

Appendix 2. METHODS

Data extraction. Two reviewers (M.P.T. and O.U.) independently and working in duplicate used a standardized form (Excel, Microsoft) to extract the data. They recorded the following data from each study: author's last name and year of publication, country, setting (primary, secondary, or tertiary care), population characteristics (age, sex, selection criteria, and clinical diagnosis of evident lesions), the number of patients included in the study, the number of lesions included in the analysis, index test and criterion standard characteristics, positivity thresholds, source of funding, financial and intellectual conflicts of interest, and diagnostic test accuracy (DTA) and patient-important outcomes. A third reviewer (A.C.L.), who acted as arbiter, clarified any discrepancies between extractors. We made efforts to contact primary study authors whenever deemed necessary.

Assessment of heterogeneity. For the pooled estimates of DTA studies, we visually assessed heterogeneity by using as a reference how close the sensitivity and specificity estimates were among studies, as well as the extension of overlap of their 95% confidence intervals. We performed this assessment in accordance with guidance from the *Cochrane Handbook for Diagnostic Test Accuracy Reviews*.¹³

Assessment of publication bias. We did not assess publication bias as recommended by the Cochrane Handbook. Heterogeneity in test accuracy is prevalent in most reviews of DTA, and interpreting statistical evidence of funnel plot asymmetry could be misleading.^{87,88}

Sensitivity analysis. In anticipation of eventual issues such as risk of bias, specifically verification bias (for example, we did not keep index test and criterion standard patient populations or when different types of lesions were tested consistent), we conducted sensitivity analysis to examine to what extent these study differences meaningfully changed summary measures. We compared the pooled estimates for sensitivity and specificity and their 95% confidence intervals, including and excluding such types of studies.

RESULTS

PVPs studies. Investigators conducted the primary studies in Australia,⁷² the United Kingdom,^{73,75,79,80} the United States,⁷⁴ Jordan,⁷⁶ Canada,⁷⁷ and Germany.⁷⁸ In all primary studies, the investigators used a cross-sectional study design and telephone interviews and self-reported and closed-ended questionnaires as a means of collecting data. Three main topics emerged from the analysis. First, fear and anxiety are identified as some of the most important barriers for seeking care. Investigators in 2 studies reported that delaying

consultation of a primary care practitioner for initial evaluation or attending a specialty clinic after referral can range between 1 and 3 months.^{72,80} Rogers and colleagues⁷⁹ found that one-third of all participants treated for oropharyngeal and oral squamous cell carcinoma (OSCC) known to be alive by the time of data collection mentioned that they did not share the finding of having a potentially malignant disorder (PMD) or OSCC with anyone during the initial evaluations.⁷¹ Second, the acceptability of conducting a clinical examination to identify PMDs was high among participants.^{71,76} Third, participants highlighted the interest of being educated about ways to reduce their risk of having oral cancer and suggested that media coverage could be an effective way to increase awareness about the early manifestation of PMDs and OSCC (eTable 5,⁷¹⁻⁸⁰ available online at the end of this article).

Risk of bias of included reviews. Using the Assessing the Methodological Quality of Systematic Reviews tool, we determined that both Cochrane reviews had the highest methodological quality that a study can have according to this tool. The reviews summarizing the evidence of salivary adjuncts for the early diagnosis of OSCC were evaluated as being of high²³ and moderate²² quality. The 2 Cochrane reviews needed to be updated, but the reviews on salivary adjuncts did not (eTables 6-9,^{4,5,16,23,24} available online at the end of this article).

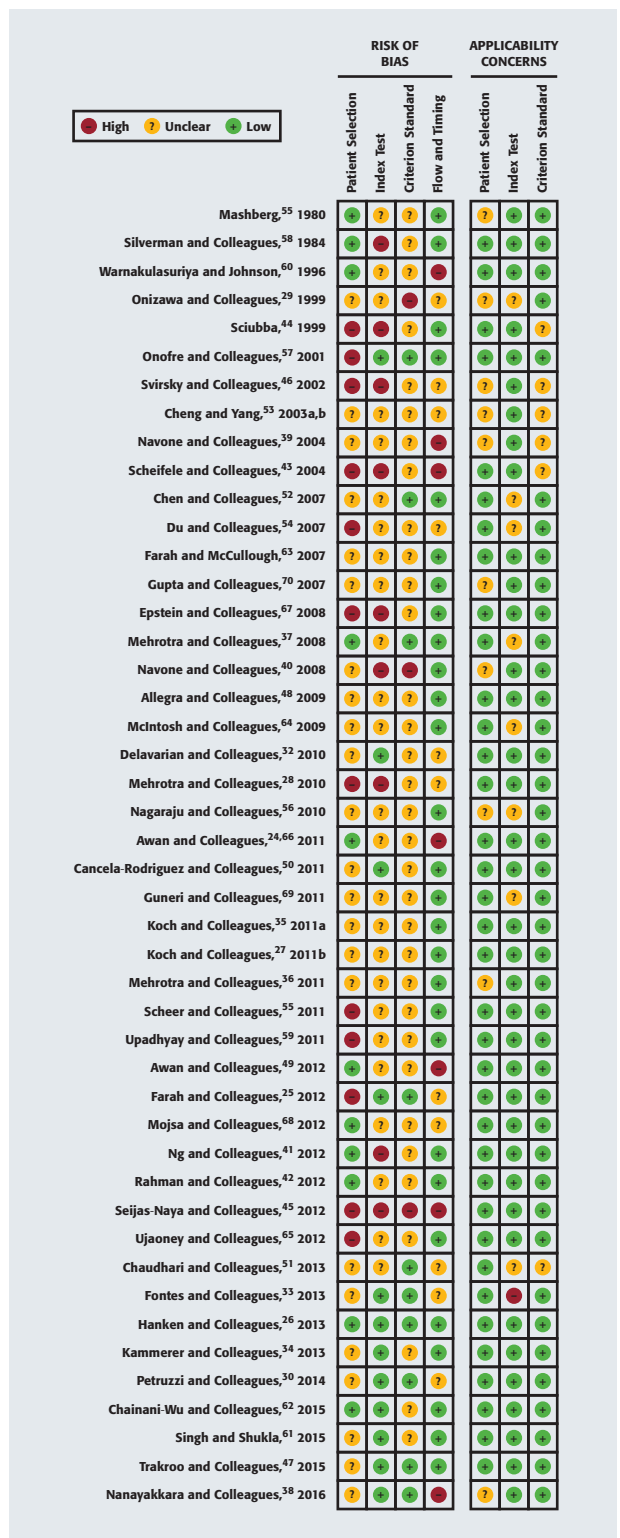
Sensitivity analysis. To evaluate the impact of verification bias from the studies contributing to the DTA pooled estimates, we pooled data for studies with and without verification bias separately. Four studies were affected by verification bias, and these studies informed 2 comparisons (vital staining and cytologic testing).^{39,45,46,51} For either comparison listed, the DTA pooled estimates seemed to show similar results (eTables 11-14,^{32-35,37-61,69} available online at the end of this article).

