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Aixplorer ShearWave Elastography for ultrasound imaging and assessing suspicious breast lesions

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Summary

Product summary and likely place in therapy	Effectiveness and safety
• The Aixplorer system's ShearWave Elastography mode adds qualitative and quantitative elasticity data to 2D and 3D ultrasound imaging, for characterising breast lesions and detecting breast cancer. • Aixplorer ShearWave Elastography is likely to be used as an adjunct to B-mode greyscale ultrasound for women who are referred to breast assessment clinics, either following positive mammography or ultrasound screening, or as a symptomatic referral from primary care.	• Fourteen diagnostic accuracy studies reporting quantitative Aixplorer ShearWave Elastography 2D parameters against a reference standard (biopsy) were identified. Of these, 5 papers that also estimated the potential impact of the technology on clinical pathways were selected for review (n=78–958). • One large study (n=939 lesions in 958 women) concluded that the addition of Aixplorer ShearWave Elastography has the potential to improve specificity of breast lesion characterisation (that is, reduce false-positive results) compared with B-mode greyscale ultrasound alone, without loss of sensitivity. • Three smaller studies (n=78 to n=142) reported that Aixplorer ShearWave Elastography has the potential to improve ultrasound specificity (reduce false-positive results) and reduce unnecessary biopsies. • One study (n=173) found that adding Aixplorer ShearWave Elastography to ultrasound improved sensitivity. • All 5 studies used retrospective analysis to set elasticity thresholds. • None of the studies showed a direct impact on clinical pathways.

	• No prospective randomised controlled trials reporting the Aixplorer system's impact on clinical pathways were identified.
Technical factors • The Aixplorer system is for use by qualified sonographers and radiologists who are familiar with ultrasound elastography and specifically trained to use the system. It is 1 of 2 ultrasound systems currently available which use dynamic shear wave elastography to quantitatively measure tissue stiffness. • The Aixplorer system conforms to the Digital Imaging and Communications in Medicine (DICOM) 3.0 standard for the communication and management of medical imaging information and related data.	**Cost and resource use** • The Aixplorer system (including the ShearWave Elastography mode) costs £80,095, including a single, reusable transducer for breast imaging. • No published evidence on resource consequences was identified.

Introduction

Breast cancer is the most common cancer in the UK, representing around one-third of all new cancers diagnosed in women (Office for National Statistics 2012). Around 55,000 people are diagnosed with breast cancer in the UK each year, about 350 of whom are men (Breast Cancer Care 2014). Around 12,000 people in the UK die from breast cancer every year, with crude mortality rates of 36 breast cancer deaths for every 100,000 females in the UK and less than 1 for every 100,000 males (Cancer Research UK 2014).

The NHS Breast Screening Programme in England screened 1.97 million women aged 45 years and over in 2012–13 (Health & Social Care Information Centre 2014). Mammographic abnormalities detected in screening are routinely subjected to further assessment through clinical examination, mammographically guided biopsy (fine-needle aspiration or core biopsy), ultrasound imaging (with or without biopsy) or MRI.

The American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) includes a system of nomenclature designed to standardise mammography reporting, reduce confusion in breast imaging interpretations, and aid outcome monitoring. BI-RADS classification can also be derived from greyscale ultrasound and MRI. BI-RADS assessment categories range from 0 to 6, with a critical decision threshold for biopsy protocols between BI RADS 3 (probably benign) and BI-RADS 4a (4 being a suspicious abnormality and 4a being a low suspicion for malignancy).

Ultrasound elastography is an adjunct to conventional greyscale (also termed 'brightness' or 'B-mode') ultrasound imaging, and is used to qualitatively or quantitatively determine the elasticity of tissue. Force is applied across the tissue, and the resulting strain causes changes in tissue dimensions. Stiffness is defined as the ability of the tissue to resist this dimensional change, and elasticity is inversely related to stiffness. Stiffer objects in softer tissue tend to move as a whole, whereas soft tissue compresses more unevenly. Tumour tissue in the breast tends to exhibit increased stiffness (lower elasticity) compared with surrounding normal glandular and fatty soft tissue.

The claimed benefits of ultrasound elastography are improved diagnostic confidence and increased specificity (fewer false positives) compared with conventional B mode greyscale ultrasound alone. The addition of ultrasound elastography data may influence clinical decision-making on lesion classification, potentially reducing the number of people who are recommended for breast tissue biopsy.

Technology overview

This briefing describes the regulated use of the technology for the indication specified, in the setting described, and with any other specific equipment referred to. It is the responsibility of healthcare professionals to check the regulatory status of any intended use of the technology in other indications and settings.

About the technology

Ultrasound elastography uses a compression source to apply force to the tissue and an imaging system to measure the resultant tissue displacement. Compression sources can be either static or dynamic. Static forces are manually applied by the operator or generated by the patient through physical movement. In the dynamic approach, forces are applied using a sequence of intense focused ultrasound pulses produced by the imaging transducer, which generate shear waves in the tissue that propagate outwards, perpendicular to the direction of each pulse. Both static and dynamic forms of compression provide qualitative imaging. Dynamic elastography provides additional quantitative data, and is claimed to be less operator-dependent and more reproducible than static elastography.

The Aixplorer system's ShearWaveElastography mode uses dynamic force to induce a shear wave, the velocity of which is used to calculate a quantitative measure of elasticity (called the Young's modulus) in units of kilopascals. Results are presented as a colour-coded, real-time ShearWave Elastography map of local tissue elasticity, overlaid on the greyscale image. Benign breast lesions, for example fibroadenomas, tend to be relatively elastic with low elasticity values of less than 30 kilopascals, shown on the elastography map as blue. Malignant breast lesions, such as invasive ductal carcinomas, tend to be stiffer with high elasticity values greater than 120 kilopascals, shown as red. Dynamic ShearWave Elastography produces quantitative elasticity values for different tissue types.

CE marking

The Aixplorer ShearWaveElastography ultrasound diagnostic imaging system ('the Aixplorer system') and its related probes were CE-marked to SuperSonic Imagine in March 2009 as a class IIa medical device. Current certification is effective from November 2013 to 2016.

Description

The Aixplorer system is a complete mains-powered ultrasound system based on a 4-wheeled cart. It comprises 4 main components:

- A central processing unit enclosed in the main body of the system, with image acquisition and analysis software and memory storage.
- An adjustable control panel with touch-screen display, trackball and gel holders.
- An adjustable LCD monitor for image viewing and analysis.

- Six ultrasound transducers, each designed for multiple clinical applications (for example abdominal, breast, genitourinary, thyroid and vascular imaging).

The use of the Aixplorer system for general purpose B-mode greyscale ultrasound imaging, doppler fluid flow analysis and non-breast clinical application areas are beyond the scope of this briefing.

The system's ultrasound transducers connect and lock into 1 of 4 ports on the main body below the control panel. Although 4 different transducers can be connected at once, only 1 can be selected and active at a time. Probe holders allow transducers to be stored when not in use.

