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TERRITORY GOVERNMENTS OF AUSTRALIA
AND THE GOVERNMENT OF NEW ZEALAND

Horizon Scanning Technology Prioritising Summary

Zilico hand-held device for rapid cervical cancer detection

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PRIORITISING SUMMARY

REGISTER ID: 000481

NAME OF TECHNOLOGY: ZILICO HAND-HELD DEVICE FOR RAPID CERVICAL CANCER DETECTION

PURPOSE AND TARGET GROUP: REAL-TIME DETECTION OF CERVICAL CANCER AND PRECANCEROUS LESIONS IN SEXUALLY ACTIVE WOMEN

STAGE OF DEVELOPMENT (IN AUSTRALIA):

- | | |
|---|---|
| <input checked="" type="checkbox"/> Yet to emerge | <input type="checkbox"/> Established |
| <input type="checkbox"/> Experimental | <input type="checkbox"/> Established <i>but</i> changed indication or modification of technique |
| <input type="checkbox"/> Investigational | <input type="checkbox"/> Should be taken out of use |
| <input type="checkbox"/> Nearly established | |

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

- | | | |
|---|-------------|----------------|
| <input type="checkbox"/> Yes | ARTG number | Not applicable |
| <input checked="" type="checkbox"/> No | | |
| <input type="checkbox"/> Not applicable | | |

INTERNATIONAL UTILISATION:

COUNTRY	LEVEL OF USE		
	Trials Underway or Completed	Limited Use	Widely Diffused
UK		✓	
Ireland		✓	
EU	✓		

IMPACT SUMMARY:

Zilico Limited provide a hand-held electrical impedance device (epitheliometer) with the aim of detecting cervical cancer and pre-cancerous changes of the cervix in real-time. It is thought that this will provide an integrated detect-and-treat model of care and help avert anxiety for women due to delay in conventional test results, and provide opportunity to treat women who are unlikely to return for results, or attend follow-up colposcopy¹. The technology which uses electrical impedance spectroscopy

¹ Reasons may include fear, ambivalence or embarrassment about the results and/or the procedure. Women in remote areas may also be less likely to receive continuity of care under current modalities.

(EIS) would serve as an alternative to Pap testing and an adjunct to colposcopy and could be made available through existing screening infrastructure to sexually active women between the age of 18 and 69 years² – the current target group of the National Cervical Screening Program.

BACKGROUND

Cervical cancer may arise from the squamous cells that cover the outer surface of the cervix (squamous cell carcinoma) or from the glandular cells in the cervical canal (adenocarcinoma). The majority of cervical cancers are squamous cell carcinoma (>60%), and approximately 20 per cent are adenocarcinomas (AIHW 2009).

Abnormal changes in the squamous cells or growth in the layers of the cervix are referred to as cervical intra-epithelial neoplasia, or CIN. Low-grade changes are referred to as CIN1, high-grade as CIN2 and CIN3 represents severe changes and is equivalent to *in situ* carcinoma (National Screening Unit 2008).

The first stage in detecting (pre) cancerous changes of the cervix is the cervical smear or Papanicolaou (Pap) test. The accuracy of the Pap test has improved significantly in recent years, but interpretation is still subjective as the assessment of cervical smears may vary between cytopathologists (Zilico 2010). This is reflected in reported specificity values for conventional cytology in the range of 95 to 98 per cent, but sensitivity of only 50 per cent (Balasubramani et al 2009). Effectiveness of the cervical screening programme in Australia thus relies on multiple opportunities at identifying and treating CIN, as reflected in the frequency of screening which is currently recommended every two years. Even with improved organisation of screening programmes, education and training, all programmes based on cervical cytology are subject to both false positives and false negatives. To a lesser degree, outcomes can be influenced by the effect of sampling and a given sample will not always provide results that reflect changes that have occurred in the cervix. The use of liquid based cytology has been shown to decrease the number of inadequate smears, but a recent systematic review and meta-analysis found this method did not show improved sensitivity or specificity compared to conventional methods (Arbyn et al 2008). Abnormal or suspect cervical smears are referred on for colposcopy. Although colposcopy is accepted as the gold standard in the evaluation of abnormal cervical cytology, results are dependent on the interpretation of the individual colposcopist as to whether normal or abnormal pathology is present. To detect any abnormality, the colposcopist applies dilute acetic acid to the cervix, and areas that turn white may indicate precancerous changes. Since a grading of ‘whiteness’ is required, colposcopic impression of any abnormality is subjective and prone to variation. The poor performance of colposcopy has been reported, with only 54.8 per cent of women with CIN3 being diagnosed in the colposcopy arm of a randomised study (Wang et al

² Or two years from commencement of sexual activity.