DISCUSSION

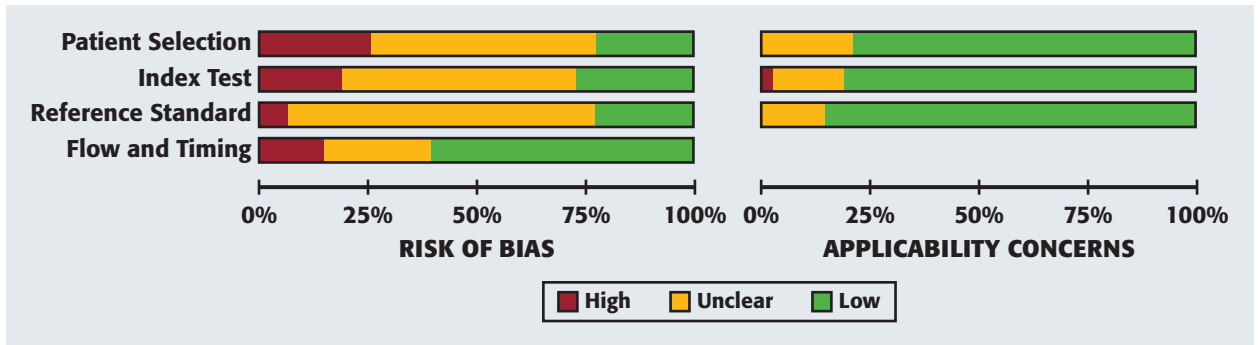
This systematic review is an update of the 2013 and the 2015 Cochrane reviews,^{5,85} but there are a few key methodological differences. First, the 2015 Cochrane review included lichen planus, actinic keratosis, hereditary disorders (no studies found), and cancers of the lip (no studies of lip cancers found) as relevant target conditions that this update did not, and we included erythroleukoplakia as a relevant target condition, which was not included explicitly in the Cochrane review. Second, for the risk of bias assessment, the authors of the 2015 Cochrane review used a modified version of QUADAS-2, whereas we used a comparable version provided in Review Manager, Version 5.3.⁴⁵ We reassessed all Cochrane risk of bias judgments during the update for the sake of consistency. Third, we needed to remove a few adjuncts that were not available in the US market, which was 1 of our inclusion criteria. Fourth, we

regrouped the comparisons, splitting the light-based category into its 2 subcategories: autofluorescence and tissue reflectance adjuncts. Fifth, we made efforts to obtain the most accurate and current estimate of the prevalence of PMDs and OSCC in the United States and used it in our analysis. We did not use the estimate calculated for the 2015 Cochrane review.

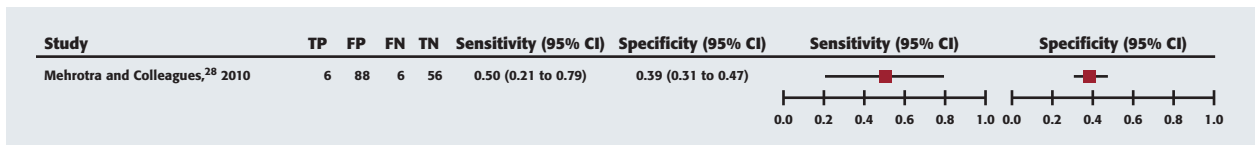
Investigators in 4 systematic reviews summarized the evidence on the use of devices to assist the diagnostic process for PMDs and OSCC, and their findings are in agreement with ours. Nagi and colleagues⁸³ and Awan and Patil⁸⁴ evaluated the clinical usefulness of autofluorescence adjuncts. The investigators in these reviews found that sensitivity and specificity for autofluorescence devices ranged from 22% to 100% and from 16% to 100%, respectively. They concluded that this type of adjunct might be helpful for the experienced clinicians in a secondary or tertiary care setting, where the prevalence is high, but of little help in primary care settings, particularly because of the inability of autofluorescence methods to help differentiate dysplasia from benign reactive or inflammatory lesions or nondysplasia. Carreras-Torras and Gay-Escoda⁸⁵ were unable to find evidence to support any diagnostic technique for the purpose of replacing biopsy. In addition, they described that the evidence to support the use of adjuncts in practice is limited. Rashid and Warnakulasuriya⁸⁶ also found variable results across autofluorescence and chemiluminescence adjuncts. They concluded that the available evidence suggests that these devices may be better suited for clinicians in specialty care settings with more clinical experience and with a higher prevalence of the condition compared with that seen in primary care settings.



