REVIEW ARTICLE

Precancerous Lesions of Oral Cavity

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Abstract

The term premalignant (precancerous) lesion has been replaced by the term potentially malignant lesion. Such lesions have as their cause, tobacco use, exposure to the human papilloma virus and the chewing of the betel nut. These substances contain carcinogens. The mucosa of the oral cavity is normally quite robust. Exposure to these substances can cause it to undergo change. These changes are usually initiated as a leukoplakic patch. While some leucoplakic patches recover and resolve, some progress into invasive squamous cell carcinoma. Oral submucus fibrosis is another such potentially malignant condition caused by the abuse of betel nut.

Keywords: Leukoplakia, potentially malignant condition, submucus fibrosis, dysplasia, keratosis, erythroplakia, huma pappilloma virus.

The terms precancer, precursor lesions, premalignant, intra-epithelial neoplasia and potentially malignant have been used in the international literature to broadly describe clinical presentations that may have a potential to become cancer.

A *precancerous lesion is* a morphologically altered tissue in which oral cancer is more likely to occur than in its apparently normal counterpart.

A *precancerous condition* is a generalized state associated with a significantly increased risk of cancer.

Precancerous lesion	*Precancerous conditions*
Leukoplakia	Submucous fibrosis
Erythroplakia	Actinic keratosis
Palatal lesions in reverse smokers	Lichen planus
	Discoid lupus erythromatosis

In a meeting of WHO working group in London in may 2005 during discussion of terminology it was decided to use the term 'Potentially Malignant Disorders (PMD)' as it conveys that not all disorders described under this term may transform into cancer.[1]

ETIOLOGY OF PMD

In the western world majority of people with PMD will have association with human papilloma virus (HPV) and 50% with Candida infection. In developing countries particularly India majority of these lesions are associated with tobacco or guthka chewing.

Betel is natural substance chewed for its psycho-stimulating effect. It produces mild psychoactive and cholinergic effect. It is composed of nut of areca palm (Areca Catechu), the leaf of betel pepper and lime (calcium hydroxide). Millions of people in South Asian subcontinent chew betel. Betel use is associated with oral submucous fibrosis, oral leukoplakia and oral squamous cell carcinoma.

A deficiency of individual or combined micronutrients e.g. vitamin A, B complex, C, D, E and minerals, e.g. iron, calcium, copper, zinc, magnesium have been demonstrated in cases with submucosal fibrosis. P53 is most commonly studied molecular marker in submucosal fibrosis and is positive in 58% of oral cancers and 60% of SMF. In studies it is also demonstrated that P53 is often present in precancerous lesions on patients who chew areca and smoke tobacco. Possibility of autoimmune reaction is also studied. Studies have shown that severity of oral submucous fibrosis was directly proportional to estimated elevated levels of measured immunoglobulins. Recent studies have found an association between copper and oral submucous fibrosis. More than 70 types of human papilloma viruses (HPV) have been suspected to play a role in development of cancer from oral PMD in particular HPV 16 and HPV 18, candida albicans is another organism associated with oral PMD.

Other causative agents reported for leukoplakia are tobacco, alcohol, chronic friction, etc. 70 to 90% of patients of leukoplakia hive history of tobacco consumption.

A. Oral Submucous Fibrosis (OSF) (Fig. 1)

Oral submucous fibrosis (OSF) is a chronic disorder characterized by fibrosis of the lining mucosa of the upper digestive tract involving the oral cavity, oropharynx and frequently the upper third of the esophagus. In 1952, Schwartz coined the term atrophica idiopathica mucosa oris to describe an oral fibrosing disease he discovered in 5 Indian women from Kenya. Joshi subsequently coined the termed oral submucous fibrosis (OSF) for the condition in 1953.[2]

Except in early forms of the disease the clinical presentation is characteristic due to fibrosis of lamina propria and submucosa with an increasing loss of tissue mobility. Different populations may show different sites of involvement within the mouth. The early and late forms of presentation are outlined below. *OSF is well-recognized as a potentially malignant disorder.*

OSF is particularly associated with areca nut chewing, the main component of betel quid. Factors including areca nut chewing, ingestion of chilies, genetic and immunologic processes, nutritional deficiencies, and other factors have been incorporated in causation of OSF. Patients with OSF have been found to have an increased frequency of HLA-A10, HLA-B7, and HLA-DR3.[3]

