Supplementary Information relating to EIS performance

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Introduction

The application of EIS to the detection of cervical neoplasia has been the subject of a number of studies that have been published since 2000[1,2,3,4]. The principal results from the most recent clinical trial of EIS in colposcopy (EpiCIN Trial) have been published as a peer-reviewed paper in the British Journal of Obstetrics and Gynaecology[5] (BJOG paper).

There is additional information, derived from the data collected during the trial, that was not included in this publication but which provides more detail on the performance of the EIS device and the potential impact of such a device on colposcopic practice and costs. This document summarises this additional information and also describes some projections on the impact of using an EIS device in clinical practice.

1. The effect of changing the threshold value

The BJOG paper describes the principles underlying the EIS device and the use of the technique to identify the likely presence of disease. It also describes the 'Probability Index' (PI) that is derived from the EIS measurements and indicates that by adjusting the threshold value for the PI it is possible to set the performance characteristics of the EIS device. This section expands upon these ideas.

The value of PI can vary from 0 to 1 and can vary continuously within this range; therefore it is possible to set a threshold value to provide specific performance characteristics. For example increasing the value of the threshold will increase the specificity and reduce the sensitivity so if a high specificity is required then a high threshold can be used.

The PI value can be calculated for all the sites in all the women enrolled into Phase 2 of the clinical trial and these can be related to the colposcopic impression (CI) determined by the colposcopist and also to the results for any biopsies that might have been taken. The CI is not a continuous variable and the opinion is either that HG-CIN may be present (CI=1) or that it is not present (CI=0). CI has been recorded in two ways, called the CI and DP methods, in the BJOG paper. The results presented in Table 2 (CI method) of the BJOG paper record a CI value of 1 if any point suggested for biopsy by the clinician was considered to be HG-CIN. In Table 3 (DP method) of the BJOG paper the CI value is recorded as 1 if the clinician decided that at least one biopsy should be taken, even though they did not consider any point to show clear evidence of HG-CIN. The two ways of recording colposcopic impression were used because both methods appear in the literature.

It was possible to produce the combined CI+PI index by adding together the separate values to produce a scale that runs from 0 to 2.

As explained in the BJOG paper this combined index was used to analyse the data from the clinical trial on a per woman basis and thereby identify threshold values that would produce particular levels of performance. The performance of colposcopy alone could be calculated from the same data because the colposcopist was blinded to the EIS results at the time they completed their examination.

In the trial the colposcopist was required to record their CI for each point where an EIS reading was taken and so the combined CI+PI value can be calculated for each reading site. So it is possible to categorise each participant in Phase 2 of the trial in the following ways:

- Abnormal (A) or Normal (N) based on whether they have biopsy-proven CIN2+
- The CI value – 1 or 0 based on the worst assessment of any part of the cervix
- The PI value – from 0 to 1 calculated from all the EIS readings taken
- The CI+PI value – the highest CI+PI value, from combining the two measures for all points.

By setting different threshold values for the CI+PI index it is then possible to assign the women into either abnormal (a) or normal (n) groups depending upon whether they have a CI+PI value above or below the threshold respectively. In this way it is possible to identify 4 groups:

Aa – biopsy-proven CIN2+ women who are above the threshold

An – biopsy-proven CIN2+ women who are below the threshold

Na – normal women who are above the threshold

Nn – normal women who are below the threshold

The numbers in these groups will vary as the threshold changes and can be used to calculate the performance characteristics of the test.

Sensitivity = Aa/(Aa+An)

Specificity = Nn/(Nn+Na)

PPV = Aa/(Aa+Na)

NPV = Nn/(Nn+An)

LR+ = sensitivity/(1-specificity)

In this way it is possible to assess how the performance characteristics of colposcopy + EIS change as the threshold is changed.

The BJOG paper presents the impact of combining EIS with colposcopy at different thresholds of the combined CI+PI index; specifically where the threshold has been chosen so that either sensitivity or specificity is identical between colposcopy alone and colposcopy + EIS. It also shows the results obtained with the PI threshold set at 0.568 which was the value determined by analysis of the Phase 1 data for use in Phase 2 of the clinical trial.

This approach can be extended to the particular requirements for selecting patients for treatment at first examination (See & Treat, S&T). There are good reasons to carry out S&T but it should not be undertaken unless there is a high confidence that the woman does require treatment. The Guidelines for the NHS Cervical Screening Programme No 20, recommend that the PPV for S&T should be >90%.

PPV is not an inherent performance characteristic of a test but is determined by both the specificity of the test and the population examined e.g. the prevalence of disease. For this reason we have determined that it would be best to choose a threshold for S&T that provides a specificity of at least 95% so that even in populations with a relatively low prevalence of disease the PPV should be >90%. We identified a CI+PI value that results in a specificity of at least 95% and so this would be the threshold that should be used in colposcopy to identify those patients that are suitable for S&T – referred to as the 'S&T Threshold'.

