The Royal College of Pathologists
Pathology: the science behind the cure

Guidelines for non-operative diagnostic procedures and reporting in breast cancer screening

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Abbreviations

AIDEP	atypical intraductal epithelial proliferation
ADH	atypical ductal hyperplasia
ALH	atypical lobular hyperplasia
DCIS	ductal carcinoma *in situ*
FNAC	fine needle aspiration cytology
LCIS	lobular carcinoma *in situ*
MRI	magnetic resonance imaging
NBSS	National Breast Screening System
NCB	needle core biopsy
NHSBSP	National Health Service Breast Screening Programme
UEH	usual epithelial hyperplasia
VAB	vacuum-assisted biopsy

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NICE has accredited the process used by The Royal College of Pathologists to produce its Cancer Datasets and Tissue Pathways guidance. Accreditation is valid for 5 years from July 2012. More information on accreditation can be viewed at www.nice.org.uk/accreditation.

For full details on our accreditation visit: www.nice.org.uk/accreditation.

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Foreword

The cancer datasets published by The Royal College of Pathologists (RCPath) are a combination of textual guidance, educational information and reporting proformas. The datasets enable pathologists to grade and stage cancers in an accurate, consistent manner in compliance with international standards and provide prognostic information thereby allowing clinicians to provide a high standard of care for patients and appropriate management for specific clinical circumstances. It may rarely be necessary or even desirable to depart from the guidelines in the interests of specific patients and special circumstances. The clinical risk of departing from the guidelines should be assessed by the relevant multidisciplinary team (MDT); just as adherence to the guidelines may not constitute defence against a claim of negligence, so a decision to deviate from them should not necessarily be deemed negligent.

Each dataset contains core data items that are mandated for inclusion in the Cancer Outcomes and Services Dataset (COSD – previously the National Cancer Data Set) in England. Core data items are items that are supported by robust published evidence and are required for cancer staging, optimal patient management and prognosis. Core data items meet the requirements of professional standards (as defined by the Information Standards Board for Health and Social Care [ISB]) and it is recommended that at least 90% of reports on cancer resections should record a full set of core data items. Other, non-core, data items are described. These may be included to provide a comprehensive report or to meet local clinical or research requirements. All data items should be clearly defined to allow the unambiguous recording of data.

The following stakeholder organisations have been consulted during the preparation of the dataset:

- National Coordinating Committee for Quality Assurance Radiologists
- National Coordinating Committee for Breast Screening Surgeons
- Royal College of Radiologists Breast Group
- Association of Breast Surgery.

Evidence for the revised dataset was obtained from updates to international tumour grading, staging and classification systems and by electronically searching medical literature databases for relevant research evidence, systematic reviews and national or international breast cancers. The level of evidence for the recommendations has been summarised (Appendix N). Unless otherwise stated, the level of evidence corresponds to ‘Good practice point (GPP): Recommended best practice based on the clinical experience of the authors of the writing group’.

No major organisational changes or cost implications have been identified that would hinder the implementation of the dataset for the core items.

A formal revision cycle for all cancer datasets takes place on a three-yearly basis. However, each year, the College will ask the authors of the dataset, in conjunction with the relevant sub-specialty advisor to the College, to consider whether or not the dataset needs to be updated or revised. A full consultation process will be undertaken if major revisions are required, i.e. revisions to core data items (the only exception being changes to international tumour grading and staging schemes that have been approved by the Specialty Advisory Committee on Cellular Pathology and affiliated professional bodies; these changes will be implemented without further consultation). If minor revisions or changes to non-core data items are required, an abridged consultation process will be undertaken whereby a short note of the proposed changes will be placed on the College website for two weeks for Fellows’ attention. If Fellows do not object to the changes, the short notice of change will be incorporated into the dataset and the full revised version (incorporating the changes) will replace the existing version on the College website.

The dataset has been reviewed by the Working Group on Cancer Services and is placed on the College website for consultation with the membership from 5 April to 3 May 2016. All comments received from the Working Group and the membership were addressed by the authors to the satisfaction of the Chair of the Working Group and the Director of Publishing and Engagement.

This dataset was developed without external funding to the writing group. The College requires the authors of datasets to provide a list of potential conflicts of interest; these are monitored by the Director of Clinical Effectiveness and are available on request. The authors of this document have declared that there are no conflicts of interest.

Introduction

The aim of assessment is to obtain a definitive and timely diagnosis of all potential abnormalities detected during screening.[1] This is best achieved by using 'triple assessment', comprising imaging (usually mammography and ultrasound), plus clinical examination, plus image-guided needle biopsy for histological examination if indicated. Definitive non-operative diagnosis of malignancy allows rapid referral for treatment, ideally in one operative procedure. Definitive non-operative diagnosis of benign conditions is equally useful, usually leading to discharge from the clinic and return to routine recall. In the early days of breast screening, fine needle aspiration cytology (FNAC) was the procedure of choice, but it is now recommended that needle core biopsy or vacuum-assisted biopsy is used for assessment of significant screening detected abnormalities.[1] This is because current evidence suggests that core biopsy has greater sensitivity and specificity in evaluating microcalcification, asymmetry and architectural distortion than does FNAC. It also aids definitive benign diagnosis. Invasive carcinoma can be distinguished from ductal carcinoma *in situ* on core biopsy (but not with FNAC). Oestrogen receptor and HER2 status can be assessed on the core biopsies because invasive carcinoma can be recognised. Histological grade can be more accurately assessed on core. FNAC may be used in addition to core biopsy if an urgent diagnosis is required or if core biopsy is not possible.[1] FNAC should not be used alone in the assessment of lesions in the breast detected by screening mammography unless core biopsy is contraindicated.

The purpose of these guidelines is to provide pathologists with an update on the role of non-operative diagnosis in breast screening assessment. A similar approach is recommended for symptomatic lesions. The document concentrates on needle core biopsy and vacuum-assisted biopsy. It also describes the mechanisms used to assure the quality of non-operative diagnosis in breast screening.

This document constitutes the third edition of guidelines for non-operative diagnosis in breast cancer screening. It updates and replaces the previous guidelines published as NHSBSP Publication No 50.[2]

1 Use of non-operative diagnostic techniques

Detailed guidance on assessment procedures is provided in the NHSBSP guidelines, *Clinical Guidelines for Breast Cancer Screening Assessment (3rd edition).*[1] All cases should be thoroughly assessed prior to needle biopsy. All needle sampling procedures carried out on screen-detected abnormalities must be discussed at a multidisciplinary meeting, where findings from all modalities are discussed and further management is decided. These guidelines also detail the methods of choice for sampling the different types of mammographic abnormality.

This approach must be adhered to in the National Breast Screening Programme as it is recognised that very rare false-positive interpretation of needle biopsy specimens can occur. All cases should be subject to multidisciplinary review to ensure concordance before proceeding to definitive treatment.

Both needle core and vacuum-assisted biopsy procedures may result in removal or destruction of the mammographically detected lesion. The lesion may therefore not be

identified in a subsequent operative specimen. In situations where such a discrepancy highlights a 'potential false-positive result', the biopsy should be reviewed according to the protocols described in *Good Practice Guide No 9: Reporting, recording and auditing B5 core biopsies with normal/benign surgery*.[3] A decision must be reached as to whether the histological findings of the core biopsy have been appropriately interpreted, whether the appropriate area of lesion has been removed in the surgical specimen or whether there is possibility that the lesion remains in the breast. The findings of such reviews should be available for discussion as part of the quality assurance process.

Core biopsy results should not be interpreted in isolation. The multidisciplinary meeting should make a judgement about whether the biopsy is concordant with radiological and clinical findings and whether the biopsy is representative of the lesion. If there is discordance, further management must be discussed. Inevitably false-negative results are significantly higher for impalpable lesions. When the imaging findings are considered to be suspicious of malignancy and the biopsy is normal or benign, management should be reviewed at a multidisciplinary meeting and a decision made whether to repeat the sampling procedure or to refer for open biopsy or localisation biopsy.

In cases where there is disagreement between modalities with a failure to achieve consensus after multidisciplinary discussion, repeat core biopsy, vacuum-assisted biopsy or surgical biopsy is the appropriate course of action. No more than two needle biopsy procedures, carried out on separate occasions, should normally be needed to achieve a non-operative diagnosis of a screen-detected abnormality. Frozen section for the diagnosis of screen-detected lesions is inappropriate, except when core biopsy is contraindicated.

Evidence from recently published series of multiple needle core biopsy (NCB) sampling has shown that for certain types of mammographic abnormality, particularly moderate- to low-level suspicion microcalcification, a larger volume of tissue is required for accurate diagnosis.[4] For such lesions, where the use of conventional 14G-core biopsy carries a high risk of an equivocal result, use of larger volume sampling techniques may increase the accuracy of biopsy. Recently published results of vacuum-assisted biopsy have demonstrated a lower equivocal sample rate and increased accuracy in the detection of small invasive tumours associated with an area of ductal carcinoma *in situ* (DCIS).[5-7] Consideration of the likely underlying histological nature of the lesion from the imaging features should therefore be taken into account when deciding on the sampling method to be used. Vacuum-assisted biopsy may also be useful after a B1, B3 or B4 diagnosis on 14G core biopsy and can be used for diagnostic excision of papillary lesions or radial scars without atypia, diagnosed on core biopsy.[8]

1.1 Image guidance for breast biopsy

Automated needle core biopsy (NCB) is now considered to be the minimum standard for breast biopsy with fine needle aspiration reserved for sampling axillary lymph nodes.[9] Core biopsy provides more reliable results and more information on which to base the diagnosis and subsequent management options. FNAC is still used for some small breast lesions, patients with implants or lesions difficult to access with a larger core device. Increasingly, vacuum-assisted biopsy (VAB) is used in circumstances where core biopsy may not be reliable.

1.1.1 When to use ultrasound guidance

Most soft tissue lesions in the breast are visible using modern high-frequency ultrasound apparatus. Ultrasound is therefore the imaging method of choice for sampling non-palpable soft tissue lesions and allows real-time demonstration of the needle traversing the lesion.

Ultrasound is also increasingly being used to guide needle biopsy of palpable masses to ensure accurate sampling. Some clusters of microcalcification, particularly coarser comedo-type calcification, are visible on high-frequency ultrasound and may therefore be sampled by

ultrasound guidance. If ultrasound guidance is used for sampling of areas of microcalcification, the specimens should be x-rayed to confirm sampling of the microcalcification. A marker should be placed at the biopsy site if it is thought that small clusters of calcification may have been completely removed, and in small lesions to confirm concordance. This will also assist future localisation for re-biopsy or surgery, should this be necessary.

1.1.2 When to use stereotactic guidance

X-ray stereotaxis is used for image-guided biopsy of most indeterminate and suspicious microcalcifications, areas of parenchymal distortion/stellate lesions and small soft tissue masses which cannot be adequately visualised by ultrasound. Stereotactic biopsy can be carried out with the patient in the upright, lateral decubitus or prone positions. Upright stereotactic units are more widely available and less expensive than dedicated prone stereotactic units. Digital imaging is now universal for x-ray guided breast biopsy equipment and this technology provides rapid acquisition of stereotactic images, manipulation of the digital images including magnification, image reversal and contrast adjustment for improved visualisation of the target abnormalities. This improves the accuracy of the technique because of the shorter image acquisition time and improved quality of the digital images.

The main problems encountered with use of the upright stereotactic units are vaso-vagal episodes and difficulty in accurately targeting lesions that are very posteriorly situated, but both can be minimised by carrying out the biopsy with the patient in the lateral decubitus position or the use of lateral arm needle guide attachments.

Tomosynthesis biopsy systems are also now available and can be used on upright systems for lesions only visible on tomosynthesis mammograms, but also has advantages for all mammographically visible lesions. Tomosynthesis is a digital-based mammography technique that involves acquisition of images from a limited angle rotation of the x-ray source around the breast that enables viewing of the breast in the conventional images planes in multiple sections, similar to CT. This allows for separation of overlapping structure that make up the conventional two-dimensional mammography image. This improves detection of abnormalities, at the same time as decreasing false-positive findings.

Dedicated prone breast biopsy systems use a table on which the patient lies in the prone oblique position and the breast passes through a rounded aperture in the table. The advantages of the prone system are the negligible risk of a vaso-vagal episode and a stable position with minimal patient movement. The disadvantages of the dedicated prone breast biopsy systems are the high capital cost of the equipment and the need for a dedicated room, which cannot be otherwise used for diagnostic mammography and the weight limit for hyperbaric patients.

A small number of women are being offered magnetic resonance imaging (MRI) as part of their high family history screening plan. MRI does detect a small number of significant abnormalities that are not seen on either mammography or ultrasound and require MRI guided biopsy. The technology for MRI guided breast biopsy is well established and the skills required are more widely available. NHSBSP protocol requires that all MRI guided breast biopsy is performed using vacuum-assisted techniques.

1.2 Sampling techniques and procedures

- Fine needle aspiration cytology (FNAC)
- Core biopsy (NCB).

Wide bore techniques:

- Vacuum-assisted biopsy (VAB)
- Large core radiofrequency assisted biopsy.

All of these procedures can be carried out by members of the breast team who have had specialist training in image-guided breast biopsy. Ultrasound guided NCB is the technique of first choice for sampling impalpable breast lesions as it is easier to perform, more comfortable for the patient and less time-consuming than the x-ray guided techniques (see above). For impalpable lesions detected by mammography, the radiologist must be certain that the abnormality seen on ultrasound is the same as the abnormality seen on mammography. Ultrasound can only be used when the radiologist is convinced that the abnormality is clearly visible using this technique. X-ray guided NCB or VAB should be used where there is any doubt about whether the ultrasound appearances correspond to the mammographic abnormality.

1.3 Core biopsy – general principles

Core biopsy of the breast is a safe and effective method for obtaining a non-operative diagnosis of breast lesions. Core biopsy should be performed with caution in patients who are anticoagulated, or on aspirin or clopidogrel. The use of these medications are not absolute contraindications and local policies should be available.[10,11] The consent process should follow local rules and the procedure and common complications should be explained to the patient. Formal written consent is not normally required. An assistant is required to compress the breast between needle passes.

Breast core biopsy should be performed with a spring-loaded device, usually 14G diameter. Local anaesthetic should be used to the skin and down to the lesion. A small (2 mm) skin nick that traverses the superficial fascia should be made with a scalpel blade (a No. 11 blade is ideal) to facilitate the passage of the needle into the breast. The skin entry site should be optimised for both cosmesis and accurate targeting. The skin nick can be visible for some months after the biopsy and approaches through the cleavage line and upper inner quadrant should be avoided; lateral, inferior and periareoalar approaches are preferable. If the breast tissue is very fibrous, insertion of the needle in a radial direction makes manipulation easier. The only major complication of breast needle biopsy is pneumothorax. To avoid this, the needle should be kept as near as possible parallel to the chest wall when fired. This means the skin entry site for deep lesions needs to be further away from the lesion than for superficial lesions. For lesions 10 mm or larger, the tip of the needle should abut the lesion before firing. When biopsying lesions less than 10 mm in diameter, the needle tip should be sufficiently short of the lesion before firing to ensure that the lesion is included in the sampling trough. It is the operator's responsibility to confirm the patient's identification and label the specimen pot before leaving the room.

After the procedure, the biopsy site should be compressed for a minimum of 5 minutes. The patient should be given written information concerning where and when they will receive the result and complications of the procedure. The patient should be advised that mild post-procedure pain, lumpiness and bruising is common and not to exercise their upper limbs for the rest of the day. Wound infection is a rare complication, but the patient should be advised to seek medical advice and for a prescription of antibiotics if the site of the biopsy becomes increasingly red or the puncture site oozes purulent material.
The patient information sheet should advise the patient to telephone the hospital (the number should be on the patient information sheet) if the breast swells appreciably or if they become short of breath.

1.4 Ultrasound guided core biopsy

The patient is positioned to provide optimal access to the area to be biopsied. This may involve, for example, raising and supporting the left side for biopsy of lesions situated in the lateral aspect of the left breast. For lesions that are situated in the lateral aspect of the right breast, it may be necessary to turn the patient on the couch so that a right-handed operator can easily access such lesions using a lateral approach. An assistant should work from the opposite side of the couch.

The lesion is demonstrated and surrounding breast tissue immobilised. Local anaesthetic is infiltrated both superficially and deeply down to and around the lesion. For posteriorly placed lesions, local anaesthetic can be infiltrated posteriorly in order to displace the lesion anteriorly. A 2–3 mm skin incision, parallel to Langer's lines, is made to allow insertion of the core biopsy needle along the direction of the long axis of the ultrasound probe. The core biopsy needle is advanced until the tip is a few millimetres proximal to the edge of the lesion. The core biopsy gun is then fired and the needle is visualised passing through the lesion. The magnification of the field of view of the ultrasound image should be set so that the tip of the needle will still be visible after taking the sample. An image showing the needle passing through the lesion is usually recorded. The needle is withdrawn and the specimen is delivered into fixative. Two or three passes are usually sufficient in most cases to obtain diagnostic material from soft tissue mass lesions. At the end of the procedure, firm pressure is applied by the assistant over the site of the biopsy to reduce bruising.

1.5 Stereotactic guided core biopsy

For needle biopsy using a stereotactic device with a conventional upright mammography machine the patient is seated. Increasingly vacuum-assisted biopsy is preferred for stereotactic breast biopsy. A superior or lateral approach with the breast in the cranio-caudal position is suitable for most lesions but latero-medial, medio-lateral or oblique approaches may be needed for lesions that are inferiorly positioned or are situated laterally in the axillary tail region. After demonstrating the lesion on a straight scout film, paired stereotactic views are obtained with the x-ray tube angled 15 degrees either side of the central straight tube position. The position of the lesion on the stereotactic views is used to determine the position of the needle guide in the X and Y axes, so that when a needle of known length is introduced through the guide into the breast the centre of the needle sampling trough will correspond to the chosen target. Digital equipment will not allow firing of the device if the lesion is too close to the detector and may damage its surface. Apparatus that facilitates a lateral approach to lesions is preferred when the breast compression thickness is small. The lateral arm approach also avoids the needle being held directly in the eye line of the patient and improved access to lesions, which are in the inferior part of the breast, and eliminates the risk of the needle tip hitting the surface of the x-ray cassette holder. An alternative approach in small breasts is to use a radiolucent spacer below the breast, to increase the distance between the lesion and the surface of the detector.

X-ray guided biopsy using tomosynthesis is also now available. The technique is largely similar to stereotactic biopsy other than that the image to select the target is acquired by continuous x-ray source arc rotation rather than from two images taken at 15 degree angles. When available, it is a quicker localisation technique and also facilitates biopsy of lesions only seen on tomosynthesis images.