Early forms	*Late forms*
Burning sensation exacerbated spicy foods.	Fibrous bands within mucosa. Limitation of mouth opening.
Vesiculation.	Narrowing of oropharyngeal orofice.
Blanching of mucosa.	with distortion of uvula.
Leathery mucosa.	Woody changes to mucosa and tongue

The disease occurs mainly in Indians and is very rare in western countries. It affects between 0-2% and 1.2% of an urban population attending dental clinics in India.[4] Epidemiological studies suggest an overall prevalence of up to 0.4% in such places as Kerala.[4]

There is a positive association between incidence of leukoplakia and oral cancer with OSF. The frequency of malignant change has been reported from 3 to 6%.The malignant potential rate in study by Pindborg et al has been reported to be up to 7.6% in 17 years follow-up.[5] 40% of 100 patients with oral cancer had oral submucosal fibrosis in a study conducted in Mumbai.[6]

Various forms of medical treatment have been tried for OSF but with poor inconsistent.

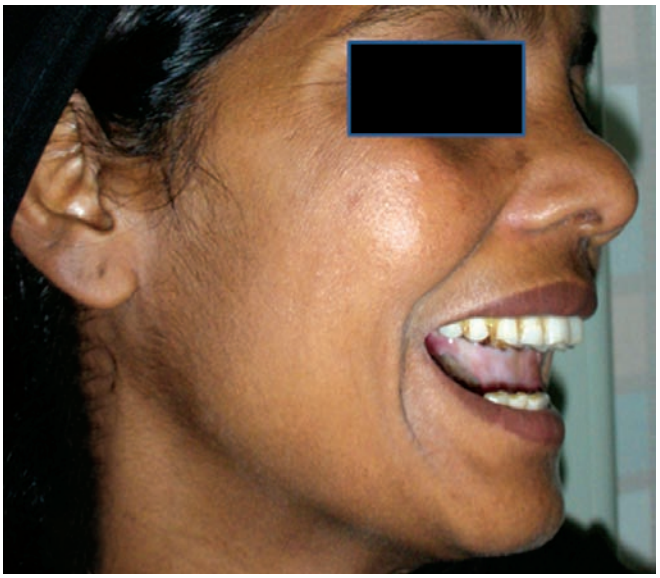


FIGURE 1: Oral submucus fibrosis with restricted opening of the mouth

Results: Local hydrocortisone injection, hyaluronidase, placental extract, and vitamin and iron supplements, have been used. Surgical treatment can be—

Simple excision of the fibrous bands: Excision can result in contracture of the tissue and exacerbation of the condition.

1. *Split-thickness skin grafting following bilateral temporalis myotomy or coronoidectomy:* Trismus associated with oral submucous fibrosis may be due to changes in the temporalis tendon secondary to oral submucous fibrosis; therefore, skin grafts may relieve symptoms.
2. *Nasolabial flaps and lingual pedicle flaps:* Surgery to create flaps is performed only in patients with oral submucous fibrosis in whom the tongue is not involved.
3. Use of a KTP-532 laser.

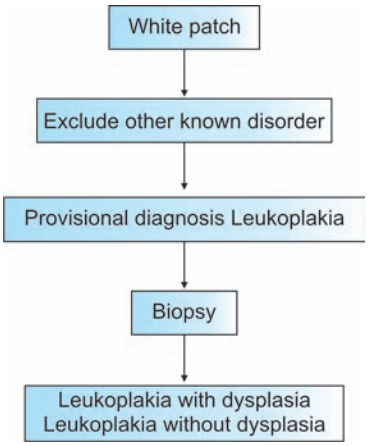
B. Leukoplakia (Fig. 2)

The term ***leukoplakia*** was first used by Schwimmer in 1877 to describe a white lesion of the tongue, which probably represented a syphilitic glossitis.

It is the *most common premalignant lesion (85%)* and the most studied PMD.

WHO working group defines leukoplakia as *'A white patch or plaque that cannot be characterized clinically or pathologically as any other disease'*. Therefore, a process of exclusion establishes the diagnosis of the disease.

Steps on the diagnosis of leukoplakia



The following lesions are commonly included in differential diagnosis for leukoplakia (See below).

Various phases of leukoplakia have been described.

Phase 1: Thin gray white translucent plaques which are soft and flat.

