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Horizon Scanning Technology Prioritising Summary Update

Velscope® for oral cancer screening

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Enquiries about the content of the report should be directed to:

HealthPACT Secretariat
Department of Health and Ageing
MDP 106
GPO Box 9848
Canberra ACT 2606
AUSTRALIA

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This Horizon scanning prioritising summary was prepared by Benjamin Ellery, Linda Mundy and Professor Janet Hiller from the National Horizon Scanning Unit, Adelaide Health Technology Assessment, Discipline of Public Health, School of Population Health and Clinical Practice, Mail Drop DX 650 545, University of Adelaide, Adelaide, SA, 5005.

PRIORITISING SUMMARY UPDATE 2010

REGISTER ID: **000396**

NAME OF TECHNOLOGY: **VELSCOPE® FOR ORAL CANCER SCREENING**

PURPOSE AND TARGET GROUP: **ORAL CANCER SCREENING DURING ROUTINE MEDICAL EXAMINATIONS**

STAGE OF DEVELOPMENT (IN AUSTRALIA):

☐	Yet to emerge	☒	Established
☐	Experimental	☐	Established *but* changed indication or modification of technique
☐	Investigational	☐	Should be taken out of use
☐	Nearly established		

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

☒	Yes	ARTG number 147035
☐	No	
☐	Not applicable	

INTERNATIONAL UTILISATION:

COUNTRY	LEVEL OF USE		
	Trials Underway or Completed	Limited Use	Widely Diffused
Canada	✓	✓	
USA	✓	✓	
Australia		✓	
India		✓	

SAFETY AND EFFECTIVENESS ISSUES

Evaluation of Velscope® in the 2008 prioritising summary was limited to evidence from case series and low-level comparative studies. These studies examined high risk groups with a history of dysplasia or oral cancer, rather than general populations. Clinical trials which investigate Velscope® as an adjunct in screening for oral cancer have not been identified for inclusion in this update. Two studies of low-level evidence are therefore discussed. The first included study considered Velscope®, while the second examined another autofluorescence visualisation device at the prototype stage.

Dental and medical specialists in India assessed 258 patients seeking dental care, all of whom had clinically innocuous lesions (Mehrotra et al 2010) (level IV diagnostic evidence). A specialist examined patients with conventional white light and each patient was assigned to screening with Velscope® or ViziLite®.The value of ViziLite®

in oral cancer detection is not well substantiated and the system differs on a number of technical details from Velscope®, therefore only results of the 156 patients screened by Velscope® are presented in this summary[1]. These 156 patients, of whom 69 were smokers, underwent scalpel biopsy to determine the sensitivity and specificity of Velscope®. On biopsy, 11 patients were found to have dysplasia and one had cancer. Five of the 11 dysplasia cases were detected by Velscope® which also detected the one cancer case. Sensitivity was 50.0 per cent (95% CI [21.1, 78.9]). Velscope® findings were negative for 56 patients with benign lesions and positive in 88 patients with benign lesions. Specificity was 38.9 per cent (95% CI [30.8, 46.9]). The positive predictive value was 6.4 per cent (95% CI [2.4, 13.4]) and the negative predictive value was 90.3 per cent (95% CI [82.8, 97.9]). According to the authors, Velscope® did not identify any lesions that were not already apparent during clinical examination with conventional light. The high false negative rate (50%) indicates likely delays in diagnosis and may mean a greater number of oral cancers are diagnosed at more advanced stages. In a screening setting, the high false positive rate means that as many as 61.1 per cent of screened individuals could undergo unnecessary biopsy, exposing them to the risk of morbidity inherent in that procedure. However, the demographic profile of participants in this study vary considerably from the general Australian population (especially in relation to smoking status), and therefore these results may have limited applicability in an Australian context.

