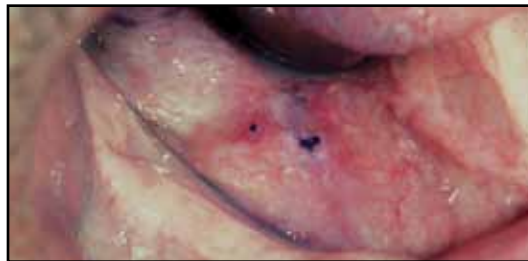


# Oral Precancer and Early Cancer Detection in the Dental Office – Review of New Technologies

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## Abstract



**Background:** New technologies have provided an exciting new array of clinical diagnostic tools for localizing or emphasizing abnormal mucosa in the dental office, especially leukoplakia and dysplasia. Some of these technologies claim to identify atypical cells prior to biopsy, even before there are clinically visible mucosal changes, hence, can allow a more confident assessment of risk and localization of the most “suspicious” area to biopsy. In essence, molecular-level detection of dysplastic oral mucosal change appears to be moving into the practitioner’s office.

**Methods:** Extensive literature review, personal experience and discussion with other professionals with clinical experience with these technologies were used in order to provide a critical summary and evaluation of available technologies.

**Conclusions:** Most technologies are beneficial but must be used with intelligence and must be considered adjunctive tests rather than stand-alone diagnostic tools. Loss of autofluorescence seems to hold the most promise for identifying mucosal dysplasia, but several non-dysplastic lesions may also be nonfluorescent and occasional false positive results do occur.

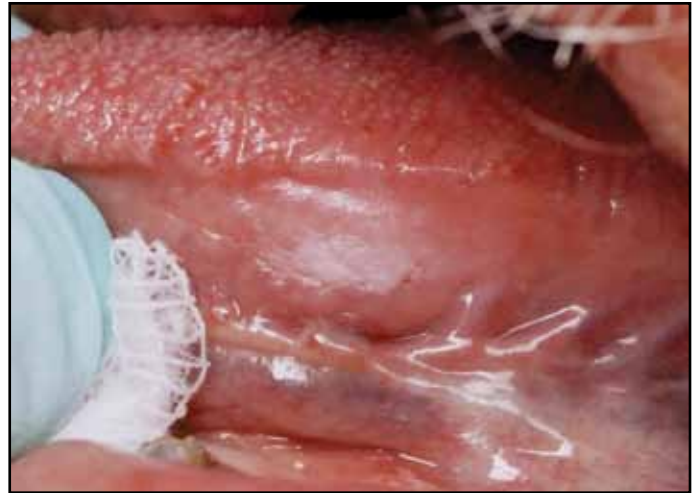
**KEY WORDS:** Oral cancer, oral diagnosis, leukoplakia, erythroplakia, cytology

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## INTRODUCTION

The idea of precancer has been a slowly changing and often confusing concept, beginning with the 1805 suggestion by an European panel of physicians that there are benign diseases which will always develop into invasive malignancy if followed long enough.<sup>1</sup> With today's definition, a precancer is considered to only hold an increased risk of cancer transformation.<sup>2</sup> Oral precancers, in particular, have a rich and fascinating literature extending as far back as the 1870s, when Sir James Paget, one of England's most renowned surgeons, proposed that "leukokeratosis" or "smoker's patch" of the hard palate (nicotine palatinus), or the tongue, in inveterate pipe smokers carried an increased risk of eventual cancer transformation.<sup>3</sup> He mentioned that he saw his first cancer transformation in this disease in 1851. Ironically, we no longer consider nicotine palatinus to be a precancer, preferring rather to think of it as a response to the heat of tobacco smoke, not the carcinogens.<sup>3,4</sup> The heavily keratinized, i.e. "protected" mucosa of the hard palate is, in fact, one of the least likely sites for oral cancer development.<sup>2</sup>

Another white keratotic lesion, leukoplakia (Figure 1), has demonstrated a far greater risk of malignant transformation, a risk which has been discussed since before 1876, when the Hungarian dermatologist, Schwimmer, first coined the term.<sup>3,5</sup> We now know that leukoplakia represents more than 80% of all oral precancers, is found in approximately 3% of U.S. adults older than 35 years of age, and shows an increasing prevalence with increasing age, as well as with increased daily usage of smoked tobacco.<sup>2,6,7</sup> Because of the continuing challenge and confusion surrounding oral precancer concepts, the World Health Organization has periodically convened interna-



**Figure 1:** Leukoplakia of the ventral tongue is seen as a well demarcated, relatively thin white keratotic patch.

tional workshops to redefine the term "precancer" and the various oral precancerous lesions. The most recent workshop, held in London in 2005, actually recommended the elimination of the term "precancer" and the use of the presumably more illuminating term "potentially malignant lesion" for oral lesions.<sup>8</sup> This panel tried to completely eliminate the term "leukoplakia" because of its progressively changing definition over time. At the end of the day, no better diagnostic term could be found.

