The ZedScan as an adjunct to colposcopy in women with suspected cervical intra-epithelial neoplasia

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Summary

The ZedScan system uses electrical impedance spectroscopy to help detect cervical cancer cells. It is intended to be used as an adjunct to colposcopy. The largest diagnostic accuracy study showed an increase in the positive predictive value compared with conventional colposcopy. The additional cost per procedure is about £30.50 plus clinician time.
The ZedScan as an adjunct to colposcopy in women with suspected cervical intra-epithelial neoplasia
(MIB20)

**Product summary and likely place in therapy**
- The ZedScan uses electrical impedance spectroscopy to detect pre-cancerous and cancerous cells in the cervix of women who have suspected cervical intra-epithelial neoplasia.
- The ZedScan is a diagnostic tool intended as an adjunct to colposcopy in women who are referred for colposcopy by the NHS Cervical Screening Programme because of an abnormal cervical cytology result.

**Effectiveness and safety**
- Five diagnostic cohort studies that used prototype versions of the ZedScan were identified (n=657 women in total).
- One diagnostic cohort study (n=196) using the most recent prototype version of the ZedScan was identified. This study used 2 standard methods to calculate the sensitivity and specificity of the ZedScan. When a cut-off value was used to give equal sensitivity to colposcopy, the ZedScan as an adjunct to colposcopy showed an increase in the positive predictive value.
- One study (n=429) reported that 1 patient fell unwell and 2 had post-biopsy bleeding. These are common complications of colposcopy and biopsy.

**Technical factors**
- The ZedScan is intended only as an adjunct to colposcopy in patient assessment. It should not be used alone as a diagnostic tool or to decide on treatment. It must be used in conjunction with other methods of assessing clinical signs and symptoms.
- The ZedScan should be used by healthcare professionals with experience in performing colposcopy.

**Cost and resource use**
- The ZedScan costs £3000, including computer software. The cost per case with the ZedScan is approximately £30.50 plus clinician time.
- One economic analysis of 1000 women suggested that using the ZedScan could result in fewer biopsies, an improvement in health-related quality of life, and a reduction in over-treatment.

**Introduction**

Cervical cancer is the 12th most common cancer in women in the UK. There were 3,064 new cases in 2011 and 919 deaths in 2012 (Cancer Research UK 2014). Cervical cancer can often be prevented by the early identification and removal of abnormal pre-cancerous cells in the cervix.
These cells can develop over many years, and while they are not an immediate risk to health they can progress to cancer if left untreated.

Almost all cases of cervical cancer are caused by the human papilloma virus (HPV), which is a sexually transmitted infection. Some types (or strains) of HPV infect the cervical epithelial cells and alter their behaviour. Eventually some of these infected cells can become cancerous and cause cervical tumours to develop. There are over 100 strains of HPV and some of these are considered high-risk strains, including 16, 18, 31, 33 and 35, because they have been linked with an increased risk of cervical cancer. HPV 16 and HPV 18 are known to cause 70% of cervical cancers (NHS Choices 2013). These strains do not cause symptoms and so women can be infected without knowing. Currently, all girls aged 12 to 13 in England are offered vaccination against HPV 16 and HPV 18 as part of the NHS childhood vaccination programme.

In order to detect cervical cancer-related changes in the cells of the cervix at an early stage, the NHS in England offers a national cervical screening programme to all women aged 25–64. Women aged 25–49 are offered cervical screening every 3 years, and women aged 50–64 offered screening every 5 years. Figures from Public Health England (NHS Cervical Screening Programme) for 2012–13 indicate that 4.24 million women were offered routine cervical screening, and 3.32 million of these attended screening appointments (78.3%).

Cervical screening involves examining a sample of cells from an area of the cervix called the transformation zone. This area is where the columnar epithelial cells are being replaced by new metaplastic squamous epithelium and is where almost all cervical cancers arise.

The collection of the cervical cell sample is usually performed in primary care by a GP or practice nurse. A small brush is used to 'sweep' around the cervix, picking up cervical cells from the transformation zone and the cells are prepared for examination by using liquid-based cytology. These cells are then checked in a pathology laboratory for abnormalities. Cytological assessment indicates the degree of cellular abnormality (dyskaryosis), based on the morphological features of the cervical cells. The degree of dyskaryosis can range from low-grade to high-grade, or borderline changes may be observed.

The results of the cytological assessment are used to decide whether further treatment should be offered. According to the NHS Cervical Screening Programme women should be referred for colposcopy after the following cytology results:

- Borderline change in squamous or endocervical cells and positive for high-risk HPV.
- Low-grade dyskaryosis and positive for high-risk HPV.
• High-grade dyskaryosis (moderate or severe), regardless of confirmed high-risk HPV infection.

• High-grade dyskaryosis or suspected invasive squamous cell carcinoma.

• Suspected glandular neoplasia of endocervical type or source not specified (women are referred to gynaecology clinic if source is likely to be from another gynaecological site or metastasis from a non-gynaecological site).

• If 3 consecutive cervical screening appointments give samples that are inadequate for testing.

Colposcopy is a procedure that involves examining the surface of the cervix using either a binocular field colposcope or a digital video colposcope. Colposcopy is performed by a British Society for Colposcopy and Cervical Pathology (BSCCP) accredited specialist called a colposcopist. To carry out a colposcopy, a 3–5% solution of acetic acid is applied to the transformation zone, which causes abnormal cells to stain white. An iodine solution may also be used to identify further abnormalities, and this stains abnormal cells yellow and normal cells dark brown. A colposcopy usually takes 15 minutes.

It has been noted by Leeson (2014), Tidy (2013) and Wade (2013) that the sensitivity and specificity of colposcopy varies between studies. Leeson (2014) noted that sensitivity has been reported to be between 49 and 61%. The 2010 Colposcopy and Programme Management guidelines for the NHS Cervical Screening Programme state that a 'satisfactory' colposcopic examination should have a predictive value of at least 65% for high-grade lesions (cervical intra-epithelial neoplasia [CIN] 2 or higher).

Cytology results should ideally be available to the colposcopist before the examination so that they can make treatment recommendations following the colposcopy.

