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Assessment of a decision making protocol to improve the efficacy of VELscope™ in general dental practice: A prospective evaluation

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SUMMARY

Background: VELscope™ is a device designed to help detect potentially malignant disorders of the oral mucosa at an early stage using direct tissue autofluorescence. Previous research indicates a high rate of false positives using this device. This study assesses a decision making protocol for the detection of oral mucosal lesions using conventional oral examination and VELscope™ in a general dental practice setting.
Materials and methods: 305 patients presenting for general dental treatment were screened by a general dental practitioner (GDP) for oral mucosal lesions using incandescent light (conventional oral examination – COE), followed by VELscope™ and then by correlating the findings from these two examinations. A decision making protocol was followed. Patients were either reviewed or referred to an Oral Medicine specialist (OMS) for consultation, and biopsy was undertaken as required for definitive diagnosis.
Results: 146 patients presented with at least one oral mucosal lesion, and a total of 222 lesions were detected. COE detected 161 oral mucosal lesions and an additional 61 lesions were detected with VELscope™. COE alone showed a sensitivity of 44.0% and specificity of 99.0% while VELscope™ alone showed a sensitivity of 64.0% and specificity of 54.3%. Using the decision making protocol, the sensitivity and specificity were 73.9% and 97.9% respectively.
Conclusion: Using the decision making protocol proposed in this study allows for the detection of additional oral mucosal lesions requiring specialist referral by incorporating VELscope™ into routine general dental practice, without compromising patient care.

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Introduction

Oral cancer ranks as the sixth most common malignancy worldwide with an estimated 263,900 new cases and 128,000 deaths in 2008 alone [1]. Ninety percent of oral cancers are designated as oral squamous cell carcinomas (OSCCs) [2]. Despite an increase in our understanding of this disease, the 5 year survival rate has remained at 50% for the past three decades [2]. The poor prognosis for oral malignancies is largely related to delayed diagnosis with localised cancers having survival rates up to 83% compared to 32% once the tumour has metastasised [3,4]. Nearly half of all oral cancers present with an advanced stage tumour despite the fact that the oral cavity is an area easily visualized by the general medical or dental practitioner [5]. Furthermore, a large percentage of OSCCs are preceded by visible changes of the oral mucosa [3].

The current standard for the detection of oral potentially malignant disorders (OPMDs) and OSCCs is visual examination [6]. White, red or mixed red–white lesions with induration and fixation are suggestive of malignancy [6]. However, 10–20.5% of the general population present with oral lesions of which the majority are benign in nature [7–9]. A conventional oral examination (COE) is poor at differentiating benign lesions from OPMDs and malignancies [10]. Further, histological evidence of dysplasia and microinvasive carcinoma has been found in clinically normal mucosa and these would evidently be missed by COE [11]. With this in mind, new technologies have been developed which highlight OPMDs to assist clinicians in detecting and treating these lesions at an early stage [12–15].

VELscope™ (LED Medical Diagnostics Inc., Barnaby, Canada) is a non-invasive, handheld device designed to visualise early mucosal changes using the principles of tissue autofluorescence [16,17]. VELscope™ emits light in the 400–460 nm spectrum which excites fluorophores intrinsic in the oral mucosa resulting in a pale green autofluorescence [16,18]. Abnormal tissue is associated with loss of autofluorescence (LAF) and appears dark in contrast to the surrounding tissue (see Fig. 1) [19]. It is proposed that dysplasia

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is associated with alterations in the stromal architecture causing LAF [18]. Lesions which completely blanch on pressure and return to a normal fluorescence pattern should be considered negative for LAF [16]. This phenomenon is termed diascopic fluorescence.

VELscope™ is marketed to the general dental or medical practitioner for use as an adjunct to COE for the detection of oral mucosal abnormalities. Previous literature has found the device to be efficacious in identifying tumour margins which extend beyond the clinically visible margin of the lesion during excision of oral malignancies [19]. It is also an effective tool for detecting dysplasia in patients with a history of OSCC [20].

VELscope™ has been shown to be highly sensitive in the detection of severe dysplasia and OSCC; however its ability in detecting dysplasia at an early stage has been questioned with a number of false negatives noted [16,21–24]. Authors have also relayed concerns that VELscope™ tends to overestimate abnormalities with a number of benign lesions displaying LAF [16,21–26]. Farah et al. stated the importance of clinical interpretation of lesions following VELscope™ examination rather than relying on LAF findings alone, and also highlighted the importance of diascopic fluorescence [16]. Studies utilising VELscope™ for routine screening have found increased rates of detection of epithelial dysplasia but with a substantial number of false positives [22,27,28]. While reviewing lesions with LAF may reduce false positives, none of the studies thus far have evaluated the significance of diascopic fluorescence in general practice [29].

The purpose of this study was to determine the value of VELscope™ as an adjunct to COE for the general dental practitioner (GDP). The main aim was to assess a model for routine screening of patients for oral mucosal lesions incorporating both COE and VELscope™, and also to test a decision making protocol for patient referral. A secondary aim was to assess the sensitivity and specificity of COE, VELscope™ and a combined examination for the detection of OPMDs and OSCC in a general practice setting.

Materials and methods

Patient recruitment

Patients presenting for general dental treatment at the University of Queensland, School of Dentistry were invited to participate in this study. Three-hundred and five consenting patients participated in the study between May 2012 and December 2013. The only exclusion criteria were patients under 18 years of age and those who were unwilling or unable to provide consent. All patients were examined in a prospective manner by a single general dental practitioner (author NB). The study was conducted according to Human Ethics Guidelines approved by the University of Queensland, School of Dentistry (project number 1204), and was designed in accordance with STARD guidelines [30].