The 3 transducers designed for breast imaging applications are:

- SuperLinear SL10-2 transducer with 192 elements and 2–10 megahertz bandwidth, used for 2D breast and deep breast imaging.
- The SuperLinear SL15-4 transducer with 256 elements and 4–15 megahertz bandwidth, used for 2D breast, deep breast and superficial breast imaging.
- The SuperLinear Volumetric SLV16-5 transducer with 192 elements and 5–16 megahertz bandwidth, used for 3D breast imaging and volumetric acquisition.

When using the Aixplorer system, the operator selects a transducer and operates the system in B-mode. This produces a 2D, greyscale, ultrasound image tissue anatomy where areas of different tissue density are shown in various shades of grey. The operator adjusts the B-mode imaging parameter controls to obtain the best possible 2D greyscale image, and then the ShearWaveElastography mode may be selected.

The ShearWaveElastography mode creates a real-time colour elasticity map which is superimposed on the greyscale image. The operator can optimise elastography resolution and penetration of the scanned area. A customisable and adjustable elasticity colour bar, displayed alongside the elastography image, provides a visual indication of tissue stiffness. In the default elasticity scale blue indicates soft tissue whereas yellow, orange and red indicate progressively stiffer tissue.

In addition to basic ultrasound imaging measurements such as distance, area and perimeter of the tissue being examined, the Aixplorer system's ShearWaveElastography mode has 4 additional measurement tools. These provide quantitative elasticity information on the stiffness of an area, expressed in kilopascals, or shear wave velocity, expressed in metres per second. The 4 tools are as follows:

- The Quantification Box (Q-Box) shows a moveable and resizable circle on the colour elasticity map. The circle is duplicated on the same region of interest on the B-mode image for reference purposes. This tool measures maximum, minimum, mean and standard deviation elasticity values in the region of interest.
- The Q-Box ratio tool displays 2 separate circles, allowing the tissue elasticity values of 2 different areas to be compared.
- The Q-Box trace tool allows the operator to manually trace around an area to measure the elasticity values within.
- The Multi Q-Box tool calculates the average of several Q-Box measurements.

After analysing the breast images and obtaining quantitative elasticity measurements, the results can be automatically classified according to the BI-RADS scale, which is included in the Aixplorer system software. Images stored on the system's internal hard drive can be sent to the integrated CD/DVD drive, USB-linked printers and memory devices, or DICOM-compatible network devices.

Optional accessories for the Aixplorer system include:

- an integrated black and white thermal printer
- an external colour printer
- a 2-pedal, USB-linked, configurable footswitch (whose function can be configured by the user).

Intended use

Aixplorer ShearWave Elastography, as described in this briefing, is intended for use in non-invasive diagnostic imaging of the breast.

Setting and intended user

Aixplorer ShearWave Elastography is intended for use in secondary care breast assessment clinics. It would be used to assess women referred from the breast screening programme with a positive or inconclusive result, and for people with symptoms or clinical signs of breast cancer referred from primary care. The device is intended for use by qualified sonographers and radiologists who are specifically trained in its use and familiar with ultrasound elastography.

Current NHS options

Ultrasound elastography may come installed as standard, or as an optional add-on for existing ultrasound imaging systems that are widely used in the NHS in breast assessment clinics (NHSBSP Publication No 49 2010). If optional, it will usually require the installation or activation of an elastography software package on the system, and may require the purchase of an additional transducer.

NICE is aware of the following CE-marked device that appears to provide a similar dynamic elastography function to the Aixplorer ShearWave Elastography system:

- Virtual Touch IQ (Siemens).

Costs and use of the technology

The Aixplorer system consists of several essential components for breast imaging and a number of optional accessories. List prices (excluding VAT) for the essential components are as follows:

- The Aixplorer system, including ShearWave Elastography (with no transducers): £74,095
- SuperLinear SL10-2 transducer: £6000
- SuperLinear SL15-4 transducer: £6000
- SuperLinear Volumetric SLV16-5 transducer: £12,000.

List prices for optional accessories (excluding VAT) are:

- Integrated black and white thermal printer: £600
- External colour printer: £1660
- 2-pedal footswitch: £260.

Standard ultrasound consumables, including water-based gels and transducer covers, can be purchased from NHS Supply Chain. Costs for alternatives to the Aixplorer system (that is, cart-based general ultrasound imaging systems with ultrasound elastography options) are also available to NHS organisations, with price on application, from the Supply Chain capital equipment framework.

The manufacturer provides at least 1 day's clinical application training with each Aixplorer system. Further training days may be customised to the needs of each installation at a cost of £500 per day.

The Aixplorer system has an anticipated lifespan of 7 to 10 years. The manufacturer offers 4 annual maintenance contract options that can be tailored to customer requirements, costing from £3000 to £8000. Each of these options can include preventative and corrective maintenance, safety and performance checks, replacement transducers and spare parts, telephone technical support and remote diagnosis, and software updates. Immediate transducer replacement in the event of accidental damage is also a contract option.

Likely place in therapy

The standard breast cancer screening test for women aged 50 to 70 years is 3-yearly X-ray mammography in the NHS Breast Screening Programme, with a rolling programme to extend the invited age range to 47 to 73 years by 2016. Women over 70 years are not routinely invited to screening, but may continue to be screened if they wish.

Any person presenting to general practice with a palpable breast mass or other clinical signs that could indicate a diagnosis of breast cancer may be referred directly for diagnostic ultrasound imaging, with or without biopsy.

Aixplorer ShearWave Elastography would be used for breast ultrasound assessment, either in those referred from a screening programme or after symptomatic referral. Using Aixplorer ShearWave Elastography mode may improve diagnostic confidence and better indicate whether a biopsy is necessary. Aixplorer ShearWave Elastography mode is not intended to replace biopsy as a diagnostic tool. It claims to improve identification of benign breast lesions with a low level of suspicion (BIRADS 4a) using elasticity information, thereby avoiding unnecessary biopsies of non-malignant tissue.

Specialist commentator comments

One specialist commentator highlighted, with reference to the BMUS 2010 ultrasound safety guidelines, that, in terms of ShearWave elastography exposure time, users should practise the 'As Low As Reasonably Achievable' (ALARA) principle during their clinical scanning. Users should be aware that the maximum thermal index values produced by the Aixplorer system's ShearWave Elastography mode are greater than those produced in B-mode, colour doppler mode and pulsed-wave doppler mode. The maximum thermal index values are given in chapter 11 of the Aixplorer user's guide.

A second specialist commentator noted that the BI-RADS classification system is not routinely used in the UK, but that the U1-U5 classification system, which is roughly analogous, is used and endorsed by both the British Society of Breast Radiology and the NHS Breast Screening Programme. Radiologists using the Aixplorer system's ShearWave Elastography mode must use the correct elasticity parameters and Q-Box size in order to accurately discriminate between benign and malignant lesions. There is no clear consensus in the evidence on which quantitative measurement (for example mean or maximum elasticity) gives the best diagnostic information, what size Q-Box should be used, or how many shear wave images of each lesion need to be assessed.

A third specialist commentator concluded that the evidence summarised in this briefing demonstrates that Aixplorer ShearWave Elastography improves the sensitivity and specificity of the breast ultrasound examination, and enables more reliable lesion classification before a biopsy is done. However, it has not yet been shown whether this actually results in fewer biopsies in clinical practice and, if so, in which patient groups. Clinical practice is unlikely to change until prospective clinical studies showing the technology's clinical impact are conducted.