Recommendations for management, treatment and follow-up after colposcopy are set out in the NHS Cervical Screening Programme guidelines. Management, treatment and follow-up decisions may be supported by histology results if biopsies were taken during the colposcopic examination. Histology is used to identify abnormal tissue changes (CIN), as CIN cells can sometimes progress to cancer. A CIN scale ranging from 1 to 3 is used to classify how many cervical cells are abnormal. CIN1 is considered to be low-grade and CIN2 and 3 are considered high-grade. Cell abnormalities can sometimes be detected in the glandular cells in the inside lining of the cervix, and these are called cervical glandular intra-epithelial neoplasia (CGIN). CGIN is less common than CIN. The possible diagnoses that can be made are:

• normal, healthy tissue
• CIN1, if up to one third of the thickness of the cervical squamous epithelium is affected
• CIN2, if up to two thirds of the thickness of the cervical squamous epithelium is affected
• CIN3, if the full thickness of the cervical squamous epithelium is affected.

If the cervix is normal or has CIN1, the management is determined by the referral cytology. A review of the cytology and management by a colposcopy multi-disciplinary team may be needed if the referral cytology was high grade. CIN1 is not always treated, and when it is not the woman will be offered cytological follow-up. CIN can be treated in different ways. The NHS Cervical Screening Program guidelines state that there is no obviously superior conservative surgical technique for treating CIN. However, the choice of treatment will depend on factors such as the visibility of the transformation zone and the CIN grade.

Laser ablation and cryotherapy destroy abnormal cells, allowing normal cells to grow back in their place. Large-loop excision of the transformation zone (LLETZ), cone biopsy, and diathermy can all be used to remove abnormal cells. LLETZ and cone biopsy remove the entire transformation zone. The tissue removed by these procedures can be used for histological examination. The most common treatment is LLETZ, which may be performed during the colposcopy appointment. It uses a heated loop of wire to remove abnormal cells from the transformation zone, and usually takes 20 minutes.

**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**

**CE marking**

The ZedScan was CE-marked as a class IIa medical device to Zilico in September 2013 as an electrical impedance spectroscopy device for the identification of cervical neoplasia.

**Description**

The ZedScan is an electrical impedance spectrometer for the examination of the cervical epithelium. It comprises:
• a handset used to examine the cervix

• a docking station used to charge the handset and connect it to a computer

• a single-use electrical impedance spectroscopy (EIS) sensor that fits over the snout of the handset for examinations

• a software application for processing and storing information from the handset.

The ZedScan works by applying a small alternating current at different frequencies to the cells lining the cervix and measuring the resulting voltage. The electrical resistance can be calculated to show the electrical impedance spectrum of the surrounding tissue. Healthy cervical epithelial tissue has a different impedance spectrum to abnormal tissue found in cervical intra-epithelial neoplasia (CIN). The ZedScan software analyses the impedance spectral data using a proprietary algorithm, and gives a value to indicate the likelihood that high-grade CIN is present.

During the colposcopy, a series of 10–12 readings are taken from points evenly spaced around the transformation zone. The exact number of readings will depend on the size of the transformation zone, but at least 10 readings should be taken to ensure adequate coverage.

To ensure that readings are taken from the right places around the transformation zone, the ZedScan handset displays a diagram of the measurement zone. This uses coloured dots to indicate the location and status of each measurement point. The colour of the dot indicates the result of the analysis:

• clear/white – no reading

• green – high-grade CIN is unlikely to be present

• amber – high-grade CIN is likely to be present

• red – the highest likelihood that high-grade CIN is present.

The treatment recommendations would depend on the results of the ZedScan, the colposcopic examination and the original cytology result.

The currently available version of the ZedScan is an update to the third generation of the device. The first-generation device (used in the studies by Brown et al. 2000 and 2005) consisted of an electrical probe hard-wired to a separate control box, which was connected to a computer. This probe was re-used and had to be cold-sterilised between patients. The β-dispersion region was
analysed at 8 frequencies to provide impedance spectra. These were used to derive parameters characteristic of the different tissue types.

The first-generation device was later modified to increase the number of frequencies from 8 to 30 and widen the frequency range. This was done to find out if it was possible to improve performance by gathering more data, particularly on the changes in the cell nucleus. This modified version was used in the Abdul et al. (2006) study.

The second-generation device (used in Balasubramani et al. 2009) was adapted so that the electronics were built into the handset, which was wirelessly connected to a PC. In addition, this version could be charged inductively. Readings were taken at 14 frequencies, but the range was narrowed again because of the poorer results obtained with a wider range. The analytical method was also changed, because the earlier studies showed that using standard electrical equations with the impedance spectra was not optimal.

The prototype third-generation device (used in the study by Tidy et al. 2013) featured on-board quality control tests to ensure accuracy of the readings, and a disposable sheath containing electrodes so that the device did not need sterilisation between patients. This version also had an LED screen to guide the user through the procedure, and came with software for recording data from the device.

The commercial version of the ZedScan incorporates further improvements identified in Tidy et al. (2013).

- Single-point mode – an additional mode used after the initial 10–12 readings are taken. In this mode the data for each point is analysed immediately and the results displayed on both the handset screen and the snout LEDs.

- LEDs on the snout – these show the status of the device so that the colposcopist can use the ZedScan while looking through the colposcope. The results in single-point mode are also displayed using these LEDs, so that the device can be held in position while a biopsy is taken. A Fresnel lens is moulded into the sleeve of the single-use sensor, to improve the visibility of the snout LEDs.

- On-board analysis – the analytical algorithm is now built into the handset, so results can be obtained without downloading the data to a PC.

- PC software – allows the user to enter patient information and maintain a searchable database of results.
Intended use

The ZedScan is intended only as an adjunct to colposcopy in patient assessment. It should not be used alone as a diagnostic tool or to decide on treatment. It must be used in conjunction with other methods of assessing clinical signs and symptoms.

Setting and intended user

The ZedScan is an adjunct to colposcopy and should be used by a colposcopist. The manufacturer states that the device should be used by medically qualified practitioners with experience in performing colposcopy, although a specialist commentator reported that the typical user in NHS practice would be a BSSCP-certified colposcopist (see following section).