1.6 Prone stereotactic core biopsy

The patient lies prone with the breast to be biopsied passed through a rounded aperture in the table. For lesions that are very posteriorly positioned or that lie in the region of the axillary tail, access can be improved by passing the ipsilateral arm and shoulder girdle through the aperture. Stereotactic views are obtained by rotating the tube 15 degrees either side of the

central position. Check films are taken during the procedure to ensure accurate positioning and that the needle has traversed the lesion.

When sampling areas of microcalcification with either conventional upright stereotactic equipment or with prone stereotactic systems, radiography of the core samples is carried out to ensure that tissue containing microcalcification has been obtained.

1.7 Large volume sampling techniques

1.7.1 Vacuum-assisted biopsy (VAB)

There are several systems available for vacuum-assisted biopsy, but all operate under similar principles. Vacuum biopsy is now recommended and preferred for sampling many types of abnormality that require stereotactic x-ray guided biopsy and is mandatory for MRI guided breast biopsy.

The biopsy probe incorporates a vacuum channel, which applies negative pressure to the biopsy port and thereby sucks the adjacent breast tissue into the port for sampling. The biopsy probe is introduced into the breast and positioned using image guidance – deep local anaesthetic, usually containing adrenaline, is used. The vacuum is activated and sucks breast tissue into the biopsy port; a rotating or oscillating cutting cylinder then passes down within the probe and separates the biopsy material from the surrounding tissue. The biopsy specimen is then delivered by withdrawing the cutting cylinder while applying negative pressure. Unlike NCB, the needle probe remains within the breast during the whole procedure. Multiple specimens can be obtained and the probe can be rotated in the breast so that the biopsy port is applied to different areas of the surrounding breast tissue.

The advantages of this system are the ability to obtain a larger volume of tissue for histological examination and the rapid evacuation of any haematoma that collects at the site of biopsy. This ensures that the specimens obtained are of good quality and are not compromised by the presence of haematoma. The larger gauge vacuum probes can retrieve 400 mg of breast tissue per core sample. Guidance is that diagnostic samples of potentially borderline lesions (e.g. microcalcification and architectural distortion) should aim to retrieve around 2 grams of tissue (five cores using a 7 gauge vacuum probe or 12 cores using a 0 gauge probe).

It is recommended that a marker should be placed at the biopsy site for all vacuum procedures. Markers that contain a metal component and can also be seen on ultrasound are preferred as these facilitate easier subsequent localisation for surgery if needed and, if not, provide future reference as to where prior biopsy has been performed. A marker is mandatory if there is any risk that the whole of the target lesion might be removed by the needle biopsy. The pathology department should be made aware of any subsequent biopsy that may contain a marker as this may influence how the tissue is prepared for sectioning.

1.7.2 Large core biopsy systems (Intact)

This device involves the insertion of a large bore probe with a radiofrequency cutting basket that can retrieve single core samples up to 25 mm in diameter. This technique is more invasive than standard core biopsy or vacuum-assisted core biopsy and requires a 10 mm skin incision for insertion of the biopsy device. The radiofrequency cutting diathermy technique means that this device has significant limitation in its use, but it does provide the advantages of a single intact large core of tissue and can potentially be used to completely excise small borderline breast lesions.[12,13]

1.8 Complications of needle biopsy

NCB and FNAC are remarkably complication-free, however some uncommon problems should be considered.

1.8.1 Pain

Pain is common on fine needle aspiration but is transitory and is not usually severe. Aspiration from painful areas of benign breast change is sometimes associated with some pain when the needle comes into contact with the painful area. Carcinomas, particularly those with abundant fibroelastotic stroma, are often also painful and this can be a guide to the aspirator that the needle has hit the lesion. If pain is anticipated for FNA, local anaesthesia to the skin and close to the sample site is recommended. FNA is now largely confined to sampling axillary lymph nodes and many prefer to routinely use local anaesthesia for this procedure. Local anaesthesia should be used for all core biopsies in the breast and axilla with sufficient anaesthetic delivered superficially at the skin entry site and around the biopsy target.

1.8.2 Haematoma

Where possible, all imaging investigations should be complete before sampling is performed as haematoma formation, if it occurs, can cause confusion on subsequent imaging. The risk of significant haematoma after FNA and NCB are about the same at 1% and this rises to approximately 4% for vacuum biopsy procedures. Haematoma is minimised by appropriate manual pressure applied over the biopsy site for 5–10 minutes. For VAB, especially when used for complete lesion excision, a compression dressing applied for 4–6 hours should be considered. Patients should be advised not to take vigorous exercise following a breast biopsy to minimise the risk of delayed haematoma.

1.8.3 Pneumothorax

This is a rare complication occurring in less than 1:10,000 breast biopsies and occurring mainly in women with small breasts, after biopsy of medial and posterior lesions, or when sampling axillary nodes. It occurs most commonly after freehand non-image-guided breast biopsy and is a very rare problem with image-guided biopsy. Large pneumothoraces should be obvious but the problem may go undetected if the pneumothorax is small. If there is any clinical concern that a pneumothorax may have occurred, the patient should be sent for a chest x-ray before being allowed home.

1.8.4 Fainting

This complication has occasionally occurred during sampling. It is of special significance during upright stereotactic procedures where the patient has to be released from the machine and laid flat. The procedure usually has to be abandoned. For women with a history of syncope, the use of sublingual lorazepam has been shown to minimise the risk.

1.8.5 Removal of lesion by core biopsy

Small lesions including foci of microcalcification may, particularly if extensively sampled, be removed by core biopsy. This risk increases when greater number of core samples are taken or with vacuum-assisted biopsy. It is recommended that markers are inserted at the site of biopsy at the time of the biopsy to ensure that the site can be identified subsequently.

On occasions, however, a sole small invasive focus in a predominant DCIS lesion may be removed in the needle biopsy samples with no further invasion in the subsequent excision specimen. In such circumstances, the core biopsy sample should be used to provide information on tumour differentiation and type.

1.8.6 Seeding of tumour

Seeding of malignant cells has become increasingly recognised as a result of the increased use of core biopsy. Rarely this may cause histopathological diagnostic difficulties in the subsequent excision. Islands of cells (sometimes showing degenerative features) are seen out with the main lesion, often within a fibroblastic and histiocyte tissue response indicating the previous sampling site. Seeding is rarely recognised more than a few millimetres from the source of the cells and the correct identification is usually straightforward. Cell groups

may be seeded from *'in situ'* papillary lesions or DCIS mimicking invasive carcinoma. The associated signs of trauma from non-operative sampling should be sought. The clinical significance of this phenomenon is not yet clear.

2 Core biopsy reporting guidelines

This section of this document is designed to assist in classification of needle core biopsy and vacuum-assisted biopsy samples. The diagnostic terminology and entities referred to are described in more detail in the *Pathology Reporting Guidelines*.[14]

2.1 Core biopsy specimen information and handling

- Proper interpretation of core biopsies requires details of history and clinical and radiological findings and this information should be provided on the request form. The completed request form should include clinical details, specifying the radiographic changes and the site of biopsies. It is not sufficient to complete the request form with R or U codes. Reliable pathological interpretation requires that radiological details such as mass lesion, deformity, calcification, etc. are recorded, as well as the radiologist's impression such as R3, R4 or R5.
- A radiograph should be taken of all biopsies performed from microcalcifications to determine the presence of calcium. Whenever possible, a radiological comment regarding the presence of representative microcalcification of the mammographic lesion in the sample should be provided to the pathologist along with the specimen x-ray. In units using digital mammography, the pathologist must be able to view the core biopsy x-rays on a monitor of suitable quality.[15] Examination of further levels should be performed if calcification in a pattern consistent with that seen on the specimen x-ray is not apparent on histological examination of initial levels. The multidisciplinary meeting should decide whether the calcification in the mammogram correlates with the calcification seen histologically.
- Optimal fixation is paramount. Biopsies should be placed immediately in a formalin fixative solution and sent promptly to the laboratory. Optimal fixation is essential for oestrogen receptor and HER-2 analysis for which a minimum of 6 hours and a maximum of 72 hours are recommended.[14] This has implications for scheduling of laboratory work. Specimens may be fixed rapidly with the aid of microwave techniques, but such techniques must be validated including assessment of immunohistochemistry.
- There are different approaches to the macroscopic description of core biopsies and vacuum-assisted biopsies. Some laboratories record the number of cores and the length of each. This has the advantage that the number of cores taken in the clinic can be confirmed and also that the number and length of cores can be checked in the histological slide. Some radiology departments weigh their VABs to ensure an adequate amount of tissue has been obtained. An alternative approach is to put the cores into containers in the clinic, so that in the laboratory the cores can be placed directly into the cassette without further handling. This reduces the risk of loss of tissue, but macroscopic description is not provided.
- After processing, it is important to ensure that the biopsy is properly embedded and that the block is adequately cut into when the sections are taken. Haematoxylin and eosin stained sections from one level are usually sufficient for core biopsies from mass lesions, but core biopsies taken for the investigation of microcalcification should have a minimum of three levels examined. In problematic cases, further levels and immunohistochemical studies may be helpful.
- Information from all core biopsies of screening-detected lesions should be entered on to National Breast Screening System (NBSS), either directly by the pathologist or using the form below.

[Level of evidence GPP.]

2.2 Recording of data on the National Breast Screening System

NBSS provides an interface for recording of pathology data related to breast screening patients. Pathologists can learn to use the system effectively for recording of non-operative and operative pathology data with a short period of training. It is recognised that most pathologists prefer to complete handwritten forms for submission to the screening office with data being input by non-medical staff or write reports in such a way that the data can be easily extracted. This is a reasonable option and provides accurate data for most patients, but for patients with complex or multiple abnormalities, steps should be taken to ensure that data is recorded accurately for the correct lesions. A copy of the form is in Appendix D.

2.2.1 Lesion identification

This should be done by the radiologist at the time of assessment. For patients with more than one abnormality, for convenience, the most suspicious or main lesion should be recorded as lesion 1 and other lesions should be recorded separately. Where lymph node assessment and needle biopsy is carried out, this should be recorded as a separate lesion. Using this information, pathologists should record information for all lesions that have been sampled using the forms provided or directly onto the system.

2.2.2 Cytology form

This is a short form and completion is straightforward. The method of localisation should be indicated – options available are palpation, stereotactic, prone stereo, x-ray, ultrasound or MRI. There is an option of 'not stated' but it should not be necessary to use this. The specimen type should also be recorded. It is important to select 'Node aspirate' if the sample is from an axillary node. The cytology opinion should be recorded using the categories C1–C5 and the pathologist has the opportunity to add comments if they are necessary.

2.2.3 Core needle biopsy form

The core needle biopsy form has scope for recording of more data in relation to the lesion and pathologists are encouraged to record as much data as possible. This will help with future analysis and audit.

The general layout of the form is similar to the cytology form. The first part of the form – including method of localisation, intention with regard to diagnostic or therapeutic with regard to VAB, whether the sample was from a node and the presence or absence of calcification on specimen x-ray – should have been completed at the time of assessment. If the pathologist has access to NBSS, it is helpful to check this information for accuracy.

The section headed 'Pathology result' should be completed by the pathologist, including specimen number, name of reporting pathologist and the B category. In the rare instance when it is not possible to distinguish between invasive and *in situ* disease, it should be recorded as 'Not assessable' rather than 'Not stated'.

These initial fields are mandatory for all biopsies; remaining fields are optional but should be completed if at all possible. There are options for recording more information with regard to benign and malignant lesions as well as grading and hormone receptor and HER-2 status if performed on the core biopsy.

Regardless of whether the intention of VABs is diagnostic or therapeutic, it is currently still necessary to complete the form with a B category. If a lesions such as a radial scar/complex sclerosing lesion or papilloma has been fully assessed using an excisional VAB and there is no epithelial atypia, it is reasonable to record this as B2 rather than B3 as would usually be the case with a diagnostic biopsy. It is planned that in future it will not be necessary to insert a B category on the NBSS for a vacuum-assisted excision.

Regardless of how data are entered on to NBSS, pathologists should be involved in quality assurance of the information entered on to the system on a regular basis.

2.3 Using the core biopsy reporting form

The core biopsy reporting forms used may be the separate reporting form (Figure 2a) or the form generated specifically by the National Breast Screening System (Figure 2b), which comes with the patient details already filled in by the computer. These both request essentially the same information, although the computer-generated form has spaces for radiographic information such as kV, mAs, side and type of localisation (palpable, ultrasound, stereotactic or other x-ray guided procedure) in the upper portion. How the national screening system treats this information has been included as Appendix 2. Information on the nature of the mammographic abnormality and clinical characteristics should be provided by the breast screening radiologist requesting the pathology examination.

2.4 RCPath dataset forms

The RCPath dataset forms include a subset of data items included in the NHSBSP form. RCPath dataset items should be collected in all cases of invasive cancer or carcinoma or *in situ*. For cases that are being collected through the breast screening programme, it is acceptable to complete the breast screening form, but for cases outside the screening programme the RCPath dataset should be followed if the NHSBSP form is not being used for all cases.

Localisation of biopsy and type of biopsy

Laterality and quadrant of breast should be indicated. The specimen type should be recorded.

Calcification present on specimen x-ray/histological calcification

If a biopsy is taken for investigation of calcification, whether calcification is present on the specimen x-ray should be indicated and whether this is identified within the biopsy.

[Level of evidence C – the presence of microcalcification within the biopsy is important information, which contributes to the discussion at the multidisciplinary meeting about whether the sample includes the desired lesion and informs assessment of adequacy of the biopsy.]

Histological/cytological opinion

Record as B1–B5 for biopsies or C1–C5 for cytology specimens as indicated. For further information, see section on core biopsy reporting categories and Appendix A on fine needle aspiration cytology reporting.

Tumour classification

If present, record the presence and type of invasive malignancy. If there is no invasive malignancy, record the presence and type of *in situ* carcinoma.

Grade

Record the tumour grade using the Elston and Ellis method. For further details on grading, see *Pathology Reporting of Breast Disease in Surgical Excision Specimens*.[14]

[Level of evidence B – Invasive tumour grade is a recognised important prognostic factor that is used in treatment planning; accurate assessment is expected.]

Oestrogen receptor status/progesterone receptor status/HER2 status

Oestrogen receptor status and progesterone receptor status predict response to endocrine therapies. Overexpression of the human epidermal growth factor receptor 2 (HER2) protein in breast cancer is predictive of response to HER2 targeted treatment.

[Level of evidence A – steroid receptor status predicts response to endocrine therapies.]

[Level of evidence A – Overexpression of HER2 predicts response to HER2 targeted treatments.]

Recording basic information

Centre/location

Give the name of the assessment centre, clinic, department, etc. where the specimen was obtained.

Side

Indicate right or left. For specimens with biopsies from multiple sites, use a separate form for each site.

Localisation technique

Please choose one of the following terms:

- palpation
- ultrasound guided
- stereotactic
- MRI.

Number of cores

If known, indicate the number of core biopsy samples taken.

Calcification present on specimen x-ray?

If the biopsy is performed for investigation of calcification, indicate whether there is calcification visible on the specimen radiograph. State if the radiograph has not been seen.

Histological calcification

Indicate whether calcification has been identified in the sample and, if present, whether it is associated with benign or malignant disease or both.

Pathologist

The name of the pathologist giving the opinion, who must be registered at the screening office.

Date

Enter the date of issuing the report.

Case for review

This is a field to indicate that a specimen has been sent for a further opinion or that the case is a particularly interesting example.

Recording the opinion

See the section on reporting categories, below.

Comment field

This free-text field is included for extra information to be recorded.

2.5 Core biopsy reporting categories

The five reporting categories are used for diagnostic biopsies. They should not be used for excision specimens including those by vacuum-assisted techniques. It is important to remember that histological examination of core biopsy samples is performed to fulfil the assessment process role by giving a pathology category classification (B1–5) and not designed to give a definitive diagnosis, although this is possible in the majority of cases. Thus whilst most core biopsy samples can be readily categorised as normal, benign or malignant, it must be recognised that a small proportion (probably less than 10%) of samples cannot. The following reporting guidelines have been devised in recognition of this and should be used for all screen-detected lesions (microcalcification, architectural deformities and mass lesions). It is recommended that this approach should also be adopted for symptomatic practice. It is important to remember that although there are five reporting categories similar to those used in fine needle aspiration cytology, these are not equivalent.

These categories are designed to take account purely of the histological nature of the specimen and not the clinical or imaging characteristics. Similarly, it is not feasible for pathology interpretation to judge independently whether a sample is adequate and from the mammographic lesion. This judgement requires multidisciplinary discussion. For these reasons, there is no inadequate biopsy category for core biopsy specimens.

A B category is not necessary for vacuum-assisted excision of a lesion that has already been diagnosed on a previous biopsy.

2.6 B1 normal tissue

This indicates a core of normal tissue whether or not breast glandular structures are present, thus this category is equally appropriate for a core including normal breast ducts and lobules or mature adipose tissue or stroma only. A B1 report should include a description of the components present and comment should be made regarding the presence of breast epithelial structures.

Normal histology may indicate that the lesion has not been sampled. This is, however, not necessarily so. In the case of certain benign lesions such as hamartomas and lipomas, apparently normal histological features would be expected on core biopsy. Minor architectural distortions seen mammographically may also result in minimal changes such as a slight increase in stromal fibrous tissue on biopsy. A minor degree of fibrocystic change is usually best categorised as B1. In these circumstances, it is the remit of the multidisciplinary meeting to determine if the lesion of interest has been sampled, if the core biopsy can be considered representative and if a B1 result can explain the clinical and radiological findings. Lactational change should be categorised as B1.

Cores with B1 diagnoses may contain microcalcification of sufficient size to be radiologically visible, for example within involutional lobules or in the stroma. It is important in these cases that discussion between pathology and radiology colleagues is undertaken to confirm whether the microcalcification in the histological specimen is representative of that seen on the mammogram. Foci of calcification within involuted lobules are common and frequently too small to be visible mammographically, thus a report that merely records the presence of this calcification without additional comment on its nature, size and site may be misleading and lead to false reassurance. It is evident that mammograms do not demonstrate microcalcification, either singly or in clusters less than 100 µm in diameter.[16] The resolution of digital mammography is lower than film/screen mammography but calcifications of similar size are more visible and easier to detect on digital mammography.

The pathologist should not categorise a biopsy as B1 because the biopsy may not reflect the clinical or radiological abnormality.[17] The pathologist should describe the histological features and base the B category on these features. Nevertheless the pathologist may make a comment in the report that the biopsy may not be representative of the lesion. It is the role of the multidisciplinary meeting to judge whether the core biopsy is adequate.