2005). The final diagnostic stage is biopsy, where there is also potential for error through sampling and subjective interpretation. In addition to the possible error inherent in each of the stages, significant waiting periods for women before receiving test results can be a cause of anxiety (Balasubramani et al 2009; Zilico 2010).



Figure 1 The Zilico system: (1) Disposable sleeve; (2) Wipe-clean surfaces; (3) Wireless operation; (4) User interface; (5) Ergonomic design; (6) Built in quality control tests (Zilico Medical Diagnostics 2010).

Technology that measures electrical impedance of tissue may provide an adjunct or alternative to conventional detection of (pre)cancerous changes to the cervix, and enable improved management of women in whom these cervical abnormalities have occurred. Biological tissue has electrical impedance, which is a function of frequency of an applied electrical current. The magnitude of impedance depends on the frequency as well as the structural composition of the tissue. Cervical epithelium is a highly structured, stratified tissue that exhibits changes associated with CIN, including increased nuclear to cytoplasmic ratio, loss of the surface layer of squamous (flattened) cells and increased volume of the extracellular space. The geometric arrangement of cells is known to affect tissue impedance, providing the basis to predict impedance spectra that are likely to be associated with CIN (Abdul et al 2006). Spectral measurements taken with a probe epitheliometer at the cervical surface can then be compared with the computed predictions to quantitatively assess whether the cervical tissue is normal or (pre)cancerous (Balasubramani et al 2009). In addition to providing a more objective way for identifying cervical neoplasia, it has been stated that Zilico's technology may reduce the number of required diagnostic biopsies, which are expensive and introduce delays in treatment. Reduction in biopsies and better selection of biopsy sites would in turn reduce over-treatment associated with colposcopy (personal communication, Zilico Medical Diagnostics). Zilico's system

consists of a hand-held wireless probe and base unit as shown with key features in Figure 1. A disposable sleeve is used for each woman undergoing the procedure.

CLINICAL NEED AND BURDEN OF DISEASE

In 1991 Australia introduced the National Cervical Screening Program. This program aims to screen all sexually active women in the age group 18-69 yrs, with testing recommended every two years. This program has led to a significant reduction in the incidence of cervical cancer and associated mortality. Cervical cancer is now the 13th most common cancer affecting Australian women, with an age-standardised³ incidence of 6.9 new cases per 100,000 women in 2005. Cervical cancer is the 19th most common cause of cancer mortality, with an age-standardised mortality of 1.9 deaths per 100,000 women in 2006. This compares favourably with 2002 worldwide figures of an age-standardised incidence of cervical cancer of 16.2 new cases per 100,000 women, and an age-standardised mortality rate from cervical cancer of 9.0 deaths per 100,000 women (AIHW 2009).

The number of colposcopies performed in Australia in the 12-month period from January 2009 to December 2009 was 8,202 (MBS item numbers 35644, 35645, 35646, 35647), with the majority (6,954) performed using the MBS item number 35647 (Fee: \$188.15).⁴ These numbers will only reflect those colposcopies performed in the private hospital setting and therefore the number of colposcopies performed in Australia is likely to be much higher. The revised NHMRC Guidelines for the management of women with screen-detected abnormalities recommend repeat cytology as follow-up for a low-grade Pap test rather than colposcopy and biopsy, with a colposcopy recommended only for women with atypical glandular cell reports. In 2007, 28,188 abnormalities were detected by histology in women aged 20–69 years, of which 13,709 were low-grade and 14,479 were high-grade, and therefore likely to be referred for a colposcopy (AIHW 2009).

A similar trend has been observed in New Zealand after the introduction of a National Cervical Screening Program in 1991. The age-standardised incidence of cervical cancer in 1991 was 12 per 100,000 and in 2002 this rate had decreased to seven per 100,000. The incidence rate is much higher in Māori women compared to non-Māori women, and was estimated to be 12.4 per 100,000 in 2002. Mortality rates have also decreased with the introduction of a national screening program. Between 1990 and 2001, mortality fell from five to two per 100,000, a decline of 60 per cent. Mortality in Māori women was also higher than in non-Māori women but has decreased from 11 per 100,000 in 1996 to six per 100,000 in 2001 (MoH 2005).

