Third Edition

Quality Resource Guide

Techniques for Early Cancer Detection

Author Acknowledgements

MICHAELL A. HUBER, DDS

Department of Comprehensive Dentistry
UT Health San Antonio
School of Dentistry
San Antonio, Texas

Dr. Huber has no relevant relationships to disclose.

Educational Objectives

Following this unit of instruction, the learner should be able to:

1. Understand the causes of delayed diagnosis of oral cavity and pharynx cancer.
2. Understand the current standard for identifying premalignant and malignant lesions.
3. Understand the essential principles for cytology-based, light-based, vital stain-based and biomarker-based diagnostic adjuncts.
4. Apply objective criteria to assess the clinical utility and value of newly marketed adjunctive aids in one's practice.
5. Develop a disciplined protocol to routinely accomplish the conventional visual and tactile examination.

MetLife designates this activity for **1.0 continuing education credits** for the review of this Quality Resource Guide and successful completion of the post test.

The following commentary highlights fundamental and commonly accepted practices on the subject matter. The information is intended as a general overview and is for educational purposes only. This information does not constitute legal advice, which can only be provided by an attorney.

Originally published June 2018. Updated and revised May 2021 and March 2024. Expiration date: March 2027.

The content of this Guide is subject to change as new scientific information becomes available.

ADA C·E·R·P® | Continuing Education Recognition Program

Accepted Program Provider FAGD/MAGD Credit **05/01/21 - 06/31/25.**

MetLife is an ADA CERP Recognized Provider. ADA CERP is a service of the American Dental Association to assist dental professionals in identifying quality providers of continuing dental education. ADA CERP does not approve or endorse individual courses or instructors, nor does it imply acceptance of credit hours by boards of dentistry. Concerns or complaints about a CE provider may be directed to the provider or to ADA CERP at https://ccepr.ada.org/en/ada-cerp-recognition.

Address comments or questions to:
DentalQuality@metlife.com - or -
MetLife Dental Continuing Education
501 US Hwy 22
Bridgewater, NJ 08807

Cancellation/Refund Policy:
Any participant who is not 100% satisfied with this course can request a full refund by contacting us.

MetLife

Navigating life together

Introduction

For the year 2024, an estimated 58,450 individuals (41,510 men and 16,940 women) will be diagnosed with oral cavity and pharynx cancer in the United States.[1] The prevalence of oral cavity cancer in those over the age of 45 years is estimated to be 0.25%.[2] In 2020, there were approximately 424,284 individuals living with oral cavity and pharynx cancer in the United States and the overall 5-year survival rate is 68.5%.[3] The stage at which it is diagnosed remains the most important prognostic factor in predicting survival.[4,5] While the dental practitioner is often in the best position to first identify these cancers,[6] only 29% of patients diagnosed with oral cavity and pharynx cancer present with localized early-stage disease.[1] Clearly, the dental profession's success in identifying oral cavity and pharynx cancers at an early stage remains a dilemma. The purpose of this Quality Resource Guide is to discuss the causes of delayed diagnosis of oral cavity and pharynx cancer, review the current standard for identifying oral cavity and pharynx cancer, and provide an assessment on currently available adjunctive devices marketed to improve the dental practitioner's ability to screen for and identify oral potentially malignant disorders (OOPMDs).

Delays in Detection of Oral Cavity and Pharynx Cancer

Patient delay: An estimated 35% of the public does not seek dental care on an annual basis[7] and patient delay is the most important factor underlying the deferred detection of oral cavity and pharynx cancer.[8,9] Patient delay is defined as the interval between the patient's first awareness of a concern and his or her seeking assessment by a healthcare provider. Estimates for patient delay range from 3.5 to 6.8 months. Psychosocial factors, health-related behaviors, socioeconomic status, education level, and health care access or availability have been proposed as important factors contributing to patient delay.[9,10]

Professional delay: The most relevant parameter of professional delay is the time from the patient's first encounter with the healthcare system to the start of definitive treatment. Factors to consider here include practitioner experience and thoroughness, and access to care issues.[11-12] A 2007 review found only 41% of patients with oral cavity cancer began definitive therapy within 30 days of their initial presentation for assessment.[13] It is accepted that prolonged professional delay compromises successful therapy.[8,9,13]

Current Standard for Identifying Oral Cavity and Pharynx Cancer

Visually inspecting the patient for oral cavity and pharyngeal cancer represents an integral component of the conventional visual and tactile examination (CVTE)* that should be afforded all patients.[14] The CVTE is accomplished after a comprehensive review of the medical, social, and dental history.[15] The CVTE, which entails the use of appropriate lighting to accomplish a thorough visual and tactile assessment of accessible extra-oral and intra-oral tissues, remains the foundation upon which lesions are discovered.[4] Findings deemed suspicious for an OPMD should be immediately biopsied or referred to a specialist. Findings deemed nonsuspicious should be monitored periodically for change and/or resolution.