An American study sequentially screened high-risk patients[2] (n=60) by white light examination (WLE) and autofluorescence visualisation (AFV) (Jayaprakash et al 2009) (level IV diagnostic evidence). The investigators used an autofluorescence imaging and point spectroscopy prototype to determine if the AFV increased the ability to detect oral premalignant lesions and oral cancers. No further details regarding the spectroscopy function of the device – or its use in the study – were given.[3] Biopsies were obtained from all suspicious areas identified during WLE and AFV (n=189), and from one control area with normal appearance per patient (n=60), giving a total of 249 samples. Sensitivity, specificity and predictive values were calculated for WLE, AFV and WLE plus AFV. Results are shown in Table 1. Sensitivity was poor with WLE alone and increased when AFV was used, however the combined use of WLE and AFV gave the highest sensitivity. Specificity was low

[1] ViziLite® is a oral cancer detection system which preceded Velscope® for oral cancer detection but relies on light reflection from tissue after use of an acetic acid mouth rinse rather than the direct visualisation of innate tissue fluorescence profiles as with Velscope®. The products are related in so far as Velscope® was granted 510(k) clearance by the FDA on the manufacturer's claim of substantial equivalence to ViziLite®. Subject to certain conditions, this means Velscope® entered the US market without more comprehensive FDA approval. Similarly, ViziLite® was previously granted 510(k) clearance on another claim of substantial equivalence to colposcopy examination lights for cervical inspection during gynaecological examinations (Mehrotra et al 2010).

[2] High risk patients were defined as those having suspicious oral lesions or recently diagnosed, untreated oral premalignant lesions or oral cancers. Sixty-five per cent were known to be former or current smokers.

[3] Due to this lack of detail, it is uncertain whether or not the device includes features similar to the device type discussed in the 'Other Issues' section.

for WLE and further decreased with use of AFV. WLE and AFV used together gave the lowest overall specificity.

Table 1 Sensitivity, specificity and predictive values for WLE, AFV and WLE + AFV for all grades of premalignant lesions and cancers. (Jayaprakash et al 2009).

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
WLE	52	70	79	40
AFV	72	50	76	46
WLE + AFV	83	38	74	50

PPV = positive predictive value, NPV = negative predictive value

Sensitivity was calculated separately for lesions classified[4] by histopathology as low-grade, high-grade and oral cancer (Table 2). Cancers and high grade lesions could be detected with 100 per cent accuracy using both methods together. However, WLE and AFV used separately or together resulted in poor sensitivity for the detection of low grade lesions. This has important implications when considering the use of AFV in general populations in which there are likely to be higher numbers of people without disease, or early disease rather than with high grade lesions or cancers.

Table 2 Sensitivity of WLE, AFV and WLE + AFV across different grades of premalignant lesions and cancers. Low grade lesions: parakeratosis with atypia, mild dysplasia. High grade lesions: moderate dysplasia, severe dysplasia, carcinoma *in situ* (Jayaprakash et al 2009).

	Low grade lesions	High grade lesions	Cancers
Sensitivity (%)			
WLE	44	71	90
AFV	63	97	93
WLE + AFV	75	100	100

Finally, given that all autofluorescence techniques evaluate changes in the optical characteristics of tissue, it is important to note that increased submucosal haemoglobin[5] can result from a number of traumatic and inflammatory conditions, or even benign conditions, which may wrongly indicate premalignant or cancerous changes (Mehrotra et al 2010, Jayaprakash et al 2009). This may partly account for the poor specificity reported with Velscope®.

ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

The study by Jayaprakash et al (2009) was conducted at a tertiary centre where prevalence of high-grade premalignant lesions and oral cancer was high. The authors claimed that the majority of patients had a high risk of oral cancer and among these patients, at least one biopsy would be warranted from the results of WLE alone. For this reason it was considered that additional morbidity due to AFV-determined

[4] Classification was based on WHO Working Group guidelines.

[5] The operation of Velscope® is possibly explained by haemoglobin's stong absorption of autofluorescent light produced by elastin, collagen and other fluorophores occurring naturally in the submucosa. Increased presence of haemoglobin rich submucosal blood, which results from cancer induced angiogenesis, may cause absorption of fluorescent light associated with collagen and elastin, thus giving a dark appearance to tissue when examined under Velscope®.

biopsies was minimal. However, an increase in biopsies due to AFV screening in a general population where disease prevalence is lower may pose an ethical issue, particularly if a screening method leads to a high number of false positive individuals who then progress to scalpel biopsy. Such a scenario is possible when testing for rare disease, in which case many false positives will occur even if the test has very high sensitivity and specificity (Lingen et al 2008). Concern about unnecessary additional morbidity (both physical and psychological) from high false positives was also raised by Mehrotra and colleagues (2010) in regard to Velscope®.