Exceptionally some specimens may be classified as uninterpretable, for example due to excessive crush artefact or composition of blood clot only. Such samples should also be classified as B1.

2.7 B2 benign lesion

A core is classified as B2 benign when it contains a benign abnormality. This category is appropriate for a range of benign lesions including fibroadenomas, fibrocystic change, sclerosing adenosis and duct ectasia and extends to include other non-parenchymal lesions such as abscesses and fat necrosis.

In some cases, it may be difficult to determine whether a specific lesion is present, for example if minor fibrocystic changes are seen. The multidisciplinary approach is once again vital in these cases to determine whether the histopathological features are in keeping with the radiological and clinical findings. It may be appropriate and prudent to classify the lesion as B1, rather than B2 if only very minor changes are present.

Sometimes skin lesions will be sampled. If a definite benign diagnosis is possible then B2 categorisation is appropriate. Sometimes a definite diagnosis is difficult, for example some adnexal tumours may be difficult to categorise on core biopsy, in which case B3 may be more appropriate.

2.8 B3 lesion of uncertain malignant potential

This category mainly consists of lesions that may provide benign histology on core biopsy, but either are known to show heterogeneity or to have an increased risk of associated malignancy (albeit lower than for B4). The level of risk is very different for the different entities. The management of B3 lesions is discussed in a separate document.[18]

It is essential that a search is made for epithelial atypia and that such atypia is reported even if there is another reason for a B3 categorisation, as the risk of malignancy associated with atypical intraductal epithelial proliferations is relatively high. For all B3 diagnoses, a comment should be made about whether epithelial atypia is present.

2.8.1 Atypical intraductal epithelial proliferations (AIDEP)

There is a range of intraductal epithelial atypia short of that required for a definite diagnosis of ductal carcinoma *in situ* that is best classified as B3 or B4. Different patterns of atypia may be seen: resembling atypical ductal hyperplasia, flat epithelial atypia, apocrine atypia and atypia that does not conform to one of these patterns. A common pattern resembles what would be called atypical ductal hyperplasia (ADH) on a surgical specimen: a monotonous proliferation of evenly spaced cells with small regular nuclei that raises the possibility of low-grade DCIS, but has insufficiently developed features or insufficient extent for this diagnosis.[14] There is a range of severity, from those which are insufficient for a definite diagnosis of DCIS but highly suspicious, to those which only show a minor degree of atypia, normally architectural, which requires further assessment and judgement of appropriate categorisation as B3 or B4 is required.

The definition of atypical ductal hyperplasia is derived from surgical resection specimens and relies on a combination of architectural, cytological and size extent criteria. For this reason, accurate diagnosis of ADH is not possible on core biopsy. It has, however, been shown that

core biopsy samples that include atypical intraductal epithelial proliferative foci, of insufficient extent for classification as DCIS, on subsequent surgical resection may form part of an established *in situ* neoplastic lesion with or without associated invasion. This view is based on several studies that describe the subsequent surgical diagnoses in cases described as ADH in non-operative core biopsy. Studies have shown that subsequent excision biopsy contains malignancy (either *in situ* or invasive) in 30–40% of these patients.[19] This is not surprising as ADH is defined as an intraductal epithelial proliferation showing the features of low-grade DCIS, but in less than two duct spaces or less than 2 mm in diameter. The limited tissue sampling that can be undertaken by core biopsy guns (often by stereotactic methods for foci of microcalcification) may thus provide insufficient material for definitive diagnosis of low-grade DCIS if only a few ducts spaces are obtained. In these cases, a diagnosis of atypical intraductal epithelial proliferation and a classification of B3 of uncertain malignant potential or B4 suspicious of malignancy should be made, dependant on the severity and extent of the lesion.

Immunohistochemistry for basal cytokeratins, such as CK14 and CK 5/6, can play a useful role in assessing epithelial proliferations. The epithelial cells in DCIS and ADH are typically completely negative, whereas usual type epithelial hyperplasia shows patchy expression. The surrounding myoepithelial cells are usually positive. However, there are pitfalls. Occasionally DCIS is positive, but this usually high grade. Columnar cell change and apocrine change are both negative, so assessment of atypia in these lesions must rely on morphology. Oestrogen receptor is typically uniformly positive in low-grade DCIS, ADH and columnar cell change and patchily positive in usual type epithelial hyperplasia. For a more detailed discussion, see the *Pathology Reporting Guidelines*.[14]

The options for B3 lesions with atypia and B4 lesions are to recommend surgical excision or vacuum-assisted biopsy to obtain more material to allow for a more definitive diagnosis. The findings in subsequent VAB specimens should be reported in conjunction with the core biopsy findings and include a comment as to whether similar changes are present in both and whether there are signs of previous biopsy to indicate sampling of the appropriate site.

2.8.2 Flat epithelial atypia

Columnar cell lesions are discussed in greater detail in the *Pathology Reporting Guidelines*.[14] Most columnar cell change, with or without hyperplasia, shows no atypia and is best categorised as B2 (or sometimes as B1 if it is very focal). Flat epithelial atypia is categorised as B3 on core biopsy. If there is a more complex architecture (usually cribriform or micropapillary), the considerations in the above section on atypical intraductal proliferations apply. Flat epithelial proliferations with high-grade nuclei should be categorised as B4 if the changes are limited, and as high-grade DCIS (B5a) only if the features are sufficient for an unequivocal malignant diagnosis. The options for B3 and B4 lesions in this category are surgical excision or vacuum-assisted biopsy to obtain more material to allow for a more definitive diagnosis.

2.8.3 Lobular neoplasia

A small to medium cell regular dyscohesive epithelial proliferation within lobules that is considered by the pathologist to represent classical lobular neoplasia (atypical lobular hyperplasia [ALH] and lobular carcinoma *in situ* [LCIS]) should be classified as B3. The distinction between ALH and LCIS cannot always be reliably made on core biopsy, so the overarching term lobular neoplasia is preferable. If wished, subcategorisation into ‘at least ALH’ and ‘LCIS’ can be made. This process does not have the same management implications as a diagnosis of DCIS or invasive malignancy and does not *per se* require therapeutic excision. Lobular neoplasia is most frequently a coincidental finding in a core biopsy from a screen-detected lesion, however, and multidisciplinary discussion is essential as the abnormality identified radiologically may not be represented. These cases must be managed cautiously.[18]

Pleomorphic LCIS is best classified as B5a (see below). Occasionally lobular neoplasia shows necrosis, but without marked nuclear pleomorphism.[20] There are only limited data on the behaviour of this variant, but in view of the overlap of features with the DCIS, it is best classified as B4.

E-cadherin immunohistochemistry can be useful to help distinguish lobular neoplasia and DCIS in difficult cases. DCIS typically shows complete membrane expression, whereas lobular neoplasia usually shows reduced or absent E-cadherin membrane expression. Basal cytokeratins are typically absent in lobular neoplasia as described above in DCIS. On occasions, it may be difficult to classify an epithelial proliferation as either lobular neoplasia or low-grade DCIS and in these circumstances a B4 classification may be appropriate.

2.8.4 Phyllodes tumour

The presence of a cellular stroma within a fibroepithelial lesion should prompt a search for other features that may aid in separating phyllodes tumour from a fibroadenoma.[21] The following favour phyllodes tumour: stromal overgrowth (x10 field of stroma with no glandular elements), fragmentation (defined as a stromal fragment with epithelium at one or both ends) and mitoses (1 or 2 per 10 high power fields favours phyllodes tumour, but can be seen fibroadenomas, and 3 or more per 10 high power fields more strongly favours phyllodes tumour). Marked atypia of stromal cells is usually only seen with other features suggestive of phyllodes tumour. If there are multiple features, a definite diagnosis of phyllodes tumour may be possible. If the features are of a benign phyllodes tumour, B3 classification is appropriate. Often the differential diagnosis lies between a cellular fibroadenoma and a benign phyllodes tumour, but definite categorisation is not possible. Such 'cellular fibroepithelial lesions' should also be designated B3 and the report should state that 'Phyllodes tumour cannot be excluded'. It is important to remember that phyllodes tumours are much less common than fibroadenomas (about 50 times) and one should not over-interpret minor changes as this will lead to excision of large numbers of fibroadenomas. Marked atypical changes may merit designation as B4 and occasionally as B5. An important pitfall is that some phyllodes tumours contain areas resembling typical fibroadenoma. Clinical factors, particularly tumour size and increase in size, should be considered in multidisciplinary discussion.

2.8.5 Papillary lesions

Papillary lesions may show significant intralesional heterogeneity and the limited sampling achieved with core biopsy may miss areas of *in situ* carcinoma. The majority of these lesions should, therefore, be designated B3. On rare occasions when a very small lesion is seen within the diameter of the core, a benign B2 classification may be considered. Conversely, when a sample of a papillary lesion in a core biopsy shows atypia, for example strongly suspicious of papillary carcinoma *in situ*, a B4 designation may occasionally be more appropriate. It is important that even focal epithelial atypia is sought as the chance of malignancy in the subsequent excision specimen is much higher than in lesions without atypia (30–40% *versus* 5–10%).[19] Vacuum-assisted excision is an alternative to surgical excision for papillary lesions with no evidence of atypia, but if atypia is present the current policy is to recommend surgical excision.[18,22]

Immunohistochemistry for myoepithelial markers can be helpful. Benign papillomas contain a myopepithelial layer both at the edge and within the lesion, whereas in papillary carcinoma *in situ* myoepithelial cells are usually absent within the lesion. Myoepithelial cells may be seen surrounding papillary DCIS, but are usually absent at the periphery of encysted or encapsulated papillary carcinoma. Benign papillomas with involvement by DCIS typically show retention of a myoepithelial layer – such lesions are usually best designated as B4 unless the atypical component is very extensive. Basal cytokeratins are useful for distinguishing usual type epithelial hyperplasia and DCIS as discussed above.

Nipple adenomas often show papillary features and so are usually best classified as B3.

2.8.6 Radial scar

Biopsies that show features of a radial scar, namely fibroelastotic stroma with entrapped glands with surrounding myoepithelial layer, should be categorised as B3. If reliable distinction from tubular carcinoma is not possible, then immunohistochemistry with a panel of myoepithelial markers is often valuable. As described above for papillary lesions, epithelial atypia should be sought as the chance of malignancy in the subsequent excision specimen is much higher if atypia is present.[19]

2.8.7 Mucocoele-like lesions

Mucin in the stroma (a mucocoele-like lesion) can be associated with benign cysts, ADH, DCIS and invasive carcinoma, particularly of mucinous type. The risk of malignancy appears to be low if there is no atypia on the core biopsy.[23] Excision of the area with a vacuum-assisted device is preferred to surgical excision if there is no atypia.[18] If atypia is present, then management as for AIDEP is recommended.

2.8.8 Rare lesions

There are some rare lesions that are usually best classified as B3 on core biopsy such as adenomyoepithelioma, microglandular adenosis, spindle cell lesions such as fibromatosis and vascular lesions that are difficult to classify.

2.9 B4 suspicious

Technical problems such as crushed or poorly fixed cores that contain probable carcinoma but cannot provide the definitive diagnosis are best included as B4. Similarly, small groups of apparently neoplastic cells contained within blood clot or adherent to the outer aspect of the sample should be classified as B4 – suspicious. Very small foci suspicious of invasive carcinoma in which there is insufficient material to allow immunocytochemical studies may also reasonably be assigned to this category.

A complete single duct space bearing an unequivocal high-grade atypical epithelial proliferative process can be classified as B5a – malignant – *in situ*. However, care must be taken if one or only part of a duct space is seen containing a highly atypical epithelial process particularly if no necrosis is present; this may be regarded as suspicious rather than definitively malignant. In particular, great care should be taken if the epithelial cells show any features of an apocrine phenotype, which may represent an atypical apocrine proliferation rather than DCIS.

Another lesion that can be allocated to this category is a non-high grade intraductal proliferation with a significant degree of atypia probably representing intermediate or low-grade DCIS, where relatively few involved duct spaces are represented in the biopsy. A pragmatic approach is usually required by reporting an atypical intraductal proliferation and qualifying this according to the degree of suspicion, i.e. ‘at least ADH, probably low-grade DCIS’, and on the basis of extent or severity of atypia allocating the case either to the B3 or to B4 category.

As discussed in the above section on lobular neoplasia, lesions that are difficult to classify as LCIS or DCIS and also non-pleomorphic LCIS with necrosis are often best classified as B4.

The management of cases classified as B4 will usually be either diagnostic excision biopsy of the area or repeat core biopsy or vacuum-assisted biopsy to obtain definitive diagnosis. Definitive therapeutic surgery should not be undertaken as a result of a B3 or B4 core biopsy diagnosis except after a definite diagnosis of a phyllodes tumour.

2.10 B5 malignant

This category is appropriate for cases of unequivocal malignancy on core biopsy. B5 category is further subdivided into B5a, B5b and B5c.

B5a should be classified for unequivocal DCIS of all grades and pleomorphic LCIS, the report stating whether the lesion is DCIS or LCIS (classical lobular neoplasia is categorised as B3).

B5b is used for all invasive primary breast carcinomas and rare invasive malignancies including malignant phyllodes, lymphomas and metastatic tumours.

B5c is used when it is not possible to say whether the carcinoma is invasive or *in situ*. This category is most frequently used when there are large fragments of carcinoma with no surrounding stroma. If there is unequivocal DCIS and features suspicious of invasion, but not sufficient for a definite diagnosis of invasive carcinoma, then B5a categorisation should be used. Fragments of papillary carcinoma are usually best categorised as B5a. In practice, the B5c category is rarely used.

2.10.1 Category B5a – *in situ*

Ductal carcinoma *in situ*

One of the benefits of core biopsy compared to FNAC is that it can allow distinction between *in situ* and invasive carcinoma. However, as a result of sampling error, approximately 20–30% of patients with a core biopsy diagnosis of DCIS will have invasive carcinoma identified in the subsequent excision specimen.[24] The nuclear grade of the DCIS should be indicated on the core biopsy. Architecture and the presence of necrosis may also be noted. The presence or absence of associated calcifications should be recorded, particularly if the biopsy was for investigation of calcification.

Paget's disease of the nipple should also be categorised as B5a. Immunohistochemistry can be helpful. Paget's disease is usually luminal cytokeratin and HER2 positive, whereas Bowen's disease expresses basal cytokeratins and melanoma is HMB45 and melan-A positive. S100 can be positive in Paget's disease as well as melanoma.

Malignant papillary lesions

Encysted or encapsulated papillary carcinoma should be categorised as B5a. Recent literature has shown that encapsulated/encysted papillary carcinomas usually lack a myoepithelial layer and probably represent an indolent form of invasive carcinoma. Regardless of whether these are invasive lesions or *in-situ* cancers, the clinical outcome is good with adequate local therapy alone similar to DCIS. The current recommendation is that these lesions should be categorised as B5a until further evidence emerges. It is recommended that the pathology report describes the lesion so that it is clear that the lesion is not conventional DCIS.

Lobular neoplasia

Pleomorphic LCIS shows marked nuclear pleomorphism like that seen in high grade DCIS. It can be confused with DCIS, particularly when associated with necrosis and calcification. These lesions should be categorised as B5a as the current recommended management is similar to high-grade DCIS. Immunostaining with E-cadherin will help differentiate between high-grade DCIS and pleomorphic LCIS. In exceptional circumstances, lobular neoplasia may be impossible to distinguish from small cell solid DCIS. Staining for E-cadherin and β catenin should be undertaken to differentiate between the two. Membrane expression of E-cadherin and β catenin is typically absent in lobular neoplasia and present in DCIS. If the distinction between classical lobular neoplasia and DCIS is not possible, then B4 categorisation is prudent.

Classical lobular neoplasia (atypical lobular hyperplasia/lobular carcinoma *in situ*) should be categorised as B3.

2.10.2 Category B5b – Invasive

Invasive carcinoma

A major advantage of core biopsy over FNAC is the ability to diagnose invasion positively. Invasive carcinoma can be unequivocally identified in core biopsy with a positive predictive value of almost 100%. False-positive diagnosis is very rare.[25] As noted above, however, the negative predictive value for invasion is only 80% when only DCIS is identified.

Microinvasive carcinoma

If the core biopsy shows a small area of invasion less than 1 mm, it is recommended that levels are examined to see if the area is larger than 1 mm. Unequivocal microinvasive carcinomas (less than 1 mm across in largest diameter) should be categorised as B5b if there is no associated DCIS, as the sample may not be representative and invasive carcinoma may be present elsewhere. If there is DCIS and definite microinvasion, categorisation as B5a is recommended, but the report must mention the microinvasion.

If there is DCIS and an area suspicious of microinvasion but no definite invasion, then categorisation as B5a is appropriate. If there is an area suspicious of microinvasion but no definite invasion and no DCIS, then categorisation as B4 is appropriate.

B5c should not be used for microinvasive carcinoma.

2.11 Assessment of prognostic and predictive factors

All invasive carcinomas should be graded and typed on core biopsy where possible. Current evidence suggests that concordance between grade on core biopsy and that in definitive excision specimen can be achieved in approximately 70% of cases.[26] It should, however, be made clear to the clinicians that the grade may differ (almost invariably by only one level) from that in the subsequent resection specimen. A phrase such as ‘Provisional (core) grade’ is suggested. In particular, mitotic count may be lower in the core biopsy than in the excision specimen, therefore leading to underestimation of grade on the core. Assessment of histological grade can also be performed on core biopsy of nodal metastases.

Assessment of histological type is useful to identity patients with invasive lobular carcinomas, who may be offered MRI if they are considering breast conserving surgery to identify multifocal disease. Grade and type are also useful when neo-adjuvant therapy is given and there may not be any residual tumour in the surgical specimen.

Oestrogen receptor and HER2 assessment on core biopsies has been shown to correlate well with subsequent surgical excision specimens.[27] As with determination on excision biopsy samples, a standard protocol and method of assessment should be used. For best results, the core biopsy should be fixed for at least six and no more than 72 hours. For detailed guidance on assessment of oestrogen receptor, progesterone receptor and HER-2 please refer to *Pathology Reporting Guidelines*.[14]

For patients undergoing neoadjuvant chemotherapy or endocrine treatment, the core biopsy must contain sufficient carcinoma for assessment of histological grade, oestrogen receptor and HER2 status.

2.11.1 Rare malignancies

Spindle cell carcinomas and metaplastic carcinomas should be designated as B5b. The use of an antibody panel including a range of anti-cytokeratin antibodies (high and low molecular weight cytokeratins and broad spectrum antibody) will assist in diagnosis. When a definite histological diagnosis cannot be made, the abnormality should be reported as spindle cell lesion of uncertain histogenesis or nature and classified as B3 or B4.