**A detailed review of the CVTE may be found in the Quality Resource Guide, "Performance of an Oral and Head and Neck Examination, 7th edition."*

Adjunctive Aids

Numerous adjunctive aids are commercially available for dental practitioner use, with the promoted goal of improving the provider's ability to identify and/or assess OPMDs. The market for adjunctive aids is dynamic, with products being introduced and/or discontinued over time. For convenience, these adjuncts (see **Tables 1-4**) may be categorized as:[15,16]

- cytology-based
- vital stain-based
- light-based
- biomarker-based

Cytology-based adjuncts are laboratory processes regulated by the Centers for Medicare & Medicaid Services (CMS) through the Clinical Laboratory Improvement Amendments (CLIA) program.[17] Vital stain-based, light-based, and biomarker-based adjuncts are all considered to be medical devices and are regulated by the Food and Drug Administration.[18] It should be noted that updated FDA regulatory guidance for biomarker-based adjuncts is pending final approval.[19]

Cytology-based Adjunct

OralCDx® is specifically promoted to allow the clinician to "painlessly test any white or red spot in the mouth to rule out the possibility that precancerous cells are present"[20] The specimen is shipped to an off-site laboratory for analysis. The appropriate CDT code to use is D7288, "brush biopsy – transepithelial sample collection."[14] Tested lesions that receive a "positive" or "atypical" result need to undergo a scalpel biopsy to determine the definitive diagnosis.

Advocates of cytology believe it can be reliably used to assess innocuous lesions for benignity, precancer and cancer, especially for patients hesitant to undergo biopsy.[31,32] Cytology may also be a useful method for assessing a patient with multiple lesions throughout the mouth, where the attainment of multiple biopsies may be impractical.[33] Detractors contend cytology represents an unnecessary and often burdensome intermediate step since all "positive" or "atypical" results must be biopsied to determine the actual diagnosis.[34,35] Furthermore, while promoted as being reassuring, cytology is not diagnostic for a persistent lesion.[36,37]

Vital Stain-based Adjuncts

Toluidine blue (TB) is a metachromatic dye of the thiazine group that has an affinity to bind with DNA. It has been promoted as a chairside lesion assessment utility for decades to assess suspicious mucosal lesions.[38,39] After rinsing with a 1% acetic acid solution, topical application of TB highlights rapidly dividing tissues such as inflammatory, regenerative, and neoplastic epithelial tissues. It also highlights exposed connective tissue.[36,38]

TB has been advocated as a utility to monitor OPMDs for progression, to assess OPMD margins, and to monitor post-cancer treatment patients.[40,41] However, false positive results are commonly encountered, especially in areas of inflammation.[33,41]

TB is not cleared by the FDA as a stand-alone adjunct. It is cleared for marketing as a follow-on case assessment marking agent for the light-based adjunct ViziLite® TBlue Annual Oral Cancer Screening System.[42] The premise is the TB allows for better visual lesion delineation of an area initially identified by the ViziLite®.[42] It may also help the provider decide which area within a lesion should be biopsied. The appropriate CDT code to apply when using TB is D0431, "adjunctive pre-diagnostic test that aids in the detection of mucosal abnormalities including premalignant and malignant lesions, not to include cytology or biopsy procedures."[14]

Light-based Adjuncts

Light-based adjuncts can be categorized into two basic groups (tissue reflectance and autofluorescence) based on the manner in which a specific spectrum of light is used to assess the reflective properties of the tissue. All are cleared for marketing by the FDA as chairside illumination aids to assist the practitioner in identifying new or potentially overlooked OPMDs.[2,43] Some are also marketed to assist the surgeon in defining the appropriate surgical margins for excision.[38,44] The appropriate CDT code to apply when using a light-based adjunct is D0431, "adjunctive pre-diagnostic test that aids in the detection of mucosal abnormalities including premalignant and malignant lesions, not to include cytology or biopsy procedures."[14]