Once applied to any and all white mucosal plaques of the mouth, leukoplakia today is defined as a "white patch or plaque that cannot be characterized clinically or pathologically as any other disease" and is not associated with an obvious etiologic agent except tobacco use.<sup>2,8</sup> This definition excludes lichen planus, frictional keratosis, smokeless tobacco keratosis, nicotine palatinus and alveolar keratosis, all diseases which were once included in the diagnosis of leukoplakia. The term is now used in a strictly clinical sense and does not imply a specific microscopic tissue alteration except, of course, the excess surface keratin



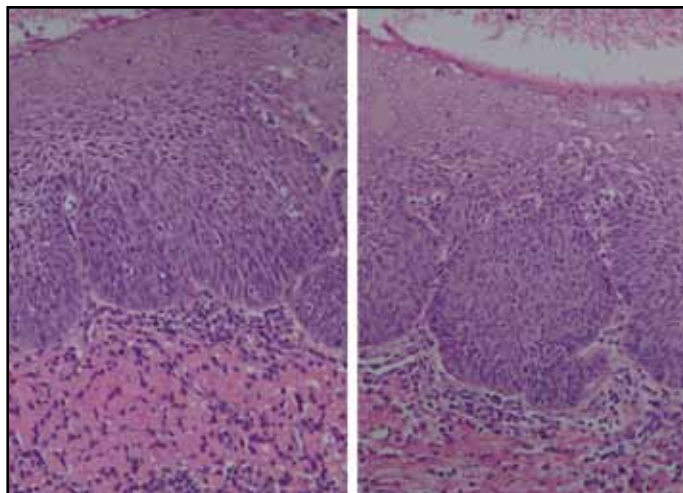
**Figure 2:** Erythroplakia of the ventral tongue is seen as a well demarcated red patch with areas of pebbled or granular surface change (some lesions have a smooth surface).



**Figure 4:** Speckled leukoplakia (erythroleukoplakia) of the oral floor shows multiple pink areas surrounded by a white keratotic plaque.

which is responsible for the white color change.

While certain clinical alterations in leukoplakia are known to increase the risk of cancer transformation, it is the microscopic features of leukoplakia and its less common but more serious red counterpart, erythroplakia (Figure 2), which are



**Figure 3:** Histopathology of moderately severe dysplasia, showing atypical keratinocytes and irregular rete tips in the lower portion of the epithelium.

the most significant prognostic indicators. For example, the clinical entity called leukoplakia is generally thought to carry a malignant transformation rate of approximately 4% (presumably a lifetime risk, although few have been followed for an entire lifetime).<sup>2,7,9</sup> The transformation rate for lesions with epithelial dysplasia is much higher, approximating 4-11% for moderately severe dysplasia and 20-35% for severe dysplasia (Figure 3), with malignant transformation usually occurring within 3 years of the dysplasia diagnosis.<sup>7-11</sup> Less dysplastic epithelium is much less worrisome in this regard and so the most significant of the oral dysplasia follow-up investigations have confined themselves to severe dysplasias or carcinoma in situ, often combining the two, since both appear to have similar biological behaviors.<sup>7,9,12</sup>

How often are dysplastic cells found in leukoplakia or erythroplakia? Overall, only 5%-25% of leukoplakias will actually show dysplastic epithelial cells when biopsied, although almost 90% of

**Table 1: Precancerous lesions of the oral, pharyngeal and laryngeal mucosa, as suggested in the literature; clinical terms only (modified from Bouquot, Farthing, Speight, 2005.<sup>7</sup>)**

<b>Disease Name</b>	<b>Malignant Transformation Potential</b>
<b>Proliferative verrucous leukoplakia (PVC)</b>	<b>*****</b>
<b>Nicotine palatinus in reverse smokers<sup>a</sup></b>	<b>*****</b>
<b>Erythroplakia</b>	<b>*****</b>
<b>Oral submucous fibrosis, with leukoplakia</b>	<b>*****</b>
<b>Erythroleukoplakia</b>	<b>****</b>
<b>Granular leukoplakia</b>	<b>****</b>
<b>Laryngeal keratosis</b>	<b>***</b>
<b>Actinic cheilosis</b>	<b>***</b>
<b>Syphilitic glossitis, with dorsal leukoplakia</b>	<b>***</b>
<b>Smooth, thick leukoplakia</b>	<b>**</b>
<b>Smokeless tobacco keratosis</b>	<b>**</b>
<b>Plummer-Vinson disease (sideropenic dysphagia, smooth tongue)</b>	<b>*</b>
<b>Lichen planus, erosive forms<sup>b</sup></b>	<b>*</b>
<b>Smooth, thin leukoplakia</b>	<b>+/-</b>
<b>Lupus erythematosus, with oral ulcers/keratosis</b>	<b>?</b>
<b>Dyskeratosis congenita, with oral leukoplakia</b>	<b>?</b>
<b>Epidermolysis bullosa, with oral leukoplakia</b>	<b>?</b>
<b>Clarke-Howel-Evans syndrome, with oral leukoplakia</b>	<b>?</b>

a. reverse smoking: smoking with the lit end of the cigarette in one's mouth

b. designated by the 2005 WHO Workshop on Oral Premalignancies as *not* a precancer<sup>8,10</sup>

erythroplakias will do so.<sup>2,8,12</sup> Therefore, we can logically consider all erythroplakias to be high risk, but the same cannot be said for leukoplakias. In fact, the great majority of leukoplakic lesions show no evidence of atypia. How then can we determine which leukoplakias are the high risk lesions?

Certain clinical features, such as large size, rough or granular surface changes, red or pink patches incorporated within the white patch of a leukoplakia (speckled leukoplakia, erythroleukoplakia), multiple leukoplakic lesions, and ulcerative mucosal breakdown are all significant in this regard (Figure 4).<sup>7,13,14</sup> Each of these suggests increased risk and, significantly, each identifies potential biopsy sites most likely to contain dysplastic cells. The latter point is extremely important for a large leukoplakia, since a negative biopsy will give a false sense of security which may, in turn, result in poor follow-up of the lesion.