The S&T Threshold could be applied so that any sites that are above this threshold would be displayed to the user with the comment that S&T should be considered. If there are no sites above this threshold then the PI values are compared against the lower threshold and any sites that are above this would be displayed to the user with the comment that biopsies should be taken. If no sites are above this lower threshold then the user would be informed that no biopsies are required. The user would consider this information in the light of clinical findings and they should use their clinical judgement and experience to make a final decision on the management of the patient.

2. Performance depending upon referral cytology result.

In current colposcopic practice the clinician takes into account the referral cytology when assessing the cervix; there is a presumption that HG-CIN will be present in women referred with a serious abnormality (e.g. moderate or severe dyskaryosis) and conversely will probably not be present in women referred with a persistent mild abnormality (e.g. repeat borderline). Zilico has looked at the effect of stratifying the study population on the basis of referral cytology and Table 1 in the BJOG paper specifies which categories of referral cytology are regarded as either high-grade or low-grade.

In Phase 2 of the study there were 196 eligible patients of whom 109 were LG referrals and 87 were HG referrals. Because the numbers in the separate referral groups are rather small for good statistical analysis, it was decided that we would identify a method of adjusting the threshold for the total population to produce separate thresholds that could be applied to the HG and LG referral populations separately. The method used was to calculate the ROC area under the curve (AUC; see Fig 3 of the BJOG paper) as a function of the difference between the thresholds applied to LG and HG referrals. The difference that maximised the ROC area was chosen to adjust the threshold for the total population and produce two new thresholds, 'HG-Threshold' and 'LG-Threshold', that could be applied to the HG and LG referrals respectively.

Table 1 (see below) sets out the performance characteristics of colposcopy alone and colposcopy + EIS both for the entire patient population and stratified by referral smear result. The thresholds applied for HG and LG referrals are derived from the threshold applied to the entire population as described in the previous paragraph.

Although these adjustments work well for the selection of patients who are likely to have HG-CIN, they are not optimal for determining the thresholds for selecting patients for S&T. Instead we have applied the same requirement that the specificity should be >95% for each referral group and also looked at the Positive Likelihood Ratio (LR+) which is another measure of test performance for selecting true positives. In this way we identified two new thresholds, 'HG-Threshold S&T' and 'LG-Threshold S&T', that can be used to identify women who might be suitable for S&T as described above. Again the results would be considered by the clinician together with the colposcopic impression and other clinical data before making a decision on the management of the patient.

TABLE 1

	Sensitivity	Specificity	LR+
Colposcopy alone (CI method)			
All Patients*	73.6%	83.5%	4.46
HG Referrals	80.3%	71.4%	2.81
LG Referrals	52.4%	86.4%	3.85
Colposcopy + EIS (CI method)			
All Patients (Sensitivity constant)*	73.6%	90.8%	8.00
All Patients (Specificity constant)*	78.2%	83.5%	4.73
S&T Thresholds (CI method)			
HG-Threshold S&T	65.2%	95.2%	13.58
LG-Threshold S&T	33.3%	98.8%	27.75
Colposcopy alone (DP method)			
All Patients‡	88.5%	38.5%	1.43
HG Referrals	89.4%	19.0%	1.10
LG Referrals	85.7%	43.2%	1.51
Colposcopy + EIS (DP method)			
All Patients (Sensitivity constant)‡	88.5%	65.1%	2.53
HG-Threshold (derived from above)	92.4%	38.1%	1.49
LG-Threshold (derived from above)	76.2%	70.5%	2.58
All Patients (Specificity constant) ‡	96.6%	38.5%	1.57
HG-Threshold (derived from above)	100%	14%	1.16
LG-Threshold (derived from above)	85.7%	44.3%	1.54

*Table 2 BJOG paper

‡Table 3 BJOG paper

3. The combination of CI and PI in clinical practice

The clinical use of the Zilico ZedScan device will be different from the protocol followed in the trial. This is in part because the clinical trial was designed so that each patient was their own control and so the clinical judgement was reached without the information from the EIS device, whereas the purpose of the ZedScan is to provide information of the likely presence of HG-CIN that the colposcopist can take into account when reaching their decision on patient management. Another key difference is that in the trial the user recorded their CI for each reading site and this is not a practical option for routine clinical practice.

The ZedScan is programmed so that the threshold used for any given patient will depend upon the referral cytology result and also whether the colposcopist has identified the presence of HG-CIN. Clearly only the PI portion of the CI+PI index is addressed in this way and so the user has to combine

the output from the device with what they have observed during the examination. An example will make this process clearer.