Current NHS options

Conventional colposcopy is the current practice for women referred with abnormal cytology results from the cervical screening programme. NICE diagnostics guidance on adjunctive colposcopy technologies for examination of the uterine cervix recommends DySIS as a clinically and cost-effective option, compared with standard colposcopy. It comprises a digital video colposcope and dynamic spectral imaging technology that are used together during the colposcopic examination. The practical requirements for using DySIS as an adjunct to conventional colposcopy in the NHS Cervical Screening Programme are described in NHSCSP Equipment Report 1201. NICE's guidance also states that current evidence is insufficient to determine whether the Niris Imaging System is a cost-effective option for use as a colposcopic adjunct.

From initial searches, NICE is not aware of any other CE-marked devices that have a similar function to the ZedScan.

Costs and use of the technology

The following are list prices for October 2014 as provided by the manufacturer. All costs exclude VAT.

- The ZedScan system – £3000 (including 1 handset, 1 docking station, 1 CD containing software with 1 user licence, and instructions for use).
- Single-use EIS Sensors – £3600 for 120 sensors (£30 each).
The ZedScan has a 1-year warranty and is estimated to have a service life of 3–5 years. Based on these list prices, each use of the technology would cost approximately £30.50, including consumables.

The manufacturer estimates that each cervical scan using the ZedScan takes 2–3 minutes. Results are automatically downloaded to a computer via the docking station, generating a report. The colposcopist’s comments can be added to the report, which can be saved or printed out.

The manufacturer provides on-site training for the ZedScan free of charge. Training takes approximately 2 hours, and the manufacturer anticipates a learning curve of around 10 patients. The device can be used alongside existing colposcopy equipment, and no additional facilities or equipment are needed. Other than routine cleaning after each use, no maintenance is needed. The device automatically carries out a calibration check before each use.

The ZedScan is intended for use alongside existing colposcopy procedures. The most recently available NHS reference costs for 2012–13 list colposcopies as outpatient procedures under currency code MA38Z and MA39Z and service code 502. The NHS reference costs suggest that colposcopic procedures fall into 3 main categories.

### Table 1 Categories of colposcopic procedures

<table>
<thead>
<tr>
<th>Description</th>
<th>Procedures</th>
<th>National average unit cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic colposcopy</td>
<td>119,198</td>
<td>£169</td>
</tr>
<tr>
<td>Diagnostic colposcopy with biopsy</td>
<td>46,837</td>
<td>£204</td>
</tr>
<tr>
<td>Therapeutic colposcopy</td>
<td>26,500</td>
<td>£214</td>
</tr>
</tbody>
</table>

The following NHS tariffs for outpatient attendance relating to consultant-led gynaecological oncology services are provided for information (Payment by results tariff 2013–14):

- first attendance, single professional: £154
- first attendance, multi-professional: £291
- follow-up attendance, single professional: £89
- follow-up attendance, multi-professional: £132.
**Likely place in therapy**

The ZedScan could be used as an adjunct to colposcopy for women who are referred for colposcopy as recommended by the NHS Cervical Screening Programme.

**Specialist commentator comments**

One specialist commentator noted that the ZedScan does not have a clear role in the practice of colposcopy until more effectiveness data becomes available. Another commentator reflected that it is important that there are agreed diagnostic criteria for evaluating adjunctive technologies and how they impact on cost effectiveness.

One commentator reported that a typical ZedScan user in the NHS would be a certified colposcopist.

One commentator reported that the ZedScan and DySIS were being evaluated in NHS clinics. One specialist commentator expressed that there is a requirement for longitudinal studies. This would allow a more accurate assessment of the effectiveness of adjunctive technologies in the earlier detection of cervical cancer. A proportion of high-grade CIN are known to regress without treatment rather than developing into cancer and the improved sensitivity offered by the ZedScan may lead to the detection and treatment of lesions that are destined to regress. However, another commentator noted that the ZedScan may be of benefit in preventing cervical cancer.

A specialist commentator highlighted that the published evidence for the ZedScan was largely based on prototype devices and not on the commercially available version. They considered that the studies on the prototypes were not informative when considering the utility of the device.

**Equality considerations**

NICE is committed to promoting equality and eliminating unlawful discrimination. In producing guidance, NICE aims to comply fully with all legal obligations to:

- promote race and disability equality and equality of opportunity between men and women
- 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 (these are protected characteristics under the Equality Act 2010).
The ZedScan would be used as part of the diagnosis of CIN in women. Sex is a protected characteristic under the Equality Act 2010. People with cancer are protected under the act from the point of diagnosis.

Evidence review

Clinical and technical evidence

Regulatory bodies

A search of the Medicines and Healthcare Products Regulatory Agency website revealed no manufacturer Field Safety Notices or Medical Device Alerts for this device. No reports of adverse events were identified from a search of the US Food and Drug Administration (FDA) database: Manufacturer and User Device Facility Experience (MAUDE).

Clinical evidence

Five diagnostic cohort studies relating to the ZedScan (Abdul et al. 2006, Balasubramani et al. 2009, Brown et al. 2000, Brown et al. 2005 and Tidy et al. 2013) were identified. These are summarised in tables 2–6. The studies evaluated different prototypes of the ZedScan and presented various outcome measures related to the development of the device.


The main changes to prototypes of the ZedScan at each point in the development of the device are summarised in about the technology. Only the Abdul et al. (2006) and Tidy et al. (2013) explicitly stated which version of the ZedScan was evaluated: these were versions MKIII and APX100 respectively.

Table 2 Versions of the ZedScan used in the published studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Prototype used</th>
</tr>
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</table>
No peer-reviewed studies were identified evaluating the commercially available model of the ZedScan. However, the manufacturer has published a non-peer-reviewed case series (Palmer et al. 2014) of 287 women carried out by a colposcopy clinic (Jessop Wing, Sheffield Teaching Hospitals NHS Trust). This study was conducted after the commercial launch of the ZedScan in January 2014.