Clinical protocol

Patients were examined using a decision making protocol designed specifically for this study (see Fig. 3).

Step 1. Background information: The age, sex, smoking history, alcohol use, mouthwash use and annual household income of all patients was recorded.
Step 2. COE: COE was performed under incandescent operatory light and details regarding any oral mucosal lesions observed were noted. The location, size, ease of visibility and border distinctness of lesions were recorded, as previously described [16]. All lesions were categorised by clinical description and then triaged into four clinical categories as previously described [16]; homogeneous leukoplakia, non-homogeneous leukoplakia, lesions with lichenoid features or 'Other'. A decision was made based on clinical presentation and features as to whether the lesion required a review or an OMS referral for further assessment. Non-homogeneous lesions were considered as suspicious for dysplasia and were marked for referral by the GDP. Lesions were photographed using a Canon A2200 camera.
Step 3. VELscope™ examination: Clinical examination was then repeated using VELscope Vx™ and all lesions with LAF were assessed for diascopic fluorescence. Details regarding all lesions visible with VELscope™ were recorded in the same manner as for COE. Lesions were then re-photographed using a Canon A2200 camera with a VELscope™ attachment. Lesions which displayed LAF with no blanching were recommended for referral to an OMS based on VELscope™ findings alone. Lesions which displayed LAF and complete blanching were recommended for review based on VELscope™ findings alone. Lesions

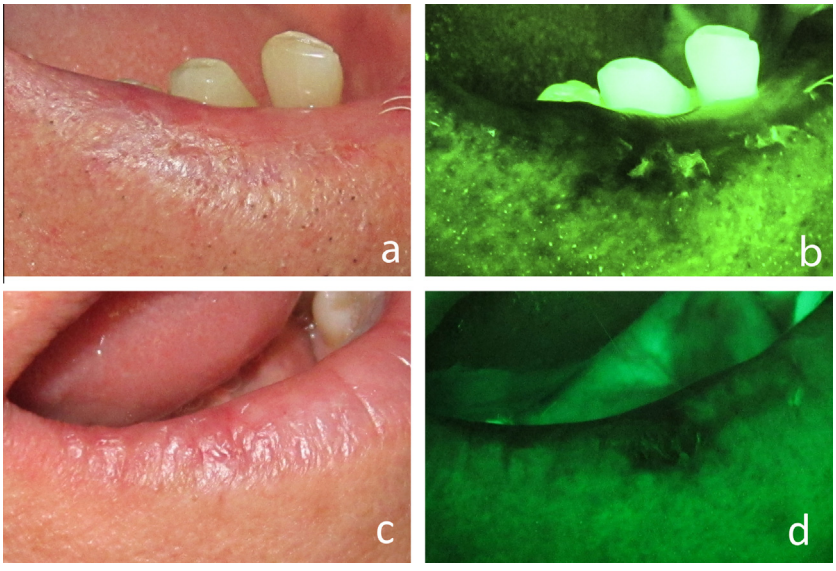

Fig. 1. Lesion on lower lip with COE (a); same lesion with VELscope™ displaying loss (dark area) and gain (lighter area) of fluorescence (b). Histopathological diagnosis was OSCC. Lesion showing poor visualisation with COE on lower lip (c); same lesion with VELscope™ displaying loss of fluorescence (d). Histopathological diagnosis was actinic cheilitis.

with partial blanching were recommended for both review by the GDP and referral based on VELscope™ findings at the initial examination alone. In addition to clinical assessment and referral decisions, answers to the following questions were recorded; (1) Did VELscope™ detect any additional lesions?, (2) Did VELscope™ enhance visibility?, (3) Did VELscope™ change provisional/clinical diagnosis category?

Step 4. Combined examination: Following VELscope™ examination, sites with LAF were re-assessed clinically at the same appointment. A further decision was then made for all lesions based on both clinical and VELscope™ findings as to whether a review was required. Where LAF could be accounted for on clinical grounds (eg: pigmentation or vascularity), no further follow up was required. Lesions which were suspicious for dysplasia based on COE were marked for referral to the OMS by the GDP. Lesions which were not suspicious for dysplasia based on COE but LAF could not be accounted for on clinical grounds were marked for review by the GDP. Patients requiring a review were reappointed after 14 days to allow for healing or resolution of lesions in case of trauma. Photos were uploaded to secure Cloud storage (Dropbox; Dropbox Inc., San Francisco, CA, USA) and assessed by an oral medicine specialist (author CSF) with extensive experience in the use of VELscope™; this procedure is termed a telemedicine request.

Step 5. Review appointment: At the review appointment (14 days after initial consultation), the combined examination was repeated. If lesions had healed, no further follow up was undertaken (Fig. 2). Lesions which persisted and could not be documented as benign were marked for referral by the GDP (termed GDP referral) (Fig. 3). Following this, the telemedicine request was reviewed by the GDP and patients were referred as determined by the OMS (author CSF).

Step 6. Referral appointment: All referred patients were assessed for oral mucosal lesions by the OMS (author CSF) and a scalpel biopsy was performed under local anaesthesia as indicated. For ethical reasons, only lesions that were clinically suspicious for malignancy or dysplasia, or those with VELscope™ findings suggestive of malignancy or dysplasia were biopsied.