2.11.2 Lymphoma

Malignant lymphoma should be classified as B5b. The majority of these lesions are of high-grade B-cell morphology and may mimic epithelial malignancy. As in other organs, the cells frequently show less cohesion and a higher nuclear to cytoplasmic ratio and do not demonstrate the architectural features of carcinoma. The correct diagnosis is supported by immnuohistochemistry (CD45, CD20, CD3, CD30, etc.) to differentiate from an epithelial or other malignancy such as melanoma (and demonstrate the appropriate phenotype).

Low-grade lymphomas may be more difficult to distinguish from a chronic inflammatory process. Infiltration of the lobular epithelium should be sought and the degree of lymphoid infiltrate if high should raise the possibility of a neoplastic process. A panel of lymphoid markers is necessary to demonstrate the phenotype of the cells present to allow correct diagnosis. Molecular tests such as looking for an IgH clone may be useful.

2.11.3 Metastasis to the breast

Metastasis to the breast from primary malignancies elsewhere is well recognised, although in practice rarely biopsied. A full clinical history is essential to avoid misdiagnosis of a metastatic adenocarcinoma as a primary carcinoma. A wide range of tumours can metastasise to the breast, but the most frequently seen are lymphomas, carcinomas of the lung, ovary (serous papillary), kidney and prostate, carcinoid tumours and malignant melanoma. The diagnosis should be considered if the features of a malignancy are not typical of mammary origin.[28]

Immunohistochemistry is often helpful, but no marker is completely sensitive or specific, so it is important to use a panel of antibodies. Breast carcinoma usually expresses cytokeratin 7 and 18 (and not cytokeratin 20), and epithelial membrane antigen. Approximately 80% of primary breast tumours are oestrogen receptor positive. TTF-1 is useful for identifying pulmonary carcinoma, WT1 for identifying ovarian carcinoma and S100, melan-A and HMB45 for identifying melanoma.

2.11.4 Sarcomas

Primary breast sarcomas are rare. Mammary sarcomas most commonly originate in association with phyllodes tumour or as part of a metaplastic carcinoma, but in a core biopsy the epithelial component may not be represented. The most common associated sarcomas are liposarcoma, fibrosarcoma, osteosarcoma, chondrosarcoma and rhabdomyosarcoma. Angiosarcoma is the most common primary breast sarcoma and most commonly arises in the dermis after previous radiotherapy. It may be the cause of false-negative diagnosis as it may be relatively subtle and bland. Primary and secondary leiomyosarcoma may be found in the breast. All these lesions can be difficult to diagnose definitively in core samples. If unequivocal malignancy is present, they should be graded as B5b. A high index of suspicion and judicious use of immunohistochemistry can facilitate or support a diagnosis.

2.12 Problems and pitfalls in diagnosis

There are recognised problem areas and potential pitfalls in core needle biopsy diagnosis.

2.12.1 Minor degrees of epithelial atypia

Mild atypia of epithelium within lobular units is one of the most common problems encountered in core biopsy samples. Care must be taken not to over-diagnose such minimal degrees of atypia, which may represent usual epithelial hyperplasia, apocrine change or reactive changes (for example adjacent to previous sampling procedure). Conversely more severe degrees of atypia must be sought which may reflect cancerisation of lobules by high-grade DCIS. The degree of atypia should be helpful in distinguishing the process and the nuclear chromatin and presence of mitoses (although rarely seen) may aid in the diagnosis.

Similarly, usual epithelial hyperplasia (UEH) and other forms of benign hyperplasia such as that of gynaecomastoid type are commonly seen in cores from benign fibroadenomas. This often shows apparent dyscohesion due to the trauma of the core biopsy sampling process and 'telescoping' of epithelium is seen within the duct spaces thus resembling a hyperplastic process. As with UEH in surgical excision specimens, the lack of uniformity and distribution/ streaming of the epithelial cells with bland nuclear features and paucity of mitoses is of assistance in reaching a diagnosis. Atypical ductal hyperplasia should not be diagnosed in these cases unless uniformity of nuclear size and shape and regular, evenly placed nuclei are seen. Usual epithelial hyperplasia of gynaecomastoid type with a micropapillary architecture should not be mistaken for micropapillary ADH/DCIS.

As discussed above, immunohistochemistry for basal cytokeratins and oestrogen receptor can be helpful in distinguishing usual epithelial hyperplasia from DCIS.

2.12.2 Apocrine atypia and apocrine DCIS

Apocrine atypia, particularly in association with a sclerosing lesion such as sclerosing adenosis, may be especially difficult to identify correctly in non-operative diagnostic samples. In core biopsy large nuclei, often with prominent nucleoli, may be mistaken for DCIS if pleomorphism is also present. The typical granular eosinophilic cytoplasmic appearance of apocrine cells should be sought. Pure apocrine DCIS is relatively rare and when an apocrine proliferation is seen within ducts in a core biopsy, additional features of malignancy such as significant atypia, intraluminal necrosis and the presence of mitoses as well as multiple duct involvement should be sought for confirmatory evidence. In addition, multiple duct involvement indicating a more extensive lesion may provide further supportive evidence. Mild or moderate degrees of apocrine proliferation with atypical features in a duct space should be assessed with caution and it may be prudent not to record a definite diagnosis but to classify such a process as B3, of uncertain malignant potential. Conversely, papillary apocrine change should not be mistakenly classified as other than benign.

2.12.3 Lactational change

Focal lactational change may be seen in women who are neither lactating nor pregnant and indeed are nulliparous and/or post-menopausal. The involved acini are usually lined by plump vacuolated cells with a 'hobnail' architecture, but may less frequently appear atypical with irregular, large or pyknotic nuclei. The epithelial cells may appear degenerative and rarely the benign nature of the process may be mistaken for cancerisation of lobules by DCIS. The recognition of the vacuolation of the cytoplasm and the typical hobnail architecture will enable the correct diagnosis to be established.

2.12.4 Sclerosing lesions/tubular carcinoma

There is a risk of over-diagnosis of invasive carcinoma when confronted by sclerosing adenosis in a core biopsy, particularly as the normal lobular arrangement may be less apparent than on an excision biopsy specimen. Immunohistochemical staining for myoepithelial markers can be useful in this situation.

2.12.5 Stromal proliferations and spindle cell lesions

Spindle cell proliferations may cause difficulties in diagnosis in core biopsy samples. The most common lesion seen on core biopsy is scarring and usually there are associated changes such as fat necrosis or haemosiderin-laden macrophages to enable a diagnosis and categorisation as B2. Occasionally, scarring may show atypical spindle cells and a definite diagnosis may not be possible on core biopsy. Myofibroblastoma is composed of short bundles of bland spindle cells with intervening collagen and sometimes adipose tissue that typically expresses CD34 and desmin. Fibromatosis is a bland spindle cell proliferation that is best categorised as B3. Nuclear expression of β catenin is frequently seen, but is not specific. Cytokeratins and CD34 are not expressed. Spindle cell or metaplastic carcinomas need to be considered in many spindle cell lesions as they can show a wide range of appearances, including resembling fibromatosis. Evidence of epithelial differentiation must be sought; this may range from small cohesive foci to conventional carcinoma. Immunohistochemistry for a panel of cytokeratins including both luminal and basal cytokeratins should be performed. Occasionally a phyllodes tumour may just show spindle cells on core biopsy and evidence for an epithelial component should be sought, for example by performing additional levels. CD34 expression supports the diagnosis of phyllodes tumour. Primary sarcomas of the breast are very rare; the least uncommon is angiosarcoma. Skin lesions such as dermatofibroma and melanoma need to be considered in the differential diagnosis of spindle cell lesions. When a definitive histological diagnosis cannot be made, the abnormality should be reported as a spindle cell lesion of uncertain nature and classified as B3 or B4.

2.12.6 Radiation induced changes

Radiotherapy changes to the breast may be difficult to differentiate from foci of recurrent or residual carcinoma, both *in situ* and invasive. The radiation induces a degree of atypia of the breast epithelium, but also in the histiocyte population, which is prominent as a result of the radiotherapy and also recent surgery. The macrophages may also show degenerative features. Thus carcinoma cells can conversely mimic macrophages. Immunocytochemistry can be helpful in difficult cases, as irradiated neoplastic cells retain cytokeratin expression whilst macrophages demonstrate a histiocytic phenotype, for example CD68 reactivity.

2.12.7 Infiltrating lobular carcinoma

Small foci of invasive lobular carcinoma can be missed in histological sections and be dismissed as chronic inflammation or stromal cells. The targetoid infiltrative pattern of classical lobular carcinoma may be of assistance but a reactive lymphocyte process can also have a peri-ductal or peri-lobular distribution. Cytokeratin immunohistochemistry to demonstrate the neoplastic cells is of value in difficult cases, but recognition of the abnormal cell proliferation requires vigilance as the features can be subtle.

3 Axillary lymph node assessment and preoperative sampling

Axillary nodal status remains the most powerful prognostic factor in patients with invasive carcinoma of the breast. Recently sentinel node biopsy has become the standard method for staging of disease. Those patients with involved nodes may then require further treatment of the axilla including surgery. A preoperative diagnosis of nodal metastasis means that patients can proceed straight to axillary clearance. Thus preoperative axillary staging can reduce the number of patients having two axillary surgical procedures.

All patients seen in symptomatic and screening assessment clinics who have suspicious mammographic and/or ultrasound findings should have detailed ultrasound assessment of the axilla. Level 1 axillary nodes are usually easily visualised in all patients and these nodes can be assessed for risk of metastatic involvement.[29]

The criteria accepted as indications for ultrasound guided needle biopsy or FNA of axillary lymph nodes are:

- longitudinal to transverse axis ratio less than two
- concentric or eccentric thickening of cortex >2–2.5 mm
- loss of fatty hilum.

Morphological lymph node abnormality is more predictive of metastatic involvement than cortical thickening. When axillary lymph nodes are involved, ultrasound and needle biopsy or FNA will detect disease in 45–50% of cases only.[30] The chances of detection are higher in high-grade invasive breast cancer and when there are four or more nodes involved. The yield from sampling normal morphology lymph nodes with no cortical thickening is very low and is not recommended.

Both core biopsy and FNA are used to sample abnormal axillary nodes. FNA is the more commonly used technique. FNA is preferred for smaller nodes and for nodes that are close to vessels. Core biopsy may be preferred when the lymph node is large (>20 mm) or when FNA is negative, inadequate or equivocal from clearly radiologically abnormal nodes. The sensitivity of core biopsy and FNA for malignancy in lymph nodes is similar.

The technique for sampling lymph nodes is the same as that used for ultrasound guided breast biopsy. Local anaesthetic is used for the skin and superficial tissues down to the node. Too much infiltration of local anaesthetic should be avoided for FNA as a pool of anaesthetic around the node makes an inadequate sample more likely. For FNA, sampling with a 21-gauge needle appears to give better results for axillary nodes. Techniques with and without suction are down to personal preference and have similar results. Core biopsy in the axilla has the potential to cause more collateral damage to adjacent structures, particularly arteries and veins, compared with the breast, Core biopsy needles that offer a two-stage sampling option may be preferred where the sampling trough can be advanced manually through the node before the cutting outer sheath is advanced. This technique minimises the risk of damaging structures around the targeted node.

The lymph node targeted on ultrasound is frequently not the sentinel node subsequently targeted at surgery.[29] Injection of microbubbles with ultrasound tracking has been shown to be successful in identifying the sentinel node[31] and current trials are investigating the role of VAB in sampling sentinel nodes identified in this way.

Specificity is high for both CB and VAB, but false-positive diagnosis has been described with FNAC of axillary nodes and is likely to be more frequent with FNAC than with core biopsy as is well recognised in sampling of lesions in the breast. About half of nodal metastases can be detected, but the sensitivity depends on how patients are selected and the number of passes. Given the necessary expertise, FNA may allow equivalent sensitivity at a lower cost. FNA is preferred by some units due to the proximity of large vessels and nerves. Core biopsy provides sections for ready identification of small volume of disease and allows immunohistochemistry in cases of equivocal morphology. With FNAC it is helpful to prepare material for immunocytochemistry, as this may be useful on occasions. Needle washings can be used for this. Limited volume disease can be missed with either technique.

Lymph node FNA and core biopsy in breast cancer patients is intended for assessment of the presence or absence of metastatic carcinoma. If there is suspicion of malignant lymphoma (axillary lymphadenopathy in the absence of a known cause or malignancy in the breast), the patient should be referred for assessment in line with local protocols for diagnosis of malignant lymphoma.

All patients with primary invasive breast cancer with negative results for metastatic disease on FNA or core of the axillary nodes are candidates for sentinel node biopsy or other axillary procedure for definitive staging.

3.1 L codes for fine needle aspiration cytology

For units using FNAC as the primary assessment of axillary lymph nodes, the following diagnostic categories should be used.

LC1 Inadequate: no lymphoid cells or technically inadequate.

LC2 Benign: benign lymphoid cells regardless of whether specific reactive features are seen or not.

LC3 Atypia: atypical cells present, lymphoid or other of uncertain nature and significance. Can be used for the atypical lymphoid proliferations – usually low-grade lymphomas where immunohistochemistry and flow samples not available.

LC4 Suspicious of malignancy: either metastasis or lymphoma. Usually only occasional cells present either singly or in small groups.

LC5 Malignant: metastatic carcinoma or other malignancy (including lymphoma).

3.2 L codes for needle core biopsy

For units using CNB as the primary method of assessment of axillary nodes, the following diagnostic categories should be used.

LB1 Inadequate: no lymph node/lymphoid tissue. Lymph node tissue with artefact that prevents interpretation should be categorised as LB1.

LB2 Benign: either normal lymph node or lymph node with benign changes such as reactive hyperplasia, dermatopathic lymphadenopathy, foreign body reaction, sarcoidosis, tuberculosis, etc.

LB3 Atypia: lymphoid tissue with atypical cells present, lymphoid or other of uncertain nature and significance.

LB4 Suspicious of malignancy, including metastatic carcinoma or other malignancy (including lymphoma).

LB5 Malignant, metastatic carcinoma or other malignancy (including lymphoma).

In instances where there is a discrepancy between the LN cytology or biopsy and the radiological impression, repeat FNAC or core biopsy should be considered as lymph node involvement may be focal.

The utility of axillary ultrasound and needle biopsy should continue to be reviewed based on current recommended practice in relation to sentinel node biopsy and axillary dissection.

3.3 Pitfalls

The primary aim of preoperative assessment of axillary nodes in patients with breast cancer is to detect nodal metastases from the mammary carcinoma. It is important to recognise other diagnoses and avoid misdiagnosis.

Other malignancies may involve the nodes. To avoid misdiagnosis, it is useful to compare the morphology of the neoplastic cells present in the lymph node FNA or core biopsy with the tumour in the preoperative core biopsy or FNA of the breast as metastases are usually similar to the primary tumour. If the tumour has a different appearance or has features unusual for a mammary carcinoma, metastasis from other sites should be considered. Melanoma should be in the differential diagnosis. Malignant lymphoma must also be considered.

Immunohistochemistry, particularly on core biopsy, can often resolve these differential diagnoses.

Benign lymph node inclusions are a diagnostic pitfall. Melanocyte rests are the most common, but epithelial inclusions and rarely mesothelial inclusions can occur.

Macrophages as part of reactive conditions such as dermatopathic lymphadenopathy or granulomatous lymphadenitis may mimic carcinoma cells. Immunohistochemistry for macrophage markers such as CD68 and epithelial markers can be helpful.

Lymphocytes from inflammatory disorders affecting adjacent structures including the skin may mimic a lymph node.

Small metastases should be reported as malignant. Occasionally after a diagnosis of malignancy on the core or FNAC of the axillary nodes, the surgical specimen may show no nodal metastasis. The original core biopsy or FNAC should be reviewed to confirm the original diagnosis. If the carcinoma is small on the core or there are only scanty cells on the the FNAC, it may be reasonable that no metastases are found in the surgical specimen. Sometimes nodes low in the axilla are missed at surgery – ultrasound of the axilla should be considered to search for such nodes.[32] If the patient has had preoperative systemic treatment, features suggesting treated carcinoma, such as fibrosis, should be sought in the nodes in the surgical specimen.

4 How to perform fine needle aspiration cytology (FNAC)

Personnel

The success of FNAC is directly related to the skill and experience of the operators. The number of staff involved should be restricted to the minimum possible. An assistant skilled in specimen preparation, preferably a biomedical scientist or a pathologist, is helpful. If a trained biomedical scientist or pathologist is available to immediately assess the adequacy of the aspirate using a rapid staining technique, recall for repeat cytology can be avoided, therefore reducing delay and distress.

Equipment

22- or 23-gauge needles of appropriate type and length. A needle with a trocar may be preferred as it is more rigid and is less likely to become blocked or contaminated during insertion. A 10 or 20 ml syringe is used to apply suction. A short extension tube between the needle and syringe is usually required for image-guided procedures. A syringe holder makes manipulation of the syringe with simultaneous suction much easier.

4.1 Aspiration procedure

1. Locate the lesion.

2. Cleanse the area with an alcohol-impregnated swab. It is important that any excess alcohol is wiped away or allowed to dry. Traces of alcohol introduced with the needle are the main cause of the burning sensation of which patients occasionally complain after aspiration.

3. Local anaesthetic may be used but may make the lesion difficult to feel. Inject the skin and immediate subcutaneous tissue only. Avoid injecting the lesion. Avoid having to pass the needle through the nipple/areola area as this is often very painful.

4. Place syringe and needle into holder if used. Make sure the plunger is fully closed to exclude air from the barrel.

5. For freehand FNA, fix the lesion between the index finger and the thumb.

6. Choosing the shortest direction, introduce the needle through the stretched skin and subcutaneous tissue into the lesion.

7. Enter lesion with needle point.

8. Aspirate by exerting gentle negative pressure through the syringe and moving the needle tip gently by short back-and-forth movements within the lesion.

9. Maintain negative pressure and withdraw the needle point just out of the lesion. Re-insert at a slightly different angle and repeat the above procedure.

10. Repeat at least twice at different angles, without withdrawing needle from skin.

11. Release negative pressure from syringe, then withdraw the needle from the skin.

Notes

If slides are smeared immediately and no check of adequacy of aspiration is available, the residue of each aspirate can be flushed into a transport solution. This sample can then be analysed after cyto-spinning if the slides fail to provide a diagnostic sample.

Bloody aspirates: clotting occurs very rapidly in the needle, making slides difficult to prepare and interpret. A small amount of a bloody aspirate should be smeared on no more than two glass slides. The remainder of the aspirate can be washed into transport medium for later cyto-spin or cell block preparation.

If there is profuse bleeding (e.g. an arteriole has been inadvertently ruptured), FNAC should be abandoned and repeated after an interval of 2–3 weeks, otherwise reactive changes may produce cytological difficulties.