Equality considerations

NICE is committed to promoting equality and eliminating unlawful discrimination. We aim to comply fully with all legal obligations to:

- promote race and disability equality and equality of opportunity between men and women, and

- eliminate unlawful discrimination on grounds of race, disability, age, sex, gender reassignment, pregnancy and maternity (including women post-delivery), sexual orientation, and religion or belief, in the way we produce our guidance (these are protected characteristics under the Equality Act [2010]).

Breast cancer is a condition which predominantly affects women, with less than 1% of cases affecting men. NHS Breast Screening Programme referrals to breast assessment clinics involve women only. Sex is a protected characteristic under the Equality Act (2010).

In both women and men, the incidence of breast cancer increases with age. Age is also a protected characteristic under the Equality Act (2010).

Patient and carer perspective

In terms of advantages for patients, Aixplorer ShearWave Elastography may more accurately differentiate between benign breast lumps and breast tumours. This would mean that fewer patients would face the pain and discomfort of unnecessary biopsies. These patients and their carers would also be spared the anxiety of waiting for biopsy results.

Evidence review

Clinical and technical evidence

Regulatory bodies

A search of the Medicines and Healthcare Products Regulatory Agency (MHRA) website revealed no manufacturer Field Safety Notices or Medical Device Alerts relating to Aixplorer ShearWave Elastography for the breast application.

No reports of adverse events were identified from the US Food and Drug Administration (FDA) Manufacturer and User Device Facility Experience (MAUDE) database.

Clinical evidence

There is a substantial body of evidence reported in the published literature describing the use of Aixplorer ShearWave Elastography to characterise suspicious breast lesions. Fourteen diagnostic accuracy studies reporting quantitative Aixplorer ShearWave Elastography parameters against a reference standard (biopsy) were assessed. Five of the 14 studies were particularly relevant to the scope of this briefing because they focused on diagnostic outcomes with the potential to change current practice in the NHS. These included the multicentre BE1 study by Berg et al. (2012) and the diagnostic accuracy studies by Evans et al. (2012), Youk et al. (2014a), Klotz et al. (2014) and Au et al. (2014). These studies reported multiple outcomes, but for the purposes of this briefing only those concerning the diagnostic capability of ShearWave Elastography and its potential impact on patient management have been summarised in detail in tables 1 to 5. The other 9 diagnostic accuracy studies are briefly summarised in table 6.

The BE1 study (Berg et al. 2012) investigated the potential diagnostic benefits of adding Aixplorer ShearWave Elastography to B-mode greyscale ultrasound imaging. More accurate classification of breast lesions at the point of imaging in the breast assessment clinic could potentially reduce the need for biopsies, although clinical practice was not changed according to the ShearWave Elastography data in this study.

This was a multicentre study of 958 women who had been referred following mammography, or who showed symptoms on referral. Nineteen women were excluded from the analysis because of there being no reference standard (n=17), presence of a skin lesion (n=1) or no mass seen on B-mode greyscale ultrasound (n=1). Therefore 939 lesions were analysed in total. The details of the study and the key results are listed in table 1. For this study, a functionally equivalent prototype (RUBI) was used, which had the same ShearWave Elastography software as the commercially available Aixplorer system.

The patients' breast lesions were first assessed and classified using BI-RADS on B-mode greyscale ultrasound imaging. The ShearWave Elastography images were then captured and saved for retrospective analysis. The final diagnosis for each lesion in which biopsy was indicated (determined by the original BI-RADS classification) was recorded from cytology or histopathology results (the reference standard).

Using retrospective analysis and modelling, the best possible ShearWave Elastography features and parameter thresholds were determined. These qualitative features and quantitative cut-offs were then applied to the stored patient images to report, hypothetically, how many BI-RADS category 3 lesions could have been upgraded and BI-RADS category 4a lesions downgraded. The diagnostic performance of this reclassification was then determined by comparing the results with those of the reference standard (biopsy).

Of the 939 lesions examined:

- 303 were classified by greyscale ultrasound as BI-RADS 3 (probably benign), 8 of which (2.6%) were later confirmed by biopsy to be malignant.
- 193 were classified as BI-RADS 4a (low suspicion for malignancy), 18 of which (9.3%) were later confirmed by biopsy to be malignant.

For the modelling element of the study, hypothetical re-categorisation resulted in an improvement in the specificity of the ultrasound examination, which increased from 61.1% to 78.5%. The authors reported that the most discriminatory ShearWave Elastography parameters were detection of a lesion with an oval shape and a maximum elasticity threshold of 80 kilopascals (5.2 metres per second) or less; with the presence of either of these parameters being associated with benign lesions. These parameters could potentially be applied in real-time imaging to maximise specificity without significantly reducing sensitivity, thereby reducing unnecessary biopsy of low-suspicion BI-RADS category 4a masses.

The authors concluded that although ShearWave Elastography has the potential to improve the diagnostic capabilities of B-mode greyscale ultrasound and reduce the rate of unnecessary benign biopsies, further prospective validation of this technique would be needed before it could be widely adopted.

Table 1 Summary of the Berg et al. diagnostic accuracy study (BE1 study, 2012)

Study component	Description
Objectives/ hypotheses	To determine whether adding Aixplorer ShearWave Elastography could increase the accuracy of B-mode ultrasonography assessment of breast masses.
Study design	Diagnostic accuracy study.

Setting	International multicentre study recruited between September 2008 and September 2010. The study took place in 16 centres, involving 32 investigators, in a setting broadly comparable to referral to NHS breast assessment clinics.
Inclusion/ exclusion criteria	**Inclusion criteria** Women aged over 21 years referred to centres following identification of suspicious breast lesion(s) on mammography, palpation, ultrasound or MRI. All women gave informed consent to have ultrasound assessment with the addition of Aixplorer ShearWave Elastography. **Exclusion criteria** Women with breast implants; who were pregnant or lactating; who were having chemotherapy or radiation therapy for any cancer; who had a history of ipsilateral breast surgery; or who were unwilling or unable to provide informed consent. Where multiple lesions were present, 1 lesion was selected at random. Method of recruitment was not reported. A power calculation was performed which indicated around 1000 lesions would be needed for analysis.
Primary outcomes	Estimates of effect of selectively upgrading BI-RADS category 3 and downgrading BI-RADS 4a masses based on Aixplorer ShearWave Elastography elasticity features. Sensitivity and specificity of BI-RADS and Aixplorer ShearWave Elastography parameters (threshold determined from ROC analysis) compared with biopsy reference standard.
Statistical methods	Logistic regression to determine effect of Aixplorer ShearWave Elastography parameters on sensitivity and specificity. Fisher's exact test for analysis of independent categorical variables. Other tests: weighted k values, McNemar test, Mann–Whitney U test, Spearman's rank correlation. Significance level of $p<0.1$ used.
Participants	958 women with 939 breast lesions.