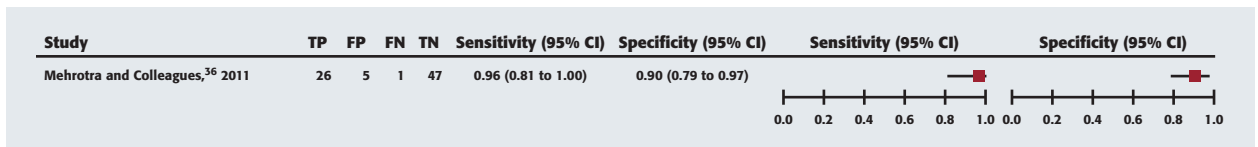
eFigure 1. Risk of bias summary: review authors’ judgments about each risk of bias item for each included study. Green indicates low risk of bias, yellow indicates unclear risk of bias, and red indicates high risk of bias.



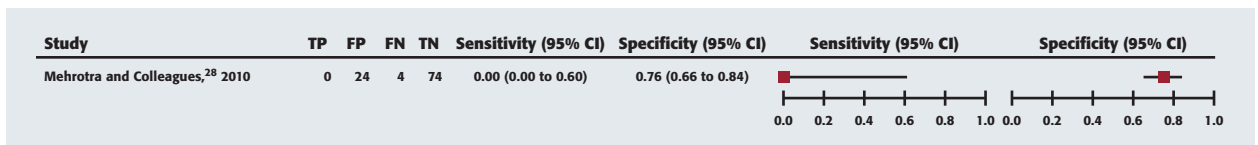
eFigure 2. Bar graph indicating percentages of risk of bias.



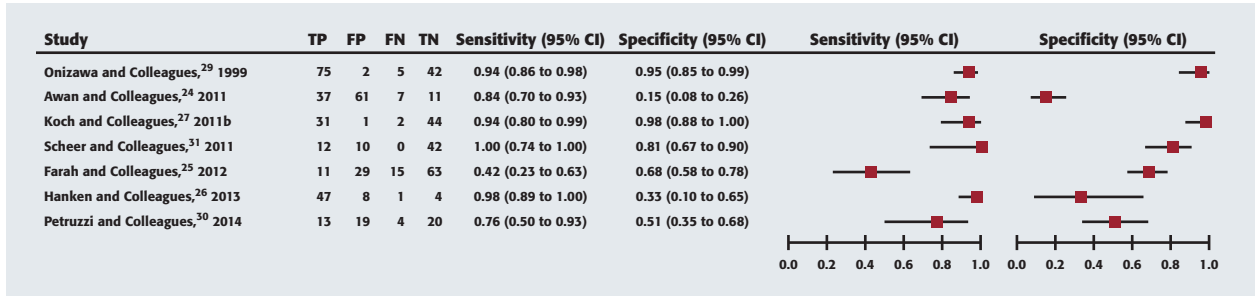
eFigure 3. Forest plot of autofluorescence for clinically evident, seemingly innocuous lesions. The thin horizontal lines indicate confidence interval (CI) magnitude. FN: False negative. FP: False positive. TN: True negative. TP: True positive.



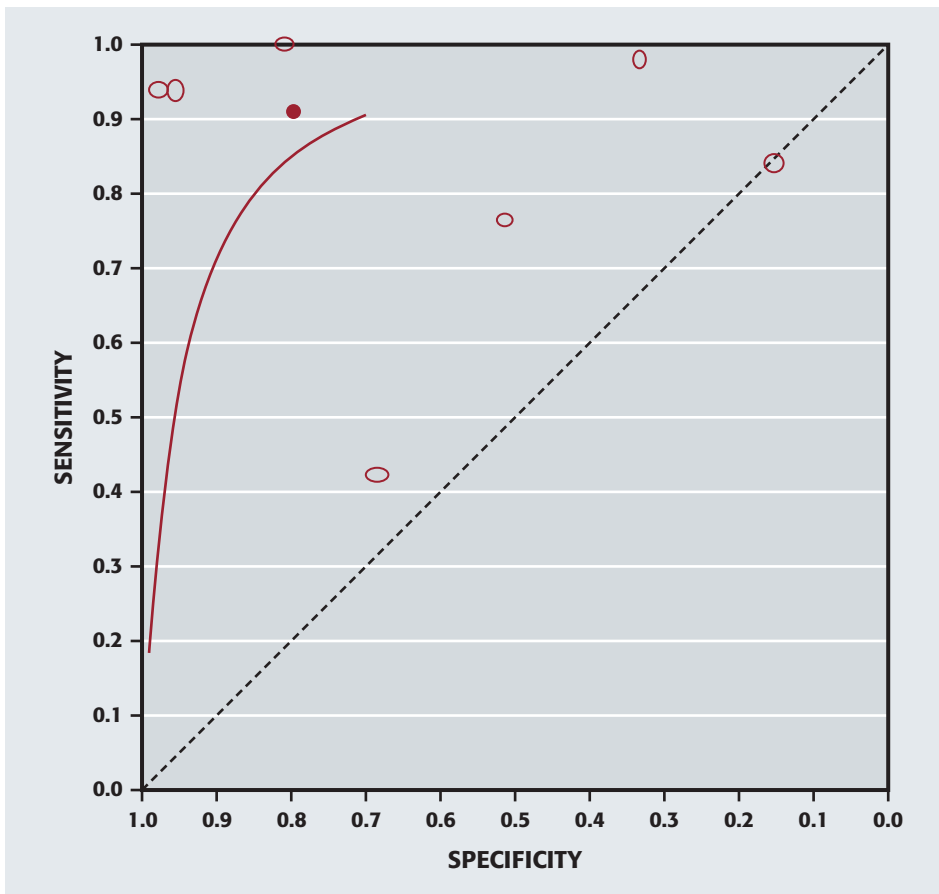
eFigure 4. Forest plot of cytology for clinically evident, seemingly innocuous lesions. The thin horizontal lines indicate confidence interval (CI) magnitude. FN: False negative. FP: False positive. TN: True negative. TP: True positive.