The tissue reflectance adjunct (ViziLite® TBlue Annual Oral Cancer Screening System) utilizes a blue-white light (wavelength of 430 and 580 nm) to analyze the tissues.[45] The light is generated through a reaction between acetylsalicylic acid and hydrogen peroxide (chemiluminescence). The protocol entails the use of a 60 second pre-rinse with a 1% acetic acid solution to remove the surface glycoprotein layer and cause cellular dehydration, to improve the exposure of cellular elements to the blue-white light.[33,45] The premise is that healthy cells absorb the blue-white light while dysplastic cells reflect the blue-white back to the examiner as "aceto-white" brightness.[36,46]

Table 1 - Available Cytology-based Adjuncts[20]

Adjunct	*Contact*
OralCDx®	CDx Diagnostics, Suffren, NY

Table 2 - Available Vital Stain-based Adjunct[21]

Adjunct	*Contact*
Toluidine chloride stain (component of ViziLite® TBlue Annual Oral Cancer Screening System)	Den-Mat Holdings, LLC Lompoc, CA

Table 3 - Available Light-based Adjuncts[21-27]

Adjunct	*Contact*
ViziLite® TBlue Annual Oral Cancer Screening System*	Den-Mat Holdings, LLC Lompoc, CA
VELscope®	LED Dental, White Rock, British Columbia, Canada
Bio/Screen®	AdDent, Inc., Danbury, CT
DOE SE Kit	DentLight Inc., Plano, TX
Identafi®	DentalEZ, Malvern, PA
OralID™	Forward Science, Houston, TX
ViziLite PRO® Oral Lesion Screening System	Den-Mat Holdings, LLC Lompoc, CA
Goccles	Pierrel S.P.A., Capua, Italy

Table 4 - Available Biomarker-based Adjuncts[28-30]

Product	*Company*	*Biomarkers Assessed*
OraRisk® HPV Complete Genotype	OralDNALabs Eden Prairie, MN	51 HPV strains, to include low, high and unknown risk strains
OralCDx®	CDx Diagnostics Suffren, NY	Immunohistochemistry testing for CDX2, MUC2, AMACR, P16, P53, KI67, HSV, *H.pylori*
CancerDetect® Oral & Throat	Viome Life Sciences, Inc. Bellevue, WA	Metatranscriptome (RNA), microbiome

Autofluorescence adjuncts (VELscope®, BioScreen®, DOE SE Kit, OralID™, ViziLite PRO® Oral Lesion Screening System, Goccles) use light spectra in the 390 – 460 nm range to assess the autofluorescent character of the mucosal tissues.[45] A narrow band filter (either in the device viewfinder or via eyewear) is used to highlight the autofluorescent character of the examined tissue. The working premise is that dysplastic or carcinogenic tissues are associated with an altered autofluorescence signature, due to increased collagen destruction, specific nuclear/

cytoplasmic ratios, and angiogenesis. Healthy tissue appears pale green during autofluorescence, while suspicious tissues appear dark (loss of fluorescence).[16,45]

Biomarker-based Adjuncts

Research to leverage biomarker profiling to develop a non-invasive saliva sourced liquid biopsy-based adjunct to assess OPMDs has accelerated over the past decade.[47-49] The number of biomarkers purportedly associated with OPMDs and oral cancer continues to evolve and grow (*e.g.,* DNAs, RNAs, proteins, metabolites and microbiota) and numerous biomarker-based panels have been proposed to interrogate OPMDs for dysplasia and carcinoma.[50-58] The development of a reliable, predictive salivary test to assess OPMDs for malignancy would be a "game changer."[2] However, most of these proposals have been based on small proof-of-concept studies comparing test performance against a cancer cohort and a healthy noncancer control cohort. Nonetheless, three biomarker-based adjunctive tests (**Table 4**) have been introduced to screen for the presence and/or risk of oral cavity and pharynx cancer. These adjuncts require shipment to an off-site laboratory for analysis.

The OraRisk® HPV Complete Genotype is a PCR–based saliva test that screens for 51 low and high risk strains of HPV in saliva.[28] A detailed review of Human Papilloma Virus (HPV) may be found in the Quality Resource Guide, *"HPV and Oral Cancer, 3rd edition."*

OralCDx® cytology submissions, when indicated, undergo immunohistochemistry screening for the biomarkers CDX2, MUC2, AMACR, P16, P53, KI67, HSV, and *H. pylori.*[29] Altered expressions of AMACR, p16, p53, and Ki67 have been noted oral cavity and pharynx cancer.[59-62]

The CancerDetect® Oral & Throat screening adjunct from Viome Life Sciences, Inc., uses high-resolution metatranscriptomic analysis to identify patients at risk for OPMD and cancer. The company claims a sensitivity and specificity of ≥90% and ≥95%, respectively.[30,62] The test is not FDA-approved or cleared.