Brown et al. (2000 and 2005) reported on the ability of the first prototype version of the ZedScan to discriminate between any grade of CIN and normal epithelial cells. In Brown et al. (2005) the 'per woman' analysis was made from a single value derived from all of the probe measurements for each woman. This gave a sensitivity and specificity of 67%.

Abdul et al. (2006) evaluated the MKIII version of the ZedScan. When performing a 'per woman' analysis to differentiate between any grade of CIN and a normal epithelium the study found a sensitivity of 66.3% (69/104), specificity of 49% (27/55), positive predictive value of 67.7% (69/96), and negative predictive value of 55% (35/63). The same analysis to identify CIN2 and CIN3 found a sensitivity of 74% (58/78), specificity of 53% (42/80), positive predictive value of 60%, and negative predictive value of 67% (42/62).

Balasubramani et al. (2009) evaluated a second-generation prototype version of the ZedScan. The study compared data obtained from cells before and after the application of acetic acid. It was reported that acetic acid application made no significant difference to the impedance spectra data. The 'per woman' analysis to detect high-grade CIN (CIN2 and above) after acetic acid was applied found a sensitivity of 89.7% and a specificity of 50%.

Tidy et al. (2013) evaluated the diagnostic performance of the APX100 prototype version of the ZedScan. The study used 2 test standard methods to calculate sensitivity and specificity, and varied the cut-off values for the EIS measurements to adjust the sensitivity or specificity of the device. To do this, a cut-off value was used for median EIS values that exceeded the median EIS value taken at

<table>
<thead>
<tr>
<th>Authors</th>
<th>Description</th>
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<tbody>
<tr>
<td>Brown et al. (2005)</td>
<td>First generation with the following modification: the construction specification of the probe was unchanged but small changes were made to the electrode spacing and the flatness of the probe face.</td>
</tr>
<tr>
<td>Tidy et al. (2013)</td>
<td>Third generation (APX100).</td>
</tr>
</tbody>
</table>
biopsy sites proven to be high-grade CIN (i.e. CIN2 or CIN3) in phase 1 of the study. Sensitivities and specificities for clinical performance were calculated using 2 methods. For the 'colposcopic impression' method, the test result was positive if high-grade CIN was suspected and a biopsy was taken for confirmation. For the 'disease present' method, the test result was positive if disease of some degree was suspected, and a biopsy was taken to confirm or exclude high-grade CIN. By using a cut-off value to give the same sensitivity as colposcopy, an increase in the positive predictive value was seen. The positive predictive value improved from 53.5% to 67% (95% confidence interval 45.0–61.8; p=0.0006) when the disease present method was used, and improved from 78.1% to 86.5% (95% confidence interval 67.5–86.4; p=0.0456) when the colposcopic impression method was used.

A case series published by Zilico (Palmer et al. 2014) evaluated 287 women attending the colposcopy clinic at Sheffield Teaching Hospitals NHS Trust between January and July 2014. The study used the ZedScan in combination with standard colposcopy. Of these women, 252 were referred with abnormal cytology, and 35 were referred with clinical indications. Of the women evaluated, 33.5% had high-grade cytology and 66.5% had low-grade cytology. The positive predictive value was 59.3%.

**Table 3 Summary of the Abdul et al. (2006) diagnostic cohort study**

<table>
<thead>
<tr>
<th>Study component</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objectives/hypotheses</td>
<td>To assess the performance of EIS in detecting CIN using the MKIII prototype of ZedScan.</td>
</tr>
<tr>
<td>Study design</td>
<td>Diagnostic cohort study.</td>
</tr>
<tr>
<td>Setting</td>
<td>One colposcopy clinic, location not specified.</td>
</tr>
<tr>
<td>Inclusion/exclusion criteria</td>
<td>Women referred to colposcopy with an abnormal Papanicolaou smear. No exclusions specified.</td>
</tr>
<tr>
<td>Primary outcomes</td>
<td>Impedance spectra were assessed to determine if there was a significant difference between values taken from CIN values taken from a normal epithelium. The probe’s ability to identify women with CIN was also assessed.</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td>Sensitivity and specificity.</td>
</tr>
<tr>
<td>---------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>Methods</td>
<td>Impedance spectra were measured using a 5.5 mm diameter pencil probe at 30 frequencies at 8 positions on the cervix, before the application of acetic acid. Colposcopy examinations, including probe positioning, were recorded by video to allow for correlation. Biopsies were taken if colposcopy alone did not allow a clear categorization of the tissue. Tissues were classified into epithelial groups using the video analysis. Impedance parameters (R/S) were calculated for each of the 8 measurement sites to provide a single indicator for each woman. The lowest value of R/S (R/S minimum) was used as the outcome for each woman, as this should identify the greatest abnormality.</td>
</tr>
<tr>
<td>Participants</td>
<td>Women referred to colposcopy with an abnormal Papanicolaou smear. Women were placed into a 'CIN' group if they had any grade of CIN (based on the colposcopy, or a 'normal' group if not. CIN group: 104 women. Normal group: 55 women. Women were excluded if less than 6 measurements were taken or if the colposcopy outcome was ambiguous. In total 17/176 women were excluded.</td>
</tr>
</tbody>
</table>
Results

A clear colposcopy result and good impedance spectra data were available for 1168 measurements made on 176 women. The total possible number of measurements was 1408 (8 measurements each on 176 women). The 240 measurements that were not assessed were excluded because the point where the probe had been placed was not clearly identified by biopsy or colposcopy to be in one histologic group (105 measurements) or the data were rejected on technical grounds (135 measurements).

*R/S minimum* was used to distinguish between a normal epithelium and CIN. The sensitivity was 66.3% (69/104), the specificity was 49% (27/55), the positive predictive value was 67.7% (69/96), and the negative predictive value was 55% (35/63).

When using *R/S minimum* to distinguish between the 2 groups, ROC was used to detect CIN2 and CIN3. This gave an AUC of 0.652. Using *R/S* as the borderline for identification of CIN2 or CIN3, the study found a sensitivity of 74% (58/78), specificity of 53% (42/80), positive predictive value of 60%, and negative predictive value of 67% (42/62). In this study, cervical cytology had a positive predictive value of 67% (103/154).

| Adverse events | Not reported. |
| Authors’ conclusions | EIS at 30 frequencies over a 2–1200 kHz frequency range has similar sensitivity and specificity to current screening methods, but with the advantage of providing real-time results. Using a wider frequency range did not improve the separation of immature metaplastic tissue from CIN. |

Abbreviations: AUC: area under the curve; EIS, electrical impedance spectroscopy; ROC, receiver operator characteristic; CIN, cervical intra-epithelial neoplasia; SIL, squamous intra-epithelial lesion.