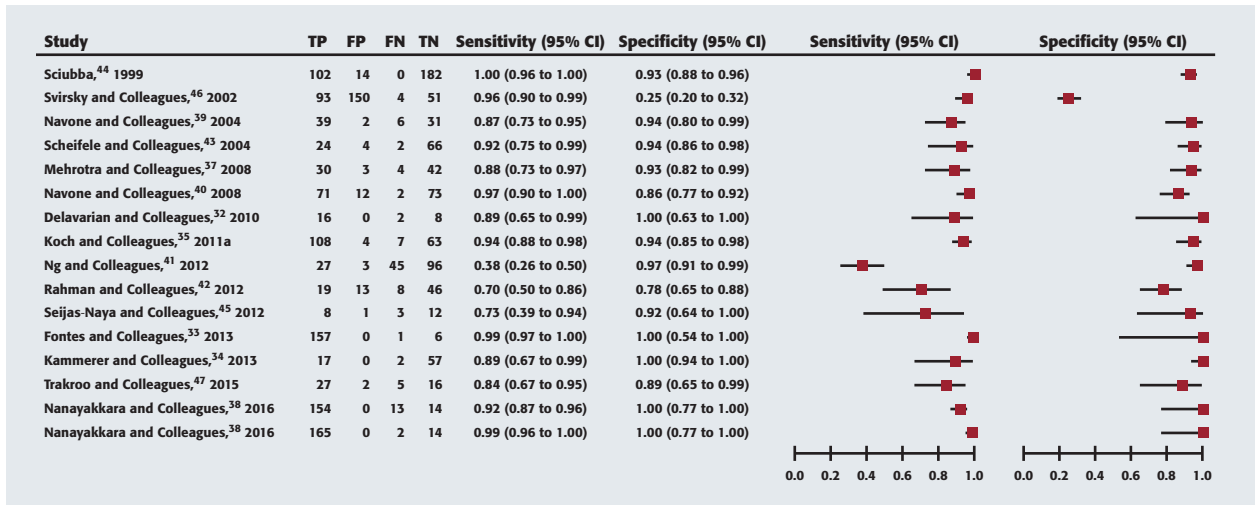
eFigure 5. Forest plot of tissue reflectance and vital staining for clinically evident, seemingly innocuous lesions. The thin horizontal lines indicate confidence interval (CI) magnitude. FN: False negative. FP: False positive. TN: True negative. TP: True positive.



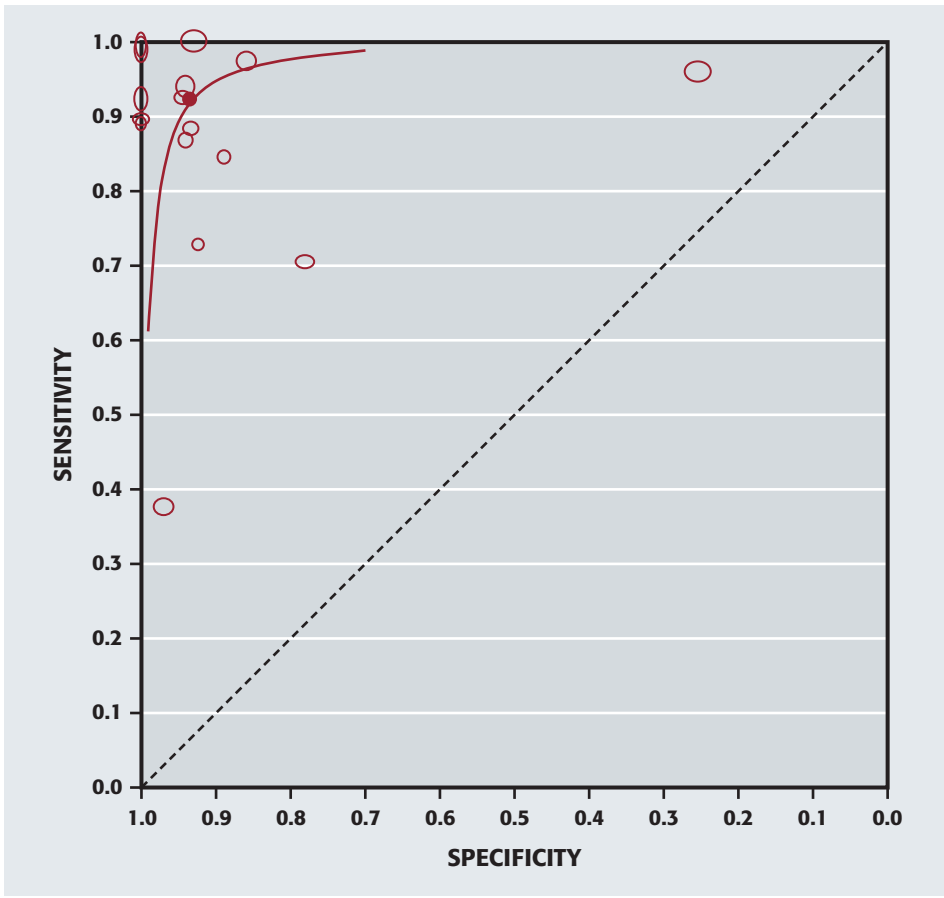
eFigure 6. Forest plot of autofluorescence for clinically evident, suspicious lesions. The thin horizontal lines indicate confidence interval (CI) magnitude. FN: False negative. FP: False positive. TN: True negative. TP: True positive.