Statistical analysis

Data was entered into a database using Microsoft Access 2010 (Microsoft, Washington, USA) and exported to Microsoft Excel 2010 (Microsoft, Washington, USA) for subsequent analysis using R software (www.r-project.org). Associations between LAF categories, clinical categories, referral and healing patterns were calculated using Fisher's exact test with corrections for multiple testing. A p value < 0.05 was considered significant. Post-hoc analysis was performed using pairwise Fisher's exact tests. The sensitivity, specificity, positive and negative predicted value of COE, VELscope™ examination alone, and combined examination at review were calculated. A decision to refer the patient was considered a positive outcome. A telemedicine request served as the soft gold standard with an indication that a consultation was required as a positive outcome; this is referred to as an OMS referral. Histopathological diagnosis served as the hard gold standard for biopsied lesions. In addition, analysis of the decision making protocol was carried out regarding how often VELscope™ enhanced detection, how often it detected new lesions, or changed provisional clinical diagnosis.

Results

A total of 305 patients were examined using the decision making protocol. Patient demographics are summarised in Table 1.

One hundred and forty-six patients (47.9%) presented with at least one oral mucosal lesion and a total of 222 lesions were detected. The majority of lesions occurred on the buccal mucosa followed by the external lip (Table 2). COE revealed 161 lesions of which 91 displayed LAF. An additional 61 lesions were discovered using VELscope™, 58 of which displayed LAF while 3

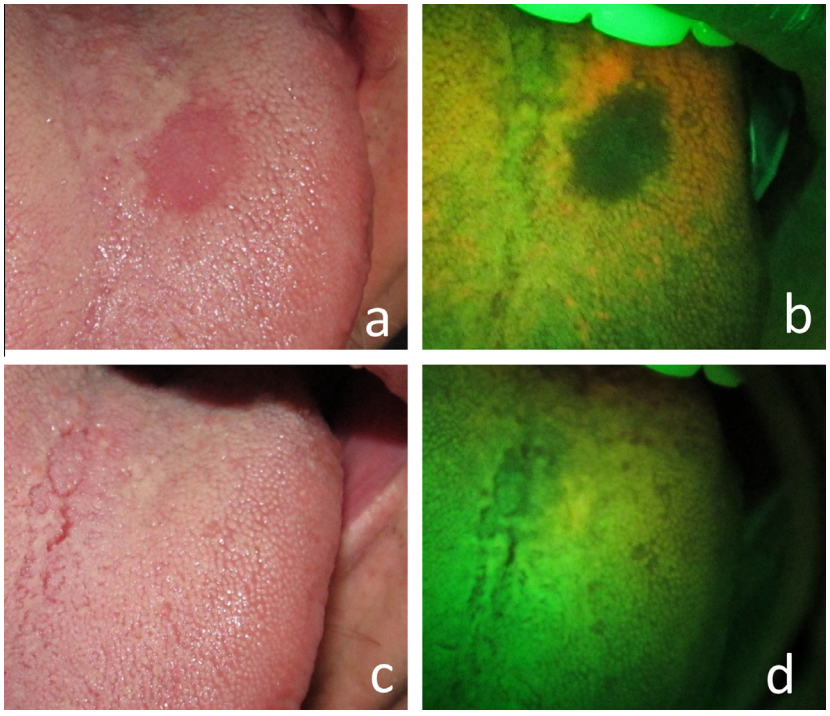

Fig. 2. Geographic tongue on dorsal tongue (a); same lesion with VELscope™ displaying loss of fluorescence (b); same area viewed with COE following 2 weeks with lesion having resolved (c); same area on follow up now shows normal fluorescence pattern with VELscope™ (d).

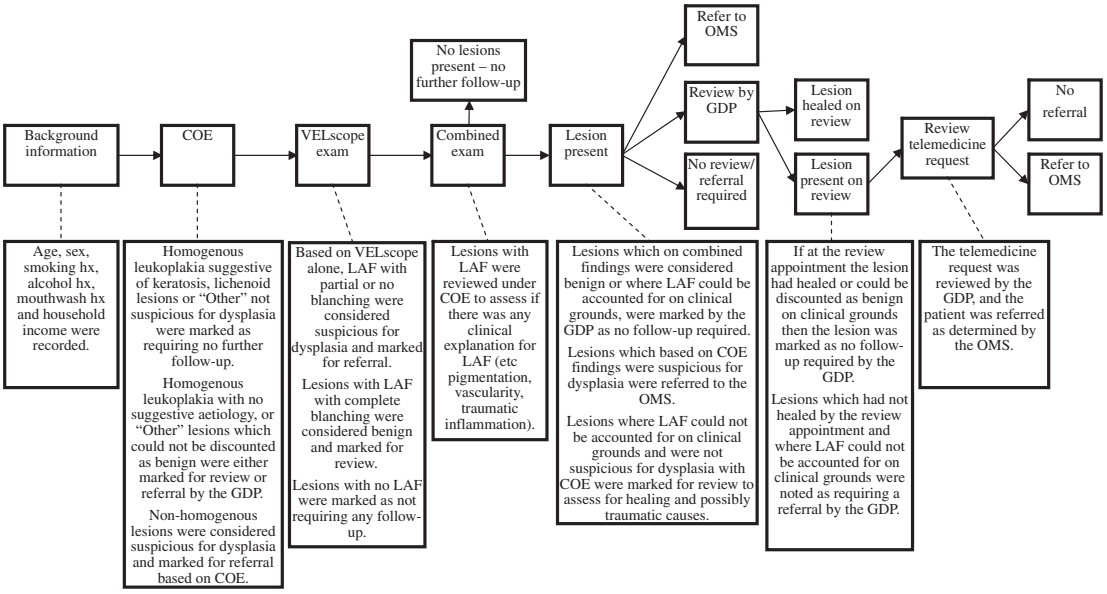

Fig. 3. Summary of decision making protocol.