Performance of Adjunctive Devices

An ideal diagnostic adjunct to assess OPMDs should:

1) be simple, safe and acceptable to the public
2) detect early stage disease
3) preferentially detect lesions likely to progress
4) detect lesions which are manageable
5) have a high positive predictive value and a low false negative value.[33]

Cytology, Vital Stain and Light-based Adjuncts

The performance of available cytology, vital stain, and light-based adjuncts was assessed in a recently published vigorous review of the available quality evidence.[2] The investigators were able to determine the estimated sensitivity and specificity values for cytology, vital stain, and light-based diagnostic adjuncts when used to assess seemingly innocuous lesions and OPMDs (**Table 5**).

In applying their values, the authors calculated that for every 100,000 patients with an OPMD, there would 250 true cancers. Thus, the use of:

- ***cytology*** to assess the OPMDs would miss 20 cancers (false negative) and misidentify 5,985 as cancers (false positive).
- ***vital staining*** would yield 33 false negatives and 28,927 false positives.
- ***tissue reflectance*** would yield 70 false negatives and 68,827 false positives.
- ***autofluorescence*** would yield 25 false negatives and 27,930 false positives.

A more recent Cochrane Library review of 63 diagnostic adjunct studies (79 data sets) determined the sensitivity and specificity for oral cytology was 0.90 and 0.94; for vital staining was 0.86 and 0.68; and for light-based was 0.87 and 0.50 to evaluate an OPMD.[64] The authors concluded none of the adjunctive tests could be recommended as a replacement for surgical biopsy and histological assessment.

The clinical implications of test accuracy are best appreciated by understanding the consequences of the results for patients. A test that yields high proportions of true positive and true negative results is the ideal. Unfortunately, most screening tests are less than completely accurate, making it important to appreciate the consequences for the patient of false positive and false negative results. A false positive occurs when the screening test labels the site as cancerous when in fact it is not. This false result subjects the patient to needless worry and possibly an unnecessary biopsy. Conversely, a false negative test result gives the patient a false sense of security that there is no cancer when there is. Given the modest to poor performance of the currently available adjuncts, the practitioner and patient need to be fully aware of these negative consequences when deciding whether to use one of these screening tests.

Table 5 - Estimated sensitivity and specificity values for adjunctive devices[2]

Adjunct	*Sensitivity/Specificity for Innocuous Lesions*	*Sensitivity/Specificity for Suspicious Lesions*
Cytology	0.96 / 0.90	0.92 / 0.94
Vital Stain	ND	0.87 / 0.71
Tissue Reflectance	0.00 / 0.76	0.72 / 0.31
Autofluorescence	0.50 / 0.39	0.90 / 0.72

ND: Not determined due to insufficient data

Biomarker-based Adjuncts

High-risk HPV prevalence in the United States is estimated at 4.0% among adults aged 18 to 69 (men, 6.8%; women, 1.2%).[65] Over 90 per cent of these infections will clear within 2 years.[66] The sensitivity and specificity of salivary HPV testing is 72 and 92, leading to a high number of false negatives and false positives when used as a screening utility in clinical practice.[67] Finally, as there are no available interventions to treat HPV infection, screening could incur significant anxiety for those who screen positive for a high-risk HPV.[68] Routine salivary screening for oral HPV is not recommended.

At present, there is insufficient evidence to adjudicate the clinical performance of the OralCDx® immunohistochemistry adjunctive test and the biomarker-based CancerDetect® Oral & Throat screening adjunct. Rigorous large-scale trials to validate their test accuracy in assessing a diverse patient cohort are necessary to endorse their use in clinical practice.

Summary

Disciplined performance of the CVTE on a regular basis remains the standard to identify OPMDs. Any OPMD or equivocal lesion should be immediately biopsied or referred to a specialist. Lesions deemed innocuous should undergo periodic monitoring for change and/or resolution. Evidence supporting the use of available adjunctive devices in clinical practice to discover or assess OPMDs is low and their use is associated with a high burden of false positive results. At present their utility is very limited and clinicians should remain skeptical about insufficiently validated marketing claims.