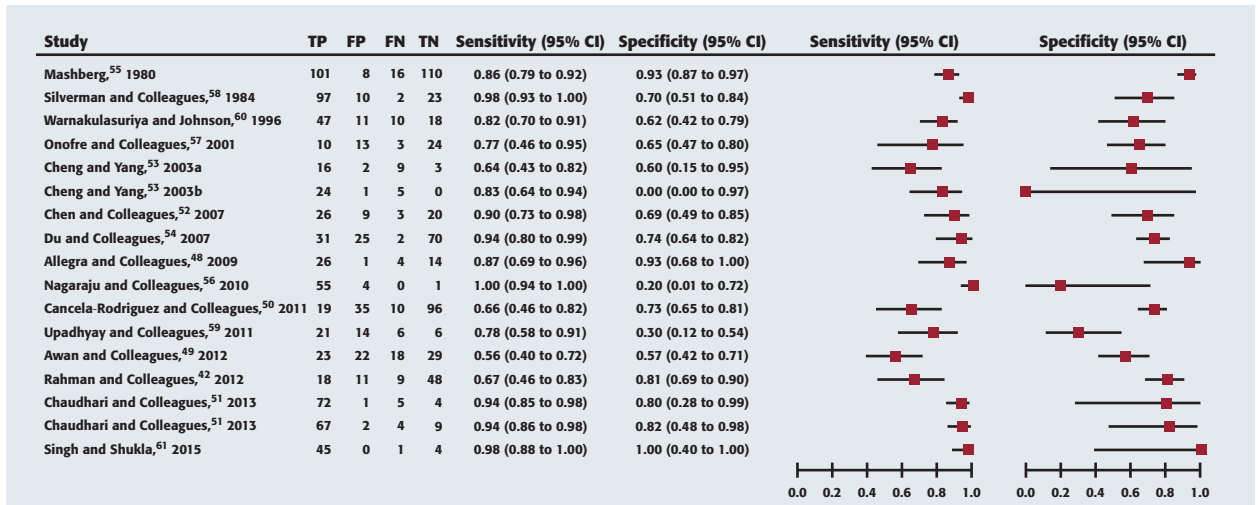
eFigure 7. Summary receiver operating characteristic curve for autofluorescence for clinically evident, suspicious lesions. Open circles indicate the individual sensitivity and specificity for each study and the filled circles indicate the pooled estimate for the particular adjunct in question.



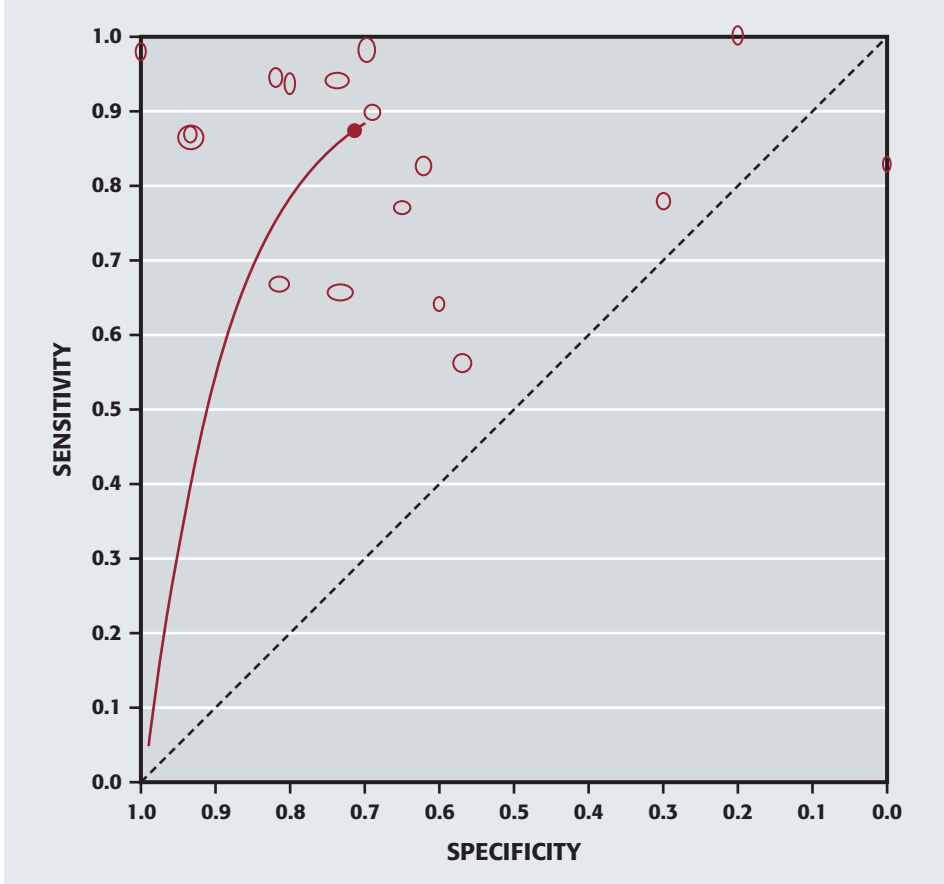
eFigure 8. Forest plot of cytology for clinically evident, suspicious lesions. The thin horizontal lines indicate confidence interval (CI) magnitude. FN: False negative. FP: False positive. TN: True negative. TP: True positive.