For several decades the above mentioned clinical features have been the only guide we have had for risk assessment of oral precancers. In the hands of an experienced clinician they have served remarkably well. Unfortunately, most of us lack the level of experience or expertise required to make ideal decisions about these lesions. Fortunately, new technologies are providing the general dentist with help that can be used in an office setting. When dysplastic cells do occur in an oral leukoplakia or erythroplakia, these technologies claim to help identify them prior to biopsy and, hopefully, to allow a more confident assessment of risk and identify a more “suspicious” area to biopsy. This point is especially significant when one knows that the biopsy is not predictive in almost half of oral precancers and that the entire oral mucosa is at risk in individuals with a precancer or cancer of the mouth.<sup>15,16</sup>

We certainly need help with this dilemma.

In essence, molecular-level detection of dysplastic oral mucosal change appears to be moving into the practitioner’s office. With these new technologies, as always, come new responsibilities and new problems.<sup>17</sup> This review will attempt to describe the pros and cons of the recent and latest of these technologies.

### The Brush Biopsy

The Pap smear, a time-honored, effective tool for finding dysplastic cells of the uterine cervix lost popularity among dentists during the 1960s because it seemed unable to find dysplastic cells in oral leukoplakias. This is undoubtedly due to the fact that oral white patches have a thicker keratin layer than their cervical counterparts. Dysplastic or immature epithelial cells arise, of course, from the bottom of the squamous epithelium, and should not be expected to be found by scraping a thick surface layer of keratin.<sup>7</sup> Today pap smears are used effectively for oral red lesions and oral ulcers to identify infections, especially candidiasis, and atypical cells in erythroplakia, a disease in which dysplastic epithelial cells are typically near the surface. They are seldom used for white keratotic lesions.

The brush biopsy or Oral CDx test has overcome this fatal shortcoming by screwing a bristle-covered wire (the “brush”) through the thick surface keratin to the basal layer of the epithelium (Figure 5A).<sup>18</sup> This relatively painless procedure captures the deeper epithelial cells on the bristles and the entire brush is sent to a pathology lab, where the cells are removed and plated on a microscopic slide. From that point on, the process is the same as a routine pap smear. A cytotechnologist, pathologist or, more recently,



**Figure 5a:** The Oral CDx brush biopsy is twisted into the mucosa.



**Figure 5b:** One of the LBC brushes in use.



**Figure 6a:** Thin leukoplakia of oral floor has a slight erythematous background.



**Figure 6b:** Toluidine blue staining identifies areas of potential biopsy (dysplasia) (photo: Dr. Hille Ephros, New Jersey Medical and Dental University, Newark, New Jersey).

a computer-associated optical scanner compares the size of each individual cell with the size of its nucleus. Large, dark nuclei are found in dysplastic or immature cells, as are abnormal nuclear shapes (pleomorphism). Results are usually reported out as one of three levels of risk.

Recently, liquid-based cytology (LBC) has become a principle methodology in cytopathol-

ogy replacing conventional smears, owing to better cell recovery and morphologic preservation. The Food and Drug Administration (FDA) has approved two LBC methods for gynecologic and non-gynecologic cytologic sample processing.<sup>19</sup> One method uses a filtration process and a computer-assisted thin layer deposition of cells (Thinprep® CYTYC Corp., Boxborough, MA),

while the other method involves a sedimentation process (TRiPath Imaging, Burlington, NC). Both of these methods produce an evenly distributed thin layer of epithelial cells devoid of blood and the ubiquitous inflammatory cells that may interfere with cytologic examination. LBC had been adopted to analyze the brush biopsy samples of oral mucosa (Figure 5B).<sup>20,21</sup> LBC methodology appears to not only increase the sensitivity and specificity of cytologic diagnosis but, significantly, also provides additional samples for immunohistochemical and other molecular studies which are not possible with conventional cytologic smears.

The brush biopsy and LBC, as with all adjunctive technologies for oral dysplasia, must be used with intelligence and its routine use requires that the clinician be relatively knowledgeable about the clinical features of precancers and can properly identify the most “severe” area to brush. It also implies that the clinician is capable of distinguishing between lesions which should be biopsied immediately and those borderline ones that should be “brush biopsied.” It is a good tool in an experienced, knowledgeable hand, with very few false positive or negative results when used appropriately.<sup>18,22</sup> However, is not a good screening procedure and no studies have correlated normal mucosa with brush biopsy results.<sup>17</sup> Perhaps more significantly, the brush biopsy is not a true diagnostic tool and cannot, therefore, provide a definitive diagnosis – an incisional biopsy is always needed for that.

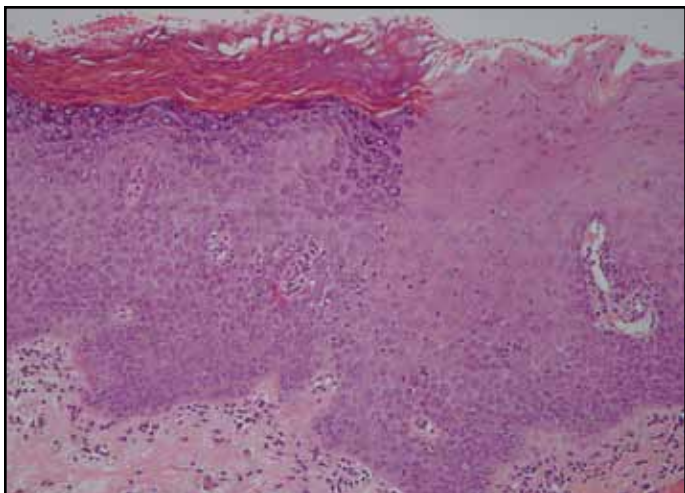
### **Toluidine Blue – in Vivo Staining of DNA in the Dental Office**