References

1. American Cancer Society. Cancer Facts & Figures 2024. Atlanta: American Cancer Society; 2024.
2. Lingen MW, Tampi MP, Urquhart O, et al. Adjuncts for the evaluation of potentially malignant disorders in the oral cavity: Diagnostic test accuracy systematic review and meta-analysis-a report of the American Dental Association. J Am Dent Assoc 2017;148:797-813.e52.
3. National Cancer Institute. SEER Cancer Stat Facts: Oral Cavity and Pharynx Cancer. Available at: https://seer.cancer.gov/statfacts/html/oralcav.html . Accessed February 22, 2024.
4. Li L, Morse DE, Katz RV. What constitutes a proper routine oral cancer examination for patients at low risk? Findings from a Delphi survey. Oral Surg Oral Med Oral Pathol Oral Radiol 2013;116:e379-86.
5. Seoane J, Alvarez-Novoa P, Gomez I, Takkouche B, et al. Early oral cancer diagnosis: The Aarhus statement perspective. A systematic review and meta-analysis. Head Neck 2016;38 Suppl 1:E2182-9.
6. Holmes JD, Dierks EJ, Homer LD, Potter BE. Is detection of oral and oropharyngeal squamous cancer by a dental health care provider associated with a lower stage at diagnosis? J Oral Maxillofac Surg 2003;61:285-91.
7. Gallop. One-Third of Americans Haven't Visited Dentist in Past Year. Available at: http://www.gallup.com/poll/168716/one-third-americans-haven-visited-dentist-past-year.aspx. Accessed February 22, 2024.
8. Purkayastha M, McMahon AD, Gibson J, Conway DI. Is detecting oral cancer in general dental practices a realistic expectation? A population-based study using population linked data in Scotland. Br Dent J 2018;225:241-246.
9. Gigliotti J, Madathil S, Makhoul N. Delays in oral cavity cancer. Int J Oral Maxillofac Surg 2019;48:1131-1137.
10. Scott SE, Grunfeld EA, McGurk M. Patient's delay in oral cancer: A systematic review. Community Dent Oral Epidemiol 2006;34:337-43.
11. Mignogna MD, Fedele S, Lo Russo L, Ruoppo E, Lo Muzio L. Oral and pharyngeal cancer: lack of prevention and early detection by health care providers. Eur J Cancer Prev 2001;10:381-3.
12. Silverman S Jr, Kerr AR, Epstein JB. Oral and pharyngeal cancer control and early detection. J Cancer Educ 2010;25:279-81.
13. Brouha XD, Tromp DM, Koole R, et al. Professional delay in head and neck cancer patients: analysis of the diagnostic pathway. Oral Oncol 2007;43:551-6.
14. American Dental Association. CDT 2024 dental procedure codes. Chicago, 2024.
15. Lingen MW, Abt E, Agrawal N, et al. Evidence-based clinical practice guideline for the evaluation of potentially malignant disorders in the oral cavity: A report of the American Dental Association. J Am Dent Assoc 2017;148:712-727.e10
16. Huber MA. Adjunctive Diagnostic Techniques for Oral and Oropharyngeal Cancer Discovery. Dent Clin North Am 2018;62:59-75.
17. Medical Learning Network Fact Sheet. Available at: https://www.hhs.gov/guidance/sites/default/files/hhs-guidance-documents/cliabrochure.pdf. Accessed February 22, 2024.
18. US Food and Drug Administration. Overview of Device Regulation. Available at: https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/overview-device-regulation. Accessed February 22, 2024.
19. Federal Register. Medical Devices; Laboratory Developed Tests. Vol. 88, No. 190/October 3, 2023/Proposed Rules. Available at: https://www.govinfo.gov/content/pkg/FR-2023-10-03/pdf/2023-21662.pdf Accessed February 22, 2024.
20. OralCDx. Available at: https://www.cdxdiagnostics.com/oralcdx. Accessed February 22, 2024.
21. ViziLite TBlue Annual Oral Cancer Screening System. Available at: https://www.denmat.com/vizilite-tblue-annual-oral-cancer-screening-system.html. Accessed February 22, 2024.
22. VELscope. Available at: https://velscope.com/. Accessed February 22, 2024.
23. Bio/Screen. Available at: https://addent.com/bio-screen-oral-cancer-screening/. Accessed February 22, 2024.
24. DOE SE Kit. Available at: https://www.dentlight.com/product/doe-se/. Accessed February 22, 2024.
25. OralID. Available at: https://forwardscience.com/oralid. Accessed February 22, 2024.
26. Vizilite PRO Oral Lesion Screening System. Available at: https://www.denmat.com/vizilite-pro-oral-lesion-screening-system.html. Accessed February 22, 2024.
27. Goccles. Available at: https://www.pierrelgroup.com/en/products/prevention/. Accessed February 22, 2024.
28. OraRisk HPV. Available at: https://www.oraldna.com/test/ohpv-complete/. Accessed February 22, 2024.
29. Cdx Laboratory Services. Available at: https://www.cdxdiagnostics.com/laboratory-services-list. Accessed February 22, 2024.
30. CancerDetect Oral & Throat. Available at: https://cancerdetect.viome.com/. Accessed February 22, 2024.