Phase 2: Homogenous thick smooth or fissured leukoplakias.

Phase 3: Nodular or granular surface or verruciform leukoplakia.

Phase 4: Ereythroplakia, specled leukoplakia, nonhomogenous leukoplakia.

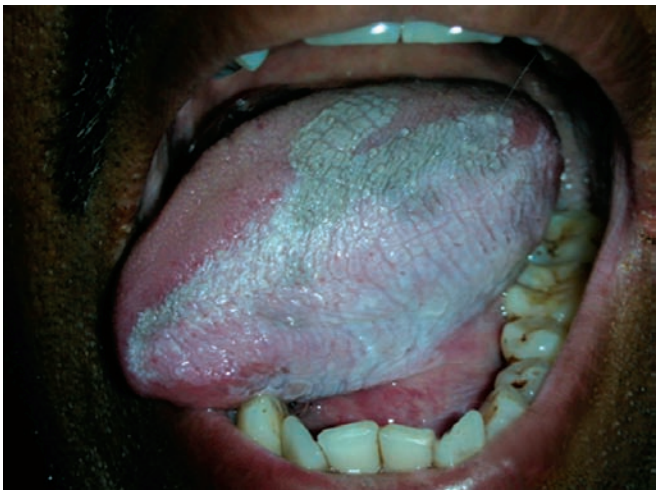


FIGURE 2: Extensive leukoplakia of the tongue

Clinically, OL falls into 1 of 2 main groups:

- **Homogenous leukoplakia:** The most common are uniformly white plaques prevalent in the buccal mucosa, which usually have low premalignant potential.
- **Nonhomogenous leukoplakia**: it may be speckled or verrucous leukoplakia, which has a higher malignant potential than homogenous leukoplakia. Speckled leukoplakia consists of white flecks or fine nodules on a erythematous base. These lesions can be regarded as a combination of or a transition between leukoplakia and erythroplasia.

Disorder	*Diagnostic features*	*Biopsy*
White sponge nevus	Noted in early life, family history, large areas involved, genital mucosa may be affected	Biopsy not indicated
Frictional keratosis	History of trauma, mostly along the occlusal plane, anetiological cause apparent, mostly reversible on removing the cause	Biopsy if persistent after elimination of cause particularly in a tobacco user
Frictional keratosis	Habitual cheek – lip biting known, irregular whitish flakes with jagged out line	Biopsy not indicated
Chemical injury	Known history, site of lesion corresponds to chemical injury, painful, resolves rapidly	Not indicated
Acute pseudomembrano-uscandidosis	The membrane can be scraped off leaving anerythematous/ raw surface	Swab for culture
Leukoderma	Bilateral on buccal mucosa, could be made to disappearon stretching (retracting), racial	Not indicated
Lichen planus (plaque type)	Other forms of lichen planus (reticular) found inassociation	Biopsy consistent with lichen planus
Lichenoid reaction	Drug history, e.g. close to an amalgam restoration	Biopsy consistent with lichen planus or lichenoid reaction
Discoid lupus erythematosus	Circumscribed lesion with central erythema, white linesradiating	Biopsy consistent with DLE supported by immunofloresence and other investigations
Hairy leukoplakia	Bilateral tongue keratosis	Specific histopathology with koilocytosis; EBV demonstrable on ISH
Leukokeratosis nicotina palate	Smoking history, greyish white palate	Not indicated

One uncommon variant, known as *proliferative verrucous leukoplakia (PVL),* is characterized by widespread, multifocal sites of involvement, often in patients without known risk factors.

The condition begins with conventional flat white patches that, over time, tend to become much thicker and papillary in nature. This papillary proliferation may progress to the point where the lesion can be categorized microscopically as a verrucous carcinoma. However, in spite of treatment, the lesions have a high recurrence rate and often eventually transform into more aggressive squamous cell carcinoma.[8,9]

There have been wide variations in incidence and prevalence of leukoplakia. In India a striking variation has been observed with 0.2% in Bihar and 4.9% in Andhra Pradesh.[10]

Gujrat has shown a prevalence rate of 11.7%.[11] In developed nations most surveys are based on hospital populations. In a community based survey in Sweden the prevalence of white lesions was 24.8% with idiopathic leukoplakia being 0.7%, tobacco associated leukoplakia 2.9% and snuff dippers lesion being 7.2%.[12] *Petti summarized the world prevalence of leukoplakia in systemic review based on 23 studies from 17 countries published between 1986 and 2002. Using statistical techniques he calculated a global prevalence of 2.6%.*[13]