OTHER ISSUES

In addition to visual autofluorescence, a technique known as autofluorescence spectroscopy has recently undergone review (Fedele 2009). Autofluorescence spectroscopy systems comprise a small optical fibre that produces various excitation wavelengths and a spectrograph that receives and records data on a computer. Dedicated software then analyses the spectral fluorescence from the tissue. Such systems have been designed to eliminate the subjective interpretation of tissue fluorescence. However, the greater number of variables, such as the combination of wavelengths and methodology of fluorescence analysis, remain to be adequately tested. Overall, it appears autofluorescence spectroscopy distinguishes lesions from healthy oral mucosa, with high sensitivity and specificity. However, the usefulness of the technique for distinguishing and classifying different types of lesion has been reported to be limited. Given the optical fibre used can sample only a small mucosal area, autofluorescence spectroscopy cannot locate new lesions or demarcate large lesions. Therefore, the use of spectroscopy is limited to small lesions, *previously identified* through visual inspection attempts to determine benign or (pre) malignant state (Fedele 2009). This highlights the apparent confusion in the literature regarding the differentiation between diagnosis and screening. The term screening designates a method or test used to discriminate those *asymptomatic* persons who are likely to have a disease from those who are not. Diagnosis, or case-finding, refers to identifying a specific disease in persons who already show an abnormality, that is, they are *symptomatic*. In the context of oral cancer, a symptomatic person will have an identified oral lesion (Lingen et al 2008). The review by Fedele (2009) and Lingen (2008) therefore indicate that autofluorescence (e.g. Velscope®) should be seen as a tool to screen for abnormalities that may later lead to diagnosis, but has no sound application in identifying cases of a specific disease. On the other hand, devices that use autofluorescence *spectroscopy* show the greatest use as a diagnostic adjunct once a suspicious lesion has been identified by other means, such as white light examination, and cannot correctly be considered as screening tools. In addition to diagnostic use, one autofluorescence spectroscopy device has shown application in delineating margins of (pre)cancerous tissue (Roblyer et al 2009) (level IV diagnostic evidence). This could reduce morbidity by improved guidance of scalpel biopsy and/or surgery.

SUMMARY OF FINDINGS

The use of AFV techniques, such as Velscope®, and autofluorescence spectroscopy have shown variable results in the detection of oral cancer. Furthermore, appropriateness of screening with devices that use spectroscopy has not been indicated in the literature reviewed. However, spectroscopy devices may serve as useful diagnostic adjuncts to help avoid unnecessary scalpel biopsy among patients with benign lesions, or providing better guidance for biopsy or surgery, when indicated. Conversely, the included study of Velscope indicated that considerable morbidity could result from false positives (through unnecessary invasive procedures) in a general population not at high risk of oral cancer, and many cancers could have delayed diagnosis as a result of cases missed by Velscope®.

HEALTHPACT ASSESSMENT:

These devices may serve as useful diagnostic adjuncts to help avoid unnecessary scalpel biopsy among patients with benign lesions, or providing better guidance for biopsy or surgery, when indicated. However, variable results were reported by studies included for assessment with the potential for increased morbidity from false positives. The levels of evidence assessed were low, and the use of Velscope® to screen for oral cancer cannot be supported on the basis of the included diagnostic evidence. Therefore no further assessment of this technology warranted.

NUMBER OF INCLUDED STUDIES

Total number of studies	3
Level IV diagnostic evidence	3

REFERENCES

Fedele, S. (2009). 'Diagnostic aids in the screening of oral cancer', *Head Neck Oncol*, 1 (1), 5.

Jayaprakash, V., Sullivan, M. et al (2009). 'Autofluorescence-guided surveillance for oral cancer', *Cancer Prev Res (Phila Pa)*, 2 (11), 966-974.

Lingen, M. W., Kalmar, J. R. et al (2008). 'Critical evaluation of diagnostic aids for the detection of oral cancer', *Oral Oncol*, 44 (1), 10-22.

Mehrotra, R., Singh, M. et al (2010). 'A cross-sectional study evaluating chemiluminescence and autofluorescence in the detection of clinically innocuous precancerous and cancerous oral lesions', *J Am Dent Assoc*, 141 (2), 151-156.