Table 1
Patient demographics (n = 305).

Characteristic	Male (n = 147)	Female (n = 158)	Total (n = 305)
Age, mean ± SD, y	49.3 ± 16.0	50.1 ± 13.8	49.7 ± 14.9
Current/past smokers, n	77 (52.4%)	68 (43.0%)	145 (47.5%)
Lifetime tobacco exposure, mean (pack years) ± SEM	16.6 ± 2.2	15.0 ± 2.0	15.9 ± 1.3
Current/past alcohol consumer, n	116 (78.9%)	96 (60.8%)	212 (69.5%)
Current smoker & alcohol consumer, n	23 (15.6%)	18 (11.4%)	41 (13.4%)

Table 2
Lesion location (n = 222).

Lesion location	Frequency, n (%)
Buccal mucosa	80 (36.0%)
External lip	36 (16.2%)
Hard palate	33 (14.9%)
Tongue	23 (10.4%)
Alveolar ridge	15 (6.8%)
Retromolar pad	9 (4.0%)
Labial mucosa	9 (4.0%)
Vestibule	7 (3.2%)
Floor of mouth	5 (2.2%)
Gingiva	4 (1.8%)
Soft palate	1 (0.5%)

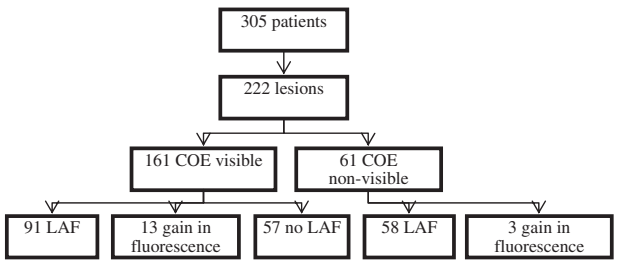

Fig. 4. Lesion visualisation under COE and VELscope™.

displayed gain in fluorescence with no LAF (Fig. 4). Homogeneous leukoplakia was the most common description of clinically visible lesions while "Other" lesions presented the most common clinical

Table 3
Lesion description on COE (n = 161).

Lesion description	Frequency, n (%)
Homogeneous	55 (34.2%)
Pigmented	21 (13.0%)
Linea alba	15 (9.3%)
Vascular	14 (8.7%)
Traumatic	11 (6.8%)
Ulcer	11 (6.8%)
Non-homogeneous	8 (5.0%)
Petechia	2 (1.3%)
Other	24 (14.9%)

category (Tables 3 and 4). Follow-up of lesions is summarised in Fig. 5. There was no significant association between the presence of an oral mucosal lesion and tobacco use, alcohol use, mouthwash use, household income or gender, however patients above the age of 45 were significantly more likely to have an oral mucosal lesion compared to those equal to or below 45 years of age (p = 0.044).

VELscope™ enhanced detection of lesions in 61 patients (20.0%) and detected additional lesions in 49 patients (16.0%). VELscope™ also changed the provisional diagnosis in 39 patients (12.8%). Among 161 lesions detected with COE, VELscope™ increased visibility of 16 (9.9%) lesions, while 7 (4.3%) were more easily visible under COE. Border visibility was also increased in 21 (13.0%) lesions with VELscope™ while COE provided greater border distinctness in 7 (4.3%) lesions.

Of the 222 lesions detected, 71 were reappointed for a review while 15 were referred to an oral medicine specialist without a review. Thirteen patients were referred to the OMS at the initial examination for lesions with clinical indications that they were

Table 4
Fluorescence characteristics as a proportion of clinical lesion category as determined by the GDP (*n*, %).

Clinical category	No LAF	LAF with complete blanching	LAF with partial blanching	LAF with no blanching	Total
Homogeneous	41 (74.5%)	8 (14.5%)	6 (11.0%)	0 (0%)	55 (100%)
Non-homogeneous	0 (0%)	1 (12.5%)	4 (50.0%)	3 (37.5%)	8 (100%)
Lichenoid	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Other	29 (29.6%)	16 (16.3%)	6 (6.1%)	47 (48.0%)	98 (100%)
Not seen clinically	3 (4.9%)	17 (27.9%)	14 (23.0%)	27 (44.2%)	61 (100%)
Total	73 (32.9%)	42 (18.9%)	30 (13.5%)	77 (34.7%)	222 (100%)