If there is any doubt about whether the correct area has been sampled, a small volume of non-ionic radio-opaque contrast medium may be injected down the aspiration needle at the end of the procedure. The site of the contrast on mammography will indicate the area aspirated.

4.1.2 Fine needle aspiration cytology

Some breast lesions give a characteristic ‘feel’ as the needle traverses the lesion. This can on occasion be a very helpful pointer as to whether the lesion has been truly sampled or not. They are conveniently described as:

No resistance	=	fatty tissue
Soft	=	fibroadenoma, mucinous carcinoma, medullary carcinoma
Rubbery	=	fibrocystic change, lobular carcinoma, fibroadenoma
Hard	=	fibrous tissue, hyalinised fibroadenoma, post-radiotherapy
Gritty	=	carcinoma, microcalcifed tissue
Cystic	=	cyst in fibrocystic change.

4.1.3 Ultrasound guided FNAC

The lesion is demonstrated and the surrounding breast tissue is immobilised by applying pressure with the palm of the hand holding the probe. Infiltration of the skin with local anaesthetic may be carried out. The FNAC needle, attached by a short connecting tube to a 10 cc syringe held by the assistant, is introduced into the breast along the line of the long axis of the ultrasound probe and will be easily visualised if it is kept parallel to the surface of

the probe. The needle tip is guided into the lesion and an image is taken to record that the needle is correctly positioned. The needle is then moved back and forth within the lesion with simultaneous rotation and with negative pressure being applied by the assistant. Aspiration is continued until material is seen within the hub of the needle. The aspirate is then delivered onto slides, and dry and wet preparations made in accordance with guidance from the pathologist. Two to three separate samples are commonly obtained in order to increase the chances of obtaining a diagnostic cellular sample. Needle washings may also be made, flushing the needle and connecting tube with 3–5 ml of cellular fixative.

Ultrasound jelly may present a problem in interpretation for pathologists seeing it for the first time and should not be confused with calcium salts or necrosis. It should not be used during the aspiration procedure and, if used previously, should be carefully removed.

4.2 Spreading the slides

A number of methods can be used to spread the slides obtained by placing a drop of aspirated material from the needle on a glass slide. Many of these are variations on a theme, but the essential aim is to get a thin layer of material on the slide to allow rapid drying for air-dried fixation without appreciable squash artefacts due to excess pressure (Figure 1).

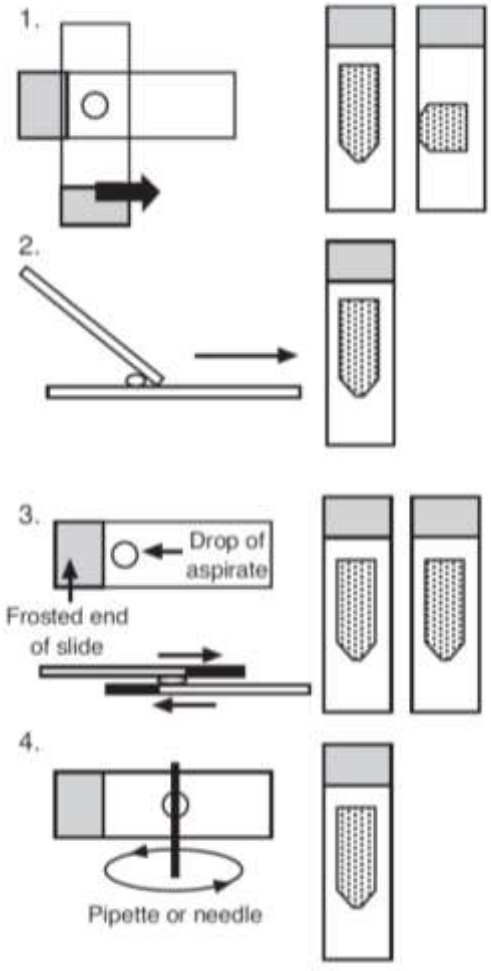

Figure 1: Spreading with a slide. Three basic methods (1, 2 or 3) can be used, all producing similar effects. Alternatively, the slide may be spread using a pipette or a needle (4).

All pathologists have received slides from clinicians where the aspirate has been well taken but has been ruined by poor spreading technique. It is sometimes difficult to remedy this, but

multidisciplinary discussion and making aspirators aware of the problems, especially visually and microscopically, often helps to alleviate the problem. Should such problems persist, alternative preparative techniques such as cytospin or thin preparations may be considered.

4.3 Fixation methods

4.3.1 Wet fixed smears

These smears must be fixed **immediately** after spreading and before they have a chance to dry, by dropping into a pot of fixative, or flooding the slide with a drop of fixative if no container is available. Spray fixation can be used.

4.3.2 Air dried smears

After spreading, the slide should be dried rapidly by waving in the air or by using a fan. Alternatively a hair dryer can be used, but this must be on a cold setting as warm air will 'cook' the cells and lead to artefacts.

4.3.3 Transport medium

In some units transport medium is used for specimens, which means that optimum preparations can be made in the laboratory after cyto-centrifugation. This method is best used where clinicians are not used to making cytological smears and do not follow proper fixation techniques. It can be superior to delayed fixation of wet preparations where air-drying can make interpretation difficult.

5 Diagnostic coding

SNOMED Topography (T) or relevant SNOMED CT code must be recorded for the anatomical site.

SNOMED Morphology (M) or relevant SNOMED CT code must be recorded for the diagnosis/tumour morphology.

A list of applicable SNOMED codes is provided in Appendix I.

6 Criteria for audit

As recommended by the RCPath as key performance indicators (see *Key Performance Indicators – Proposals for implementation*, July 2013, https://www.rcpath.org/profession/clinical-effectiveness/key-performance-indicators-kpi.html):

- English Trusts are required to implement the structured recording of core pathology data in the COSD by January 2016.

  Standard: 95% of reports must contain structured data

- Histopathology cases that are reported, confirmed and authorised within seven and ten calendar days of the procedure.

  Standard: 80% of cases must be reported within seven calendar days and 90% within ten calendar days.

The following standard is also suggested:

- Completeness of histopathology core items recorded. The standard is that reports should contain 100% of the core items.

Please see also Appendix C (Quality assurance) for details on auditing core biopsy performance.

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Appendix A Fine needle aspiration cytology reporting guidelines

This section of the document is designed to assist classification and reporting of FNAC samples. It should, however, be noted that FNAC alone is not an appropriate method of assessment of abnormalities detected by breast screening. FNAC does provide the advantage of providing a rapid diagnosis compared to core biopsy and may be used in conjunction with core needle biopsy where the necessary expertise exists. It can also be used for assessment of symptomatic patients.

Reporting categories

In ideal circumstances, one should aim for a definitive benign or malignant diagnosis. The proportion where this is possible will increase with experience of both the pathologist and aspirator.

C1 inadequate

The designation of an aspirate as 'inadequate' is, to a certain extent, a subjective matter and may depend on the experience of the aspirator and/or the interpreter. It is generally based on the presence of sufficient numbers of epithelial cells to provide a sample adequate for confident assessment. There are a number of reasons for labelling a smear as inadequate. These fall into three main groups:

- hypocellularity
- error in aspiration, spreading or staining
- excessive blood.

In some cases, diagnostic information may be present and may be conveyed in the accompanying text description, for example, adipose tissue fragments could support a clinical diagnosis of lipoma. Aspirates from certain lesions, such as cysts, abscesses, intramammary lymph nodes, fat necrosis and nipple discharge specimens may not contain epithelial cells but should not be classified as inadequate.

Preparative artefacts include:

- crush, when too much pressure is used during smearing
- drying, when the dry smears are allowed to dry too slowly (dry smears should be dried quickly, wafting in the air can speed up drying) or when the wet-fixed smears have been allowed to dry out before fixation
- thickness of smear, when an overlay of blood, protein rich fluid or cells is obscuring the picture, making assessment impossible.

It is helpful to make a comment explaining why the specimen is inadequate.

C2 benign

- Indicates an adequate sample showing no evidence of malignancy or specific lesions regarded as atypical and, if representative, a negative report can be issued.
- The aspirate in this situation is poorly to moderately cellular and tends to consist mainly of regular duct epithelial cells. These are generally arranged as monolayers and the cells have the characteristic benign cytological features. The background is usually composed of dispersed individual and paired naked nuclei. Should cystic structures be a component of the aspirated breast, a mixture of foamy macrophages and regular apocrine cells may be part of the picture. Fragments of fibrofatty and/or fatty tissue are common findings.
- A positive diagnosis of specific conditions, e.g. fibroadenoma, fat necrosis, granulomatous mastitis, breast abscess, lymph node, etc., may be suggested if sufficient specific features are

present to establish the diagnosis with confidence and may be helpful in multidisciplinary correlation.

- Care should be taken when correlating cytology features and radiology. For example, a few cohesive groups of epithelial cells in an aspirate from a well-defined lesion thought to be a cyst may not be representative of the lesion.

C3 atypia probably benign

The aspirate here can have all the characteristics of a benign aspirate as described in the previous paragraph. There are, however, also certain features not commonly seen in benign aspirates. These could be any, or a combination, of the following:

- nuclear pleomorphism
- some loss of cellular cohesiveness
- nuclear and cytoplasmic changes resulting from, for example, hormonal (pregnancy, pill, HRT) or treatment influences (see diagnostic pitfalls)
- increased cellularity accompanying the above features.

In addition, specific lesions that are regarded as showing an increased risk of malignancy can be identified on FNAC and should be reported as C3. These include papillary lesions and suspected phyllodes tumours. In both of these lesions, there may not be any cytological atypia, but the possibility of malignancy in a focal area of these lesions warrants a report of C3.

C4 suspicious of malignancy

This category should be used for those aspirates where there are atypical features in the smear, such that the pathologist is almost certain that they come from a malignant lesion, although a confident diagnosis cannot be made.

This may be for three main reasons

1. The specimen is scanty, poorly preserved or poorly prepared, but some cells with features of malignancy are present.
2. The sample may show some malignant features without overt malignant cells present. The degree of abnormality should be more severe than in the previous category.
3. The sample has an overall benign pattern with large numbers of naked nuclei and/or cohesive sheets of cells, but with occasional cells showing distinct malignant features.

If an aspirate is reported as C4 because of low cellularity, repeat aspiration is often helpful. If, however, the aspirate is cellular but considered to be suspicious of malignancy, it is unlikely that repeat aspiration will be helpful.

Definitive therapeutic surgery should **not** be undertaken as a result of a C3 or C4 diagnosis.

C5 malignant

- This indicates an adequate sample containing cells characteristic of carcinoma, or other malignancy.
- The pathologist should feel at ease in making such a diagnosis. Malignancy should not be diagnosed on the basis of a single criterion. Combination of the features listed in Table 3 will be necessary to achieve this diagnosis.

Calcification

FNAC should not be carried out on mammographic calcifications in the absence of a mass detected on ultrasound or clinical examination. The reasons for this are twofold: it is difficult to confirm that calcification is present in the sample and also it is not possible to reliably distinguish between *in situ* and invasive malignancy on FNAC, rendering a C5 diagnosis in these circumstance of limited use in planning treatment.

General diagnostic patterns

The essential role of cytological diagnosis is to distinguish benign from malignant processes. The common general criteria used are illustrated in Table 1. It is important to bear in mind that the morphological and histological patterns seen in both benign and malignant breast disease are quite varied, and this is reflected in the cytological appearances. For this reason, it is useful to have a working understanding of breast histology before approaching breast FNAC. This knowledge can improve recognition of rare lesions and reduce numbers of false-positive and false-negative diagnoses.

Table 1: General diagnostic criteria for the recognition of benign and malignant conditions

Criterion	**Benign**	**Malignant**
Cellularity	Usually poor or moderate	Usually high
Cell-to-cell cohesion	Good with large defined clusters of cells	Poor with cell separation resulting in dissociated cells with cytoplasm or small groups of intact cells
Cell arrangement	Even, usually in flat sheets (monolayers)	Irregular with overlapping and three-dimensional arrangement
Cell types	Mixtures of epithelial, myoepithelial and other cells with fragments of stroma	Usually uniform cell population
Bipolar (elliptical) bare nuclei	Present, often in high numbers	Not conspicuous
Background	Generally clean except in inflammatory conditions	Occasionally with necrotic debris and sometimes inflammatory cells including macrophages
Nuclear characteristics		
Size (in relation to RBC diameter)	Small	Variable, often large, depending on tumour type
Pleomorphism	Rare	Common
Nuclear membranes (PAP stain)	Smooth	Irregular with indentations
Nucleoli (PAP stain)	Indistinct or small and single	Variable but may be prominent, large and multiple
Chromatin (PAP stain)	Smooth or fine	Clumped and may be irregular
Additional features	Apocrine metaplasia, foamy macrophages	Mucin, intracytoplasmic lumina

Appendix B Cytological features of specific lesions diagnosed on FNAC

Benign lesion

1 Fibroadenoma

Typical fibroadenomas are characterised by three features: numerous staghorn branching groups of epithelial cells, frequent bipolar bare nuclei and stromal fragments resembling the stroma seen on histology of fibroadenomas. On occasions, aspirates from fibroadenoma may contain atypical epithelial cells but identification of the pattern at low power examination will prevent false-positive diagnoses (C3 and above). Fortunately this usually happens in actively growing lesions in teenage women, rather than in the screening age range. The clue to the diagnosis is the presence of 'stripped' bipolar nuclei. Smears containing these in significant numbers should not be diagnosed as malignant unless there are clear features of a benign epithelial lesion (with benign epithelial clumps) and also malignant clumps and dissociated malignant cells recognisable as a distinctly separate cell population. These smears, where the needle has passed through both a benign and a malignant lesion, may be very difficult but the two distinct populations of epithelial cells should aid their recognition. Smears from some malignant tumours contain bare nuclei. These bare or stripped nuclei are not bipolar and have obvious malignant features identical to co-existing intact tumour cells. Often in fibroadenomas two cell types can be recognised in the cell clumps, even in the atypical examples.

It is recognised that LCIS, DCIS and invasive carcinoma may arise in fibroadenomas, like any other breast tissue, and the presence of significant atypia in a fibroadenoma-like lesion should result in a C3 or C4 diagnosis.

2 Apocrine cells

Apocrine cells in smears may appear pleomorphic and may dissociate. Degenerate apocrine cells in cyst fluids may also have an atypical appearance. Recognition of the dusty blue cytoplasm, with or without cytoplasmic granules with air dried slides or pink cytoplasm on wet fixed slides, coupled with the prominent central nucleolus is the key to identifying cells as apocrine. Awareness of the marked pleomorphism which may occur in degenerate apocrine cells and careful assessment of the cellularity and chromatin pattern should allow the distinction from the rare apocrine carcinoma. If there is doubt about the nature of apocrine cells, it is better to err on the side of caution and give a suspicious or atypical report.

One particularly difficult lesion is atypical apocrine change in sclerosing adenosis, especially if this is associated, as it often is, with a complex sclerosing lesion or radial scar, giving a mammographically worrying appearance. In this case, the highly pleomorphic apocrine cells may not always appear obviously apocrine in smears. Features that may be helpful are the abundant cytoplasm with granules and the absence of necrosis. Spindling of cells in the centre of the clumps (myoepithelial cells from the sclerosing adenosis) surrounded by or intermingled with the atypical apocrine cells may be seen.

3 Spreading artefacts

Excessive pressure during spreading of slides may produce dissociation of cells from benign clumps. If the cells within these clumps are also somewhat pleomorphic due to degenerative or atypical changes, the dissociation may cause the cells to resemble dissociated malignant cells. The clue to this is often the finding of nuclear lysis and trails of chromatin due to the over-spreading artefact. Fibroadenomata are the most likely lesions to produce these problems when over-spread.

4 Papilloma

Aspiration of papillomas usually produces cellular aspirates with ‘staghorn’ or ‘antler horn’ clusters of cells similar on low-power appearance to those seen in fibroadenomas, although they may appear three-dimensional. In some cases connective tissue cores may be seen within these clusters. These may be diagnostic of papilloma but are not a common feature. Fibroadenomas do not contain large numbers of foam cells. Bare nuclei are seen in papilloma but there are generally not as many as in fibroadenomas. Apocrine metaplasia may also be present. While it is important clinically to distinguish papilloma from intracystic papillary carcinoma, this may not be possible on cytological grounds. Some features of malignancy, such as nuclear pleomorphism, increased nuclear cytoplasmic ratio and cellular crowding or overlapping, may occur with some benign forms of papilloma. No single feature can differentiate the two conditions. Papillary lesions with no epithelial cell atypia should be reported as C3 on FNAC. If there is epithelial cell atypia of significant degree or loss of cohesion not due to overspreading, a report of C4 is appropriate. Due to limited sampling it is difficult to make a C5 diagnosis on papillary lesions on FNAC.

5 Atypical lobular hyperplasia and lobular carcinoma *in situ*

It is not possible to distinguish atypical lobular hyperplasia, lobular carcinoma *in situ* and even invasive lobular carcinoma reliably on fine needle aspiration smears alone. The difference between lobular carcinoma *in situ* and atypical lobular hyperplasia is one of extent of lobule involvement seen in histological sections and is not based on the cytological appearances of the cell. The cells are similar or identical in morphology. The cytological features of ALH have been well described.[33] Cytologically dissociated small epithelial cells with rounded or squared-off nuclei are seen. These are present singly or in small groups with nuclear moulding. The cells may contain intracytoplasmic lumina (private acini), seen best on mucin staining where they appear like a ‘bulls eye’ with an alcian blue stained microvillous membrane and a periodic acid Schiff (PAS) stained mucin droplet in the centre. Atypical lobular hyperplasia and LCIS are usually seen as a chance finding in association with another lesion, which can result in complex appearances in fine needle aspiration smears.

6 Atypical ductal hyperplasia

Atypical ductal hyperplasia is most often encountered in breast screening in patients who present with microcalcification on mammography. As stated earlier, FNAC is of very limited or no benefit in this situation and, if not carried out, the potential pitfalls can be avoided.

Most cases of ductal carcinoma *in situ* detected by breast screening are of the ‘comedo’ or large cell type and these do not present a problem as, if they are aspirated, the characteristic features of malignant cells are present along with necrosis and dissociation. The difficulty comes in the distinction of low-grade ductal carcinoma *in situ* of cribriform or micropapillary type from atypical ductal hyperplasia. Low-grade cribriform or micropapillary ductal carcinoma *in situ* does not produce necrosis or large numbers of dissociated cells and is mainly recognised by its architectural pattern within the cell clusters. Atypical ductal hyperplasia is similar but unlike the monotony of the cell clusters in cribriform ductal carcinoma *in situ*, the clusters of atypical ductal hyperplasia still show a biphasic pattern at least in part. They differ from the cell groups found in benign breast lesions in that they have a three-dimensional appearance and usually show some cytological atypia, which may be severe in some cases.