Primary results	**ROC analysis** AUC of BI-RADS: 0.950. AUC of BI-RADS combined with quantitative Aixplorer ShearWave Elastography: 0.962 (p=0.005). **Re-categorisation outcomes** Incorporating visual colour stiffness and lack of stiffness improved specificity from 61.1% to 78.5% (p<0.001) compared with BI-RADS classification using B-mode greyscale ultrasound alone. Oval shape on Aixplorer ShearWave Elastography images and quantitative maximum elasticity of 80 kPa or less improved specificity from 69.4% to 77.4% (p<0.001) compared with BI-RADS classification using B-mode greyscale ultrasound alone.
Conclusions	The authors concluded that the addition of Aixplorer ShearWave Elastography had the potential to improve specificity (reduce false-positive results) compared with B-mode greyscale ultrasound alone. This could reduce the number of unnecessary biopsy referrals. However, prospective clinical studies would be needed to validate this hypothesis and determine any detrimental effects (such as missed diagnoses of breast cancer).
Abbreviations: AUC, area under curve; kPa, kilopascals; MRI, magnetic resonance imaging; ROC, receiver operating characteristic.	

The diagnostic accuracy study by Evans et al. (2012) primarily investigated the potential of Aixplorer ShearWave Elastography to improve the diagnostic accuracy of lesion classification using BI-RADS. Additionally, the inter-operator reproducibility of Aixplorer ShearWave Elastography was investigated. The study was done between April and December 2010 in Dundee, Scotland. A description of the study and its primary results is included in table 2.

A total of 173 women were recruited consecutively after a suspicious breast lesion was identified at mammography or clinical examination. The breast lesions were then classified using the BI-RADS system through B-mode greyscale ultrasound, and also measured for elasticity using Aixplorer ShearWave Elastography. A predetermined threshold value of 50 kilopascals or over for mean elasticity was used to classify a malignant lesion, a value that was taken from a previous study (Evans et al. 2010). The results of the benign/malignant shear wave elastography classifications were then directly compared with the

BI-RADS classification using B-mode greyscale ultrasound. The results of these 2 tests were then combined, so that a positive result for either BI-RADS on B-mode greyscale ultrasound or Aixplorer ShearWave Elastography was considered a positive indicator for malignancy. All women enrolled in the study were referred for biopsy. A subset of 30 lesions was also used to assess the inter-operator reproducibility of the Aixplorer ShearWave Elastography examination.

The mean elasticity result using Aixplorer ShearWave Elastography was found to have a sensitivity of 95% and a specificity of 77% for the detection of malignancy, compared with a sensitivity of 95% and specificity of 69% for BI-RADS using greyscale ultrasound. When the results were combined, the sensitivity was 100% (statistically superior to either test alone) and the specificity was 61%. The inter-operator reproducibility element of the study showed high levels of agreement between operators, with an intraclass correlation coefficient of 0.87. The authors concluded that the combination of BI-RADS classification with elastography was an extremely sensitive diagnostic test for detecting breast cancer.

Table 2 Summary of the Evans et al. diagnostic accuracy study (2012)

Study component	Description
Objectives/hypotheses	The aim of the study was to assess the performance of Aixplorer ShearWave Elastography combined with BI-RADS classification of B-mode greyscale ultrasound images for benign/malignant differentiation in a large group of patients.
Study design	Diagnostic accuracy study with reproducibility subgroup.
Setting	The study was set in a breast cancer assessment environment. Women were recruited consecutively in 2010 following detection of a suspicious breast lesion at mammography, or through clinical examination.

Inclusion/exclusion criteria	**Inclusion criteria** Women with suspicious breast lesions and informed consent. All women had BI-RADS classification using B-mode greyscale ultrasound, Aixplorer ShearWave Elastography and a biopsy reference standard. **Exclusion criteria** 30 women (aged under 25 years) were excluded because their lesions were considered benign on B-mode greyscale ultrasound, therefore they were not referred for biopsy.
Primary outcomes	Diagnostic performance of Aixplorer ShearWave Elastography mean elasticity parameter (50 kPa threshold) compared with B-mode greyscale ultrasound BI-RADS classification. Diagnostic accuracy of combined BI-RADS and Aixplorer ShearWave Elastography. Inter-operator reproducibility of Aixplorer ShearWave Elastography.
Statistical methods	Intraclass correlation coefficients. Fisher's exact test for diagnostic parameters.
Participants	173 women aged 18–94 years with 175 breast lesions. 130 (74%) were symptomatic and 45 (26%) were referred from the breast screening programme.

Results	Reference testing showed that 64 lesions were benign and 111 were malignant. **Combined Aixplorer ShearWave Elastography mean elasticity and BI-RADS*** Sensitivity: 100% (CI 100% to 100%). Specificity: 61% (CI 49% to 73%). PPV: 82% (CI 75% to 88%). NPV: (CI 100% to 100%). Diagnostic accuracy: 86%. **B-mode greyscale ultrasound BI-RADS vs Aixplorer ShearWave Elastography mean elasticity** Sensitivity: 95% (CI 92% to 99%) vs 95% (CI 92% to 99%). Specificity: 69% (CI 57% to 80%) vs 77% (CI 66% to 87%). PPV: 84% (CI 78% to 91%) vs 88% (CI 82% to 94%). NPV: 90% (CI 81% to 98%) vs 91% (CI 83% to 99%). Diagnostic accuracy 86% to 89%. **Reproducibility** Intraclass correlation coefficient 0.87 (n=30).
Conclusions	The authors concluded that the Aixplorer ShearWave Elastography mean elasticity parameter was highly sensitive for the detection of malignancy and, when combined with BI-RADS classification on B-mode greyscale ultrasound, was highly specific for malignancy. If these results were representative of clinical practice, then Aixplorer ShearWave Elastography combined with BI-RADS from B-mode greyscale ultrasound could be used to reduce the number of unnecessary biopsies and follow up.
Abbreviations: CI, confidence interval; kPa, kilopascals; n, number of patients; NPV, negative predictive value; PPV, positive predictive value. * Compared with reference standard.	

The diagnostic accuracy study by Youk et al. (2014a) aimed to compare the diagnostic accuracy of Aixplorer ShearWave Elastography (specifically dynamic elastography) combined with B-mode greyscale ultrasound, with strain (static) elastography combined with B-mode greyscale ultrasound. As all patients in this study also had diagnostic biopsy, the diagnostic accuracy of Aixplorer ShearWave Elastography can be directly inferred from this study.

This study recruited 78 consecutive women with 79 breast lesions classified on B-mode greyscale ultrasound as BI-RADS category 3 or 4. As a result of this classification, the women were also scheduled to have ultrasound-guided core needle biopsy or surgical excision of their lesions. Prior to biopsy, patients were examined with Aixplorer ShearWave Elastography and images were saved for retrospective analysis. Receiver operating characteristic curves were formulated to generate cut-off thresholds for a variety of shear wave parameters, to estimate diagnostic accuracy. The study characteristics and results are discussed in table 3.

The authors reported that for BI-RADS class 4a lesions, the sensitivity of the Aixplorer ShearWave Elastography mean elasticity parameter compared with the reference standard (biopsy) was 90.5%, and specificity was 100%. These values were the same as for B-mode greyscale ultrasound alone compared with the reference standard. The authors also found that, in this population, 56% of benign BI-RADS class 4a lesions could be downgraded following analysis of the ShearWave Elastography images, without producing false-negative results. The authors concluded that the use of Aixplorer ShearWave Elastography could potentially reduce the need for tissue biopsy.