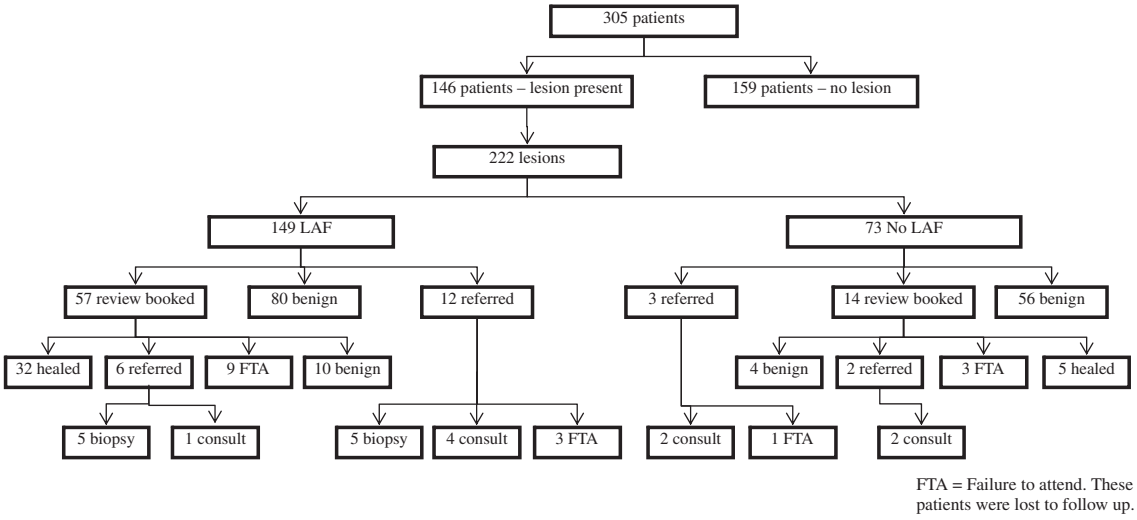

Fig. 5. Results of screening displaying follow-up and outcomes of lesions discovered with the use of the decision making protocol.

long standing, or where the patient refused review for logistical reasons, and a referral was warranted on initial examination. No associations were found between patient demographics or lesion size with LAF (Table 5). There was no significant association between rates of healing and LAF category ($p = 0.12$) (Table 6) or clinical category ($p = 0.08$) although lesions with LAF and no blanching tended to show a higher rate of healing on review. A total of 23 lesions in 18 patients were referred. Ten biopsies were performed and are summarised in Table 7. One patient opted to undertake a biopsy privately for logistical reasons. Under COE, 13 lesions were marked for referral by the GDP while an additional 9 lesions were marked for referral following the decision making protocol. Among these, one case was actinic cheilitis with mild dysplasia. One case of actinic cheilitis with mild dysplasia was not marked for referral by the GDP but was referred following an OMS telemedicine request. A telemedicine request with photographs was available for 152 lesions including all lesions which were referred. A telemedicine request based on clinical description alone was available for the remaining 70 lesions.

A significant association was found between clinical category and LAF ($p < 0.001$). Homogeneous lesions were significantly more likely to present with no LAF ($p < 0.001$) while non-homogeneous lesions had an increased likelihood of presenting with LAF although this did not reach significance ($p = 0.055$). An association was found between clinical category and GDP referral ($p < 0.001$) and OMS referral ($p < 0.001$). In both cases, non-homogeneous lesions were significantly more likely to require referral ($p < 0.001$) while lesions categorised as "Other" were unlikely to require referral ($p < 0.001$). LAF category was associated with both GDP referral ($p < 0.001$) and OMS referral ($p < 0.004$). Lesions displaying LAF with partial blanching were associated with a higher likelihood of referral by both GDP ($p < 0.001$) and OMS ($p < 0.001$) although other fluorescence categories did not show any significant associations. Lesion site was also significantly associated with referral by the GDP ($p < 0.001$) and the OMS ($p < 0.001$) with lesions on the external lip presenting with a significantly increased likelihood of requiring referral by both practitioners ($p < 0.001$).

Table 5
Association between clinical and demographic parameters, and LAF status of lesions ($n = 222$).

Variable	No LAF	LAF	
Gender			$p = 0.57$
Male	41	73	
Female	32	76	
Age			$p = 0.35$
⩽45 years	26	34	
>45 years	47	115	
Annual household income ($AUD) ($n = 217$)			$p = 0.57$
<$20,000	17	26	
$20,000–40,000	19	46	
$40,000–60,000	11	32	
$60,000–80,000	16	21	
$80,000–100,000	7	13	
>$100,000	1	8	
Smoking			$p = 0.57$
Never	38	72	
Current or past	34	77	
Alcohol use			$p = 0.57$
Never	30	49	
Current or Past	43	100	
Mouthwash use			$p = 0.57$
Never	43	101	
Current or past	30	48	
Lesion size			$p = 0.35$
⩽200 mm^2	68	2	
>200 mm^2	81	10	

Table 6
Review and referral patterns based on LAF category as determined by the GDP.

LAF category	Total	No follow up required	Reviewed	Changes on review	GDP referral	OMS referral
No LAF	73	56 (76.7%)	11 (15.1%)	5 (6.8%)	3 (4.1%)	5 (6.8%)
LAF – complete blanching	42	27 (64.3%)	11 (26.2%)	6 (14.3%)	3 (7.1%)	4 (9.5%)
LAF – partial blanching	30	8 (26.6%)	14 (46.7%)	8 (26.7%)	10 (33.3%)	11 (36.7%)
LAF – no blanching	77	43 (55.8%)	26 (33.8%)	21 (27.3%)	5 (6.5%)	5 (6.5%)
Total	222	134 (60.4%)	79 (35.6%)	40 (18.0%)	21 (9.5%)	25 (11.3%)

Table 7
Histopathological diagnoses and clinical characteristics as determined by GDP of lesions which underwent biopsy (n = 10).