7 Columnar cell change

This may produce dissociation and some authors have noted that the cells may resemble lobular carcinoma cells. Some of the cells are columnar in nature, resembling bronchial epithelial cells. Again, this change is most often seen in association with mammographic microcalcification and FNAC should not be performed in these circumstances.

8 Lactational change

Even in the screening age group, focal lactational changes can occur. This is uncommon but can produce occasional dissociated cells within an otherwise benign-appearing smear. The dissociated cells may possess nucleoli and have larger nuclei than the surrounding benign cells. They do, however, have a moderate quantity of pale blue cytoplasm on Giemsa staining with lipid droplets in the cytoplasm. Caution in interpreting occasional dissociated cells in an otherwise benign pattern should be exercised even in the screening age range and the question, 'Could these be lactational/secretory cells?', should be specifically asked in these cases. Outside the screening age, a history of pregnancy/lactation should always be sought and clinicians should always tell the pathologist of lactation or pregnancy.

9 Radiotherapy changes

These can lead to a false-positive cytological diagnosis, especially when the history of previous irradiation is not provided. However, the aspirate is usually not very cellular and the interpretation of poorly cellular smears, especially with a history of irradiation, should be undertaken with caution, as in item 3. Irradiation can cause marked nuclear pleomorphism and dissociation. Mammography may also not be helpful or even false positive in this situation, which may lead to an inaccurate clinical impression.

10 Intra-mammary lymph nodes.

These should not cause a problem if the pathologist recognises the cells as lymphoid. Awareness that these can occur and can be aspirated should be enough to avoid an error. Lymphomas may be more difficult to distinguish from carcinoma, but the lack of clumps should suggest the possibility. Careful assessment including immunocytochemistry should distinguish the occasional carcinoma which shows almost complete dissociation with a plasmacytoid appearance. Examples of bone marrow in aspirates of lesions stated to be in the breast are rarely seen; the origin of these is assumed to be rib or myelo-lipoma.

11 Degenerate cells in cyst fluids

Degeneration of cells within cysts or nipple discharge specimens can give pleomorphic appearances, especially when these are larger apocrine cells. Cautious interpretation of cells within degenerate cysts is advised.

Uncommon lesions

1 Granulomatous mastitis

Epithelioid macrophages in granulomatous mastitis can mimic carcinoma cells. They are associated with other inflammatory cells in the smear and numerous macrophages may be seen. The smear is also very cellular. In the presence of inflammation and a cellular smear, the finding of multinucleate macrophages should alert the observer to the possibility of granulomatous mastitis. The rare cribriform carcinomas with multinucleate giant cells do not usually contain other inflammatory cells and are therefore distinguishable from granulomatous mastitis by their dimorphic picture of small malignant cells in clumps and singly and more basophilic 'osteoclast-like' giant cells with larger nuclei and prominent nucleoli. Mononuclear forms of the multinucleate cells may also be present.

2 Granular cell tumour

This can present a worrisome appearance in smears: there may be marked dissociation of cells with pink cytoplasm which, although they have small nuclei generally, may contain occasional larger nuclei, giving a pleomorphic appearance. However, the cells do not look

epithelial and benign epithelial clumps are seen between the dissociated cells of the tumour. The cells have eosinophilic granular cytoplasm on Papanicolaou or haematoxylin and eosin staining and a mottled pale mauve cytoplasm on Giemsa stains, looking similar to apocrine cells.

3 Adenomyoepithelial lesions

These lesions can show malignant cytological features because of dissociation of pleomorphic cells, which are in fact myoepithelial. However, obvious benign clumps and bipolar bare nuclei are present. Malignancy can arise within these lesions.

4 Collagenous spherulosis

This lesion produces rounded globules staining a granular purple colour on Giemsa stains with surrounding spindle cells. There is a resemblance to adenoid cystic carcinoma, with which the lesion can be confused. The globules can also be seen in papilloma and ductal adenoma. Biopsy in these rare conditions is advised.

Potential false-negative diagnosis

The most common cause of false-negative cytological diagnosis is an aspiration miss. There are, however, types of carcinoma which by their nature may lead to a false-negative cytological diagnosis.

1 Tubular carcinoma

Tubular carcinoma cells often have much in common with benign breast epithelial cells, including uniformity, nuclear size and, often, absence of immediately obvious nuclear abnormalities. Knowledge of the mammographic findings, a lack of bare nuclei, individual cells with cytoplasm and occasional tubular profiles are pointers to the diagnosis. Paradoxically the nuclei are often more regular and orderly than benign ductal epithelium and there is a single cell population in the clumps. Often it is not possible to give an unequivocal diagnosis but care should always be taken in interpreting smears from stellate opacities to avoid false-negative results from this type of tumour. It should be noted that tubules can occasionally be obtained from benign lesions including radial scars, tubular adenomas and fibroadenomas.

2 Lobular carcinoma

Aspirates from this type of carcinoma are often difficult to interpret. The cellularity of these specimens is usually less than that seen in ‘ductal’ carcinoma and due to the growth pattern of this tumour there is often a mix of benign and malignant cells in an aspirate. A number of patterns can be observed, ranging in cytological appearance from benign-looking uniform cells to atypical cells not dissimilar to those seen in invasive ‘ductal’ carcinoma. The presence of small three-dimensional collections of cells with only slightly enlarged nuclei is helpful. A large number of cells with intracytoplasmic lumina (private acini) in association with the above features is an indication of lobular carcinoma, although not specific. Nuclear irregularities and small protrusions from the nucleus (‘noses’) may also be seen.

3 Apocrine carcinoma

This rare type of carcinoma produces cellular smears. Difficulty in interpretation is related to the subtle appearance of the neoplastic apocrine cells and their resemblance to benign apocrine cells with degenerative changes. Clustering of cells and papillary formations are seen in benign as well as malignant lesions and are of little help. The key features of a malignant aspirate are the uniform cell population with nuclear atypia, which one should not confuse with degenerative changes. Necrosis is also a helpful feature. Until one is aware of the marked

atypical changes associated with apocrine cells in fibrocystic change, the diagnosis of apocrine carcinoma should always be approached with caution.

4 Ductal carcinoma *in situ*

It should be noted that ductal carcinoma *in situ* and invasive 'ductal' carcinoma cannot be distinguished accurately by cytology alone. While some of the cases of ductal carcinoma *in situ* are overtly malignant, low-grade DCIS may present difficulties. A clue in some cases can be obtained from the architectural pattern within the rigid and monomorphic clumps. In some cases, a report of intraductal proliferation (atypical or suspicious) may be all that can be given and in such cases biopsy may be the only way to resolve the problem.

5 Carcinoma with extensive fibro-elastosis

These tumours may give sparsely cellular smears, which can lead to difficulties in diagnosis. Often it is not possible to be definitive and the need for caution in the interpretation of poorly cellular smears is again emphasised.

Other unusual lesions

1 Silicone, soya oil or paraffin granuloma

This may occasionally be problematic because of cell dissociation, but the appearances are made easier with the recognition of multinucleate cells and oil or silicone droplets in the cytoplasm of the macrophages. Clinical data will be helpful here and clinicians should understand the need to supply the pathologist with proper clinical information on all breast lumps sampled by FNAC.

2 Benign stromal lesions

These lesions are occasionally aspirated when they produce an irregular mass on mammography or palpation. One of the more usual lesions to be mistaken for carcinoma radiologically is fibromatosis. Nodular fasciitis may, however, also be sampled. On aspiration, there are small numbers of stromal cells that are dissociated from each other. The cells are spindle in shape and have regular nuclear characteristics.

3 Phyllodes tumours

The benign variants of phyllodes tumour may not be recognised as such on fine needle aspiration and may give a picture similar to fibroadenoma. Clues to the diagnosis include the presence of intact stromal cells, occasionally with nuclear abnormalities and the finding of pieces of cellular mucoid connective tissue in the aspirate. Fibroadenomas can also show both these features, however, and the recognition of benign phyllodes tumours often depends on clinical and sonographic features.

Occasionally phyllodes tumours can also produce false-positive diagnosis of malignancy. Malignant phyllodes tumours show a pattern of benign-appearing epithelial clumps, with spindle cells showing obvious malignant nuclear features.

4 Metastatic tumours

Metastatic tumours in the breast should always be considered in FNAC where a peculiar pattern unusual for breast tumours is seen. Melanoma and oat cell carcinoma are the most common. In melanoma, pigment and large intranuclear cytoplasmic inclusions may be visible. Ovarian metastases are often papillary with psammoma bodies (an uncommon feature of breast tumours), large clear cells full of glycogen may suggest a renal metastasis, squamous

carcinoma cells may be from a primary breast lesion but may also be from a metastatic lesion, etc. The triple approach may often resolve this problem.

5 Lymphoma

The recognition of the lymphoid nature of an apparent primary breast tumour depends on the recognition of the spectrum of lymphoid cell types and the absence of clumps of cells. Immunocytochemistry may be necessary in some cases.

6 Malignant stromal tumours

The most common sarcoma to be aspirated from the breast is the angiosarcoma. This can show variable cytological features but is often accompanied by a large amount of blood. Clumps of cells may occasionally be seen but the pattern is often that of malignant-appearing spindle or ovoid cells.

Sarcomas also give a picture of dissociated malignant spindle cells. The major diagnostic dilemma is between spindle cell carcinoma and sarcoma. When this is a problem immunocytochemistry for epithelial markers may be necessary.

Appendix C Quality assurance

Background

Accurate non-operative diagnosis is an essential component of a successful breast screening programme. Accurate diagnosis of malignancy allows for patients with cancer to have a therapeutic procedure as the first surgical procedure. Accurate diagnosis of benign lesions means that most patients avoid surgery completely, important to reduce the morbidity associated with screening.

Screening detects many borderline lesions and it is not possible to achieve 100% diagnostic accuracy, but it should be possible to achieve performance in line with that of other similar units. To this extent, comparisons using standard reports are invaluable, but only as part of an effective overall quality assurance (QA) programme.

Definitions

The definitions shown in Table 2 are intended to relate to the clinical evaluation of the effectiveness of core biopsy, rather than specifically related to evaluation of the laboratory component. Thus normal (B1) core biopsy results are not excluded from the calculations, as in some evaluations in the literature. Pathologists wishing to evaluate their statistics purely to see their own accuracy in diagnosis may wish to calculate the figures slightly differently.

Table 2: Definitions of QA standards for core biopsy

QA standard	Definition
Absolute sensitivity	The number of carcinomas diagnosed as such (B5), expressed as a percentage of the total number of carcinomas sampled.
Complete sensitivity	The number of carcinomas that were not definitely negative on core, expressed as a percentage of the total number of carcinomas.
Specificity (full)	The number of correctly identified benign lesions (the number of B2 results minus the number of false negatives), expressed as a percentage of the total number of benign lesions sampled.
Positive predictive value of a B5 diagnosis	The number of correctly identified cancers (number of B5 results minus the number of false-positive results), expressed as a percentage of the total number of positive results (B5).
Positive predictive value of a B4 diagnosis	The number of cancers identified as suspicious (number of B4 results minus the number of false suspicious results), expressed as a percentage of the total number of suspicious results (B4).
Positive predictive value of a B3 diagnosis	The number of cancers identified as atypia (number of B3 results minus the number of benign atypical results), expressed as a percentage of the total number of atypical results (B3).
False-negative case	A case that over the next 3 years turns out to be carcinoma, having had a negative (B2) core result. (This will by necessity include some cases where a different area from the lesion was sampled but who present with an interval cancer.)
False-positive case	A case that was given a B5 result who turns out at open surgery to have a benign lesion (including atypical hyperplasia).
False-negative rate	The number of false-negative results, expressed as a percentage of the total number of carcinomas sampled.
False-positive rate	The number of false-positive results, expressed as a percentage of the total number of carcinomas sampled.

How to calculate quality assurance statistics (BQA)

Pathology statistics for the National Health Service Breast Cancer Screening Programme (NHSBSP) can be produced automatically from data input onto the national breast screening system (NBSS) database, which cross-references the core biopsy result with the histology or subsequent outcome. A crystal report can generate the wide bore needle statistics (BQA, which are used to monitor performance for QA purposes.

Further rules used in deriving quality assurance statistics

Cases with both a non-invasive and invasive cancer should count as invasive unless they are in opposite breasts, in which case they should be counted twice (once for each breast).

In cases with a malignant and a benign diagnosis, the malignant result overrides the benign result unless they are from opposite breasts.

Cases with open episodes are listed at the bottom of the report.

Tables 3 and 4 can be produced for internal QA purposes for all clients, all tests, all cases/tests performed by one person, all cases/tests reported by one pathologist, and all cases/tests performed by any localisation method (palpable, ultrasound or stereotactic). The tables can also be produced for any date range (using the date of biopsy or, if not available, the date of reporting), any geographic location and for any or all of the radiological appearances (speculated mass, rounded opacity, microcalcification, stellate lesion or asymmetrical density).

It is possible to request a report that lists the screening numbers of clients involved in any of the cells in Table X. For example, a list of cases in cell box 41 is produced with the title: 'Cases with B4 results not biopsied but with closed episodes – please check'. Note that all cases in box 37 are regarded as malignant and that all cases in box 42 are regarded as benign.

Total cases screened in period .....

Total assessed .....

Total WBN performed .....

Table 3: Core biopsy QA standard report (BQA)

	Core biopsy diagnosis								
Final histology	B5	B5a	B5b	B5c	B4	B3	B2	B1	**Total**
Total malignant	Box 1	Box 2	Box 3	Box 4	Box 5	Box 6	Box 7	Box 8	Box 9
Invasive	Box 10	Box 11	Box 12	Box 13	Box 14	Box 15	Box 16	Box 17	Box 18
Non-invasive	Box 19	Box 20	Box 21	Box 22	Box 23	Box 24	Box 25	Box 26	Box 27
Total benign	Box 28	Box 29	Box 30	Box 31	Box 32	Box 33	Box 34	Box 35	Box 36
No histology	Box 37	Box 38	Box 39	Box 40	Box 41	Box 42	Box 43	Box 44	Box 45
Total C results	Box 46	Box 47	Box 48	Box 49	Box 50	Box 51	Box 52	Box 53	Box 54

The entry in each box in Table 3 is calculated from the numbers of core biopsies with a B code (B1, B2, etc.) and cross-referenced with the worst histology diagnosis.

The table and calculations (see below) should be produced for all core biopsy tests (headed 'all tests') and also for all clients (headed 'all clients); if two core biopsy results are present, the higher B number is used. Only closed episodes should be used.

The figures in the tables are then used to calculate values for each of the BQA measures. The calculations are shown in Table 4 (numbers in bold correspond to the box numbers in Table 3).

It is recognised that the specificities and false-negative rates are approximate and will be more accurate the longer the date range of analysis is from the date of calculation.

Table 4: Calculation of biopsy performance measures

Absolute sensitivity (this assumes that all unbiopsied B5 results are carcinoma and are treated with primary chemotherapy or hormonal therapy)	$\frac{\mathbf{(1 + 37)}}{\mathbf{9 + 37}} \times 100$
Complete sensitivity	$\frac{\mathbf{(1 + 5 + 6 + 37)}}{\mathbf{9 + 37}} \times 100$
Specificity (biopsy cases only)	$\frac{\mathbf{34}}{\mathbf{36}} \times 100$
Specificity (full) (this assumes that all cases of atypia (B3) that are not biopsied are benign)	$\frac{\mathbf{(34 + 43)}}{(36+42+43+44)} \times 100$
Positive predictive value (B5 diagnosis)	$\frac{\mathbf{(46 – 28)}}{46} \times 100$
Positive predictive value (B4 diagnosis)	$\frac{\mathbf{5}}{\mathbf{(50 – 41)}} \times 100$
Positive predictive value (B3 diagnosis)	$\frac{\mathbf{6}}{\mathbf{51}} \times 100$
Negative predictive value (B2) (at present this parameter is not calculated by the various BQA routines)	$\frac{\mathbf{(52 – 7)}}{\mathbf{52}} \times 100$
False-negative rate	$\frac{\mathbf{7}}{\mathbf{9 + 37}} \times 100$
False-positive rate	$\frac{\mathbf{28}}{\mathbf{9 + 37}} \times 100$
B1 core biopsy rate	$\frac{\mathbf{53}}{\mathbf{54}} \times 100$
B1 core biopsy rate from cancers	$\frac{\mathbf{8}}{\mathbf{9 + 37}} \times 100$
Suspicious rate	$\frac{\mathbf{50 + 51}}{\mathbf{54}} \times 100$
Core biopsy miss rate from cancers	Sum of false-negative rate and B1 core biopsy rate from cancers

Table 5: Suggested thresholds for core biopsy performance

	Minimum (%)	**Preferred (%)**	**Current median (%)* 2011–2014**
Absolute sensitivity (AS) for all carcinomas	> 92	> 95	96.7
Absolute sensitivity (AS) for DCIS after maximum of two attempts	> 85	> 90	
Complete sensitivity (CS)	> 99	> 99.5	99.8
Specificity (full) (SPEC) (including non-biopsied cases)	> 75	> 85	79.5
Positive predictive value B5 (+PV)	> 99.5	> 99.9	100
False-positive rate (F+)	< 0.2	< 0.1	0
False-negative rate (B2 from cancer)	< 0.5	< 0.2	0.1
B1 core biopsy rate from cancers	< 0.5	< 0.3	0.1
Miss rate (B1 + B2) from cancer at first attempt	< 5	< 1	
Suspicious rate (B3 + B4)	< 10	< 5	7.8
B3 rate	4 to 9	4.5 to 8.5	7.0
B4 rate	< 1.5	< 1	0.7
Positive predictive value B4	–	–	72.2
Positive predictive value B3	–	–	14.6

* Figures from audit of *National Breast Screening Pathology Audit 2015***.**[34]

How to interpret the results

The figures are inter-related and a strategy to improve one figure will affect others – thus attempts to improve the sensitivity may increase the false-positive rate, attempts to improve the specificity will increase the false-negative rate and so on. Also attempts to reduce the benign biopsy rate by not biopsying the majority of lesions called benign on core biopsy will reduce the specificity where this is based on benign surgical histology results rather than on all biopsied cases.

In general, the performance of pathologists as assessed by the positive predictive values is good, although some pathologists are more cautious in diagnosis. This caution can be inferred from the statistics in the units with high positive predictive values for B4 and B3 diagnoses and also in units that have a high suspicious rate.