Toluidine blue (tolonium chloride) is a metachromatic dye long used in histology laboratories to stain nuclear material, since it stains DNA very

well. For several decades now it has also been used, primarily outside the United States, for oral precancer detection by staining, in the dental office, the nuclei of immature, living cells. This test is premised on the fact that mucosal cells with extra DNA, i.e. large nuclei, attract and retain the stain, even after the bulk of the stain has been washed off with acetic acid (Figures 6a,6b).<sup>17</sup> It has recently been FDA cleared for use within the United States, and has been added to another technology, the ViziLite(R) system to improve the effectiveness of that test (see following). It is also used in the U.S. to find “outlier” areas of dysplasia prior to definitive oral cancer surgery. Unfortunately, this dye test is awkward to use, requiring an acetic acid (vinegar) rinse before and after, and there are high proportions of false positives and false negatives.<sup>23-25</sup> It frequently needs to be repeated because the false positive tests are often trauma- or inflammation-related. Moreover, the dysplastic cells lying deeply in a thick keratotic lesion will likely not be stained adequately. Even with its limitations, however, the toluidine blue test can be a good adjunctive test in the hands of an experienced, knowledgeable clinician, and is especially effective with erythroplakia and carcinoma in situ.<sup>23,24</sup> It should not be considered a stand-alone test and will not give a diagnosis, but it can help to localize areas to biopsy or to brush biopsy.

### **The ViziLite – Highlighting the Keratin**

Gynecologists have long been aware of the ability of acetic acid to enhance regions of thickened surface keratin of the uterine cervix. In the oral environment, likewise, it makes the keratin more white and, therefore, more visible to the naked eye. A thin leukoplakia which might otherwise have been missed could be detected after a min-



**Figure 7:** The ViziLite is good at emphasizing keratotic surface change, hence, should more readily identify the hyperkeratosis on the left, but underlying epithelial atypia is seen on both right and left sides.

ute of contact with acetic acid. The ViziLite(R) system takes advantage of this and adds bright blue light to even further enhance keratin detection.<sup>26-28</sup> This technology uses reflected light solely and so can only give us information from the most superficial cell layers. Dysplasia, of course, begins in the lowest layers of the epithelium and so reflected light will identify such cells only if they are associated with surface hyperkeratosis, e.g. leukoplakia (Figure 7). With this caveat, however, it does well, with a very high ability to enhance identification of keratotic patches.<sup>17,26,29</sup> The light is derived from either chemical tubes (chemiluminescence) or a laser and, recently, toluidine blue has been added to the kit (ViziLite Plus(R)) for identification of superficial nuclear abnormalities.

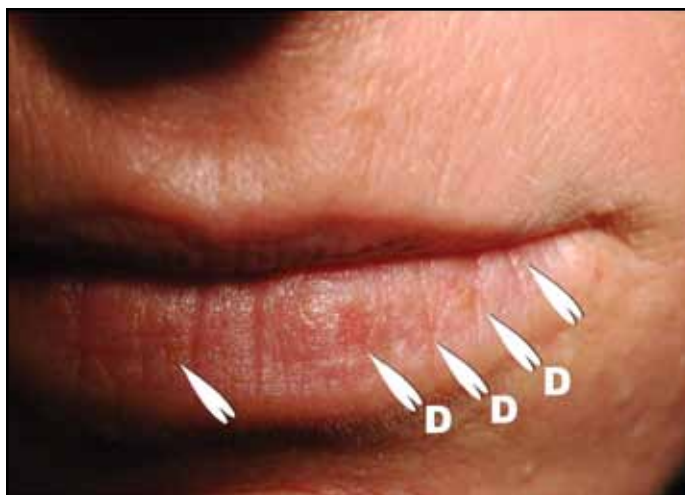
As with other adjunctive diagnostic technologies, the ViziLite(R) exam has disadvantages. It seems to have a high proportion of false positive and false negative tests, relative to identification of dysplastic cells rather than hyperkeratosis.<sup>28,29</sup>



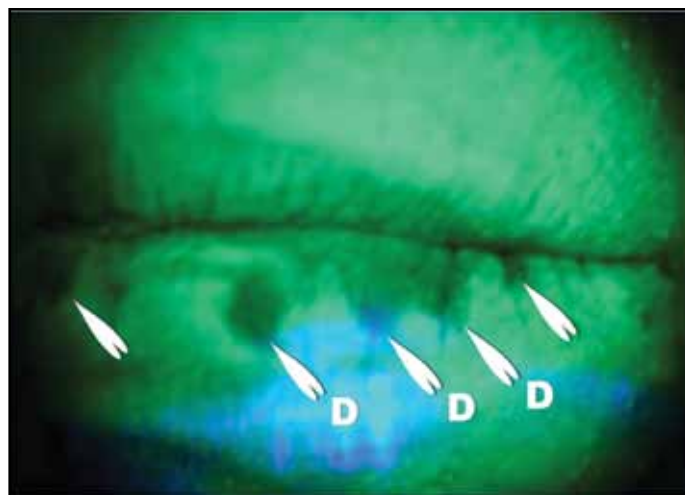
**Figure 8:** The ViziLite will make this leukoedema much more noticeable, despite the fact that there are never dysplastic cells in the affected epithelium.

It would constantly, for example, intensify innocuous keratotic lesions such as smokeless tobacco keratosis and leukoedema (Figure 8). Additionally, it requires a swish with acetic acid before and after the light examination. It is best performed in a completely dark room, which is often difficult in today's dental offices. And the relatively limited clinical research related to the ViziLite(R) has not looked at the microscopic appearance of oral mucosa which is "normal" according to the test.