Lesion ID	Location	COE category	LAF category	COE referral	GDP referral	Histopathology
124	Lower external lip	Non homogeneous	Partial blanching	No	No	Actinic cheilitis with mild dysplasia
127	Buccal mucosa	Non homogeneous	Partial blanching	Yes	Yes	Lichenoid reaction
193	Lower external lip	Homogeneous	Partial blanching	Yes	Yes	Actinic cheilitis with mild dysplasia
107	Lower external lip	Not seen clinically	Partial blanching	No	No	Actinic cheilitis
112	Hard palate	Homogeneous	Partial blanching	Yes	Yes	Papillary hyperplasia
170	Lower external lip	Homogeneous	Complete blanching	Yes	Yes	Actinic cheilitis
171	Lower external lip	Non homogeneous	Partial blanching	Yes	Yes	OSCC
175	Lower external lip	Not seen clinically	Complete blanching	No	Yes	Actinic cheilitis with mild dysplasia
197	Lower external lip	Non homogeneous	Complete blanching	Yes	Yes	Actinic cheilitis with mild dysplasia
219	Lower external lip	Non homogeneous	No blanching	Yes	Yes	Moderately dysplastic actinic cheilitis

The sensitivity and specificity for COE and VELscope™ are summarised in Table 8. The sensitivity and specificity for a combined examination was calculated using the findings of COE and VELscope™ on review if available. For patients where lesions were considered benign at the initial examination and no review was conducted, or a referral was made without review, combined COE and LAF findings at the initial appointment were used. Patients who did not return for scheduled reviews were excluded from the combined findings leaving 210 lesions. The sensitivity of COE, when compared with the soft gold standard was 44.0% while the sensitivity of VELscope™ examination was 64.0%. However, the sensitivity for a combined examination was greater than either examination alone at 73.9%. This was associated with only a small drop in specificity from 99.0% for COE to 97.9% for combined findings.

Discussion

It is commonly believed that early diagnosis of OPMDs and active intervention may prevent the progression of disease to malignancy and provides the highest standard of care [3,31]. In a recent study, we have shown that one in five people present with an oral mucosal lesion [9]. However it is often difficult to differentiate benign lesions from OPMDs with COE [10]. For this reason, a number of adjunctive optical techniques have been devised to assist the general practitioner to detect oral mucosal lesions and also to differentiate benign lesions from OPMDs. Of these, autofluorescence devices appear to show promise in this regard. Among devices incorporating autofluorescence for oral mucosal screening, VELscope™ enjoys the greatest amount of supporting literature.

The majority of research associated with VELscope™ assesses its diagnostic potential in a specialist environment [16,21,23,25,26,32,33]. The consensus appears to be that while VELscope™ is efficacious at highlighting dysplasia, using the device alone overestimates abnormalities. Reported sensitivities and specificities for the device in specialist practice range from 30% to 100% and 15% to 81% respectively [12]. These values however, cannot be extrapolated to general dental practice where the prevalence of oral mucosal lesions is significantly lower than a secondary referral centre.

Table 8
Sensitivity and specificity of COE, VELscope™ and combined examination following the decision making protocol. OMS referral used as soft gold standard. (%, 95% CI).

	COE	VELscope	Combined
Sensitivity	44.0% (24.4–65.1%)	64.0% (42.5–82.0%)	73.9% (51.6–89.7%)
Specificity	99.0% (96.4–99.9%)	54.3% (47.1–61.4%)	97.9% (94.6–99.4%)
PPV	84.6% (54.4–97.6%)	15.1% (8.9–23.4%)	81.0% (58.1–94.4%)
NPV	93.3% (89.0–96.3%)	92.2% (85.8–96.4%)	96.8% (93.2–98.8%)

Furthermore, previous studies have focused on the diagnostic accuracy of VELscope™ and its ability to detect dysplasia. However, the device is intended to be used as an adjunct to a clinical examination and not as a stand-alone diagnostic tool [17]. The role of a general practitioner is not necessarily to diagnose dysplasia, but to make appropriate clinical decisions and referrals to a specialist centre where the patient can be diagnosed and managed appropriately. This means referring lesions that appear suspicious, but also knowing when not to refer, to maintain the highest standard of patient care. Therefore in general practice, while assessing the ability to detect dysplasia can be one outcome measure, the ultimate aim of an oral mucosal examination should not be to detect dysplasia, but to detect and appropriately refer oral mucosal abnormalities.

Given the low specificity associated with the use of VELscope™, there is concern that this would result in a significant increase in the number of specialist referrals which may lead to patient harm through unnecessary stress, and wasted time and financial costs. This was the concern expressed by McNamara et al. who found that a number of benign lesions displayed LAF [22]. This is in agreement with findings from the current study, in that a number of lesions which were clinically benign displayed LAF. We found that clinical interpretation is extremely important when utilising VELscope™ as relying on LAF findings alone is unreliable. Pigmented lesions, vascular lesions and inflammatory lesions in particular may confound the operator as they also present with LAF [16,29]. A common finding in this study was the presence of areas of LAF under dentures in clinically normal tissue displaying chronic inflammation [34]. In contrast to our protocol, McNamara et al. biopsied all lesions with LAF which did not resolve [22]. As can be seen in the current study, this is unwarranted.

With this in mind, similar to the present study, Laronde et al. introduced a three week review to allow for resolution of inflammatory lesions [29]. Lesion colour and texture were found to be

associated with LAF with red or mixed red/white lesions as well as pigmented lesions, more likely to demonstrate LAF compared to white lesions. Whether the lesion was homogeneous or non-homogeneous did not show any significant associations [29]. This is in contrast to the present study, where a non-homogeneous appearance was associated with LAF as well as an increased likelihood of referral. We have previously shown that a non-homogeneous appearance is associated with oral epithelial dysplasia, and so it would be assumed that non-homogeneous lesions would also be associated with LAF [35].