Quality assurance and key performance indicators relating to core biopsy

National medians and use of control charts

Control charts, also known as funnel plots, are helpful in identifying where variation in performance is significantly different to the average and are used in the national breast screening pathology

audit.[34] Both the upper and lower control limit lines are plotted at 95% (2 standard deviations from the mean) and 99% (3 standard deviations from the mean) confidence intervals. Any data points within the control limits are deemed to be subject to natural variation. Data points outside of the control limits (either above or below the control limit lines) are significantly different and are deemed to be a result of special cause variation. Breast screening services or pathologists (if individual performance statistics are produced) falling outside of the control limits are referred to as outliers. As expected, the confidence intervals narrow as the number of cases increase. Hence, it is sensible to examine the numerator and denominator that comprise the statistic when looking at key performance indicators (KPIs). In some cases, even over an aggregated period of several years, the numbers are very small and the addition or reduction of one or two cases may be sufficient for a service no longer to remain an outlier. Also, whilst performance on an indicator may be statistically significant, it does not always mean that it will have clinical relevance.

The BQA reports produce statistics on 12 key indicators, some of which have minimum and achievable standards. Control charts may identify outliers that represent statistically high or low levels of performance in comparison to the average. Depending on the indicator being assessed, being a high or low outlier may demonstrate optimal performance, whilst for others, investigations should take place to determine the nature of this special cause variation. Causes of special cause variation could be attributable to a number of different factors, such as data inaccuracies, population/case mix, staff, laboratory procedures, processing, protocols or equipment (both for radiology and pathology).

Where there are no core performance targets for an indicator, it may be useful to assess the performance of a screening service against the national median value.

The Quality Assurance (QA) service (QA coordinator for pathology and the Quality Assurance Reference Centre [QARC]) should be contacted for advice on undertaking audit where the service is deemed to be performing significantly less well in comparison to other services nationally. Where data is produced at the screening service level, this will pertain to the laboratories that provide pathology support for that service. The majority of units nationally have pathology provision at one laboratory. However, just under 20% of units send specimens to multiple laboratories. In these circumstances, it is important that the statistics are produced by individual hospital location to assess whether all laboratories are performing similarly, to identify if performance is different at any particular lab.

As pathology performance is operator dependent, it may be advisable to seek advice from the QA coordinator for radiology to audit certain cases where there is suspicion that the target lesion has been missed or where there is perceived to be a very low threshold for needle biopsies at a service.

The BQA reports

The NBSS computer system can produce BQA reports by all tests or by client (which gives the most significant needle biopsy result only). The latter should be used to assess the performance of the screening service and the related laboratory or laboratories. See Table 2 for definitions of standards and Table 5 for suggested thresholds and current median values.

Absolute and complete sensitivity

If a service is a high outlier for absolute sensitivity, this demonstrates optimal performance due to the unequivocal identification of malignancy. Low outliers on this indicator should examine rates of complete sensitivity. If this is not also low, or conversely it is identified as being a high outlier, the pathologist may possibly be categorising lesions with sufficient features for a B5 diagnosis as B3 or B4. This is problematic as it may result in unnecessary diagnostic open biopsies. This may not be a pathology issue and the diagnostic equipment used for targeting the lesion should be assessed as lack of vacuum-assisted biopsies (VAB) may result in less tissue for examination, resulting in more B3 or B4 diagnoses, which may have yielded a B5 outcome with a larger specimen. If absolute and complete sensitivity are low, the B1 core biopsy rate from cancers and false-negative rate should be

examined as cancers may have been reported non-operatively as B1 or B2, which requires investigation by the radiologist to assess whether the operator has correctly identified the target lesion or whether the cancer has been missed by the pathologist. Also it may be helpful to review the MDT decision process to identify why no further needle biopsies were undertaken.

Specificity (full)

Full specificity demonstrates the most variation in performance at the service level. Much of this is due to the variability in access to and use of VACB within assessment clinics. Full specificity is more likely to be high with accurate identification of benignity and this is not problematic. Low outliers should assess the availability of VACB as this will sometimes lead to more definitive B3 diagnoses which may not require further investigation in the absence of atypia. The B1 core biopsy rate should also be examined as this may be high and could indicate sub-optimal or mis-sampling by the operator or may demonstrate a low threshold for sampling by the radiologist or advanced practitioner. The proportion of women assessed undergoing needle tests could be compared to the national average and the PPV of referral (the number of cancers detected expressed as a proportion of all women referred from screening for assessment), which may indicate this could be contributory factor. If the PPV of referral is low, this may be due to radiological aspects of performance. It is suggested that a sample (proportionate to the size of the service) of B1–B3 slides are anonymised and reviewed to confirm correct diagnosis. Another factor is the distinction between B1 and B2 by the pathologist, in particular how minor changes such as mild fibrocystic change is classified (as highlighted by the national B1/B2 audit). Also some pathologists inappropriately use the B1 category if the biopsy may not explain the radiological or clinical abnormality. The multidisciplinary meeting should judge whether the core biopsy has adequately sampled the lesion.

Positive predictive value of B5 diagnosis

Most services and laboratories are high outliers for PPV B5 as there are very few false-positive outcomes in the NHSBSP. Services who do not achieve 100% should carefully review all potential false-positive cases, which are on the increase due to the detection of small cancers that are removed in their entirety non-operatively by VACB or needle core biopsy and also the increasing use of neo-adjuvant chemotherapy. Any true false-positive cases should be reviewed as recommended by national guidance, which includes review of the pathology specimen followed by review of the MDT decision.[3] Any proven error should be reported within the Trust and pathology department via the established clinical governance procedures. It should also be reported to the local director of breast screening, who should escalate details of the review to the QA service via the established reporting channels. It is good practice to share the specifics of these rare cases with the National Coordinating Committee for Breast Pathology.

Positive predictive value of B4 diagnosis

Many services and laboratories will not report many specimens with an outcome of B4 on either an annual basis or over a longer aggregated period. Less than 1% of all needle biopsy specimens are reported as B4. As a result, the confidence intervals of this statistic for an individual service are wide. Consequently, caution must be exercised when reviewing it. Low and high outliers, whilst statistically significant, may not be clinically relevant. A high PPV could indicate over-caution in reporting of malignancy, whilst a low PPV may indicate a low threshold for reporting the suspicious category. It is recommended that the proportion of B3 lesions are examined to assess whether there is an excess use of this category that is not explained by VACB use and, if the PPV B3 is high, this may represent over-caution by the pathologist or sub-optimal sampling by the operator.

Positive predictive value of B3 diagnosis

Low outliers should relate this information with the overall percentage of the B3 category and benign biopsy rates. A low threshold for reporting biopsies as B3 will result in a high B3 rate and a subsequent increased benign biopsy rate. This in turn will lead to a low PPV for B3. Pathology services should also investigate the use of VAB at the associated breast service. A high volume of VAB procedures may result in no further diagnostic intervention following a B3 result, especially

when no epithelial atypia is present. High outliers should examine the number, and type, of needle biopsies undertaken at assessment, as adequate diagnostic work-up in the first instance may have prevented an unnecessary surgical biopsy with malignant histology. In future the proportion of B3 diagnoses with and without atypia will be recorded and analysis of the PPVs for these two groups will be performed.

Negative predictive value of B2 diagnosis

This indicator measures the percentage of B2 results that were not malignant in the surgical specimen. Many services will be high outliers for negative predictive value, which indicates that no cancers had a definitive outcome of B2 non-operatively. Services who are a low outlier on this indicator should review the MDT decision to establish why further needle biopsies were not undertaken prior to open surgical biopsy.

False-negative rate

Many services will be low outliers on this indicator, which demonstrates good performance and accurate targeting of the lesion by the operator. Services who are high outliers should review the MDT decision-making process to assess the targeting of the lesion and the reasons for failure to repeat core biopsies.

False-positive rate

The majority of services will be low outliers on this indicator as true false-positives are an exceptionally rare occurrence in the programme. Any potential false-positive cases should be reviewed according to national guidance, which includes review of the pathology specimen followed by review by the relevant MDT.[3] In most potential false-positive cases, the malignancy has been removed by the NCB or VAB or the patient received preoperative systemic treatment with complete pathological response. Any proven error should be reported within the Trust and pathology department via the established clinical governance procedures. It should also be reported to the local director of breast screening, who should escalate details of the review to the QA service. It is good practice to share the specifics of these rare cases with the National Coordinating Committee for Breast Pathology.

B1 Core biopsy rate from cancers

Most services are low outliers on this indicator with no cancers having the most significant core result of B1, which demonstrates good performance. It is recommended that a review of the MDT process is undertaken at services for any cancers that had a B1 outcome reported non-operatively. It is possible that the correct diagnosis was missed by the pathologist or the target lesion may not have been sampled.

Suspicious rate

High outliers should examine the proportion of cases that are B3 and B4 to establish whether the service are outliers for the reporting of both categories. The availability and use of VACB could be partly attributable for high rates of B3 outcomes and the benign biopsy rate should be examined as high B3 rates in conjunction with a high suspicious rate may indicate over-caution by the pathologist or MDT decision-making process. A high suspicious rate may also correlate with a low absolute sensitivity. Lack of or underutilisation of VACB may prevent a more definitive diagnosis by the pathologist.

Low outliers on this indicator may demonstrate good performance if this is in conjunction with high PPV B5 and B4. If levels of complete sensitivity are low, the service are underutilising the B3/B4 categories, which may be due to the operator missing the target lesion or a pathology issue.

In future there will be separate analyses of the proportion of B3 diagnoses and the proportion of B4 diagnoses.

Education and training

The Training and Education Sub-group of the National Coordinating Committee for Breast Screening Pathology is responsible for organising breast screening pathology courses, including a biannual non-operative diagnosis course. Information on these courses can be obtained from Nottingham International Breast Education Centre. Additional experience may be gained by secondment to neighbouring centres of expertise and participating in EQA schemes.

It is recognised that courses can only provide baseline knowledge and acceptable levels of performance, particularly in core biopsy and cytological diagnosis, can only be realistically achieved by experience on in routine practice. Regular self-audit of non-operative diagnosis results should be undertaken and is of educational value.

Appendix D NHSBSP wide bore needle biopsy form

Surname ..... Forenames ..... Date of birth .....

Screening no ..... Hospital no ..... NHS no .....

Date performed ..... Location ..... …..Operator ..... Centre .....

Kv ..... Total exposures ..... Total films .....

Projection ..... Marker ..... Localisation type .....

Side: Right □ Left □

Quadrant: Upper outer quadrant □ Lower outer quadrant □
Upper inner quadrant □ Lower inner quadrant □
Retroareolar □ Axilla □

Localisation type: Palpation □ Stereotactic □ Ultrasound □

Number of cores .....

Specimen type: Core biopsy □ Vacuum-assisted *excision* biopsy □
Vacuum-assisted *diagnostic* biopsy □
Vacuum-assisted biopsy – not further specified □
Nipple/skin biopsy □

Calcification present on specimen x-ray? Yes □ No □ Radiograph not seen □

Comment.....

.....

Date reported .....Pathologist ..... Report number .....

Histological opinion B1 Unsatisfactory/normal tissue only □
B2 Benign □
B3 Uncertain malignant potential with epithelial atypia □
B3 Uncertain malignant potential without epithelial atypia □
B4 Suspicious □
B5 Malignant type (a) *in situ* □
(b) invasive □
(c) not assessable □

Histological calcification Absent □ Benign □ Malignant □ Both □

Optional further information

Benign lesion

Complex sclerosing lesion/radial scar □ Fibroadenoma □ Multiple papilloma □

Periductal mastitis/duct ectasia □ Fibrocystic change □ Solitary papilloma □

Sclerosing adenosis □ Solitary cyst □ Columnar cell change □

Other (please specify) ……

Epithelial proliferation Not present □ Present without atypia □

Present with atypia (ductal) □ Present with atypia (lobular) □

Malignant lesion

In situ carcinoma Not present □ Ductal □ Lobular □ Pagets □

DCIS grade High □ Intermediate □ Low □ Not assessable □

Invasive carcinoma Present □ Not present □

Size invasive tumour .....mm (largest dimension, if available)

Type: No special type (ductal NST) □

Pure special type (90% purity specify components present below) □:

Mixed tumour type (50–90% special type component, specify components present below) □:

Other malignant tumour (please specify) .....

Specify type component(s) present for pure special type and mixed tumour types:

Tubular/cribriform □ Lobular □ Mucinous □ Medullary/atypical medullary □

Ductal/no special type □ Other (please specify) .....

Invasive grade 1 □ 2 □ 3 □ Not assessable □

Oestrogen receptor status Positive (≥1%) □ Negative (<1%) □

Percentage positive tumour cells …….

On-slide positive control material: Present □ Absent □

Progesterone receptor status (optional): Positive (≥1%) □ Negative (<1%) □

Percentage positive tumour cells …….

On-slide positive control material: Present □ Absent □

HER2 immunohistochemical score: 0 negative □ 1+ negative □ 2+ Borderline □ 3+ Positive □

FISH/ CISH ratio: .....

Status: Amplified □ Non-amplified □ Borderline □ Not performed □

HER2 copy no: …… Chromosome 17 no: ……..

Final HER2 status[†]: Positive □ Negative □

Appendix E RCPath proforma for reporting of breast core biopsy

Surname: …… Forenames: …… Date of birth: ……..…

Sex: ……. Hospital: ……..…….. Hospital no: ...……..…...

NHS no: …… ……...Date of surgery: ……..Date of report: ……...…...

Authorisation: ……..…… Report no: ……Date of receipt:…….…….

Pathologist: ……..…… Surgeon: ……..……... …

Side†: Left □ Right □

Quadrant†: Upper outer quadrant □ Lower outer quadrant □
Upper inner quadrant □ Lower inner quadrant □
Retroareolar □

Number of cores if known .....

Specimen type†: Needle core biopsy □
Vacuum-assisted *excision* biopsy □
Vacuum-assisted *diagnostic* biopsy □
Vacuum-assisted biopsy – not further specified □

Calcification present on specimen x-ray? Yes □ No □ Radiograph not seen □

Comment
.....

Histological opinion† B1 (Normal) □
B2 (Benign) □
B3 (Uncertain malignant potential with epithelial atypia) □
B3 (Uncertain malignant potential without epithelial atypia) □
B4 (Suspicious) □
B5a (Malignant *in situ*) □
B5b (Malignant invasive) □
B5c (Malignant not assessable) □

If biopsy taken for assessment of calcification:
Histological calcification: Not identified □ Benign □ Malignant □ Both benign and malignant □

In situ carcinoma† Not identified □ Ductal □ Lobular□

DCIS grade† High □ Intermediate □ Low □ Cannot be assessed □

Invasive carcinoma† Not identified □ Present □

Type†: No special type (ductal NST) □
Pure special type (90% purity specify components present below) □
Mixed tumour type (50–90% special type component, specify components present below) □
Other malignant tumour (please specify) .....

† Data items which are currently part of the Cancer Outcomes and Services Dataset (COSD) version 6

Specify type component(s) present for pure special type and mixed tumour types†:

Tubular/cribriform □ Lobular □ Mucinous □ Medullary/atypical medullary □
Ductal/no special type □ Other □ (please specify) .....

Invasive carcinoma grade†: 1 □ 2 □ 3 □ Cannot be assessed □

Oestrogen receptor status†: Positive (≥ 1%) □ Negative (<1%) □
Percentage positive tumour cells =……..
On-slide positive control material: Present □ Absent □

HER2 IHC score†: 0 negative □ 1+ negative □ 2+ Borderline □ 3+ Positive □

FISH/ CISH ratio: .....

Status†: Amplified □ Non-amplified □ Borderline □ Not performed □

HER2 copy no: …… Chromosome 17 no: ……..

Final HER2 status†: Positive □ Negative □

SNOMED† codes: T ……. M ……

Date reported ..... Pathologist .....

† Data items which are currently part of the Cancer Outcomes and Services Dataset (COSD) version 6

Appendix F RCPath proforma for reporting of breast FNAC

Surname: …… Forenames: …… Date of birth: ……..…

Sex: …….. Hospital: ……. Hospital no: ...……..…..

NHS no: …… ……...Date of surgery: ……...Date of report: ……...…..

Authorisation: ……..…… Report no: ……Date of receipt:…….……..

Pathologist: ……..…… Surgeon: ……..…….. …

Side†: Left □ Right □

Location†: Upper outer quadrant □ Lower outer quadrant □
Upper inner quadrant □ Lower inner quadrant □
Retroareolar □

Cytological opinion† C1 □ (Inadequate/unsatisfactory)
C2 □ (Benign)
C3 □ (Uncertain)
C4 □ (Suspicious)
C5 □ (Malignant)

Comment

.....

.....

SNOMED† codes: T ……. M …..……

Date reported ..... Pathologist .....

† Data items which are currently part of the Cancer Outcomes and Services Dataset (COSD) version 6

Appendix G RCPath proforma for reporting of axillary FNAC

Surname: …… Forenames: …… Date of birth: ……..…
Sex: ……. Hospital: ……. Hospital no: ...……..…..
NHS no: …… ……...Date of surgery: ……...Date of report: ……...…..
Authorisation: ……..…… Report no: ……Date of receipt:…….…….
Pathologist: ……..…… Surgeon: ……..…….. …

Side†: Left □ Right □

Location†: Axillary LN □

Cytological opinion† LC1 □ (Inadequate/unsatisfactory)
LC2 □ (Benign)
LC3 □ (Uncertain)
LC4 □ (Suspicious)
LC5 □ (Malignant)

Comment

.....

.....

SNOMED† codes: T ……. M …..……

Date reported ..... Pathologist .....

† Data items which are currently part of the Cancer Outcomes and Services Dataset (COSD) version 6

Appendix H RCPath proforma for reporting of axillary core biopsy

Surname: …… Forenames: …… Date of birth: ……..…

Sex: ……. Hospital: ……. Hospital no: ...……..…..

NHS no: …… ……...Date of surgery: ……..Date of report: ……...…..

Authorisation: ……..…… Report no: ……Date of receipt:…….…….

Pathologist: ……..…… Surgeon: ……..……... …

Side†: Left □ Right □

Location†: Axillary LN □

Opinion† LB1 □ (Inadequate/Unsatisfactory)
LB2 □ (Normal/Benign)
LB3 □ (Uncertain)
LB4 □ (Suspicious)
LB5 □ (Malignant)

Comment

.....

.....

SNOMED† codes: T ……. M ……..……

Date reported ..... Pathologist .....

