. 2009;15(11):3802-11.
73. Fisher CS and Margenthaler JA. A look into the ductoscope: its role in pathologic nipple discharge. Ann Surg Oncol. 2011;18(11):3187-91.
74. Kamali S, Harman Kamali G, Akan A, et al. Use of ductoscopy as an additional diagnostic method and its applications in nipple discharge. Minerva Chir. 2014;69(2):65-73.
75. Khan SA, Mangat A, Rivers A, et al. Office ductoscopy for surgical selection in women with pathologic nipple discharge. Ann Surg Oncol. 2011;18(13):3785-90.
76. Liu GY, Lu JS, Shen KW, et al. Fiberoptic ductoscopy combined with cytology testing in the patients of spontaneous nipple discharge. Breast Cancer Res Treat. 2008;108(2):271-7.
77. Moncrief RM, Nayar R, Diaz LK, et al. A comparison of ductoscopy-guided and conventional surgical excision in women with spontaneous nipple discharge. Ann Surg. 2005;241(4):575-81.
78. Simpson JS, Connolly EM, Leong WL, et al. Mammary ductoscopy in the evaluation and treatment of pathologic nipple discharge: a Canadian experience. Can J Surg. 2009;52(6):E245-8.
79. Waaijer L, van Diest PJ, Verkooijen HM, et al. Interventional ductoscopy in patients with pathological nipple discharge. Br J Surg. 2015;102(13):1639-48.
80. McCavert M, O'Donnell ME, Aroori S, et al. Ultrasound is a useful adjunct to mammography in the assessment of breast tumours in all patients. Int J Clin Pract. 2009;63(11):1589-94.
81. Osako T, Iwase T, Takahashi K, et al. Diagnostic mammography and ultrasonography for palpable and nonpalpable breast cancer in women aged 30 to 39 years. Breast Cancer. 2007;14(3):255-9.
82. Garg S, Mohan H, Bal A, et al. A comparative analysis of core needle biopsy and fine-needle aspiration cytology in the evaluation of palpable and mammographically detected suspicious breast lesions. Diagn Cytopathol. 2007;35(11):681-9.
83. Homesh NA, Issa MA and El-Sofiani HA. The diagnostic accuracy of fine needle aspiration cytology versus core needle biopsy for palpable breast lump(s). Saudi Med J. 2005;26(1):42-6.
84. Pisano ED, Fajardo LL, Caudry DJ, et al. Fine-needle aspiration biopsy of nonpalpable breast lesions in a multicenter clinical trial: results from the radiologic diagnostic oncology group V. Radiology. 2001;219(3):785-92.
85. American College of Radiology. ACR Appropriateness Criteria: palpable breast masses. http://www.acr.org/SecondaryMainMenuCategories/quality_safety/app_criteria/pdf/ExpertPanelonWomensImagingBreastWorkGroup/PalpableBreastMassesDoc3.aspx. . Accessed: Oct 25.
86. Pearlman MD and Griffin JL. Benign breast disease. Obstet Gynecol. 2010;116(3):747-58.
87. Yeow KM, Lo YF, Wang CS, et al. Ultrasound-guided core needle biopsy as an initial diagnostic test for palpable breast masses. J Vasc Interv Radiol. 2001;12(11):1313-7.
88. Steinberg JL, Trudeau ME, Ryder DE, et al. Combined fine-needle aspiration, physical examination and mammography in the diagnosis of palpable breast masses: their relation to outcome for women with primary breast cancer. Can J Surg. 1996;39(4):302-11.