In developed nations majority of leukoplakia occurred in 4th to 7th decade of life while in developing countries they occurred 5 to 10 years earlier. Majority of leukoplakia are seen in men (80 to 98%). The systemic review by Petti confirmed that oral PMD affects males atleast 3 times as often as females.[13]

Leukoplakias are known to occur at almost all places in oral cavity. However, they are most frequent in buccal mucosa and mandibular mucosa. 2/3 rd of the oral leukoplakia occur at vermillon, buccal mucosa and gingival surface. In Gujarat where smoking is common 43.9% occurred on buccal mucosa while 35.4% at commissure. In kerala where chewing is common 64.8% were on buccal mucosa, 24.3% at commissures and 6% on tongue. In Andhra Pradesh where smoking is common 71.3% were on palate, 8.1% on commissure, 16.9% on buccal mucosa and 2.7 on tongue.[10] In Swedish study buccal mucosa or commissure was involved in 90% of cases. In Hungarian study tongue was involved in 36.5%, buccal mucosa in 27.9%, alveolar ridge in 13.6% and commissure in 12.5%.[12]

The lesions in floor of mouth, lateral tongue and lower lip are more likely to show dysplatic or malignant changes. Histopathological nature of leukoplakia by site in 3,360 biopsy specimens.[14]

Site	*%of leukoplakia at this site*	*%of leukoplakia showing dysplasia*
Lips	10.3	24
Upper alveolus	10.7	14.8
Lower alveolus	25.2	14.6
Palate	10.7	18.8
Buccal mucosa	21/9	16.5
Tongue	6.8	24.2
Floor of mouth	8.6	42.9
Retromolar trigone	5.9	11.7
Total	100	19.9

The prognosis of leukoplakia varies. In a study conducted in Mumbai 42.5% untreated leukoplakias diseappeared in 5 years, 45.3% in 10 years in tobacco chewing group.[15] In Gujarat 11% of leukoplakias re-examined after 2 years had increased in size 31.6% had decreased in size or disappeared and 57.3% had remained unchanged.[16] In study from developed world only 20.1% had disappeared, 17.8% had reduced in size and 3.3% had increased at 10 years follow-up.[17]

The possibility of malignant transformation of leukoplakias depend on multiple factors.

The frequency of dysplastic or malignant alterations in oral leukoplakia has ranged from 15.6 to 39.2 percent in several studies.

Source	*Country*	*Year*	*n*	*% of patients with malignant transfor-mation*
Einhorn and Wersäl[18]	Sweden	1967	782	4.0
Silverman[19]	USA	1968	117	6.0
Pindborg et al[20]	Denmark	1968	248	4.4
Kramer[21]	England	1969	187	4.8
Roed-Petersen[22]	Denmark	1971	331	3.6
Bánóczy[23]	Hungary	1977	670	6.0
Silverman et al[24]	USA	1984	247	17.5
Lind[25]	Norway	1987	157	8.9
Bouquot and Gorlin[26]	USA	1988	463	10.3

In Indian studies the rate of malignant transformation ranges from 0.13 to 2.2% per year. In Swedish study 0.2% developed oral cancer in 2 years, 0.4% in 5 years in tobacco users while in nontobacco users the transformation rate was 1.1% and 3.1% at 2 and 5 years respectively.[27] In Danish study a maximum transformation rate of 4.4% per annum was calculated.[17] *In systemic review Petti has calculated a global transformation rate for oral leukoplakia of 1.36% per year.*[13]

When compared with "conventional leukoplakia," proliferative verrucous leukoplakia is a particularly high-risk condition. In a follow-up study of 54 cases of proliferative verrucous leukoplakia, Silverman and Gorsky found that 70.3 percent of the patients subsequently developed squamous cell carcinoma.[8]

Although leukoplakia is more common in men than women, several studies have shown that women with leukoplakia have a higher risk of developing oral carcinoma. Another disturbing finding is that leukoplakias in nonsmokers are more likely to undergo malignant transformation than leukoplakias in patients who do smoke.[28]

C. Erythroplakia

WHO23 WHO Collaborating center for oral precancerous lesions, definition of leukoplakia and related lesions: An aid to studies on oral precancer, *Oral Surg* 46 (1978), pp. 518–539. defined erythroplakia as "any lesion of the oral mucosa that presents as bright red velvety plaques which cannot be characterized clinically or pathologically as any other recognizable condition".