Is this a worthwhile screening test? The manufacturer claims that "light from ViziLite(R) is absorbed by normal tissue and reflected by dysplastic tissue, which will appear white."<sup>30</sup> However, this seems counter-intuitive; reflected light should have no effect on our ability to see dysplasia unless associated with excess surface keratin, although the addition of toluidine blue of the ViziLite Plus(R) system is capable of identifying dysplastic or immature cells when they are close enough to the surface.<sup>29</sup> As an adjunctive



**Figure 9a:** Actinic cheilosis in a 37 year old woman has an innocuous appearance.



**Figure 9b:** The VELscope shows considerable loss of autofluorescence in multiple areas (arrows), with dysplasia (marked "D") seen microscopically in three sites.

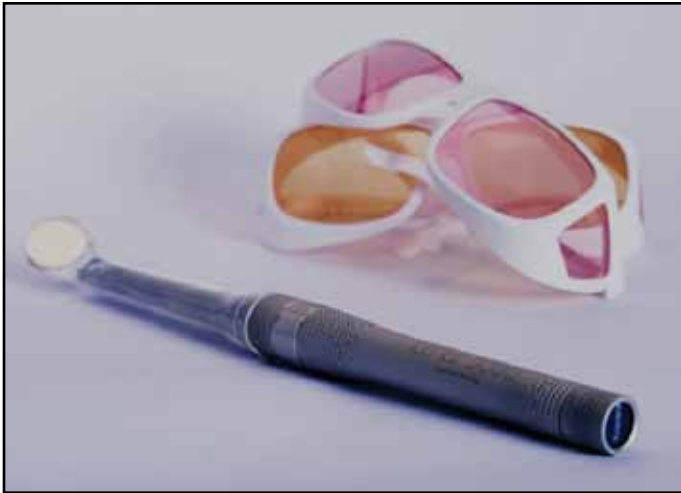
test, this system is valuable in that it increases awareness of the oral cancer and precancer detection dilemma for both the clinician and the patient, and it should, certainly, find hyperkeratotic patches that may have been missed with routine visual inspection. Whether or not it can detect dysplastic cells without toluidine blue staining, and in the absence of surface keratin, has not been adequately proven and, certainly, there are those who considered the technology to add little or nothing to the routine visual examination.<sup>28</sup>

### **Oral Autofluorescence – When the Mucosa Doesn't Glow**

Two optical devices, the VELscope(R) (LED Dental, Inc. White Rock, BC, Canada) introduced three years ago, and the new Identafi(R) 3000 Ultra (Trimira, LLC, Houston, Texas), take advantage of the fact that, to a certain degree, we all glow. Each of our cells contain molecules capable of self-fluorescence, especially when activated (excited) by

specific light waves.<sup>31-35</sup> Excitation and emission of fluorescence depends on how light is scattered and absorbed in tissue: scattering is caused by differences in the index of refraction of different tissue components, while absorption is dependent on the molecular composition of the same components.<sup>32,35</sup> In humans, these fluorescing products are numerous: tryptophan, porphyrins, collagen cross-links, elastin, NADH (nicotinamide adenine dinucleotide), and flavins (FAD, flavin adenine dinucleotide).<sup>34</sup> This fluorescent signaling has been used to assess the metabolic state of tissues and to identify primitive/dysplastic cells. The discovery and harnessing of fluorescent proteins, together with the subsequent biological and medical research have been significant enough to have culminated in a Nobel Prize in Chemistry.

The amount of fluorescence given off from living tissues is very slight; certainly not capable of being seen under normal conditions. However, if violet or blue light is used in a darkened



**Figure 10a:** The Identafi<sup>®</sup> 3000 Ultra with filtering goggles to be worn by the clinician.



**Figure 10b:** Using the green light during an oral examination.



**Figure 11a:** The VELscope autofluorescence device.



**Figure 11b:** In clinical use, the operator looks through the eyepiece, which is mounted in the hand-held light emitting "gun," while the patient wears protective eye gear.

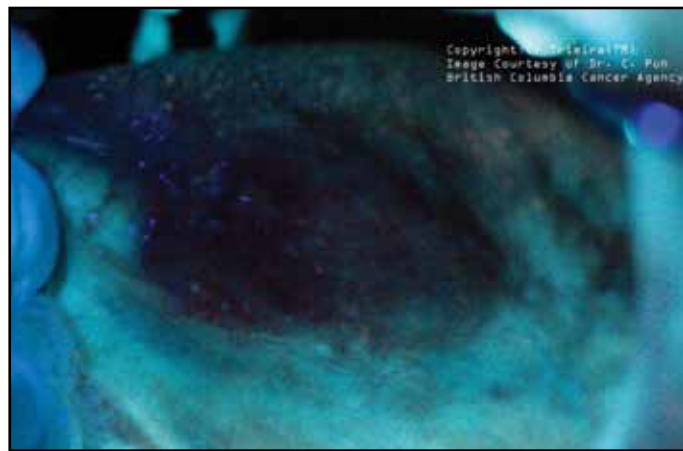
room and the clinician peers through an eyepiece or pair of glasses which filter out virtually all reflected light and only allows transmission of light of the wavelength(s) of the fluorescing tissues, the autofluorescence is easily seen (Figures 9a,9b). The wavelengths which excite the greatest fluorescence in oral mucosa range

from 400 to 460 nm, i.e. violet and blue light.