Table 3 Summary of the Youk et al. diagnostic accuracy study (2014a)

Study component	Description
Objectives/ hypotheses	The authors aimed to compare the diagnostic performance of Aixplorer ShearWave Elastography with strain elastography, both in combination with B-mode greyscale ultrasound. The ability of these 2 techniques to differentiate benign from malignant breast lesions was analysed.
Study design	Diagnostic accuracy study.
Setting	Women having biopsy or surgery consecutively recruited between September and October 2012.

Inclusion/exclusion criteria	**Inclusion criteria** Women who consented for biopsy or operation. **Exclusion criteria** 8 women were excluded because pathology results were not available (n=3) or elastography values were not obtained (n=5).
Primary outcomes	Sensitivity and specificity of Aixplorer ShearWave Elastography. Number of category 4a BI-RADS lesions that can be safely downgraded to category 3.
Statistical methods	AUC analysis to obtain cut-off thresholds for calculation of diagnostic parameters.
Participants	78 women with 79 breast lesions.
Results	**Diagnostic accuracy of Aixplorer ShearWave Elastography** Mean elasticity sensitivity 90.5% (CI 77.4% to 97.3%). Mean elasticity specificity 100.0% (CI 96.9% to 100%). **Diagnostic accuracy of B-mode greyscale ultrasound** Sensitivity 90.5% (CI 77.4% to 97.3%). Specificity 100.0% (CI 96.9% to 100%). Proportion of benign BI-RADS category 4a lesions that can be downgraded to category 3 using Aixplorer ShearWave Elastography: 56%.
Conclusions	The authors concluded that the use of Aixplorer ShearWave Elastography could potentially reduce the need for biopsies in low-risk lesions.
Abbreviations: AUC, area under the curve; CI, confidence interval; n, number of patients; RR, relative risk.	

The diagnostic accuracy study by Klotz et al. (2014) recruited 142 women who had previously had breast lesions classified on B-mode greyscale ultrasound according to the BI-RADS system. The women had Aixplorer ShearWave Elastography, and the data generated were retrospectively compared with data from conventional B-mode greyscale ultrasound. In total, 167 lesions were analysed, with 164 of these having the reference standard (biopsy). Thresholds for quantitative measures were calculated through receiver operating characteristic analysis, and these were used to model hypothetical changes in patient management. The characteristics of this study and a summary of the key results are included in table 4.

Histological analysis showed that 61% of the identified lesions were malignant and 39% were benign. The authors found that for quantitative Aixplorer ShearWave Elastography, the maximum elasticity parameter for malignant lesions was 187.1±37.6 kilopascals, compared with 61.6±10.9 kilopascals for benign lesions. The authors also found that by using the B-mode greyscale ultrasound combined with quantitative Aixplorer ShearWave Elastography (maximum elasticity parameter): the sensitivity was 95.1%; the specificity was 84.6% (double that of greyscale ultrasound alone); the positive predictive value was 90.7%; and the negative predictive value was 91.7%. The authors concluded that by combining Aixplorer ShearWave Elastography with conventional B-mode greyscale ultrasound, specificity could be considerably improved without a loss in sensitivity.

Table 4 Summary of the Klotz et al. diagnostic accuracy study (2014)

Study component	Description
Objectives/ hypotheses	The authors aimed to determine the diagnostic performance of Aixplorer ShearWave Elastography in differentiating benign and malignant breast lesions, and to suggest alternative management of breast lesions using the combination of B-mode greyscale ultrasound and Aixplorer ShearWave Elastography.
Study design	Diagnostic accuracy study incorporating retrospective analysis.
Setting	Single-centre study in women who had breast lesions categorised according to the BI-RADS system and histopathological confirmation of malignancy status.
Inclusion/ exclusion criteria	**Inclusion criteria** Women with BI-RADS score of 3, 4 or 5 who had had histopathological testing for malignancy. **Exclusion criteria** None stated. Recruitment method was not stated.

Primary outcomes	Quantitative thresholds for Aixplorer ShearWave Elastography. Diagnostic parameters for combined Aixplorer ShearWave Elastography and B-mode greyscale ultrasound.
Statistical methods	Chi-squared test, t-test, ANOVA test, Kruskal–Wallis H test, correlation analyses.
Participants	142 women with 167 suspicious breast lesions.
Results	Maximum elasticity malignant lesion 187.1±37.6 kPa; maximum elasticity benign lesion 61.6±10.9 kPa. **Combined B-mode greyscale ultrasound and Aixplorer ShearWave maximum elasticity diagnostic parameters** Sensitivity: 95.1%. Specificity: 84.6%. PPV: 90.7%. NPV: 91.7%.
Conclusions	The authors concluded that the combination of B-mode greyscale ultrasound and Aixplorer ShearWave Elastography can improve the management of breast lesions.
Abbreviations: ANOVA, analysis of variance; kPa, kilopascals; NPV, negative predictive value; PPV, positive predictive value.	

The diagnostic accuracy study by Au et al. (2014) recruited 112 women with 123 solid breast masses identified by ultrasound. The masses were classified to BI-RADS using conventional B-mode greyscale ultrasound, followed by examination using Aixplorer ShearWave Elastography and reference standard diagnosis using ultrasound-guided core biopsy. ShearWave was quantified using measures of mean elasticity, maximum elasticity and elasticity ratio. The diagnostic accuracy of B-mode greyscale ultrasound was compared with Aixplorer ShearWave Elastography alone or in combination with B-mode greyscale ultrasound. Thresholds for diagnosing breast masses as benign or malignant were calculated retrospectively using receiver operator characteristic analysis, and these were used to hypothetically reclassify BI-RADS 4a lesions downwards and BI-RADS 3 lesions upwards (without affecting actual patient management). The characteristics of this study and a summary of the key results are included in table 5.

The optimal thresholds for Aixplorer ShearWave Elastography were retrospectively calculated as 42.5 kilopascals for mean elasticity, 46.7 kilopascals for maximum elasticity and 3.56 for the elasticity ratio. Applying these cut-offs, all 3 parameters – alone or combined with B-mode greyscale ultrasound – had better specificity than B-mode greyscale ultrasound alone, without affecting sensitivity. The area under the receiver operator curve was highest for the elasticity ratio combined with B-mode greyscale ultrasound, suggesting that this may offer the greatest improvement in diagnostic performance. Using Aixplorer ShearWave Elastography and ultrasound combined improved the BI-RADS classification when compared with the reference standard. However, it was noted that using the combined methods, hypothetically, 1 out of 2 malignant BI-RADS 4a lesions in the study would have been incorrectly downgraded (false-negative), and 1 out of 28 lesions with BI-RADS category 3 would have been incorrectly upgraded (false-positive).

It should be noted that that although this represents a high rate of false-negative results, the sample size of this study was very small and so results must be interpreted with caution.

The authors concluded that using Aixplorer ShearWave Elastography combined with B-mode greyscale ultrasound could improve diagnostic accuracy, with the elasticity ratio being the most discriminatory quantitative measure. Hypothetically, by correctly downgrading about 90% of lesions from BI-RADS 4a to category 3, the technology would have avoided unnecessary biopsies.