References (continued)

31. Eisen D, Frist S. The relevance of the high positive predictive value of the oral brush biopsy. Oral Oncol 2005;41:753-5.
32. Mehrotra R, Mishra S, Singh M, Singh M. The efficacy of oral brush biopsy with computer-assisted analysis in identifying precancerous and cancerous lesions. Head Neck Oncol 2011;24;3:39.
33. Lingen MW, Kalmar JR, Karrison T, Speight PM. Critical evaluation of diagnostic aids for the detection of oral cancer. Oral Oncol 2008;44:10-22.
34. Bhoopathi V, Kabani S, Mascarenhas AK. Low positive predictive value of the oral brush biopsy in detecting dysplastic oral lesions. Cancer 2009;115:1036-1040.
35. Fedele S. Diagnostic aids in the screening of oral cancer. Head Neck Oncol 2009 Jan 30;1:5.
36. Cheng YS, Rees T, Wright J. Updates Regarding Diagnostic Adjuncts for Oral Squamous Cell Carcinoma. Tex Dent J 2015;132:538-49.
37. Koch FP, Kunkel M, Biesterfeld S, Wagner W. Diagnostic efficiency of differentiating small cancerous and precancerous lesions using mucosal brush smears of the oral cavity--a prospective and blinded study. Clin Oral Investig 2011;15:763-9.
38. Chhabra N, Chhabra S, Sapra N. Diagnostic modalities for squamous cell carcinoma: an extensive review of literature-considering toluidine blue as a useful adjunct. J Maxillofac Oral Surg 2015;14:188-200.
39. Silverman S Jr, Migliorati C, Barbosa J. Toluidine blue staining in the detection of oral precancerous and malignant lesions. Oral Surg Oral Med Oral Pathol 1984;57:379-82.
40. Epstein JB, Güneri P. The adjunctive role of toluidine blue in detection of oral premalignant and malignant lesions. Curr Opin Otolaryngol Head Neck Surg 2009;17:79-87.
41. Zhang L, Williams M, Poh CF, et al. Toluidine blue staining identifies high-risk primary oral premalignant lesions with poor outcome. Cancer Res 2005;65:8017-21.
42. FDA website. Premarket notification K033033. Available at: http://www.accessdata.fda.gov/cdrh_docs/pdf3/K033033.pdf . Accessed March February 22, 2024.
43. Huber MA, Epstein JB. Marketing versus science: a call for evidence-based advertising in dentistry. Oral Surg Oral Med Oral Pathol Oral Radiol. 2015;120:541-3.
44. Poh CF, Zhang L, Anderson DW, et al. Fluorescence visualization detection of field alterations in tumor margins of oral cancer patients. Clin Cancer Res 2006;12:6716- 22.
45. Rashid A, Warnakulasuriya S. The use of light-based (optical) detection systems as adjuncts in the detection of oral cancer and oral potentially malignant disorders: a systematic review. J Oral Pathol Med 2015;44:307-28.
46. Huber MA, Bsoul SA, Terezhalmy GT. Acetic acid wash and chemiluminescent illumination as an adjunct to conventional oral soft tissue examination for the detection of dysplasia: a pilot study. Quintessence Int 2004;35:378-84.
47. Liu J, Duan Y. Saliva: A potential media for disease diagnostics and monitoring. Oral Oncol 2012;48:569-577.
48. Ferrari E, Pezzi ME, Cassi D, et al. Salivary Cytokines as Biomarkers for Oral Squamous Cell Carcinoma: A Systematic Review. Int J Mol Sci. 2021;22:6795
49. Adeoye J, Brennan PA, Thomson P. "Search less, verify more"-Reviewing salivary biomarkers in oral cancer detection. J Oral Pathol Med 2020;49:711-719.