† Data items which are currently part of the Cancer Outcomes and Services Dataset (COSD) version 6

Appendix I RCPath proforma for reporting of breast core biopsy in list format

Element name	Values	Implementation notes
Side	Single selection value list: • Left • Right	
Quadrant	Single selection value list: • Upper outer quadrant • Lower outer quadrant • Upper inner quadrant • Lower inner quadrant • Retroareolar	
Number of cores	Integer	
Specimen type	Single selection value list: • Needle core biopsy • Vacuum-assisted excision biopsy • Vacuum-assisted diagnostic biopsy • Vacuum-assisted biopsy – not further specified	
Calcification present on specimen x-ray	Single selection value list: • Yes • No • Radiograph not seen	
Histological opinion	Single selection value list: • B1 (Normal) • B2 (Benign) • B3 (Uncertain malignant potential with epithelial atypia) • B3 (Uncertain malignant potential without epithelial atypia) • B4 (Suspicious) • B5a (Malignant *in situ*) • B5b (Malignant invasive) • B5c (Malignant not assessable)	
Histological calcification	Single selection value list: • Not identified • Benign • Malignant • Both benign and malignant • Not applicable	

Element name	Values	Implementation notes
***In situ* carcinoma**	Multiple select value list: • Not identified • Ductal • Lobular	
DCIS grade	Single selection value list: • High • Intermediate • Low • Cannot be assessed • Not applicable	Not applicable if '*In Situ* carcinoma' is 'Not identified' or 'Lobular' only.
Invasive carcinoma	Single selection value list: • Not identified • Present	
Type	Single selection value list: • No special type (ductal NST) • Pure special type (90% purity specify components present below) • Mixed tumour type (50–90% special type component, specify components present below) • Other malignant tumour	
Type, Other – specify	Free text	Only required if 'Type, Other' – 'Malignant tumour' is selected.
Specify type component(s) present for pure special type and mixed tumour types	Multiple select value list: • Tubular/cribriform • Lobular • Mucinous • Medullary/atypical medullary • Ductal/no special type • Other	
Specify type component(s) present for pure special type and mixed tumour types, Other – specify	Free text	Only required if 'Specify type component(s) present for pure special type and mixed tumour types, Other' is selected.
Invasive tumour grade	Single selection value list: • 1 • 2 • 3 • Cannot be assessed	

Element name	Values	Implementation notes
Oestrogen receptor status	Single selection value list: • Positive • Negative • Not performed	
Oestrogen receptor, percentage positive tumour cells	Integer, range 0–100	
On-slide control material	Single selection value list: • Present • Absent	
HER2 IHC score	Single selection value list: • 0 • 1+ • 2+ • 3+ • Not performed	
FISH/CISH ratio	Number	
FISH/CISH Status	Single selection value list: • Amplified • Non-amplified • Borderline • Not performed	
HER 2 copy no	Number	
Chromosome 17 no	Number	
Final HER2 status	Single selection value list: • Positive • Negative • Not performed	
Comment	Free text	
SNOMED Topography code	May have multiple codes. Look up from SNOMED tables.	
SNOMED Morphology code	May have multiple codes. Look up from SNOMED tables.	

Appendix J RCPath proforma for reporting of breast FNAC in list format

Element name	Values	Implementation notes
Side	Single selection value list: • Left • Right	
Quadrant	Single selection value list: • Upper outer quadrant • Lower outer quadrant • Upper inner quadrant • Lower inner quadrant • Retroareolar	
Cytological opinion	Single selection value list: • C1 (Inadequate/unsatisfactory) • C2 (Benign) • C3 (Uncertain) • C4 (Suspicious) • C5 (Malignant)	
Comment	Free text	
SNOMED Topography code	May have multiple codes. Look up from SNOMED tables.	
SNOMED Morphology code	May have multiple codes. Look up from SNOMED tables.	

Appendix K RCPath proforma for reporting of axillary FNAC in list format

Element name	Values	Implementation notes
Side	Single selection value list: • Left • Right	
Cytological opinion	Single selection value list: • LC1 (Inadequate/unsatisfactory) • LC2 (Benign) • LC3 (Uncertain) • LC4 (Suspicious) • LC5 (Malignant)	
Comment	Free text	
SNOMED Topography code	May have multiple codes. Look up from SNOMED tables.	
SNOMED Morphology code	May have multiple codes. Look up from SNOMED tables.	

Appendix L RCPath proforma for reporting of axillary core biopsy in list format

Element name	Values	Implementation notes
Side	Single selection value list: • Left • Right	
Opinion	Single selection value list: • LB0 • LB1 • LB2 • LB3 • LB4 • LB5	
Comment	Free text	
SNOMED Topography code	May have multiple codes. Look up from SNOMED tables.	
SNOMED Morphology code	May have multiple codes. Look up from SNOMED tables.	

Appendix M Recommended SNOMED codes for breast pathology

Neoplasms

The following are SNOMED3 equivalents of the ICD-O codes that are recognised internationally. Codes marked with an asterisk (*) are proposed codes that have not yet been formally included in ICD-O.

The licensing rights to SNOMED are held by IHTSDO.

Morphological codes	SNOMED code	SNOMED CT terminology	SNOMED CT code
Adenocarcinoma NOS	M-81403	Adenocarcinoma, no subtype (morphologic abnormality)	35917007
Adenoid cystic carcinoma	M-82003	Adenoid cystic carcinoma (morphologic abnormality)	11671000
Adenoma of nipple	M-85060	Adenoma of the nipple (morphologic abnormality)	65787003
Adenomyoepithelioma (benign)	M-89830	Adenomyoepithelioma (morphologic abnormality)	128765009
Adenomyoepithelioma (malignant)	M-89833*	Adenomyoepithelioma with carcinoma (morphologic abnormality)	703644009
Angiosarcoma	M-91203	Hemangiosarcoma (morphologic abnormality)	39000009
Apocrine carcinoma	M-85733	Adenocarcinoma with apocrine metaplasia (morphologic abnormality)	22694002
Atypical medullary carcinoma	M-85133	Atypical medullary carcinoma (morphologic abnormality)	128698005
Carcinoma with osteoclast-like giant cells	M-80353	Carcinoma with osteoclast-like giant cells (morphologic abnormality)	128631001
Cribriform carcinoma	M-82013	Cribriform carcinoma (morphologic abnormality)	30156004
DCIS	M-85002	Intraductal carcinoma, non-infiltrating, no International Classification of Diseases for Oncology subtype (ICDO) (morphologic abnormality)	86616005
Ductal adenoma	M-85030	Intraductal papilloma (morphologic abnormality)	5244003
Ductal carcinoma/NST	M-85003	Infiltrating duct carcinoma (morphologic abnormality)	82711006
Encysted papillary carcinoma	M-85042	Noninfiltrating intracystic carcinoma (morphologic abnormality)	89277004

Morphological codes	SNOMED code	SNOMED CT terminology	SNOMED CT code
Fibroadenoma	M-90100	Fibroadenoma, no ICDO subtype (morphologic abnormality)	65877006
Fibroadenoma juvenile	M-90300	Juvenile fibroadenoma (morphologic abnormality)	46212000
Fibromatosis-like carcinoma	M-85723	Adenocarcinoma with spindle cell metaplasia (morphologic abnormality)	68358000
Granular cell tumour	M-95800	Granular cell tumour (morphologic abnormality)	12169001
Haemangioma	M-91200	Hemangioma, no ICDO subtype (morphologic abnormality)	2099007
Hamartoma	M-90203	Hamartoma (morphologic abnormality)	51398009
Inflammatory carcinoma	M-85303	Inflammatory carcinoma (morphologic abnormality)	32968003
Intraductal papilloma	M-85030	Intraductal papilloma (morphologic abnormality)	5244003
Intraductal papilloma with DCIS	M-85032	Noninfiltrating intraductal papillary adenocarcinoma (morphologic abnormality)	30566004
Invasive micropapillary carcinoma	M-85073*	Invasive micropapillary carcinoma of breast (morphologic abnormality)	703578005
Invasive papillary carcinoma	M-85033	Intraductal papillary adenocarcinoma with invasion (morphologic abnormality)	64524002
LCIS	M-85202	Lobular carcinoma *in situ* (morphologic abnormality)	77284006
Lipoma	M-88500	Lipoma, no ICDO subtype (morphologic abnormality)	46720004
Lobular carcinoma	M-85203	Lobular carcinoma (morphologic abnormality)	89740008
Low-grade adenosquamous carcinoma	M-85703	Adenocarcinoma with squamous metaplasia (morphologic abnormality)	15176003
Lymphoma NOS	M-95903	Malignant lymphoma, no ICDO subtype (morphologic abnormality)	21964009
Medullary carcinoma	M-85103	Medullary carcinoma (morphologic abnormality)	32913002
Metaplastic carcinoma NOS	M-85753	Metaplastic carcinoma (morphologic abnormality)	128705006

Morphological codes	SNOMED code	SNOMED CT terminology	SNOMED CT code
Metastatic carcinoma	M-80106	Carcinoma, metastatic (morphologic abnormality)	79282002
Mixed carcinoma	Specify subtypes		
Mucinous carcinoma	M-84803	Mucinous adenocarcinoma (morphologic abnormality)	72495009
Myoepithelial carcinoma	M-89823	Malignant myoepithelioma (morphologic abnormality)	128884000
Myofibroblastoma	M-88250	Myofibroblastoma (morphologic abnormality)	128738002
Neuroendocrine carcinoma (poorly differentiated)	M-80413	Small cell carcinoma (morphologic abnormality)	74364000
Neuroendocrine carcinoma (well differentiated)	M-82463	Neuroendocrine carcinoma (morphologic abnormality)	55937004
Nodular fasciitis	M-88280*	Nodular fasciitis (morphologic abnormality)	703616008
Pagets disease of nipple	M-85403	Paget's disease, mammary (morphologic abnormality)	2985005
Papillary carcinoma *in situ*	M-85032	Noninfiltrating intraductal papillary adenocarcinoma (morphologic abnormality)	30566004
Papilloma multiple	M-85050	Intraductal papillomatosis (morphologic abnormality)	32296002
Phyllodes benign	M-90200	Phyllodes tumour, benign (morphologic abnormality)	16566002
Phyllodes malignant	M-90203	Phyllodes tumour, malignant (morphologic abnormality)	87913009
Phyllodes borderline	M-90201	Phyllodes tumour, borderline (morphologic abnormality)	71232009
Pleomorphic carcinoma	M-80223	Pleomorphic carcinoma (morphologic abnormality)	16741004
Pleomorphic LCIS	M-85192*	Pleomorphic lobular carcinoma *in situ* (morphologic abnormality)	444591006
Secretory carcinoma	M-85023	Juvenile carcinoma of the breast (morphologic abnormality)	41919003
Signet ring carcinoma	M-84903	Signet ring cell carcinoma (morphologic abnormality)	87737001
Spindle cell carcinoma	M-80323	Spindle cell carcinoma (morphologic abnormality)	65692009

Morphological codes	SNOMED code	SNOMED CT terminology	SNOMED CT code
Squamous cell carcinoma	M-80703	Squamous cell carcinoma, no ICDO subtype (morphologic abnormality)	28899001
Syringomatous adenoma of nipple	M-84070	Syringoma (morphologic abnormality)	71244007
Tubular adenoma	M-82110	Tubular adenoma, no ICDO subtype (morphologic abnormality)	19665009
Tubular carcinoma	M-82113	Tubular adenocarcinoma (morphologic abnormality)	4631006
Undifferentiated carcinoma	M-80203	Carcinoma, undifferentiated (morphologic abnormality)	38549000

Other conditions

Term	SNOMED code	SNOMED CT terminology	SNOMED CT code
Abscess	M-41610	Abscess (morphologic abnormality)	44132006
Accessory/ ectopic breast	D4-48012	Accessory breast (disorder)	18166000
Apocrine metaplasia	M-73310	Apocrine metaplasia (morphologic abnormality)	81274009
Atypical apocrine hyperplasia	M-73315	Atypical apocrine metaplasia (morphologic abnormality)	103673004
Atypical ductal hyperplasia	M-72175	Atypical intraductal hyperplasia (morphologic abnormality)	6660000
Atypical lobular hyperplasia	M-72105	Atypical lobular hyperplasia (morphologic abnormality)	33889003
Calcification	M-55400	Calcified structure (morphologic abnormality)	54497001
Collagenous spherulosis	M-72171	Collagenous spherulosis (morphologic abnormality)	447298005
Columnar cell atypia	M-67020	Columnar cell atypia (morphologic abnormality)	55465005
Columnar cell lesions	M-74240	Blunt duct adenosis (morphologic abnormality)	58811002
Complex sclerosing lesion	M-78731	Radial scar (morphologic abnormality)	133855003
Cyst NOS	M-33400	Cyst (morphologic abnormality)	12494005
Duct ectasia	M-32100	Duct ectasia (morphologic abnormality)	110420004

Morphological codes	SNOMED code	SNOMED CT terminology	SNOMED CT code
Epithelial hyperplasia without atypia	M-72170	Intraductal hyperplasia (morphologic abnormality)	67617000
Excision margins tumour free	M-09400	Surgical margin uninvolved by tumour (finding)	55182004
Fat necrosis	M-54110	Fat necrosis (morphologic abnormality)	79682009
Fibrocystic change	M-74320	Fibrocystic disease (morphologic abnormality)	28092006
Fibromatosis	M-76100	Angiomatosis (morphologic abnormality)	14350002
Fistula	M-39300	Acquired fistula (morphologic abnormality)	51711001
Foreign body reaction	M-44140	Foreign body giant cell granuloma (morphologic abnormality)	37058002
Galactocoele	M-33220	Galactocele associated with hildbirth (disorder)	87840008
Gynaecomastia	M-71000	Hypertrophy (morphologic abnormality)	56246009
Infarction	M-54700	Infarct (morphologic abnormality)	55641003
Inflammation acute	M-41000	Acute inflammation (morphologic abnormality)	4532008
Inflammation chronic	M-43000	Chronic inflammation (morphologic abnormality)	84499006
Inflammation granulomatous	M-44000	Granulomatous inflammation (morphologic abnormality)	6266001
Involutional change	M-79140	Menstrual involution of breast (morphologic abnormality)	33429008
Juvenile hypertrophy	D7-90404	Pubertal breast hypertrophy (disorder)	198113009
Lactational change	M-82040	Lactating adenoma (morphologic abnormality)	128651002
Metaplasia atypical	M-73005	Atypical metaplasia (morphologic abnormality)	125544002
Metaplasia chondroid	M-73600	Cartilaginous metaplasia (morphologic abnormality)	112671001
Metaplasia epithelial (clear cell, etc.)	M-73200	Epithelial metaplasia (morphologic abnormality)	54725001
Metaplasia osseous	M-73400	Osseous metaplasia (morphologic abnormality)	38109001
Metaplasia squamous	M-73220	Squamous metaplasia (morphologic abnormality)	83577005

Morphological codes	SNOMED code	SNOMED CT terminology	SNOMED CT code
Microglandular adenosis	M-72480	Microglandular hyperplasia (morphologic abnormality)	2953007
Microglandular hyperplasia	M-72450	Adenofibromyomatous hyperplasia (morphologic abnormality)	88000003
Morphological description only	M-09350	Morphologic description only (finding)	85728002
Mucocoele-like lesion	M-33440	Mucous cyst (morphologic abnormality)	19633006
Normal: NOS	M-00100	Normal tissue (finding)	30389008
PASH	M-72430	Stromal hyperplasia (morphologic abnormality)	75235002
Plasma cell mastitis	M-43060	Plasma cell inflammation (morphologic abnormality)	26246006
Pregnancy	M-68080	Pregnancy pattern (morphologic abnormality)	68737009
Radial scar	M-78731	Radial scar (morphologic abnormality)	133855003
Radiotherapy effect	M-11600	Radiation injury (morphologic abnormality)	81018009
Sclerosing adenosis	M-74220	Fibrosing adenosis (morphologic abnormality)	50916005
Surgical wound or cavity	M-14020	Surgical wound (morphologic abnormality)	112633009
Weddelite	M-55400	Calcified structure (morphologic abnormality)	54497001

Appendix N Summary table – Explanation of levels of evidence

(Adopted from Palmer K *et al. BMJ* 2008; 337:1832.)

Level of evidence	**Nature of evidence**
Level A	At least one high-quality meta-analysis, systematic review of randomised controlled trials or a randomised controlled trial with a very low risk of bias and directly attributable to the target cancer type or A body of evidence demonstrating consistency of results and comprising mainly well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias, directly applicable to the target cancer type.
Level B	A body of evidence demonstrating consistency of results and comprising mainly high-quality systematic reviews of case-control or cohort studies and high-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relation is causal and which are directly applicable to the target cancer type or Extrapolation evidence from studies described in A.
Level C	A body of evidence demonstrating consistency of results and including well-conducted case-control or cohort studies and high quality case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relation is causal and which are directly applicable to the target cancer type or Extrapolation evidence from studies described in B.
Level D	Non-analytic studies such as case reports, case series or expert opinion or Extrapolation evidence from studies described in C.
Good practice point (GPP)	Recommended best practice based on the clinical experience of the authors of the writing group

Appendix O AGREE compliance monitoring sheet

The cancer datasets of The Royal College of Pathologists comply with the AGREE II standards for good quality clinical guidelines (www.agreetrust.org). The sections of this dataset that indicate compliance with each of the AGREE II standards are indicated in the table.

AGREE standard	Section of dataset
Scope and purpose	
1. The overall objective(s) of the guideline is (are) specifically described	Foreword, 1
2. The clinical question(s) covered by the guidelines is (are) specifically described	1
3. The patients to whom the guideline is meant to apply are specifically described	1
Stakeholder involvement	
4. The guideline development group includes individuals from all the relevant professional groups	Foreword
5. The patients' views and preferences have been sought	n/a
6. The target users of the guideline are clearly defined	1
7. The guideline has been piloted among target users	Foreword
Rigour of development	
8. Systematic methods were used to search for evidence	Foreword
9. The criteria for selecting the evidence are clearly described	Foreword
10. The methods used for formulating the recommendations are clearly described	Foreword
11. The health benefits, side effects and risks have been considered in formulating the recommendations	Foreword
12. There is an explicit link between the recommendations and the supporting evidence	2
13. The guideline has been externally reviewed by experts prior to its publication	Foreword
14. A procedure for updating the guideline is provided	Foreword
Clarity of presentation	
15. The recommendations are specific and unambiguous	2–4
16. The different options for management of the condition are clearly presented	1–4
17. Key recommendations are easily identifiable	2, 3
18. The guideline is supported with tools for application	Appendices A–M
Applicability	
19. The potential organisational barriers in applying the recommendations have been discussed	Foreword
20. The potential cost implications of applying the recommendations have been considered	Foreword
21. The guideline presents key review criteria for monitoring and/or audit purposes	6
Editorial independence	
22. The guideline is editorially independent from the funding body	Foreword
23. Conflicts of interest of guideline development members have been recorded	Foreword