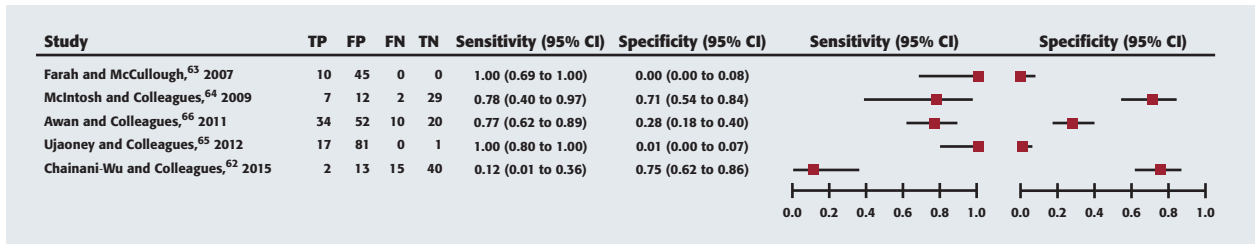
eFigure 9. Summary receiver operating characteristic curve for cytology for clinically evident, suspicious lesions. Open circles indicate the individual sensitivity and specificity for each study and the filled circles indicate the pooled estimate for the particular adjunct in question.



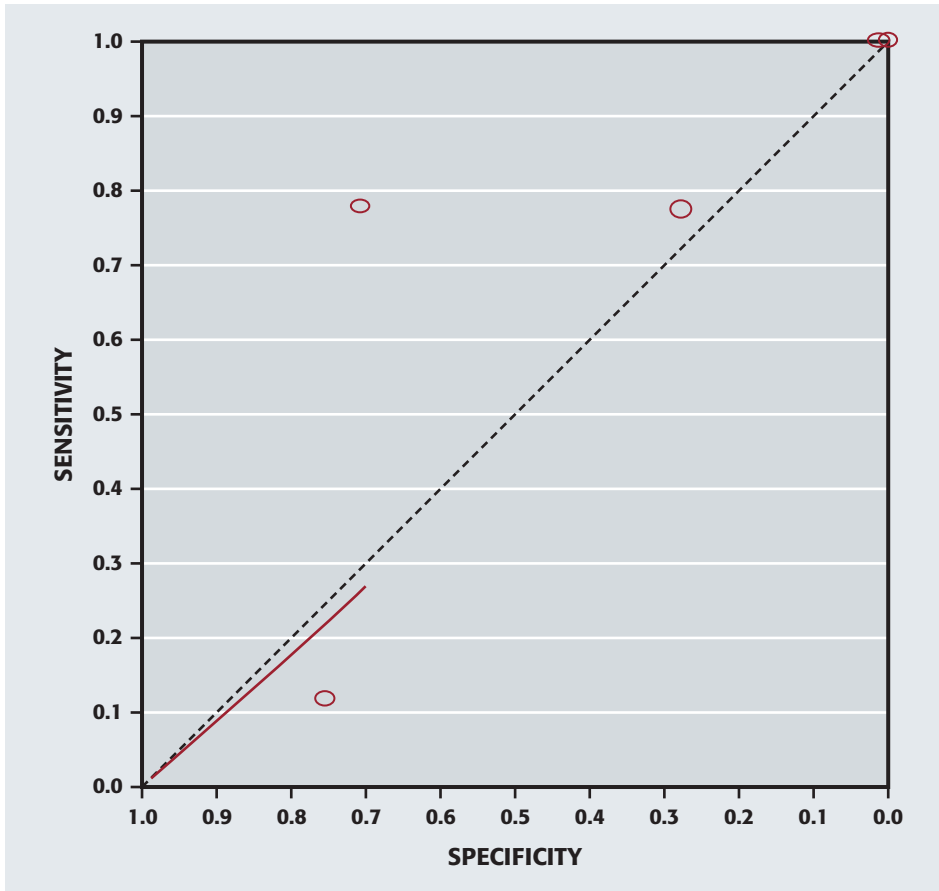
eFigure 10. Forest plot of vital staining for clinically evident, suspicious lesions. The thin horizontal lines indicate confidence interval (CI) magnitude. FN: False negative. FP: False positive. TN: True negative. TP: True positive.