50. Assad DX, Mascarenhas ECP, de Lima CL, et al. Salivary metabolites to detect patients with cancer: a systematic review. Int J Clin Oncol 2020;25:1016-1036.
51. Chattopadhyay I, Verma M, Panda M. Role of Oral Microbiome Signatures in Diagnosis and Prognosis of Oral Cancer. Technol Cancer Res Treat 2019;18:1533033819867354.
52. Dikova V, Jantus-Lewintre E, Bagan J. Potential Non-Invasive Biomarkers for Early Diagnosis of Oral Squamous Cell Carcinoma. J Clin Med 2021;10:1658.
53. Fadhil RS, Wei MQ, Nikolarakos D, et al. Salivary microRNA miR-let-7a-5p and miR-3928 could be used as potential diagnostic bio-markers for head and neck squamous cell carcinoma. PLoS One 2020;24;15:e0221779.
54. Ferrari E, Pezzi ME, Cassi D, et al. Salivary Cytokines as Biomarkers for Oral Squamous Cell Carcinoma: A Systematic Review. Int J Mol Sci 2021;22:6795.
55. Jain A, Kotimoole CN, Ghoshal S, et al. Identification of potential salivary biomarker panels for oral squamous cell carcinoma. Sci Rep 2021;11:3365.
56. Kang JW, Eun YN, Lee YC. Diagnostic Value of Salivary miRNA in Head and Neck Squamous Cell Cancer: Systematic Review and Meta-Analysis. Int J Mol Sci 2021;22:7026.
57. Li Q, Ouyang X, Chen J, et al. A Review on Salivary Proteomics for Oral Cancer Screening. Curr Issues Mol Biol 2020;37:47-56.
58. McRae MP, Kerr AR, Janal MN, et al. Nuclear F-actin Cytology in Oral Epithelial Dysplasia and Oral Squamous Cell Carcinoma. J Dent Res 2021;100:479-486.
59. Hong-Lin He, Ying-En Lee, Min-Te Chang, et al. AMACR overexpression acts as a negative prognostic factor in oral squamous cell carcinoma. Int J Med Sci 2018;15: 638–644.
60. Lewis JS, Thorstad WL, Chernock RD, et al. p16 Positive Oropharyngeal Squamous Cell Carcinoma: An Entity With a Favorable Prognosis Regardless of Tumor HPV Status. Am J Surg Pathol 2010;34:1088-96.
61. Sinevici N, O'sullivan J. Oral cancer: Deregulated molecular events and their use as biomarkers. Oral Oncol 2016;61:12-8.
62. Takkem A, Barakat C, Zakaraia S, et al. Ki-67 Prognostic Value in Different Histological Grades of Oral Epithelial Dysplasia and Oral Squamous Cell Carcinoma. Asian Pac J Cancer Prev 2018;19:3279-3286.
63. Banavar G, Ogundijo O, Toma R,et al. The salivary metatranscriptome as an accurate diagnostic indicator of oral cancer. NPJ Genom Med 2021;6:105. Published online 2021 Dec 8.
64. Diagnostic tests for oral cancer and potentially malignant disorders in patients presenting with clinically evident lesions. Cochrane Database Syst Rev. 2021; 2021:CD010276.
65. McQuillan G, Kruszon-Moran D, Markowitz LE, Unger ER., Paulose-Ram R. Prevalence of HPV in adults aged 18–69: United States, 2011–2014. NCHS data brief, no 280. Hyattsville, MD: National Center for Health Statistics. 2017.
66. Beachler DC, Sugar EA, Margolick JB, et al. Risk factors for acquisition and clearance of oral human papillomavirus infection among HIV-infected and HIV-uninfected adults. Am J Epidemiol. 2015;181:40-53.
67. Gipson BJ, Robbins HA, Fakhry C, D'Souza G. Sensitivity and specificity of oral HPV detection for HPV-positive head and neck cancer. Oral Oncol. 2018;77:52-56.
68. Rettig E, Kiess AP, Fakhry C. The role of sexual behavior in head and neck cancer: implications for prevention and therapy. Expert Rev Anticancer Ther 2015;15:35-49.