Table 4 Summary of the Balasubramani et al. (2009) diagnostic cohort study

<table>
<thead>
<tr>
<th>Study component</th>
<th>Description</th>
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To evaluate the efficacy of an EIS probe (Epitheliometer, a prototype of ZedScan) for diagnosing high-grade CIN (CIN2 or CIN3) in women referred with cervical smear abnormalities, and to assess the effect of acetic acid and tissue boundaries on the measurements. The comparator was colposcopy examinations and histopathology.

| Study design | Diagnostic cohort study. |
| Setting | Location not specified. |
| Inclusion/exclusion criteria | Women with an abnormal cervical smear result or clinical indication for colposcopy. pregnant women and postmenopausal women were excluded. |
| Primary outcomes | Evaluation of the ability of ZedScan to discriminate between tissue types, and the potential use of ZedScan as an adjunct to colposcopy. |
| Secondary outcomes | To determine whether applying acetic acid altered tissue impedance and to assess whether the probe could identify tissue boundaries. |
| Methods | Impedance measurements were made using a 5.5 mm diameter pencil probe at 16 frequencies at 12 positions on the cervix. A further 12 measurements made after 5% acetic acid was applied to the cervix. Colposcopy was performed and biopsies taken if clinically indicated. The procedure was recorded by video for subsequent correlation of data. Boundary data was collected and analysed from 41 women after acetic acid was applied, to assess if the probe could differentiate between tissue boundaries. ROC curves were drawn to evaluate whether the probe could differentiate high-grade CIN from all other classifications of the cervical epithelium. A per-woman analysis was performed using the probe results, classifying the epithelium either as 'normal' or 'high-grade CIN'. |
Participants
Women (n=165) aged 20–55 years attending the colposcopy clinic with any cervical smear abnormality or a clinical indication for colposcopy. About 73% were non-smokers. The main study included 124 women and the boundary detection section included 41. A learning curve was noticed in the first 20 women to have their impedance measurements taken, and so these women were excluded from further analysis.

Reason for referral to colposcopy clinic: 34 women had mild dyskaryosis, 16 had moderate dyskaryosis, 27 had severe dyskaryosis, 20 had borderline dyskaryosis, 5 had post-coital bleeding, 1 had inflammation and 1 had glandular neoplasia.

Results
Comparison of data before and after acetic acid was applied demonstrated that acetic acid does not cause a large change in impedance spectra.

For the data after acetic acid application, the ROC curves showed an AUC of 0.79, with a sensitivity of 78.9% and a specificity of 66%. The AUC for high-grade CIN compared with all other classifications was 0.74, with a sensitivity of 73.6% and a specificity of 63%. The per-woman analysis gave an AUC of 0.74, with a sensitivity of 89.7% and a specificity of 50%.

Comparison of ZedScan diagnosis with histology: at all sites the ZedScan and histological diagnosis matched, with 18 sites identified by both as high-grade CIN and 4 sites identified by both as non-CIN. This suggests a 100% sensitivity and specificity, although on a small sample set. The probe distinguished between tissue boundaries from homogenous tissue points.

Adverse events
Not reported.

Authors’ conclusions
The authors concluded that ZedScan had the potential to be used as an adjunct to colposcopy for diagnosing high-grade CIN, and that by giving real-time results it could decrease the need for diagnostic cervical biopsies.

Abbreviations: AUC, area under the curve; CIN, cervical intra-epithelial neoplasia; EIS, electrical impedance spectroscopy; ROC, receiver operating characteristic.

Table 5 Summary of the Brown et al. (2000) diagnostic cohort study

<table>
<thead>
<tr>
<th>Study component</th>
<th>Description</th>
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<table>
<thead>
<tr>
<th>Objectives/hypotheses</th>
<th>To assess the agreement between EIS measurements using a prototype of ZedScan and predictions made by taking into account the known cell arrangements in cervical tissue.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td>Diagnostic cohort study.</td>
</tr>
<tr>
<td>Setting</td>
<td>Colposcopy clinic, location not specified.</td>
</tr>
<tr>
<td>Inclusion/exclusion criteria</td>
<td>Consecutive women with moderate or severe dyskaryosis. Three women with borderline changes and 2 with mild dyskaryosis were also included.</td>
</tr>
<tr>
<td>Primary outcomes</td>
<td>Cervical impedance measurements.</td>
</tr>
<tr>
<td>Methods</td>
<td>Impedance measurements were made at 8 positions on the cervix before acetic acid was applied. Colposcopy examinations, including probe positioning, were recorded by video to allow for correlation between results obtained from colposcopic impression, biopsy histopathology, and impedance measurements. Impedance parameters, $R/S$, were calculated for each of the 8 measurement sites to provide a single indicator for each woman. The lowest value of $R/S$ ($R/S_{minimum}$) was used as the outcome for each woman, as this should identify the greatest abnormality.</td>
</tr>
<tr>
<td>Participants</td>
<td>124 women (756/992 impedance measurements).</td>
</tr>
<tr>
<td>Results</td>
<td>Comparing impedance measurements with colposcopic and histological results: 370 showed normal epithelium, 1 showed invasive cancer, 126 showed CIN2 or CIN3, 63 showed CIN1, 64 showed mature metaplasia, 98 showed immature metaplasia and 34 showed columnar tissue. When comparing the $R/S_{minimum}$ results with the CIN 'normal' classification, the ROC curve showed an AUC of 0.819 (116/124 women). Categorising on the basis of impedance results and using the 75% centile (0.81) for $R/S_{minimum}$ as the borderline, the sensitivity was 75% (66/88), the specificity was 71% (20/28), the PPV was 89% (66/74) and the NPV was 45% (20/44). In this study cervical cytology had a positive predictive value of 76% (88/116).</td>
</tr>
<tr>
<td>Adverse events</td>
<td>None reported.</td>
</tr>
</tbody>
</table>
Authors’ conclusions

Characteristics of the electrical impedance spectra of tissues can be explained by changes in cell arrangements (layering) and in the size of the nuclei.