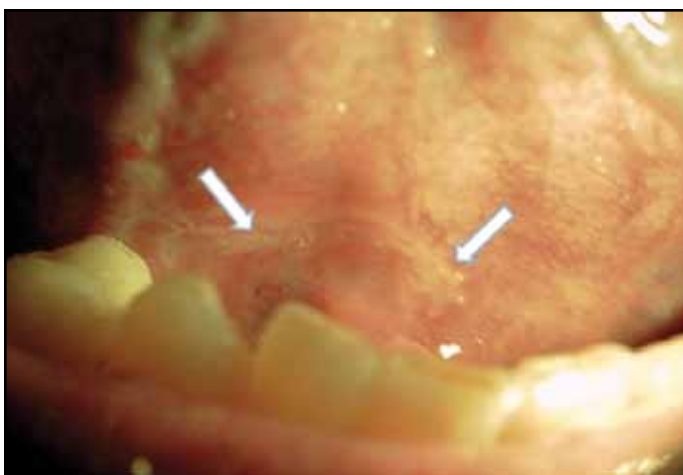
The Identafi(R)3000 Ultra shines a violet light of approximately 405 nm, which especially stimulates a blue/violet fluorescence. The light shines from a battery-powered device roughly the size, shape and weight of a dental hand-piece; the user looks through special filtering



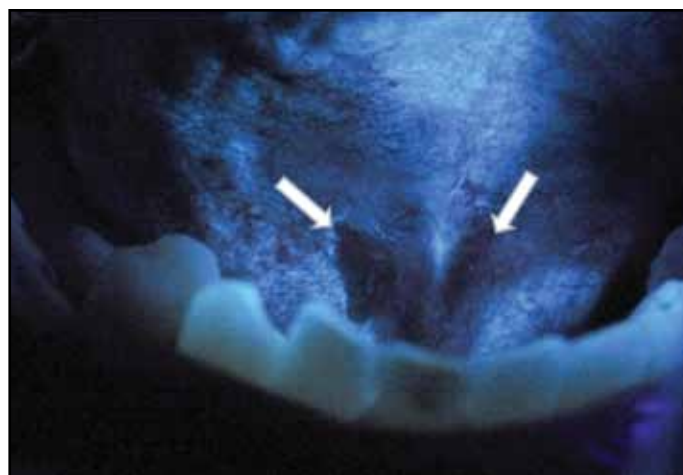
**Figure 12a:** Squamous cell carcinoma of the left ventral and lateral tongue presents as an innocuous, somewhat pebbled patch.



**Figure 12b:** Entire lesions show a considerable loss of autofluorescence (using Identafi<sup>®</sup> 3000 Ultra violet light) (photo: Dr. Catherine Poh, University of British Columbia, Vancouver, British Columbia, Canada).



**Figure 13a:** Poorly visualized whitish change of the anterior oral floor was diagnosed as severe dysplasia by biopsy.



**Figure 13b:** Well demarcated loss of autofluorescence in area of dysplasia (photo: Dr. Anne Gillenwater, M.D. Anderson Cancer Center, Houston, Texas).

glasses (Figures 10a, 10b). This device also provides two other types of light: a white light suitable for a conventional visual examination, and a green-amber light that highlights keratinized mucosa and submucosal blood vessels. The generated light is less intense or bright than that of the VELscope(R) but this does not seem to influ-

ence the amount of tissue fluorescence given off.

The VELscope(R) uses a blue light with peak intensity at approximately 436 nm; this wavelength especially stimulates a green fluorescence. The device shines light out of a handheld “gun” that is tethered to a light source which typically remains on a cart or counter

**Table 2: Autofluorescence outcomes with various oral lesions, using a 0-4 point scale, with 4 equally complete loss of fluorescence (very dark region of mucosa). These outcomes are based on the anecdotal experience of numerous clinicians with extensive experience using autofluorescing devices.**

<b>Disease/Lesion</b>	<b>Amount of Autofluorescence Loss (Maximum = 4)</b>
<b>Leukoplakia with epithelial dysplasia</b>	<b>3-4</b>
<b>Dysplasia without white or red color</b>	<b>3-4</b>
<b>Melanosis</b>	<b>3-4</b>
<b>Amalgam tattoo</b>	<b>3-4</b>
<b>Tonsil tag (lymphoid aggregate)</b>	<b>3-4</b>
<b>Focal epithelial hyperplasia (FEH)</b>	<b>3-4</b>
<b>Hemangioma/venous lake</b>	<b>3-4</b>
<b>Geographic tongue (depapillated area)</b>	<b>2-4</b>
<b>Lichen planus (erosive type only)</b>	<b>2-4</b>
<b>Irritation fibroma (with continued surface</b>	
<b>irritation, subepithelial congestion) *</b>	<b>2-3</b>
<b>Squamous papilloma</b>	<b>1-3</b>
<b>Inflammatory congestion</b>	<b>1-3</b>
<b>Mild cheek bite (with or without hyperkeratosis)</b>	<b>1-2</b>
<b>Mild tongue thrust habit (lateral margins)</b>	<b>1-2</b>
<b>Leukoplakia without epithelial dysplasia</b>	<b>0-1</b>

\* fibromas without such surface irritation are brightly fluorescent

top plugged to the wall (Figures 11a, 11b), and the user looks through a filtered eyepiece that disallows reflective and ambient light.