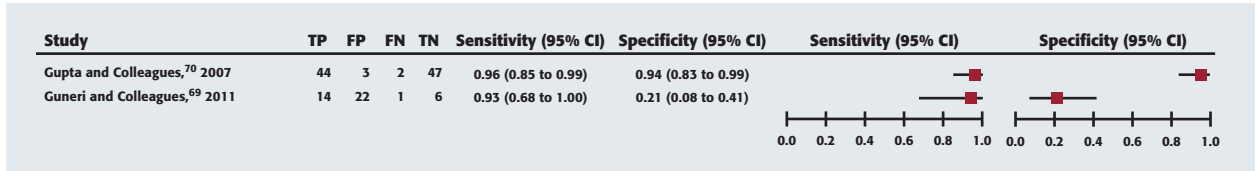
eFigure 11. Summary receiver operating characteristic curve for vital staining for clinically evident, suspicious lesions. Open circles indicate the individual sensitivity and specificity for each study and the filled circles indicate the pooled estimate for the particular adjunct in question.



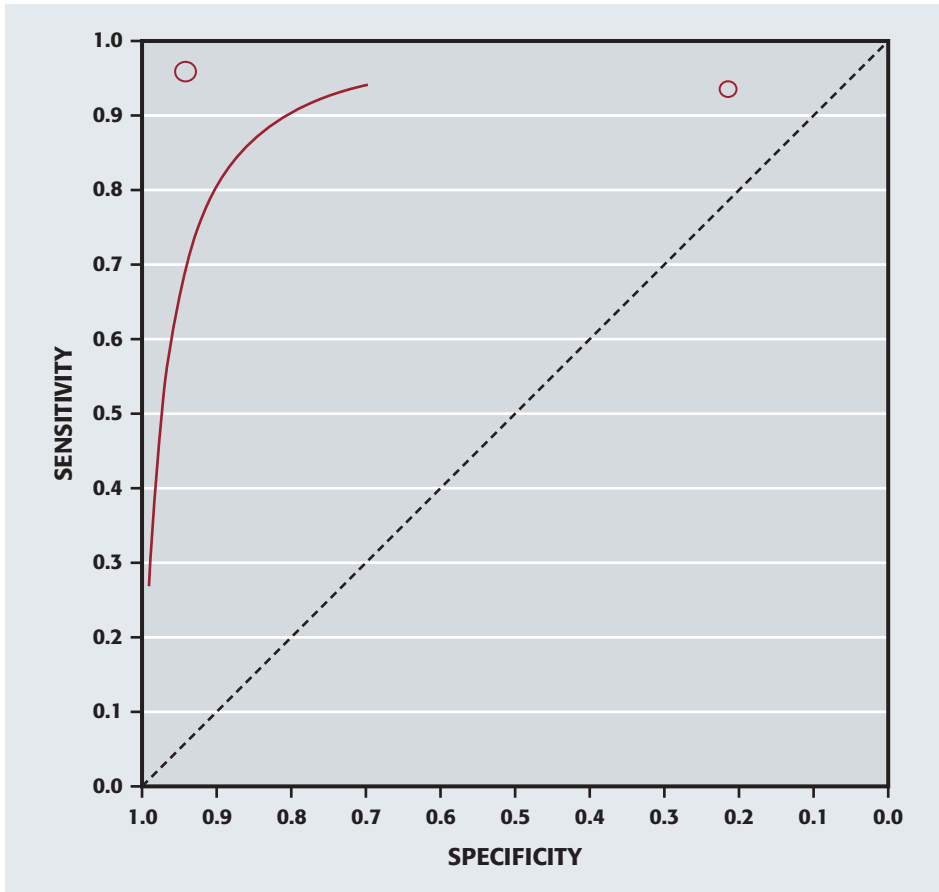
eFigure 12. Forest plot of tissue reflectance for clinically evident, suspicious lesions. The thin horizontal lines indicate confidence interval (CI) magnitude. FN: False negative. FP: False positive. TN: True negative. TP: True positive.



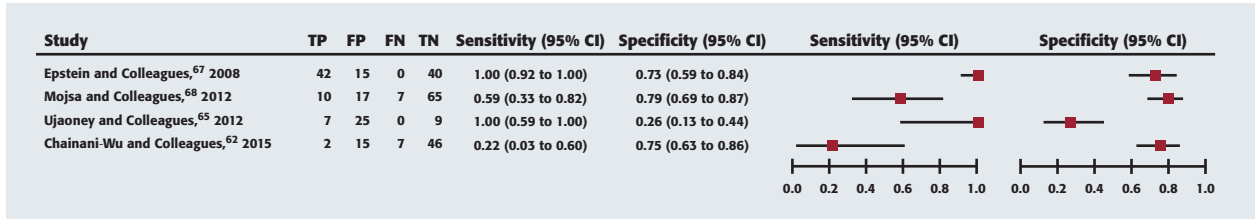
eFigure 13. Summary receiver operating characteristic curve for tissue reflectance for clinically evident, suspicious lesions. Open circles indicate the individual sensitivity and specificity for each study and the filled circles indicate the pooled estimate for the particular adjunct in question.