Abbreviations: AUC, area under the curve; CIN, cervical intra-epithelial neoplasia; EIS, electrical impedance spectroscopy; ROC, receiver operator characteristic.

Table 6 Summary of the Brown et al. (2005) diagnostic cohort study

<table>
<thead>
<tr>
<th>Study component</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objectives/hypotheses</td>
<td>To improve the performance of the EIS probe (prototype of ZedScan) in measuring the impedance spectrum of the cervical epithelium, in women with CIN or with a normal epithelium. In addition, to address practical issues with using probe to help introduce it into routine clinical use.</td>
</tr>
<tr>
<td>Study design</td>
<td>Diagnostic cohort study.</td>
</tr>
<tr>
<td>Setting</td>
<td>One hospital-based colposcopy clinic in Sheffield.</td>
</tr>
<tr>
<td>Inclusion/exclusion criteria</td>
<td>Women referred for colposcopy with moderate or severe dyskaryosis. Three women with mild dyskaryosis were also included. Postmenopausal women were excluded.</td>
</tr>
<tr>
<td>Primary outcomes</td>
<td>Electrical impedance measurements, to determine if there were differences between values from CIN and from a normal epithelium.</td>
</tr>
</tbody>
</table>
| Methods                  | A pencil probe with 4 gold electrodes was used to measure an electrical impedance spectrum in the cervical epithelium. Measurements were made before acetic acid was applied. Colposcopy examinations, including probe positioning, were recorded by video to allow for correlation between results obtained from colposcopic impression, biopsy histopathology, and impedance measurements.

Impedance parameters \( R/S \) were calculated for each of the 8 measurement sites, to provide a single indicator for each woman. The lowest value of \( R/S \) \( (R/S\ minimum) \) was used as the outcome for each woman, as this should identify the greatest abnormality.

Participants

Women for whom there were data from at least 6/8 probe measurements (82/87).
Results

When comparing the $R/S_{\text{minimum}}$ results with the CIN 'normal' classification, the ROC curve showed an AUC of 0.707. Both the sensitivity and specificity were 67%.

Categorising on the basis of impedance results and using the 75% centile (0.70) for $R/S_{\text{minimum}}$ as the borderline, the sensitivity was 75% (46/61), the specificity was 43% (9/21), the positive predictive value was 79% (46/58) and the negative predictive value was 38% (9/24).

When CIN was defined using the 25 and 75 centiles for $R/S$ (<0.55), the sensitivity was 75% (46/61), the specificity was 71% (15/21), the positive predictive value was 88% (46/52) and the negative predictive value was 50% (15/30).

In this study cervical cytology had a positive predictive value of 74% (61/82).

Adverse events

None reported.

Authors’ conclusions

Cervical impedance spectrometry provides a potentially promising screening tool, with similar sensitivity and specificity to current screening tests, but with the potential advantage of providing instant results.

Abbreviations: AUC, area under the curve; EIS, electrical impedance spectroscopy; CIN, cervical intra-epithelial neoplasia; ROC, receiver operator characteristic.

Table 7 Summary of Tidy et al. (2013) diagnostic cohort study

<table>
<thead>
<tr>
<th>Study component</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objectives/hypotheses</td>
<td>To determine if EIS improves the diagnostic accuracy of colposcopy when used as an adjunct.</td>
</tr>
<tr>
<td>Study design</td>
<td>Diagnostic cohort study.</td>
</tr>
<tr>
<td>Intervention</td>
<td>ZedScan prototype APX 100 EIS device. Comparator: colposcopy examinations and histopathology.</td>
</tr>
<tr>
<td>Setting</td>
<td>Hospital-based colposcopy clinics (Manchester, Sheffield and Dublin) between April 2009 and May 2011.</td>
</tr>
</tbody>
</table>
### Inclusion/exclusion criteria
All women referred with abnormal cervical cytology, as directed by English and Irish cervical screening programmes. Referrals were non-consecutive. Pregnant and menstruating women were excluded from the study.

### Primary outcomes
To assess ZedScan when used as an adjunct to improve colposcopic performance, as measured by positive predictive value.

### Methods
Phase I: ZedScan was compared with colposcopic impression and biopsy histopathology. A probability index and cut-off value for detecting high-grade CIN (CIN2 or CIN3) was derived to indicate sites for biopsy in phase 2. ZedScan data collection and analyses were performed in real time and blinded to the clinician.

Phase 2: measurements made after acetic acid was applied but before formal colposcopic impression. Data were analysed using different cut-off values, to assess the performance of ZedScan as an adjunct. Sensitivities and specificities for clinical performance were calculated using 2 methods. In the 'colposcopic impression' method, the test result was positive if high-grade CIN was suspected and a biopsy was taken for confirmation. In the 'disease present' method, the test result was positive if disease of some degree was suspected and biopsy was taken to confirm or exclude high-grade CIN.

A colposcopic impression for all biopsies was recorded at the same time as the ZedScan measurements, and videos were reviewed to evaluate concordance.

ROC analysis was used to assess the performance of ZedScan on its own and as an adjunct to colposcopy. The AUC was calculated to measure the ability of ZedScan to separate women with and without high-grade CIN. ROC curves were plotted using MATLAB. P values were calculated by comparing colposcopy with and without ZedScan, using a 2-tailed non-parametric Z-test.
474 women were recruited to the study. In phase 1 there were 247 women. 31 women were excluded as part of the training, and 2 because of incomplete data. The median age was 31.3 years (range 20–60). There were 7 (3.3%) postmenopausal women, and 195 (91%) white women. There were 159 (74.3%) women at the Sheffield clinic, 55 (25.7%) women at the Manchester clinic and no women at the Dublin clinic. There were 113 (52.8%) women referred for high-grade CIN.