Roblyer, D., Kurachi, C. et al (2009). 'Objective detection and delineation of oral neoplasia using autofluorescence imaging', *Cancer Prev Res (Phila Pa)*, 2 (5), 423-431.

PRIORITISING SUMMARY (2008)

REGISTER ID: **000396**

NAME OF TECHNOLOGY: **VELSCOPE® FOR ORAL CANCER SCREENING**

PURPOSE AND TARGET GROUP: **ORAL CANCER SCREENING DURING ROUTINE MEDICAL EXAMINATIONS**

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☒	Yes	ARTG number 147035
☐	No	
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COUNTRY	LEVEL OF USE		
	Trials Underway or Completed	Limited Use	Widely Diffused
Canada	✓		
USA	✓		
Australia		✓	

IMPACT SUMMARY:

INLINE Systems - Australia markets the Velscope® as a device for screening for oral cancer. Oral cancer has a low survival rate mostly due to late stage diagnosis. A device to screen non-invasively for oral cancers at an early stage may facilitate a lower death rate from the disease.

BACKGROUND

Oral cancer is under diagnosed and is often mistaken for non-cancerous oral manifestations such as ulcers. By the time oral cancer is symptomatic the disease has progressed too far and the prognosis is poor. Normal diagnosis is initiated only if a medical practitioner suspects a lesion is potentially malignant. As the manifestation of oral cancer is similar to other frequent, and non-life threatening mouth abnormalities, such as ulcers, true oral cancer may not be properly investigated. It is not feasible to biopsy and diagnose every potential lesion as the vast majority of suspected lesions

are benign. Performing unnecessary biopsies would impact negatively on the patient and also increase health care costs.

The Velscope® device is marketed as a screening tool for use by medical practitioners to investigate potentially malignant lesions in the clinic. The device consists of a light source and a visualisation handpiece through which suspect tissue is examined. The diagnostic capability of the device is based on the differing fluorescence profiles of normal and abnormal (potentially cancerous) tissue within the oral cavity. A blue light is shone into the oral cavity and the resulting fluorescence of the tissue is visualised through the handpiece. Normal tissue appears with a bright apple-green glow, and abnormal tissue appears dark under the blue light. If abnormal tissue is discovered a biopsy can be performed on the patient for definitive histological diagnosis.

CLINICAL NEED AND BURDEN OF DISEASE

Oral cancer rates in Australia have been published in several studies and range from 2,000 to 2,500 new cases per year (Cox 2000; Sugerman & Savage 2002). The AIHW data for 2004 reports approximately 2,300 new cases of oral cancer (AIHW 2004). The 5-year survival rate for oral cancer diagnosed patients is approximately 50 per cent. In Australia, approximately 400-500 deaths, or one per cent of all cancer deaths, occur annually from oral cancer (Farah & McCullough 2008).

Data available from New Zealand reports on rates of lip, mouth and pharynx (LMP) cancer. The number of new LMP cancer registrations are declining with the corresponding decline in tobacco consumption. In 1996, the number of new cases recorded for the New Zealand population was 179 and 89 for males and females, respectively, reflecting the difference in cigarette consumption between the sexes. These numbers translate to an age standardised incidence rate of 12 and five per 100,000 males and females, respectively. In 1997 the age standardised mortality rate was four (68 deaths) and two (35 deaths) per 100,000 for males and females, respectively. Taking into account the expected rise in the New Zealand population, it was estimated that by 2012 the age standardised mortality rate for LMP cancer would decrease to three (65 deaths) and one (39 deaths) per 100,000 for males and females respectively (Public Health Intelligence Unit 2002).

DIFFUSION

The device has TGA approval (see footnote above) and private clinicians are using the Velscope® in Australia. (personal communication INLINE Systems - Australia).

COMPARATORS

No current screening methods for oral cancer diagnosis are extant in Australia. If a general practitioner or dentist suspects a lesion has potential for becoming or is cancerous a biopsy is taken and sent to a pathology lab for histological diagnosis (Scully et al 2005).