An immature or dysplastic epithelial cell has much less NADH and FAD activity than a normal cell and so mucosal areas with such cells will not fluoresce, thereby appearing black (actually blackish-green or blackish-blue) through the eyepiece or glasses (Figures 9,12,13).<sup>35</sup> Additionally, data also suggests that the cross-links in subepithelial collagen fibers beneath dysplastic cells also lose fluorescent activity, contributing to the “black spot” seen through the filter.<sup>35</sup> Research has shown that the difference in self-fluorescence between normal oral mucosa and dysplastic epithelium, e.g. in carcinoma, can be as much as 12x (Figures 12a, 12b), and biopsies of border regions between green and black mucosa have shown that the green/blue fluorescent mucosa is very unlikely to contain dysplastic cells, while black mucosa is highly likely to contain such cells (Figures 13a, 13b).<sup>34,35,37</sup>

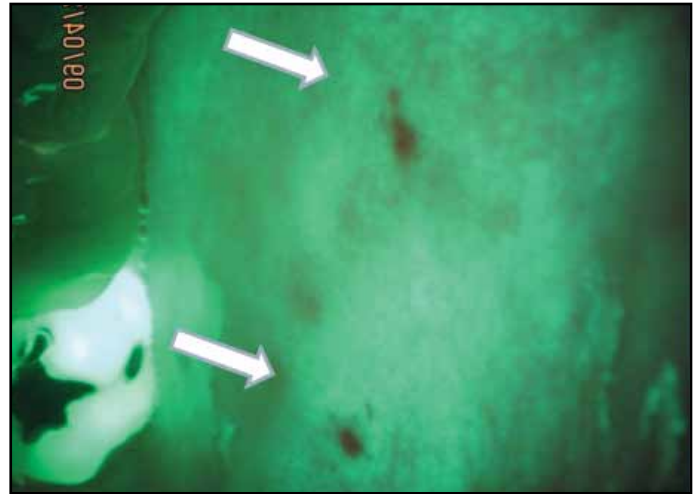
The beauty of the self-fluorescence test is that the light used to excite the oral cells penetrates to the deepest part of the epithelium and so easily reaches dysplastic cells in the lower regions of the epithelium, as well as the subepithelial collagen fibers. This deep penetration can, however, prove to be a bit of a disadvantage in certain settings, since several nondysplastic tissue changes are also positive with this test (Table 2). These additional positive lesions are not true “false positives” but they do require a basic understanding of common oral lesions and a closer evaluation with visible light. For example, the excellent light-absorbing qualities of hemoglobin (Figures 14a, 14b) and melanin deposition produce the impression of loss of fluorescence. If there are numer-

ous dilated superficial blood vessels immediately beneath the epithelium, as can easily occur in mild trauma or inflammation, a mimicked loss of fluorescence (black spot) might result. The Identafi(R) 3000 attempts to address this issue by providing a green-amber light which highlights vascularity. Relative to the dark patches from melanin pigmentation, this can easily be identified with routine visual or white light examination.

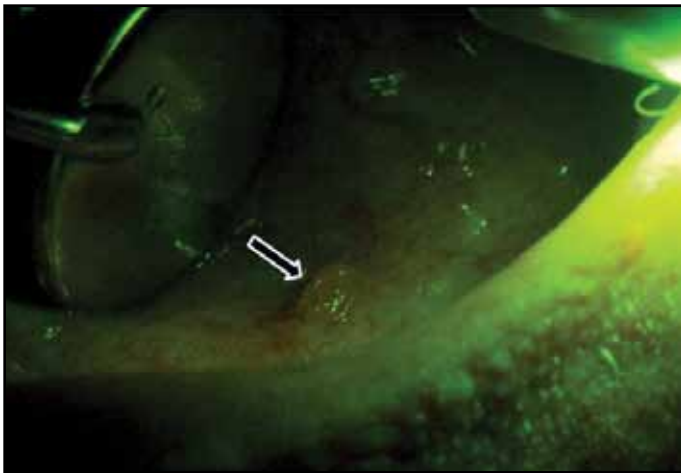
Aggregates of benign lymphoid tissue, such as tonsils or oral tonsil tags, lack collagen almost entirely and leukocytes may lack the autofluorescence molecules influenced by the wavelengths use by the oral devices in use today; such aggregates are typically dark when viewed with the VELScope(R) or Identafi(R)3000 Ultra (Figures 15a, 15b). Bacteria using different fluorescent cytosol molecules will give off a red, pink or orange or yellow fluorescence (Figures 16a, 16b). Fungal microorganisms, such as candida, may fluoresce yellow or yellow/orange (Figure 17a, 17b). Lesions of focal epithelial hyperplasia also typically show a moderate loss of fluorescence, for reasons unknown. The irritation fibroma with secondary surface irritation and increased subepithelial vascularity may appear dark, even though more typical, less irritated fibromas fluoresce very, very well because they are comprised almost completely of mature collagen with many cross links. And finally, our own personal experience suggests that the erythematous background of erosive (atrophic) lichen planus typically lacks self-fluorescence (Figures 18a, 18b). The reason for this is unknown but may have to do with epithelial influence on the subepithelial stroma or the replacement of dense subepithelial collagen fibers by less fluorescent leukocytes.



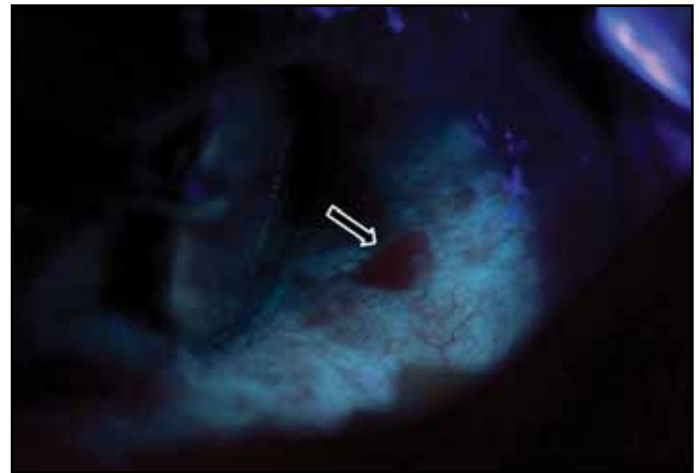
**Figure 14a:** Buccal mucosa with two small telangiectasias.