In phase 2 there were 227 women. 9 women were excluded because of incomplete data, 1 because of the inclusion criteria, 1 because the colposcopic examination could not be completed, and 1 because of protocol violation. Phase 2 evaluated 196/215 women. The median age was 29.5 years (range 20–64). There were 9 (4.2%) postmenopausal women and 194 (90%) white women. There were 76 (35.3%) women at the Sheffield clinic, 68 (31.6%) women at the Manchester clinic and 71 (33.1%) women at the Dublin clinic. There were 94 (43.7%) women referred for high-grade CIN.

<p>| Experience of colposcopist | One BSCCP-certified colposcopist at each centre performed all examinations. Colposcopists were trained to use ZedScan, but it is not clear if this training was done outside of this study. |</p>
<table>
<thead>
<tr>
<th>Results</th>
<th>ZedScan as adjunct to colposcopy using colposcopic impression method to detect high-grade CIN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Using the cut-off from phase 1 (0.568), the positive predictive value improved from 78.1% to 91.5% (95% CI 67.5 to 86.4; p=0.0012). The specificity increased from 83.5% to 95.4% (95% CI 75.2 to 89.9; p=0.0010), and the sensitivity was significantly reduced from 73.6% to 62.1% (95% CI 63.0 to 82.5; p=0.0394). The negative predictive value was not statistically different. The positive likelihood ratio for colposcopic impression alone was 4.46, and this increased to 13.5 with ZedScan as an adjunct (p&lt;0.0001).</td>
</tr>
<tr>
<td></td>
<td>Using a cut-off to give the same sensitivity as colposcopy, the positive predictive value improved from 78.1% to 86.5% (95% CI 67.5 to 86.4; p=0.0456). The specificity increased from 83.5% to 90.8% (95% CI 75.2 to 89.9; p=0.0226). The negative predictive value was not statistically different. The positive likelihood ratio for colposcopic impression alone was 4.46, and this increased to 8 with ZedScan as an adjunct (p=0.0308).</td>
</tr>
<tr>
<td></td>
<td>Using a cut-off to give ZedScan the same specificity as colposcopy, there was no statistically significant difference in sensitivity, negative predictive value, positive predictive value or positive likelihood ratio.</td>
</tr>
<tr>
<td></td>
<td>ZedScan as adjunct to colposcopy when using DP method</td>
</tr>
<tr>
<td></td>
<td>Using the cut-off from phase 1 (0.568), the specificity increased from 38.5% to 51.6% (95% CI 29.2 to 48.3; p=0.0076). The positive likelihood ratio for colposcopic impression alone was 1.43, and this increased to 1.90 with ZedScan as an adjunct (95% CI 1.24 to 1.69; p=0.0002). There was no statistically significant difference in sensitivity, positive predictive value or negative predictive value.</td>
</tr>
<tr>
<td></td>
<td>Using a cut-off to give the same sensitivity as colposcopy, the positive predictive value improved from 53.5% to 67%, (95% CI 45.0 to 61.8; p=0.0006). The specificity increased from 38.5% to 65.1% (95% CI 29.4 to 48.3; p&lt;0.0001). There was no statistically significant difference in the negative predictive value. The positive likelihood ratio for colposcopic impression alone was 1.43, and this increased to 2.53 with ZedScan as an adjunct (95% CI 1.24 to 1.69; p&lt;0.0001).</td>
</tr>
<tr>
<td></td>
<td>Using a cut-off to give the same specificity as colposcopy, the sensitivity increased from 88.5% to 96.6% (95% CI 79.9 to 94.4; p=0.0060). The negative predictive value improved from 80.8% to 93.3% (95% CI 67.5 to 90.4; p=0.0094). There was no statistically significant difference in the positive predictive value or positive likelihood ratio.</td>
</tr>
</tbody>
</table>
The ROC for ZedScan as an adjunct to colposcopy to detect high-grade CIN had an AUC of 0.887 (95% CI 0.840 to 0.934).

### Adverse events
One patient felt unwell and 2 had problems with bleeding after the biopsy. In 5 cases ZedScan had technical problems that prevented the collection of EIS data.

### Authors' conclusions
The addition of ZedScan could lead to more appropriate management and lower intervention rates.

**Abbreviations:** AUC, area under the curve; BSCCP, British Society for Colposcopy and Cervical Pathology; CI, confidence interval; CIN, cervical intra-epithelial neoplasia; EIS, electrical impedance spectroscopy; ROC, receiver operator characteristic.

### Recent and ongoing studies
No ongoing or in-development trials of ZedScan were identified.

### Costs and resource consequences
The most recently available NHS reference costs for 2012–13 indicate that if the ZedScan avoided the need for a biopsy during a colposcopy the saving would be £45. If using the ZedScan prevented unnecessary follow-up appointments, the saving would be £89 per patient.

### Published cost studies
An economic evaluation of the ZedScan (funded by the manufacturer) was carried out in July 2013 by the School of Health and Related Research (Bessey et al. 2013).

The report analysed the cost and health impacts of the device on colposcopy services in the NHS. A model was built and run to simulate 1,000,000 women treated over a 3-year pathway. Probabilistic sensitivity analysis and one-way sensitivity analyses were performed. Base-case results were presented for 1000 women attending under 3 scenarios, each with and without using the ZedScan. These aimed to represent the variations in treatment options at colposcopy appointments:

- **Treat later clinic** – no treatment at initial colposcopy appointment. Biopsy taken for confirmation, before treatment at a later date.
- **See and treat clinic** – women treated at initial colposcopy appointment if diagnosis indicates that this is appropriate.

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- Triage clinic – low-grade referrals seen as in the 'see and treat' clinic, high-grade referrals seen as in the 'treat later' clinic.

Table 8 Summary of results from the Bessey et al. 2013 economic evaluation

<table>
<thead>
<tr>
<th></th>
<th>Treat later clinic</th>
<th>See and treat clinic</th>
<th>Triage by cytology result</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Standard colposcopy</td>
<td>Colposcopy with ZedScan</td>
<td>Standard colposcopy</td>
</tr>
<tr>
<td>Cost per woman with CIN2 or CIN3 treated</td>
<td>£1351</td>
<td>£1308</td>
<td>£1478</td>
</tr>
<tr>
<td>Total number of colposcopy appointments over 3 years (for 1000 women)</td>
<td>1942</td>
<td>1821</td>
<td>1545</td>
</tr>
</tbody>
</table>

Abbreviations: CIN, cervical intra-epithelial neoplasia.