Laronde et al. also found that lesion persistence was best predicted using a combination of clinical examination and VELscope™ findings than with either screening modality alone [29], a finding echoed in the current study where the combined examination provided a more accurate assessment. In the present study, using the decision making protocol an additional five patients were identified for referral beyond COE, of which one patient proved to have mild dysplasia. While there was a small drop associated in specificity of referrable lesions from 99.0% to 97.9%, this was not as significant as previously reported when diagnosis of dysplasia was used as an outcome measure [16,22]. Compared to the specificity of VELscope™ alone, the combined protocol removed a large portion of over-referrals. The use of the decision making protocol is also associated with an increase in sensitivity from 44.0% to 73.9%, while the sensitivity of VELscope™ was 64.0%. The importance of COE cannot be understated as VELscope™ itself may not detect all significant lesions as it has been found that not all cases of dysplasia display LAF [16].

While previous studies have stated the importance of diascopic fluorescence [16], the significance of blanching has not been assessed in general practice. In the present study, lesions which partially blanched were associated with the highest rate of referrals. Among reviewed lesions, those with LAF and no blanching tended to show the highest rates of healing although this did not reach significance. This highlights the importance of reviewing patients with LAF and not acting on initial findings. Epithelial dysplasia can be associated with inflammation and changes in underlying vasculature which can contribute to the problem of partial blanching [36]. The higher rate of healing among reviewed lesions with no blanching may be due to the presence of extravasated haemoglobin in acute traumatic events which are a frequent occurrence in the oral environment. Accurate blanching can be difficult to perform and is highly dependent on operator interpretation; however it forms an essential part of assessment of lesions using autofluorescence. Blanching was more easily performed using the back of a periodontal or sickle probe rather than the back of a mirror particularly with smaller lesions and in difficult to access areas.

One of the limitations of this study is that it is a single centre study performed in a uniform population. All cases of dysplasia found in this screening study were located on the lower lip which is not surprising given that the highest incidence of OSCC in this population occurs on the lower lip due to high levels of sun exposure [37,38]. In other populations, where other factors such as the use of betel quid play a more prominent role in the development of OSCC, results may vary and LAF patterns of lesions such as submucous fibrosis need to be taken into account. Nonetheless, the results of our study utilising the decision making protocol are generalizable to other populations.

It is possible that significant oral mucosal lesions were missed since not all patients were seen by a specialist practitioner. However, this more closely simulates a real world environment where only patients with lesions deemed to be significant by the primary clinician are seen in a secondary referral centre. Further testing of this decision making protocol with multiple practitioners in multiple centres is required to confirm its applicability and generalizability.

Conclusion

Using VELscope™ alone to screen patients in routine general dental practice over-estimates the burden of significant oral mucosal abnormalities and may lead to over-referral. Using the decision making protocol presented in this study, with particular emphasis on careful clinical interpretation and reviewing lesions where appropriate, can result in a decrease in the number of unnecessary referrals which may occur if relying on LAF alone. In addition, VELscope™ may aid in the detection of dysplasia which may not be identified by COE alone. Future research should focus on large scale multi-centre trials to assess what additional benefits this technology brings to COE.

Conflict of Interest statement

None declared.

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References

[1] Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011;61(2):69–90.
[2] Warnakulasuriya S. Global epidemiology of oral and oropharyngeal cancer. Oral Oncol 2009;45(4–5):309–16.
[3] Mignogna MD, Fedele S, Lo Russo L, Ruoppo E, Lo Muzio L. Costs and effectiveness in the care of patients with oral and pharyngeal cancer: analysis of a paradox. Eur J Cancer Prev 2002;11(3):205–8.
[4] Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin 2010;60(5):277–300.
[5] Gómez I, Seoane J, Varela-Centelles P, Diz P, Takkouche B. Is diagnostic delay related to advanced-stage oral cancer? A meta-analysis. Eur J Oral Sci 2009;117(5):541–6.
[6] Farah CS, McCullough MJ. Oral cancer awareness for the general practitioner: new approaches to patient care. Aust Dent J 2008;53(1):2–10.
[7] Bouquot JE. Common oral lesions found during a mass screening examination. J Am Dent Assoc 1986;112(1):50–7.
[8] Al-Mobeeriek A, AlDosari AM. Prevalence of oral lesions among Saudi dental patients. Ann Saudi Med 2009;29(5):365–8.
[9] Do L, Spencer A, Dost F, Farah C. Oral mucosal lesions: findings from the Australian National Survey of Adult Oral Health. Aust Dent J 2014.
[10] Epstein JB, Guneri P, Boyacioglu H, Abt E. The limitations of the clinical oral examination in detecting dysplastic oral lesions and oral squamous cell carcinoma. J Am Dent Assoc 2012;143(12):1332–42.
[11] Thomson PJ. Field change and oral cancer: new evidence for widespread carcinogenesis? Int J Oral Maxillofac Surg 2002;31(3):262–6.
[12] Bhatia N, Lalla Y, Vu AN, Farah CS. Advances in optical adjunctive aids for visualisation and detection of oral malignant and potentially malignant lesions. Int J Dent 2013;2013:194029.
[13] McCullough MJ, Prasad G, Farah CS. Oral mucosal malignancy and potentially malignant lesions: an update on the epidemiology, risk factors, diagnosis and management. Aust Dent J 2010;55:61–5.
[14] Lingen MW, Kalmar JR, Karrison T, Speight PM. Critical evaluation of diagnostic aids for the detection of oral cancer. Oral Oncol 2008;44(1):10–22.
[15] Rethman MP, Carpenter W, Cohen EE, Epstein J, Evans CA, Flaitz CM, et al. Evidence-based clinical recommendations regarding screening for oral squamous cell carcinomas. J Am Dent Assoc 2010;141(5):509–20.
[16] Farah CS, McIntosh L, Georgiou A, McCullough MJ. Efficacy of tissue autofluorescence imaging (VELScope) in the visualization of oral mucosal lesions. Head Neck 2012;34(6):856–62.
[17] VELscope Vx: Enhanced Oral Assessment. LED Dental Inc. <http://www.velscope.com/> [accessed 25.10.13].
[18] Pavlova I, Williams M, El-Naggar A, Richards-Kortum R, Gillenwater A. Understanding the biological basis of autofluorescence imaging for oral cancer detection: high-resolution fluorescence microscopy in viable tissue. Clin Cancer Res 2008;14(8):2396–404.
[19] Poh CF, Zhang L, Anderson DW, Durham JS, Williams PM, Priddy RW, et al. Fluorescence visualization detection of field alterations in tumor margins of oral cancer patients. Clin Cancer Res 2006;12(22):6716–22.