Table 5 Summary of the Au et al. diagnostic accuracy study (2014)

Study component	Description
Objectives/ hypotheses	The researchers aimed to assess the diagnostic performance of quantitative Aixplorer ShearWave Elastography parameters (mean elasticity, maximum elasticity and elasticity ratio) in evaluating benign and malignant solid breast masses and determining the most discriminatory parameter.
Study design	Diagnostic accuracy study incorporating retrospective analysis.
Setting	Single-centre study with women aged over 18 years consecutively recruited between July 2011 and July 2012.

Inclusion/ exclusion criteria	**Inclusion criteria** Women with BI-RADS score of 3, 4 or 5 determined by ultrasound who had had histopathological testing for malignancy. **Exclusion criteria** None stated.
Primary outcomes	Quantitative thresholds for Aixplorer ShearWave Elastography (mean and maximum elasticity, elasticity ratio). Diagnostic parameters for Aixplorer ShearWave Elastography and B-mode greyscale ultrasound, alone and combined. ROC AUC analysis. Reclassification of BI-RADS scores according to input of elasticity data (using Aixplorer ShearWave Elastography alone or combined with ultrasound).
Statistical methods	Student t-test for continuous variables. Logistic regression and ROC analysis. McNemar test.
Participants	112 women with 123 suspicious breast lesions. BI-RADS category 3 23.6%; category 4a 35.8%; category 4b 15.4%; category 4c 4.9%; category 5 20.3%.

Results	**Elasticity thresholds** Mean elasticity 42.5 kPa. Maximum elasticity 46.7 kPa. Elasticity ratio 3.56. **ROC analysis** Addition of any elasticity parameter improved ROC AUC (all $p<0.001$). **Diagnostic parameters** All elasticity parameters (Aixplorer ShearWave Elastography alone or in combination) improved specificity compared with ultrasound alone (all $p<0.0001$) without significantly worsening sensitivity. **Reclassification of BI-RADS** Addition of elasticity parameters allowed for 90% of BI-RADS 4a to be downgraded to 3, but half of patients with malignancy were misclassified (false-negative results).
Conclusions	The authors concluded that the combination of B-mode greyscale ultrasound and Aixplorer ShearWave Elastography can improve the management of breast lesions.
Abbreviations: AUC, area under curve; kPa, kilopascals; ROC, receiver operating characteristic.	

The authors of this briefing identified 9 other diagnostic accuracy studies that included a reference standard and reported diagnostic results, but did not describe the potential impact of Aixplorer ShearWave Elastography on diagnostic pathways and the clinical implications of this. These studies are briefly summarised in table 6.

Table 6 Brief summary of the 9 additional Aixplorer ShearWave Elastography diagnostic accuracy studies

Reference	Study aims	Setting and number of patients	Selected results and conclusions

Chang et al. (2011)	To assess the quantitative elasticity values of various benign and malignant breast lesions and to evaluate the diagnostic performance of Aixplorer ShearWave Elastography in differentiating breast masses compared with conventional ultrasonography, using histological analysis as the reference standard.	Hospital in South Korea. n=186 breast masses in 162 consecutive women.	The mean elasticity values were significantly higher in malignant masses (153.3±58.1 kPa) than in benign masses (46.1±42.9 kPa, p<0.0001). The optimal cut-off value for mean elasticity, yielding the maximal sum of sensitivity and specificity, was 80.17 kPa, and the sensitivity and specificity of Aixplorer ShearWave Elastography were 88.8% and 84.9% respectively. The authors concluded that Aixplorer ShearWave Elastography has the potential to aid in the differentiation of benign and malignant breast lesions.
Chang et al. (2013)	To compare the diagnostic performances of Aixplorer ShearWave Elastography and strain elastography for differentiating benign and malignant breast lesions.	Single centre, South Korea. n=153 breast lesions in 130 consecutive women.	Using the optimal threshold of 80 kPa for mean elasticity on Aixplorer ShearWave Elastography, the sensitivity was 95.8% and specificity was 84.8%. The authors concluded that Aixplorer ShearWave Elastography can improve overall diagnostic performance in differentiating benign and malignant lesions when combined with B-mode greyscale ultrasound.

Evans et al. (2010)	To determine the reproducibility of Aixplorer ShearWave Elastography. To correlate the elasticity values of a series of solid breast masses with histological findings. To compare Aixplorer ShearWave Elastography with B-mode greyscale ultrasound for benign/malignant classification.	Hospital in Dundee, Scotland. n=53 solid breast lesions in 52 consecutive adults.	At a mean elasticity threshold of 50 kPa, Aixplorer ShearWave Elastography compared with B-mode greyscale BI-RADS performance was as follows: Sensitivity: 97% vs 87%. Specificity: 83% vs 78%. Positive predictive value: 88% vs 84%. Negative predictive value: 95% vs 82%. Accuracy: 91% vs 83%. These differences were not statistically significant. The authors concluded that Aixplorer ShearWave Elastography gives quantitative and reproducible information on solid breast lesions with diagnostic accuracy at least as good as B-mode greyscale ultrasound with BI-RADS classification.

Lee et al. (2013a)	To evaluate which Aixplorer ShearWave Elastography parameter proves most accurate in the differential diagnosis of solid breast masses.	Single centre, South Korea. n=156 breast lesions in 139 consecutive women.	At the optimum maximum elasticity cut-off of 82.3 kPa, sensitivity was 88.9%, specificity was 77.5% and accuracy was 80.1%. The authors concluded that the maximum elasticity parameter at a threshold of 82.3 kPa provided the best diagnostic performance in differentiating solid breast masses. However, the overall diagnostic performance of ultrasound and Aixplorer ShearWave Elastography combined was not significantly better that that of conventional ultrasound alone.
Lee et al. (2013b)	To compare the diagnostic performances of 2D and 3D Aixplorer ShearWave Elastography for differentiating benign from malignant breast masses.	Hospital in South Korea. n=144 breast masses in 134 consecutive women.	At a maximum elasticity threshold of 80 kPa, 2D Aixplorer ShearWave Elastography statistically significantly improved the specificity of B-mode ultrasound from 29.9% to 71.4% without a significant change in sensitivity. The authors concluded that 2D Aixplorer ShearWave Elastography improved the specificity of B-mode greyscale ultrasound.

Olgun et al. (2014)	To determine correlations between Aixplorer ShearWave Elastography elasticity values of solid breast masses and biopsy findings, and to define cut-off elasticity values differentiating malignant from benign lesions.	Hospital in Turkey. n=115 solid breast lesions in 109 consecutive adults.	The cut-off values were: 45.7 kPa for mean elasticity (sensitivity, 96%; specificity, 95%). 54.3 kPa for maximum elasticity (sensitivity, 95%; specificity, 94%). 37.1 kPa for minimum elasticity (sensitivity, 96%; specificity, 95%). The authors concluded that Aixplorer ShearWave Elastography adds useful quantitative data and may help in the diagnosis of breast lesions, but that long-term clinical studies are needed to accurately select lesions for biopsy.