Clinical Variations

1. Homogeneous erythroplakia.
2. Erythroplakia interspersed with patches of leukoplakia.
3. Granular or speckled erythroplakia (embracing the lesion described as speckled leukoplakia).

Differential diagnosis of erythroplakia

Nature of condition	*Diagnostic category*
Inflammatory/immune disorders	Desquamative gingivitis Erythematous lichen planus Discoid lupus erythematosus Pemphigoids Hypersenstivity reactions Reiter's disease.
Infections	Erythematous candidiasis Histoplasmosis.
Hamartomas/neoplasms	Hemangioma Kaposi's sarcoma

Although erythroplakia is not nearly as common as leukoplakia, it is much more prone to show dysplasia or carcinoma. In a sister study to their large series of leukoplakia cases, Shafer and Waldron also analyzed their biopsy experience with 65 cases of erythroplakia. All erythroplakia cases showed some degree of epithelial dysplasia; 51 percent showed invasive squamous cell carcinoma, 40 percent were carcinoma in situ or severe epithelial dysplasia, and the remaining 9 percent demonstrated mild-to-moderate dysplasia.[29]

Therefore, true clinical erythroplakia is a much more worrisome lesion than leukoplakia.

D. Nicotine Stomatitis

Nicotine stomatitis is a thickened, hyperkeratotic alteration of the palatal mucosa that is most frequently related to pipe smoking.

The palatal mucosa becomes thickened and hyperkeratotic, sometimes developing a fissured surface. The surface often develops popular elevations with red centers, which represent the inflamed openings of the minor salivary gland ducts.

The term nicotine stomatitis is actually a misnomer because it isn't the nicotine that causes the changes; the changes are caused by the intense heat generated from the smoking. Nicotine stomatitis is seen more often in pipe smokers because of the great amount of heat that is generated from the pipestem. Although nicotine stomatitis is a tobacco related it is *not considered to be premalignant* and it is readily reversible with discontinuation of the tobacco habit.

E. Palatal Lesions in Reverse Smokers

In some Southeast Asian and South American countries, individuals practice a habit known as reverse smoking in which the lit end of the cigarette or cigar is placed in the mouth. This habit creates a more severe heat related alteration of the palatal mucosa known as *reverse smoker's palate*, which has been associated with a significant risk of malignant transformation.[30,31]

F. Actinic Keratosis

Actinic keratosis is considered to represent a potentially malignant condition which arises in many sites including lips. It is commonly associated with exposure to sun.
In Actinic keratosis average rate of progression to invasive cancer ranges from 0.025 to 16% per year.[32]

A provisional diagnosis may be made on clinical grounds, but definitive diagnosis requires biopsy.

G. Tobbacco Pouch Keratosis

Another specific tobacco-related oral mucosal alteration occurs in association with smokeless tobacco use, either from snuff or chewing tobacco. Such lesions typically occur

in the buccal or labial vestibule where the tobacco is held, but they can also extend onto the adjacent gingiva and buccal mucosa.

Early lesions may show slight wrinkling that disappears when the tissues are stretched.

Other lesions may appear as hyperkeratotic, granular patches. Advanced lesions exhibit greatly thickened zones of grayish white mucosa with well-developed folds and fissures.

Overall, it is estimated that 15 percent of chewing tobacco users and 60 percent of snuff users will develop clinical lesions.

Microscopically, smokeless tobacco keratoses show hyperkeratosis and acanthosis of the mucosal epithelium. True epithelial dysplasia is uncommon; when dysplasia is found, it is usually mild in degree.[33] However, significant dysplasia or squamous cell carcinoma occasionally may be discovered. Most tobacco pouch keratoses are readily reversible within two to six weeks after cessation of the tobacco habit.

H. Hereditary Disorders with Increased Risk

Two conditions that may have an increased risk of malignancy in the mouth are dyskeratosis congenital (DC) and Epidermolysis Bullosa. They are rare hereditary conditions. Most cases of DC are X-linked and affect males. Patients with DC often develop white plaques on the dorsal tongue which may be confused with leukoplakia, but the absence of habits and their young age may point to the hereditary nature of this disorder. Malignant change within the areas of white patches is reported.