POST-TEST

Internet Users: This page is intended to assist you in fast and accurate testing when completing the "Online Exam." We suggest reviewing the questions and then circling your answers on this page prior to completing the online exam.

(1.0 CE Credit Contact Hour) Please circle the correct answer. 70% equals passing grade.

1. **In 2020 the number of individuals living with oral cavity and pharynx cancer in the United States was estimated to be:**
   a. 225,000
   b. 325,000
   c. 425,000
   d. 525,000

2. **The most important factor contributing to the delayed diagnosis of oral cavity and pharynx cancer is:**
   a. the clinician's failure to use innovative technologies on a routine basis.
   b. the patient's tardiness to obtain an evaluation.
   c. lack of examination consistency.
   d. professional delay.

3. **Components of a proper examination to identify an OPMD include all of the following EXCEPT:**
   a. A comprehensive review of the medical, dental, and social history
   b. A thorough visual and tactile extra-oral and intra-oral examination
   c. Referral or biopsy of any discovered lesion deem suspicious
   d. Saliva testing for the presence of a high-risk HPV

4. **All of the following statements regarding TB are true, EXCEPT for one. Which one is the exception?**
   a. It is a metachromatic dye with an affinity to bind DNA.
   b. It is marketed as a case-assessment utility with the ViziLite® tissue reflectance product.
   c. It is cleared by the FDA as a standalone adjunctive screening aid.
   d. The presence of inflammation is associated with increased false positive results.

5. **Of the available adjunctive devices to improve the clinician's ability to identify a potentially malignant disorder, which one uses the principle of tissue reflectance?**
   a. ViziLite® TBlue Annual Oral Cancer Screening System
   b. Goccles
   c. Bio/Screen®
   d. ViziLite PRO®

6. **When using an autofluorescent adjunctive device, healthy tissues should appear:**
   a. dark blue.
   b. pale magenta.
   c. pale green.
   d. bright white.

7. **All of the following statements regarding biomarker-based adjuncts are true, except for one. Which one is the exception?**
   a. Potential biomarkers include DNAs, RNAs, proteins, metabolites, and microbiota.
   b. Numerous biomarker-based panels have been proposed to interrogate OPMDs for dysplasia and carcinoma.
   c. Biomarker-based adjuncts are not regulated by the FDA.
   d. Large scale trials to determine the accuracy of biomarker-based adjuncts are lacking.

8. **A positive result from OraRisk® HPV testing means:**
   a. the oral mucosa contains dysplastic cells.
   b. the oral mucosa contains cancerous cells.
   c. the oral mucosa will develop cancer.
   d. the oral mucosa contains HPV DNA.

9. **For which category of screening adjuncts is there insufficient evidence to assess their true value in clinical practice?**
   a. Cytology-based
   b. Light-based
   c. Vital stain-based
   d. Biomarker-based

10. **Which category of screening adjuncts generates the lowest number of false positives results?**
    a. Cytology-based
    f. Light-based
    g. Vital stain-based
    h. Biomarker-based

Registration/Certification Information (Necessary for proper certification)

Name (Last, First, Middle Initial): _____

PLEASE PRINT CLEARLY

Street Address: _____ Suite/Apt. Number _____

City: _____ State: _____ Zip: _____

Telephone: _____ Fax: _____

Date of Birth: _____ Email: _____

State(s) of Licensure: _____ License Number(s): _____

Preferred Dentist Program ID Number: _____ ☐ Check Box If Not A PDP Member

AGD Mastership: ☐ Yes ☐ No

AGD Fellowship: ☐ Yes ☐ No Date: _____

Please Check One: ☐ General Practitioner ☐ Specialist ☐ Dental Hygienist ☐ Other

FOR OFFICE USE ONLY

Evaluation - Techniques for Early Cancer Detection 3rd Edition

Providing dentists with the opportunity for continuing dental education is an essential part of MetLife's commitment to helping dentists improve the oral health of their patients through education. You can help in this effort by providing feedback regarding the continuing education offering you have just completed.

Please respond to the statements below by checking the appropriate box, using the scale on the right.

	1 = POOR 1	2	3	4	5 = Excellent 5	
1. How well did this course meet its stated educational objectives?	☐	☐	☐	☐	☐	
2. How would you rate the quality of the content?	☐	☐	☐	☐	☐	
3. Please rate the effectiveness of the author.	☐	☐	☐	☐	☐	
4. Please rate the written materials and visual aids used.	☐	☐	☐	☐	☐	
5. The use of evidence-based dentistry on the topic when applicable.	☐	☐	☐	☐	☐	☐ N/A
6. How relevant was the course material to your practice?	☐	☐	☐	☐	☐	
7. The extent to which the course enhanced your current knowledge or skill?	☐	☐	☐	☐	☐	
8. The level to which your personal objectives were satisfied.	☐	☐	☐	☐	☐	
9. Please rate the administrative arrangements for this course.	☐	☐	☐	☐	☐	

10. How likely are you to recommend MetLife's CE program to a friend or colleague? *(please circle one number below:)*

10 **9** **8** **7** **6** **5** **4** **3** **2** **1** **0**

extremely likely — neutral — not likely at all

What is the primary reason for your 0-10 recommendation rating above?

11. Please identify future topics that you would like to see:

Thank you for your time and feedback.

MetLife

To complete the program traditionally, please mail your post test and registration/evaluation form to:
MetLife Dental Quality Initiatives Program | 501 US Highway 22 | Bridgewater, NJ 08807