³ Australian standard population

⁴ <http://www9.health.gov.au/mbs/search.cfm>

DIFFUSION

The Zilico impedance device is not currently in use in Australia or New Zealand.

COMPARATORS

Precancerous abnormalities of cervical cells may be detected before progression to cancer occurs by screening with the Pap test (AIHW 2009). While the Pap test is problematic and unreliable in many respects it has been the backbone of the most successful cancer reduction program in the Australian health system. The main failing of the Pap test is its sensitivity which has been estimated to be as low as 30 per cent (30-87%), while the specificity – more important for a screening test - is much higher, falling in the range of 86-100 per cent (Nanda et al 2000). Although the success of the Australian Cervical Cancer Screening program is well substantiated, reaching 73 per cent of eligible women in each three year period, many women do not participate in the screening program for a variety of reasons and the impact of this is evident in the fact that 50 per cent of invasive cervical cancers occur in women not adequately screened (Sasieni et al 1996). Given cervical screening is a staged process that refers women with Pap tests showing high-grade (or multiple low-grade abnormalities) to colposcopy (CCV 2010), EIS has been developed with a dual purpose in mind. It is firstly envisaged that EIS will be used as an adjunct to colposcopy, and secondly as an alternative to Pap testing. Development of the system to provide a quantitative test with greater sensitivity than the Pap test, which relies on subjective interpretation of cytology, is proposed by Zilico (personal communication). However, studies to date focus on application in women referred for colposcopy.

SAFETY AND EFFECTIVENESS ISSUES

A UK study investigated the efficacy of a prototype Zilico EIS device for diagnosing high-grade CIN in women (n=165) aged 20 to 55 years (Balasubramani et al 2009) (level III-2 diagnostic evidence). All women had been referred to a colposcopy clinic with cervical smear abnormalities, and the EIS device was used to take 12 measurements from the cervix of each woman. Colposcopy was performed and biopsies taken where clinically indicated. Of the 165 women recruited, 104 provided data for the main study analysis, generating 889 measurement points with clear colposcopy results and good impedance data. Of these points, the EIS device determined that the tissue types were squamous (636), immature metaplasia (113), high-grade CIN (85) and columnar (45). Ten points were classified as human papilloma virus infection, inflammation, mature metaplasia, or low-grade CIN. Measurements were also taken after administration of five per cent acetic acid solution to assess any influence acetic acid application during standard colposcopy may have on the efficacy of the device. There was no significant difference between measurements before or after acetic acid application.

A per woman analysis was undertaken using impedance results which classified women as either normal or having high-grade CIN. Using receiver operating characteristic curves (ROC) derived with a statistical package to discriminate squamous cells from high-grade CIN for comparison with the colposcopy results, an area-under-curve (AUC) analysis gave results corresponding to a sensitivity and specificity of 88.4 and 63.9 per cent, respectively. The diagnosis of tissue type and histological diagnosis at the biopsy site were also compared and found to be in 100 per cent agreement. Eighteen sites were identified by both as high-grade CIN and four sites were non-CIN. While this is suggestive of 100 per cent sensitivity and specificity, the small sample size for this part of the study needs consideration (Balasubramani et al 2009). No specific assessment of safety was evident in the study, however, it appears unlikely that the process of taking measurements with the device would result in harm more substantial than during colposcopy, and the commercialised form has no sharp edges that could confer injury.

COST IMPACT

Zilico have estimated the cost of their EIS system at £2000, with a consumable cost of £20 per patient for each disposable sleeve. The anticipated life-span of the system is three years based on an average use of five to ten times per day. It is claimed there are no associated service or maintenance costs for the equipment. The cost benefit of the technology would be seen in reduced laboratory costs, especially if the detect-and-treat model of care (which the technology facilitates) were to be widely adopted, as adoption of such practice should lead to a reduction in the number of necessary colposcopy clinic appointments. Training of colposcopists in the use of EIS would be an additional cost, but could feasibly be incorporated into existing re-accreditation requirements (personal communication, Zilico Medical Diagnostics).

ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

No issues were identified/raised in the sources examined.

OTHER ISSUES

A multicentre clinical trial of the Zilico device has commenced in the EU. This study will investigate safety and effectiveness of the EIS, and determine tissue recognition thresholds. In contrast to previous studies, ethical approval to biopsy from sites determined by the device has been granted (personal communication, Zilico Limited).

SUMMARY OF FINDINGS

The early evidence suggests that the EIS probe could effectively distinguish between tissue types and assist as a more objective means to identify (pre)cancerous changes to the cervix. The technology may also assist in improved selection of sites for biopsy, especially where colposcopy and EIS results are in agreement.

HEALTHPACT ASSESSMENT:

Colposcopy is a subjective technique which relies to a great extent on operator skill. The Zilico device is objective as it identifies regions of abnormal impedance, therefore the operator knows that an abnormal area exists and sampling should proceed until that area has been identified. Although this technology may increase costs initially, this should be offset by improvements in the performance of colposcopy. HealthPACT have recommended that this technology be assessed for further information in 24-months time when the results if clinical trials are likely to have been published.

NUMBER OF INCLUDED STUDIES

Total number of studies	1
Level III-2 diagnostic evidence	1

REFERENCES:

Abdul, S., Brown, B. H. et al (2006). 'The use of electrical impedance spectroscopy in the detection of cervical intraepithelial neoplasia', *Int J Gynecol Cancer*, 16 (5), 1823-1832.

AIHW (2009). *Cervical screening in Australia 2006-2007*, Australian Institute of Health and Welfare and the Australian Government Department of Health and Ageing for the National Cervical Screening Program, Canberra

Arbyn, M., Bergeron, C. et al (2008). 'Liquid compared with conventional cervical cytology: a systematic review and meta-analysis', *Obstet Gynecol*, 111 (1), 167-177.

Balasubramani, L., Brown, B. H. et al (2009). 'The detection of cervical intraepithelial neoplasia by electrical impedance spectroscopy: the effects of acetic acid and tissue homogeneity', *Gynecol Oncol*, 115 (2), 267-271.

CCV (2010). *The colposcopy* [Internet]. The Cancer Council Victoria. Available from: <http://www.papscreen.org.au/browse.asp?ContainerID=b12> [Accessed 5 August 2010].

MoH (2005). *Cervical screening in New Zealand: A brief statistical review of the first decade.*, New Zealand Ministry of Health, Wellington.

Nanda, K., McCrory, D. C. et al (2000). 'Accuracy of the Papanicolaou test in screening for and follow-up of cervical cytologic abnormalities: a systematic review', *Ann Intern Med*, 132 (10), 810-819.

National Screening Unit (2008). *Guidelines for Cervical Screening in New Zealand*, New Zealand Ministry of Health, Wellington.

Sasieni, P. D., Cuzick, J. & Lynch-Farmery, E. (1996). 'Estimating the efficacy of screening by auditing smear histories of women with and without cervical cancer. The National Co-ordinating Network for Cervical Screening Working Group', *Br J Cancer*, 73 (8), 1001-1005.

Wang, S. S., Walker, J. L. et al (2005). 'Evaluating the risk of cervical precancer with a combination of cytologic, virologic, and visual methods', *Cancer Epidemiol Biomarkers Prev*, 14 (11 Pt 1), 2665-2668.

Zilico (2010). *Interview with clinical founder* [Internet]. Zilico Medical Diagnostics. Available from: http://www.zilico.co.uk/about_zilico/interview_with_clinical_founder [Accessed 4 August 2010].

Zilico Medical Diagnostics (2010). *Zilico Products* [Internet]. Zilico Medical Diagnostics. Available from: <http://www.zilico.co.uk/products/> [Accessed 5 Aug 2010].

SEARCH CRITERIA TO BE USED:

Cervix, cancer/neoplasia/carcinoma

Cervical cancer

EIS

HEALTH PACT DECISION:

- | | |
|--|--|
| <input type="checkbox"/> Horizon Scanning Report | <input type="checkbox"/> Full Health Technology Assessment |
| <input type="checkbox"/> Monitor | <input type="checkbox"/> Archive |
| <input type="checkbox"/> Refer | <input type="checkbox"/> Decision pending |

PRIORITY RATING

- High** **Medium** **Low**