MANAGEMENT

Conservative surgical excision remains the treatment of choice for leukoplakia. However excision of leukoplakia has not shown to decrease the rate of malignant transformation.

There was no obvious difference in the malignant transformation rate between patients who received any surgical treatments (5.5%, 5/91) and those who did not (7.8%, 4/51).[34,35] Also surgical treatment of leukoplakia may not reduce malignant transformation rate.[38,39]

A study comparing different laser techniques, CO_2 laser, NdYAG laser, and KTP, demonstrated differences in recurrence rates (34.2%, 28.9%, and 17.0%, respectively); however, only six patients were included in the KTP group whereas the CO_2 and NdYAG groups comprised 38 and 36 patients, respectively.[34]

Cryosurgery does not seem to be of particular benefit, recurrence rates of 20-71.4% being reported, along with malignant transformation rates of 7-25%.[36]

In the update of a Cochrane review (27), nine RCTs testing medical therapy for management of leukoplakia were found following an extensive literature search. The chemopreventive agents employed included local and systemic vitamin A and retinoids, systemic beta carotene, lycopene a carotenoid, ketorolac (as mouthwash), local bleomycin , and a mixture of tea used both topically and systemically. Only two studies reported useful data on malignant transformation (31, 35) and unfortunately none of the three treatments tested (topical bleomycin, systemic vitamin A, and systemic beta carotene) were of benefit when compared with placebo.

Data on complete resolution of the oral lesions were available from all the nine studies included in the review. Two studies showed a small but significant benefit for the systemic treatment with beta carotene or lycopene when compared with the controls. Vitamin A or retinoids were also of some benefit.

Unfortunately, the recurrence rates among those who responded to treatment were high (20-64%) when reported (20-64%), as well as adverse effects (up to 100%). The current conclusion of the systematic review is that none of the treatments investigated are effective in preventing malignant transformation of oral leukoplakia.[37]

RECENT ADVANCES IN DETECTION OF ORAL PRECANCEROUS LESIONS

Vital tissue staining with Tolonium chloride (TB). It is a metachromatic vital dye that may bind preferentially to tissues undergoing rapid cell division (such as inflammatory, regenerative and neoplastic tissue), to sites of DNA change associated with oral PMD or both. The binding results in the staining of abnormal tissue in contrast to adjacent normal mucosa. A meta-analysis summarized 12 studies conducted between 1964 and 1984 and reported an overall sensitivity of 93.5 percent and specificity of 73.3 percent.[40]

Visualization adjuncts. They function under the assumption that mucosal tissues undergoing abnormal metabolic or structural changes have different absorbance and reflectance profiles when exposed to various forms of light or energy.

Described as a chemiluminescent light detection system, **ViziLite** was developed from predicate devices to detect cervical neoplasia. After receiving an application of acetic acid, sites of epithelial proliferation, having cells with altered nuclear structure, are purported to preferentially reflect the low energy blue-white light emitted by a device generating an "acetowhite" change. The ViziLite system is a part of the ViziLite Plus with Tolonium chloride system.

The Microlux DL system is a multiuse system developed from a blue-white light-emitting diode (LED) and a diffused fiberoptic light guide that generates a low-energy blue light.

The Orascoptic DK system is sold as a three-in-one, battery-operated, hand-held LED instrument with an oral lesion screening instrument attachment that is used in concert with a mild acetic acid rinse promoted to improve visualization of oral lesions.

The VELscope system is a multiuse device with a hand-held scope through which the clinician can scan the mucosa visually for changes in tissue fluorescence. The proposed mechanism of tissue fluorescence is that mucosal tissues have a reflective and absorptive pattern based on naturally occurring fluorophores in the tissue.

Cytopathology. The oral CDx Brush test system uses a specialized brush that collects transepithelial cellular samples composed of free cells and clusters. These samples are fixed onto a glass slide and sent to a laboratory where they are stained (via a modified Papanicolaou test), scanned and analyzed microscopically by means of a computer-based imaging system that can rank cells on the basis of degree of abnormal morphology. A cytopathologist interprets the computerized results. Results are reported as "negative or benign," "positive" or "atypical.

Oral CDx has been shown to be very accurate All Oral CDx "atypical" and "positive" results should be referred for scalpel biopsy and histology to completely characterize the lesion.[41]

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