Wang et al. (2013)	To evaluate Aixplorer ShearWave Elastography in the diagnosis of breast tumours.	Hospital in China. n=114 breast lesions in 108 consecutive women.	Malignant lesions showed significantly higher maximum and mean elasticity (111.57±69.29 kPa and 54.49±33.70 kPa) than benign lesions (59.00±45.35 kPa and 36.64±26.18 kPa, p<0.01). For maximum elasticity compared with BI-RADS, performance results were: Sensitivity: 60.9 % vs 78.3%. Specificity: 85.3% vs 98.5%. Positive predictive value: 73.7% vs 97.3 %. Negative predictive value: 76.3% vs 87.0%. Accuracy: 75.4% vs 90.3%. The authors concluded that Aixplorer ShearWave Elastography gives quantitative elasticity information that could help characterising breast lesions, but it cannot replace conventional BI-RADS in differentiating breast lesions.

Youk et al. (2014b)	To evaluate and compare the performance of Aixplorer ShearWave Elastography for breast masses using the local shear wave speed (m/s) compared with Young's modulus (kPa).	Single centre, South Korea. n=130 breast lesions in 123 consecutive women.	The estimated optimal cut-off values were as follows: Maximum elasticity: 63.4 kPa and 4.6 m/s. Mean elasticity: 63.7 kPa and 4.8 m/s. At these threshold values, there was no statistically significant difference in sensitivity or specificity between shear-wave speed and Young's modulus. The authors concluded that the quantitative elasticity values measured in kPa and m/s on Aixplorer ShearWave Elastography showed good diagnostic performance.

Zhou et al. (2014)	To analyse the diagnostic performance of Aixplorer ShearWave Elastography in differentiating between benign and malignant breast lesions compared with conventional ultrasonography.	Single centre hospital, China. n=193 breast lesions in 193 consecutive women.	The optimal cut-off values were as follows: 33.26 kPa for mean elasticity (sensitivity, 55.4%; specificity, 85.4%). 49.57 kPa for maximum elasticity (sensitivity, 76.8%; specificity, 78.1%). 4.8 kPa for minimum elasticity (sensitivity, 51.8%; specificity, 86.1%). The combination of conventional ultrasound features plus all Aixplorer ShearWave Elastography features resulted in sensitivity of 98.2% and specificity of 72.3%, compared with sensitivity of 69.6% and specificity of 94.2% for conventional ultrasound alone. The authors concluded that adding Aixplorer ShearWave Elastography features to conventional ultrasound has the potential to improve the differentiation of breast lesions.
Abbreviations: kPa, kilopascals; m/s, metres per second; n, number.			

Recent and ongoing studies

Three ongoing or in-development trials of Aixplorer ShearWave Elastography for breast applications were identified in the preparation of this briefing:

- ShearWave Elastography of Breast Lesions in Chinese Patients (BE3) (NCT02226081)
- Combined Elastography and Color Doppler Ultrasonography for Breast Screening With Ultrasound (NCT01963624)
- Contrast Enhanced Ultrasound and Shear Wave Elastography in Measuring Response in Patients With Breast Cancer Receiving Chemotherapy Before Surgery (NCT02067884)

Costs and resource consequences

In 2012–13, 7.6% of women aged 45 years and over attending the NHS Breast Screening Programme for the first time ('prevalent screening') were referred for further assessment. Of those women who had a routine invitation in 2012–13 and had been screened in the last 5 years ('incident screening'), 2.9% were referred for further assessment. The total number of women referred for further assessment in 2012–13 following any imaging modality or clinical examination was 81,876; 37,573 of whom also went on to have a fine needle aspiration (with or without biopsy) (Health & Social Care Information Centre 2014). The national figure for symptomatic referrals from primary care to breast assessment clinics is not known.

Of the 1,728,671 women aged 50 to 70 years who had X-ray mammography screening in 2012–13, 7 in every 10,000 had a benign biopsy result (Health & Social Care Information Centre 2014). This equals 2,470 benign biopsies per year in these patients.

Costs and resource consequences of Aixplorer ShearWave Elastography may be judged against avoided costs of unnecessary biopsies. In the published studies, addition of Aixplorer ShearWave Elastography to B-mode greyscale ultrasound took about 2 to 5 extra minutes. No other changes to the way in which current services or facilities are organised would be needed.

The 2013–14 Payment by Results tariff (hospital income) for an outpatient ultrasound scan (less than 20 minutes) is £45 (Department of Health 2014). Biopsy procedures are not unbundled from the outpatient attendance tariff, so a figure for comparison cannot be given.

No published evidence on resource consequences was identified.

Strengths and limitations of the evidence

The evidence base for Aixplorer ShearWave Elastography for evaluating suspicious breast lesions is good in terms of both quantity and quality. The evidence for the technology is dominated by diagnostic accuracy studies, and this briefing has focused on the studies that described outcomes that could directly influence clinical practice and alter clinical pathways in the NHS. All the studies described benefited from having a recognised reference standard (fine needle aspiration or histopathology through core biopsy or surgical section), allowing for diagnostic parameters to be calculated for the intervention and its comparator. However, caution should be applied when interpreting the results because diagnostic results were often reported for the whole cohort studied, rather than focusing specifically on the relevant subgroups the management of whose disease may change with introduction of the system (BI-RADS categories 3 and 4a).

A significant limitation of all studies was that the results were analysed retrospectively, and thus the clinical and health care system benefits of improved diagnostic accuracy are implied rather than demonstrated. This approach also led to different threshold estimates, and there is no agreement between studies on which thresholds are optimal. Longer-term prospective studies with predefined thresholds and hard clinical outcomes are needed to demonstrate any potential for misdiagnosis and possible benefits of the altered diagnostic pathways associated with Aixplorer ShearWave Elastography for this indication.

The 2012 study by Berg et al. (the BE1 study) was the largest study included in this briefing, and benefited from the greatest statistical power. However, the operators were already aware of the BI-RADS status of each patient before using Aixplorer ShearWave Elastography, and they made a conscious effort to recruit women with category 3 or 4 lesions. For this reason there may have been selection bias and the study may not be fully generalisable to NHS practice. A technical limitation was that Aixplorer ShearWave Elastography was performed in 1 view only, which could have resulted in suboptimal results. Lesions were reclassified retrospectively, following receiver operating characteristic analysis to establish optimal thresholds, which does not reflect clinical practice. Thus a truly prospective study is needed to validate the positive results of this study.

The study by Evans et al. (2012) was done in the UK and so may be more relevant to an NHS setting. However, an unusually large proportion of women were referred because they were symptomatic, which might account for the high proportion of malignancy and relatively high negative predictive values seen. In this study, the operator was blinded to other test results, which may have limited bias. The use of a minimum of 2 views using Aixplorer ShearWave Elastography may have optimised performance, but it is unclear whether this is how the device would be used in practice (Berg et al. 2012). Evans et al. was the only study that incorporated a pre-set cut-off threshold for quantitative Aixplorer ShearWave Elastography (mean elasticity 50 kilopascals, derived from an earlier study) which avoided the use of retrospective analysis. However, this is not yet a recognised threshold value for the differentiation of malignant and benign lesions. The diagnostic results of the study did not change clinical pathways, thus further prospective validation would be recommended.