**Figure 14b:** Vascular lesions show dark areas mimicking loss of fluorescence (using VELscope) (photos: Dr. Robert Anderson, Houston, Texas).



**Figure 15a:** Lymphoid aggregate (tonsil tag) of oral floor viewed with amber/green light of the Identafi<sup>®</sup>.



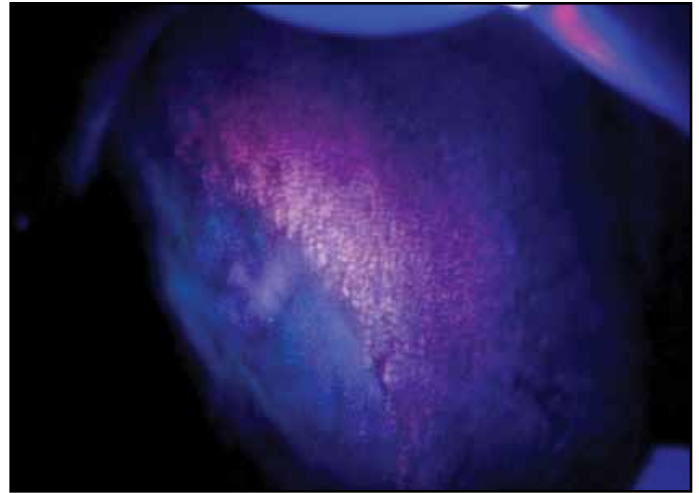
**Figure 15b:** Lesion appears very dark with the violet light of the Identafi<sup>®</sup>.

Autofluorescence technology has been extensively used in endoscopic instruments for bronchoscopy, esophageal examination, colonoscopy and skin evaluation. Each anatomic site requires slight variations in wave length and other factors, but the greatest hurdle

to overcome for the routine oral use of this technology appears to be the need for a dimmed environment. This makes evaluation very much more efficient and without it there is bound to be a larger number of true false negatives. Our experience suggests that these numbers



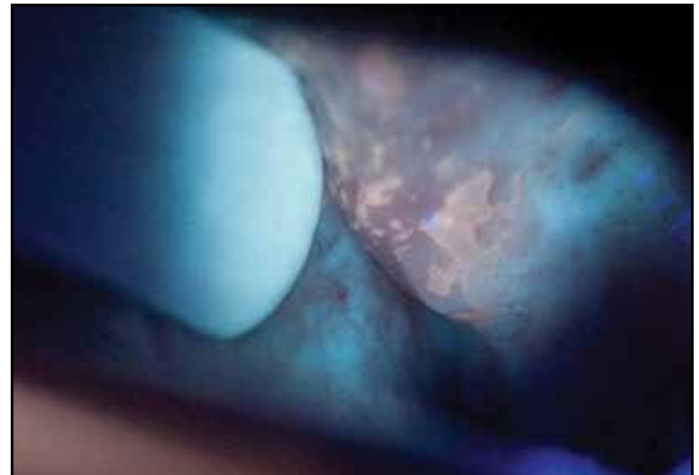
**Figure 16a:** Leukoplakia of the right dorsal tongue.



**Figure 16b:** The leukoplakia shows minimal loss of fluorescence; lingual bacteria fluoresce pink using the blue light of the Identafi<sup>®</sup> (photos: Dr. Anne Gillenwater, M.D. Anderson Cancer Center, Houston, Texas).



**Figure 17a:** Pseudomembranous candidiasis of left buccal mucosa.



**Figure 17b:** Yellow autofluorescence with the blue light of the Identafi<sup>®</sup> (photos: Dr. Anne Gillenwater, M.D. Anderson Cancer Center, Houston, Texas).

are quite low when the devices are properly used as part of an overall clinical examination.

This, of course, again brings to mind the premise mentioned previously: these are adjunctive tests only, and all such tests require the clinician to use his or her intelligence. A second

concern is that the equipment can be relatively expensive, ranging from \$3,000 to \$7,000. The only two published papers dealing with routine use of autofluorescence have come to opposite conclusions, with Huber<sup>35</sup> feeling that it adds nothing and Huff<sup>36</sup> feeling that it picked up dys-



**Figure 18a:** Erosive, bullous lichen planus of the left buccal mucosa.

plastic lesions missed by routine examination. To be fair, this degree of opposing conclusions is seen in all of the technologies discussed here, but our own opinion is that it is a good idea to use autofluorescence on an annual basis as a screening tool in the dental office. Certainly, in our experience this technology has identified dysplastic, even microinvasive lesions that were completely “normal” looking with visible light, even to the suspicious eye of an oral pathologist.

## CONCLUSIONS

Our intention is not to recommend one of these technologies over another, but the future looks most bright for the optical autofluorescence technology (pardon our pun), combined with either a biopsy, brush biopsy or LBC. All devices have limitations and the published research is sparse, but until other methods are developed, such as the use of molecular markers in salivary proteomics or genomics, it is heartening to know that relatively acceptable in-office devices are already available and can be used as adjunctive



**Figure 18b:** Severe loss of fluorescence of erythematous background using the violet light of the Identafi<sup>®</sup>.

diagnostic tools. Refinements and continued research will undoubtedly improve our ability to detect, at the earliest possible stage, dysplastic changes in our patients, and new technologies may emerge quickly which will prove much more valuable. Until then, it is refreshing to be practicing dentistry during a time of such exciting emerging technologies attempting to address one of the most frustrating and serious of our oral diagnostic dilemmas. ●

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