The model showed that using the ZedScan resulted in lower total cost and lower costs per woman with treated CIN2 or CIN3 for all 3 scenarios. However, the base case did not support moving from 'treat later' to 'see and treat' clinics, as the cost per woman with treated CIN2 or CIN3 was lower in the 'treat later' clinic using standard care than in the 'see and treat' option using the ZedScan. For both the 'see and treat' and 'triage' clinics, the model showed a reduction in overtreatment, adverse events and related treatment costs. Lower biopsy rates were associated with the ZedScan, with 1–1.02 biopsies per woman having colposcopy with the ZedScan compared with 1.72 with standard care, and this reduced related costs. A cost saving was also illustrated from the reduction in follow-up colposcopy appointments over the timeframe of the model. Based on figures collected from the NHS Cervical Screening Programme the model may underestimate the number of follow-up appointments, and therefore the economic impact of the ZedScan.

There was an estimated reduction in probable overtreatment from 14% to 2% with the ZedScan. A sensitivity analysis using a higher sensitivity while maintaining specificity resulted in a lower colposcopy cost per woman with treated CIN2 or CIN3, and more treated CIN2 or CIN3 than standard colposcopy. The results are sensitive to changes in colposcopy costs.
Strengths and limitations of the evidence

No randomised controlled trials of the ZedScan or its prototypes were identified. The available evidence comprises 5 diagnostic cohort studies, 1 non peer-reviewed case series and 1 economic evaluation.

It was unclear whether the studies by Abdul et al. (2006), Balasubramani et al. (2009) or Brown et al. (2005) recruited consecutive patients. Tidy et al. (2013) stated that recruitment was non-consecutive, and this could result in selection bias. It was unclear in Abdul et al. (2006) if any women were excluded.

The studies by Abdul et al. (2006), Balasubramani et al. (2009), Brown et al. (2000), and Brown et al. (2005) did not provide details of the training that the colposcopist using the ZedScan had received.

All of the studies apart from Tidy et al. (2013) were limited in that they were conducted in single centres. This limitation may mean that the results are not generalisable to other populations and settings. The sample size may be too small to observe a true effect size. The study by Tidy et al. (2013) was conducted in 3 centres, but only 1 colposcopist performed the examinations at each of the 3 centres. This colposcopist could have been highly experienced with the ZedScan compared with colposcopists at other centres.

The studies evaluated different versions of the ZedScan, and none of the peer-reviewed studies used the commercially available version of the device. Each reported different analyses of the data.

Tidy and Brown (authors on all 5 of the diagnostic accuracy studies) hold patents related to the technology, are shareholders of the manufacturer and receive consultancy fees, so their studies should be treated with some caution. However, the data collection and study monitoring in Tidy et al. (2013) was done by Medvance. No statement was included on conflicts of interest or funding in Abdul et al. (2006), Brown et al. (2000) or Brown et al. (2005).

The methodology for the case series (Palmer et al. 2014) published by the manufacturer has not been fully reported, and so cannot be fully critically appraised. It is a non-comparative study and so the findings could be subject to bias.

The non-peer reviewed economic evaluation was well executed, with a clear statement of limitations and assumptions. Long-term costs of failing to identify and treat CIN2 or CIN3 are not captured because of the 3-year follow up. Some inputs were based on data from small studies, and others were estimated.
The use of the ZedScan is not currently planned into any NICE guidance programme.

NICE has issued the following guidance which is relevant to this briefing:

- Adjunctive colposcopy technologies for examination of the uterine cervix – DySIS and the Niris Imaging System (2012) NICE diagnostics guidance 4

References


Cancer Research UK (September 2014) Cervical Cancer: Key Facts [online; accessed 21 October 2014]

Department of Health (2013) Payment by Results 2013-2014, Payments by Result (PbR) in the NHS [online; accessed 21 October 2014]


NHS Cancer Screening Programme (2012) NHS Cervical Screening [online; accessed 20 October 2014]


NHS Choices (February 2013) Cervical Cancer [online; accessed 21 October 2014]

Palmer JE, Lyon RE and Tidy JA (2014) ZedScan delivers improvements in clinical performance and more effective patient management at Sheffield Teaching Hospitals NHS Foundation Trust: Increased detection of high grade CIN (HG CIN) in a high throughput colposcopy clinic [online; accessed 22 October 2014]


The ZedScan as an adjunct to colposcopy in women with suspected cervical intra-epithelial neoplasia (MIB20)


Zilico (October 2014) ZedScan NHS Case Study [online; accessed 22 October 2014]

Zilico (April 2014) ZedScan Sales Brochure [online; accessed 23 October 2014]

Search strategy and evidence selection

Search strategy

A strategy was designed in Medline and adapted for the following databases:

Medline In Process, Embase, PsycINFO, Cochrane library (CDSR, CENTRAL, DARE, HTA, NHS EED), Web of Science core collection (including conference proceedings), NHS Evidence, Pubmed (for 'epub ahead of print' publications only) and HEED.

Additional searches were also conducted of the following:

- Clinicaltrials.gov, ICTR, FDA MAUD, MHRA and Google
Evidence selection

References were imported into Reference Manager and screened independently in duplicate by title and abstract. The full publications of selected references were also screened independently in duplicate, when available. Data from each of the studies were extracted by 1 reviewer and independently checked for accuracy by a second reviewer. Disagreements were resolved through discussion. Studies were assessed for quality using an adapted version of the QUADAS-2 tool, as directed by the NICE medical innovation briefings interim process and methods statement. Assessment was performed by one reviewer and independently checked by a second reviewer and disagreements resolved by discussion.

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 Cedar. 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.

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

- Miss Theresa Freeman-Wang, Consultant Gynaecologist, Whittington Health.
- Mr Simon Leeson, Consultant Obstetrician and Gynaecologist, Betsi Cadwaladr University Health Board.

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