[20] Poh CF, Ng SP, Williams PM, Zhang L, Laronde DM, Lane P, et al. Direct fluorescence visualization of clinically occult high-risk oral premalignant disease using a simple hand-held device. Head Neck 2007;29(1):71–6.
[21] Awan KH, Morgan PR, Warnakulasuriya S. Evaluation of an autofluorescence based imaging system (VELscope) in the detection of oral potentially malignant disorders and benign keratoses. Oral Oncol 2011;47(4):274–7.
[22] McNamara KK, Martin BD, Evans EW, Kalmar JR. The role of direct visual fluorescent examination (VELscope) in routine screening for potentially malignant oral mucosal lesions. Oral Surg Oral Med Oral Pathol Oral Radiol 2012;114(5):636–43.
[23] Mehrotra R, Singh M, Thomas S, Nair P, Pandya S, Nigam NS, et al. A cross-sectional study evaluating chemiluminescence and autofluorescence in the detection of clinically innocuous precancerous and cancerous oral lesions. J Am Dent Assoc 2010;141(2):151–6.
[24] Koch FP, Kaemmerer PW, Biesterfeld S, Kunkel M, Wagner W. Effectiveness of autofluorescence to identify suspicious oral lesions – a prospective, blinded clinical trial. Clin Oral Investig 2011;15(6):975–82.
[25] Scheer M, Neugebauer J, Derman A, Fuss J, Drebber U, Zoeller JE. Autofluorescence imaging of potentially malignant mucosa lesions. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011.
[26] Rana M, Zapf A, Kuehle M, Gellrich NC, Eckardt AM. Clinical evaluation of an autofluorescence diagnostic device for oral cancer detection: a prospective randomized diagnostic study. Eur J Cancer Prev 2012;21(5):460–6.
[27] Truelove EL, Dean D, Maltby S, Griffith M, Huggins K, Griffith M, et al. Narrow band (light) imaging of oral mucosa in routine dental patients. Part I: Assessment of value in detection of mucosal changes. Gen Dent 2011;59(4):281–9. quiz 290–281, 319–220.
[28] Huff K, Stark PC, Solomon LW. Sensitivity of direct tissue fluorescence visualization in screening for oral premalignant lesions in general practice. Gen Dent 2009;57(1):34–8.
[29] Laronde DM, Williams PM, Hislop TG, Poh C, Ng S, Bajdik C, et al. Influence of fluorescence on screening decisions for oral mucosal lesions in community dental practices. J Oral Pathol Med 2014;43(1):7–13.
[30] STARD statement: STAndards for the Reporting of Diagnostic accuracy studies. <http://www.stard-statement.org/> [accessed 24.02.14].
[31] Neville BW, Day TA. Oral cancer and precancerous lesions. CA Cancer J Clin 2002;52(4):195–215.
[32] Marzouki HZ, Tuong Vi Vu T, Ywakim R, Chauvin P, Hanley J, Kost KM. Use of fluorescent light in detecting malignant and premalignant lesions in the oral cavity: a prospective, single-blind study. J Otolaryngol Head Neck Surg 2012;41(3):164–8.
[33] Lane PM, Gilhuly T, Whitehead P, Zeng H, Poh CF, Ng S, et al. Simple device for the direct visualization of oral-cavity tissue fluorescence. J Biomed Opt 2006;11(2):024006.
[34] Sharma AK, Mirza FD. Palatal mucosa under dentures: a qualitative histologic and histochemical analysis. J Prosthet Dent 1986;56(5):574–82.
[35] Dost F, Le Cao KA, Ford PJ, Farah CS. A retrospective analysis of clinical features of oral malignant and potentially malignant disorders with and without oral epithelial dysplasia. Oral Surg Oral Med Oral Pathol Oral Radiol 2013;116(6):725–33.
[36] Raica M, Cimpean AM, Ribatti D. Angiogenesis in pre-malignant conditions. Eur J Cancer 2009;45(11):1924–34.
[37] Ariyawardana A, Johnson N. Trends of lip, oral cavity and oropharyngeal cancers in Australia 1982–2008: overall good news but with rising rates in the oropharynx. BMC Cancer 2013;13(1):333.
[38] Farah C, Simanovic B, Dost F. Oral cancer in Australia 1982–2008: a growing need for opportunistic screening and prevention. Aust Dent J 2014;59. http://dx.doi.org/10.1111/adj.12198 [in press].