SAFETY AND EFFECTIVENESS ISSUES

Several studies have investigated the Velscope® device for diagnosing oral cancer in different populations of patients. The initial pilot study by Lane et al reported on a population of 44 subjects. Histology of the suspected lesions was used as the gold standard. Normal mucosa was able to be distinguished from severe dysplasia/carcinoma in situ or invasive carcinoma with a sensitivity of 98 per cent and a specificity of 100 per cent (Lane et al 2006) (Level III-2 diagnostic evidence).

A small case series of only three patients conducted in an oral dysplasia clinic, investigated the Velscope® as a screening tool to identify tissue that has loss of autofluorescence and has therefore the potential to be cancerous or precancerous. The three patients were being monitored after having previous procedures to remove dysplasias or carcinomas. The oral cavities of all three cases appeared normal under ordinary light inspection. When the Velscope® was used, regions of abnormal tissue were evident and biopsies were taken. Histopathology revealed that all three cases had clinically significant pathology with severe dysplasia in the first patient and cancer in the second and third patient (Poh et al 2007) (Level IV diagnostic evidence).

A second study by Poh et al (2006) investigated the ability of the Velscope® to identify cancerous tissue in patients with known cancers and also to identify the margins of abnormal tissue around the known lesion. Twenty patients were consecutively recruited as they were being assessed prior to removal of a known cancer. The Velscope® was used to assess the cancer and its margins. Biopsies of tissue with abnormal and normal fluorescence were then taken for histopathology. All tumours showed loss of fluorescence and this extended outside the normal visual margin for all tumours except one. When the fluorescing and non-fluorescing tissue was analysed 32 of 36 non-fluorescing tissue samples were found to be histologically abnormal, whereas of the 66 fluorescing samples, only one was histologically abnormal. Using an arbitrary resection margin of 10mm around the tumour would have left 6/20 cases with cancerous or highly abnormal tissue remaining, making recurrence a high probability. This study demonstrates that the Velscope® is useful to identify abnormal tissue that may appear normal under regular lighting (Level III-2 diagnostic evidence).

No safety issues were reported in the literature examined.

The studies reviewed in this summary demonstrate that the Velscope® has the potential to diagnose abnormal tissue that appears normal using standard inspection techniques. Tissue flagged as abnormal by the Velscope® has a high likelihood of being histologically abnormal e.g. showing dysplasia or cancerous properties. Conversely, tissue flagged as normal by the Velscope® is rarely abnormal by histopathology. Despite this promising data, there is a need for the device to undergo further trials with larger groups of subjects and better study designs.

COST IMPACT

The Velscope® kit includes: Velscope® unit, operation manual, examination guide, training DVD, PowerPoint presentation, patient brochures, patient mailer inserts, waiting room posters.

ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

No issues were identified/raised in the sources examined.

OTHER ISSUES

No issues were identified/raised in the sources examined.

SUMMARY OF FINDINGS

Several small scale studies show the Velscope® has good potential to identify abnormal oral tissue that appears normal under standard inspection and to also allow better planning of surgical resection of known tumours. The device may have potential as a screening device in the future.

HEALTHPACT ACTION:

The Velscope® shows promise to fill a necessary gap in current diagnostic capabilities. Yet there is a need for more and higher quality data to demonstrate better patient outcomes. HealthPACT therefore recommended that this technology should be monitored for further information in 24-months time.

NUMBER OF INCLUDED STUDIES

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

REFERENCES:

AIHW (2004). *Number of new cases and age-standardised rates of cancer* [Internet]. Australian Institute of Health and Welfare. Available from: http://www.aihw.gov.au [Accessed 10th July].

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Lane, P. M., Gilhuly, T. et al (2006). 'Simple device for the direct visualization of oral-cavity tissue fluorescence', *J Biomed Opt*, 11 (2), 024006.

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Scully, C., Newman, L. & Bagan, J. V. (2005). 'The role of the dental team in preventing and diagnosing cancer: 3. oral cancer diagnosis and screening', *Dent Update,* 32 (6), 326-328, 331-322, 335-327.

Sugerman, P. B. & Savage, N. W. (2002). 'Oral cancer in Australia: 1983-1996', *Aust Dent J,* 47 (1), 45-56.

SEARCH CRITERIA TO BE USED:

Mouth Neoplasms/ diagnosis/genetics/ surgery
Risk Assessment
Tumor Markers, Biological/genetics
Fluorescence