The study by Youk et al. (2014a) was designed to compare Aixplorer ShearWave Elastography with strain elastography, but because it used a reference standard relevant data could be extracted. This was a small study, including only 79 lesions in total. Only 2 false-positive cases were reported, and so a larger study population would be needed to draw meaningful results. In addition, blinding was not used, introducing a potential source of bias. As with other studies, the analysis was conducted retrospectively and did not influence medical decision-making, emphasising the need for a prospective clinical study.

The study by Klotz et al. (2014) compared prospectively obtained Aixplorer ShearWave Elastography data with retrospective BI-RADS data obtained through B-mode greyscale ultrasound. This raised the possibility of selection bias, and prevented the use of live analysis using B-mode greyscale ultrasound (as happens in clinical practice). Additionally, the proportion of malignant lesions identified in the study was high (61%), limiting the generalisability of the study to NHS breast assessment clinics. The limited population recruited meant that lesion numbers were very small for elements of the subgroup analysis. The reported specificity of B-mode greyscale ultrasound used alone (43.1%) was also lower than for other studies.

In the study by Au et al. (2014), a single operator who knew the BI-RADS scores of the breast masses did the Aixplorer ShearWave Elastography and B-mode greyscale ultrasound examination, which could have introduced bias and limited interpretation of inter-operator variability. Retrospective receiver operating characteristic curve analysis was used to calculate the elasticity thresholds, which is not generalisable to real-life clinical practice. This was a relatively small study and was underpowered to adequately perform the intended subgroup analysis. For instance, only 2 out of 44 lesions classified using B-mode greyscale ultrasound as BI-RADS 4a were subsequently confirmed by biopsy to be malignant.

Relevance to NICE guidance programmes

The use of Aixplorer ShearWave Elastography is not currently planned into any NICE guidance programme.

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Search strategy and evidence selection

Search strategy

The search strategy was designed to identify evidence on the clinical and cost effectiveness of ultrasound elastography for breast imaging. It comprised 2 concepts: the population (breast imaging) and the intervention (ultrasound elastography). The strategy excluded animal studies and non-English language publications. No additional filters for study design were applied. The results were limited to studies published from 2005 to the time of publication, reflecting that the manufacturer was founded in 2005.

The final strategy was peer-reviewed by an independent information specialist.

The following databases were searched:

- Cochrane Central Register of Controlled Trials (Cochrane Library, Wiley)
- Cochrane Database of Systematic Reviews (Cochrane Library, Wiley)
- Database of Abstracts of Reviews of Effect (Cochrane Library, Wiley)
- Embase (Ovid SP)
- Health Technology Assessment Database (Cochrane Library, Wiley)
- MEDLINE and MEDLINE in Process (Ovid SP)
- NHS Economic Evaluation Database (Cochrane Library, Wiley).

The manufacturer also provided a bibliography of 53 studies of peer-reviewed publications reporting results of clinical studies which looked at the use of Aixplorer ShearWave Elastography in breast imaging. This identified 3 additional papers which were published too recently to have been included in any of the databases searched.

Evidence selection

A total of 1305 records were retrieved from the literature search (1302 from the database searches and 3 provided by the manufacturer). After de-duplication, 842 records remained. An initial 262 records were excluded at first pass as being animal or plant studies, obviously irrelevant interventions or obviously irrelevant populations. The remaining 580 records were sifted against the inclusion criteria at title and abstract level.

Records were sifted independently by 2 researchers. Any disagreements were discussed and agreement was reached in all cases, so a third independent arbiter was not required. The first sift removed 532 records based on the following exclusion criteria:

- articles of poor relevance against search terms
- publication types that were out of scope
- non-English language studies
- conference abstracts
- review articles.

Full articles were retrieved for 47 of the remaining 48 studies, with 1 ordered but not received within the briefing production timeline. Full text assessment was done independently by 2 researchers to identify relevant primary research addressing the key outcomes of interest (that is, diagnostic accuracy studies reporting quantitative Aixplorer ShearWave Elastography parameters against a reference standard [biopsy]). Papers excluded at this stage included:

- studies on different commercial or experimental systems: 8
- studies focusing on intra- and inter-observer outcomes: 3
- studies reporting only qualitative data (visual colour map): 4
- correlation studies and/or other post hoc analyses: 5
- population has wrong pathology (e.g. malignancy already diagnosed): 2
- technical study (phantom tissue): 1
- secondary study (e.g. review): 4
- conference abstracts: 4
- non-English paper: 2
- total: 33.

Fourteen studies remained, which were all diagnostic accuracy studies that included a reference standard. This was judged to be disproportionate number for the purposes of a briefing, and so a further exclusion was applied in order to focus this briefing only on diagnostic accuracy studies against a reference standard which also estimated the potential impact of the technology on clinical pathways (for example, with data on BI-RADS reclassification of lesions between categories 3 and 4a and/or estimated change in biopsy rates). This additional step excluded a further 9 diagnostic accuracy studies. These 9 papers all reported threshold Aixplorer ShearWave Elastography parameters for determining malignancy in breast lesions, but the authors did not describe clinical impact as a primary outcome of interest. This left 5 diagnostic accuracy studies with reported outcomes relevant to clinical pathways.

About this briefing

Medtech innovation briefings summarise the published evidence and information available for individual medical technologies. The briefings provide information to aid local decision-making by clinicians, managers, and procurement professionals.

Medtech innovation briefings aim to present information and critically review the strengths and weaknesses of the relevant evidence, but contain no recommendations and **are not formal NICE guidance**.

Development of this briefing

This briefing was developed for NICE by Newcastle and York External Assessment Centre. The interim process and methods statement sets out the process NICE uses to select topics, and how the briefings are developed, quality assured and approved for publication.

Project team

Newcastle and York External Assessment Centre

Medical Technologies Evaluation Programme, NICE

Peer reviewers and contributors

- Iain Willits, Medical Technologies Evaluator, Newcastle upon Tyne Hospitals NHS Foundation Trust
- Helen Cole, Head of Service – Clinical Scientist, Newcastle upon Tyne Hospitals NHS Foundation Trust
- Derek Bousfield, Senior Clinical Technologist, Newcastle upon Tyne Hospitals NHS Foundation Trust
- Roseanne Jones, Research Scientist, Newcastle upon Tyne Hospitals NHS Foundation Trust
- Kim Keltie, Research Scientist, Newcastle upon Tyne Hospitals NHS Foundation Trust
- Hannah Wood, Information Specialist, York Health Economics Consortium
- Andrew Sims, Centre Director, Newcastle upon Tyne Hospitals NHS Foundation Trust

Specialist commentators

The following specialist commentators provided comments on a draft of this briefing:

- Professor Erika Denton, National Clinical Director of Diagnostics, NHS England and Honorary Professor of Radiology, University of East Anglia and Norfolk & Norwich University Hospital
- Dr Andrew Evans, Professor of Breast Imaging, University of Dundee and Honorary Consultant Radiologist, NHS Tayside
- Dr Barry Ward, Head of Service – Clinical Scientist, Newcastle upon Tyne Hospitals NHS Foundation Trust

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