A woman has been referred with severe dyskaryosis and the colposcopist has seen what they believe to be HG-CIN during the examination. The ZedScan has been used to take a series of readings around the cervix and at least one of these has a PI value above the 'HG-Threshold S&T'. The user sees on the handset display that at least one site is indicated as above the higher threshold and that S&T could be appropriate. The user considers whether the location of this site(s) coincides with the area of HG-CIN that they identified and if it does, then the CI+PI index is high enough that the specificity is >95% and S&T should be considered; the ultimate decision about whether S&T is carried out resides with the colposcopist and, if they decide not to carry out an excision, they can still take a biopsy. If the site(s) identified by the ZedScan do not coincide with the HG-CIN identified by the colposcopist then the CI+PI index is not sufficiently high for S&T to be appropriate but a biopsy should still be taken, using the single point mode of the ZedScan to better identify the precise site.

4. Impact on the number of biopsies required

All the calculations of the performance of colposcopy + EIS presented in the BJOG paper are based on taking a single biopsy at the site with the highest CI+PI value, so in principle the use of the ZedScan device could completely remove the need for multiple biopsies and would also reduce the number of women who would require a biopsy at all. Since one of the costs of providing a colposcopy service is the cost of processing, examining and reporting the histopathology of the biopsies taken during examination, reducing the total number of biopsies could provide an important cost saving.

In order to estimate the potential impact of ZedScan on the number of biopsies the following assumptions can be made.

1. Where there is at least 1 site which is above the appropriate threshold and which coincides with the clinician's opinion that HG is present then a single biopsy will be taken at that site.
2. Where no sites coincide with the clinician's opinion of HG being present but there is at least one site elsewhere which is above the cut-off then a single biopsy may be taken at the site with the highest PI and/or the clinician may still take a biopsy at a site of their choice.
3. Where there are no sites above the cut-off then the clinician might not take any biopsies or may take at least one at a site of their choice
4. The lowest possible estimate is based upon the clinician being extremely conservative and not taking any biopsies that are not indicated by both CI and the APX, whereas the highest possible estimate is where the clinician may take one biopsy at a clinically chosen site and may also take one biopsy per woman at a site indicated by the APX.

The impact of these assumptions was calculated using the data from Phase 1 of the clinical trial because the protocol more closely represented normal clinical practice with regard to the number of biopsies taken than was the case in Phase 2. Each patient was considered in the light of the above assumptions to determine whether and how the number of biopsies might change.

Table 2 (below) shows that, by combining EIS with colposcopy, there will be an overall reduction in the number of biopsies required, even though for some patients the use of the device will lead to an

additional biopsy e.g. 19 women who had no biopsy taken by conventional colposcopy would be identified as requiring a single biopsy. Conversely at least 12 women who had either 1 or 2 biopsies taken would have avoided biopsy based on the data from the device.

	Phase 1 Results		Colposcopy + EIS										
			lowest possible estimates					highest possible estimates					
			Number of biopsies					**Number of biopsies**					
			0	**1**	**2**	**3**	All	**0**	**1**	**2**	**3**	All
	0	35	16	19			35	16	19			35
	1	61	33	28			61	9	49	3		61
	2	109	32	77			109	3	84	22		109
	3	8		8			8		5	3		8
	4	1		1			1		1			1
			81	133	0	0	214	28	158	28	0	214
Total women		214	214					214				
Total biopsies		307	133					214				

Table 2. Impact of EIS on the number of biopsies.

The calculation was made with a threshold of 0.39 (see Table 3 of the BJOG paper) and applied to the whole population without stratification into HG and LG referrals.

[1] Brown BH, Tidy J, Boston K, Blackett AD, Smallwood RH and Sharp F. The relationship between tissue structure and imposed electrical current flow in cervical neoplasia. *Lancet* 2000; 355: 892–95.

[2] Brown BH, Milnes P, Abdul S, Tidy J. Detection of cervical intraepithelial neoplasia using impedance spectroscopy – prospective study. Br J Obstet Gynaecol 2005; 112: 802–6.

[3] Abdul S, Brown BH, Milnes P, Tidy J The use of electrical impedance spectroscopy in the detection of cervical intraepithelial neoplasia. Int J Gynecol Cancer 2006; 16: 1823–32.

[4] Balasubramani L, Brown BH, Healey J, Tidy JA. The detection of cervical intraepithelial neoplasia by electrical impedance spectroscopy: The effects of acetic acid and tissue homogeneity. Gynecol Oncol; 2009; 115: 267–71.

[5] Tidy JA, Brown BH, Healey TJ, Daayana S, Martin M, Prendiville W. & Kitchener HC. Accuracy of detection of high-grade cervical intraepithelial neoplasia using electrical impedance spectroscopy with colposcopy BJOG 2013, 120:400-11