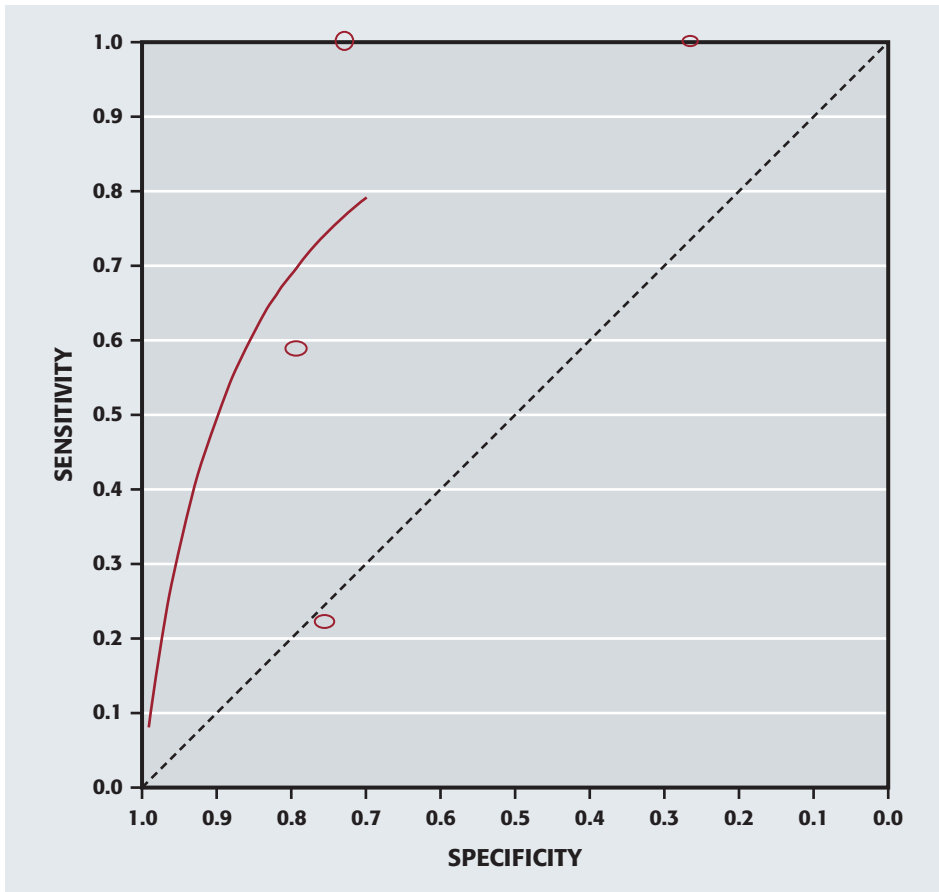
eFigure 14. Forest plot of cytology and vital staining for clinically evident, suspicious lesions. The thin horizontal lines indicate confidence interval (CI) magnitude. FN: False negative. FP: False positive. TN: True negative. TP: True positive.



eFigure 15. Summary receiver operating characteristic curve for cytology and vital staining for clinically evident, suspicious lesions. Open circles indicate the individual sensitivity and specificity for each study and the filled circles indicate the pooled estimate for the particular adjunct in question.



eFigure 16. Forest plot of tissue reflectance and vital staining for clinically evident, suspicious lesions. The thin horizontal lines indicate confidence interval (CI) magnitude. FN: False negative. FP: False positive. TN: True negative. TP: True positive.



eFigure 17. Summary receiver operating characteristic curve for tissue reflectance and vital staining for clinically evident, suspicious lesions.



eFigure 18. No clinically evident lesion or other symptoms.



eFigure 20. Seemingly malignant lesion.



eFigure 19. Clinically evident, seemingly-innocuous or non-suspicious lesion.



eFigure 21. Clinically evident suspicious lesion.

eTABLE 1

Glossary of terms.	
TERM	DEFINITION
Target Condition	A target condition is a disease or health outcome of interest.
Screening Versus Evaluation	Screening is the process by which a practitioner surveys a patient without symptoms to determine whether he or she is likely or unlikely to have a condition or disease. In mass screening programs, also known as <i>community-based screening</i> or <i>population-based screening</i> , the target group is invited to participate specifically for the purpose of detecting disease. In the dental care setting, the act of screening for oral cancer usually occurs when a patient reports for routine care, a form of opportunistic screening. Evaluation generally involves a broader survey of patients, both with and without symptoms, including a review of their medical, social, and dental history and a physical assessment. In the dental care setting, this is accomplished through an intraoral and extraoral visual and tactile examination to detect any tissue abnormalities, including potentially malignant and seemingly malignant disorders.
CVTE*	CVTE is the systematic visual inspection of the head and neck. This includes examination of the face, lips, and mouth tissues under white light illumination for any signs or clinically detectable tissue abnormality or morphologic change, such as changes in size, color, and texture. This is combined with regional palpation with gloved fingers to detect changes in consistency and temperature of mucosa, skin, bone, joints, and lymph nodes. Patient-reported symptoms could include globus sensation, unexplained ear pain or oropharyngeal pain, hoarseness, and so on.
No Clinically Evident Lesions	No clinically evident lesions or symptoms are the absence of any clinically detectable tissue abnormality or symptoms during the CVTE of the dental patient.
Clinically Evident Lesions	Clinically evident lesions are morphologically altered tissue noted at CVTE.
Clinically Evident, Seemingly Innocuous, or Nonsuspicious Lesions	Clinically evident, seemingly innocuous, or nonsuspicious lesions are areas of morphologically altered tissue noted at examination for which the clinician considers a clinical diagnosis of a PMD [†] with features suggestive of dysplasia or malignancy to be a remote possibility.
Clinically Evident, Suspicious Lesions	Clinically evident, suspicious lesions are morphologically altered tissue noted at CVTE for which the clinician considers a definitive diagnosis of a PMD (lesion with features suggestive of malignancy) or even a malignant disorder to be a distinct possibility. These are likely to occur in the following anatomic sites: ventrolateral part of the tongue, floor of mouth, and anterior tonsillar pillar and soft palate complex.
Seemingly Malignant Lesions	Seemingly malignant lesions are a clinical diagnosis reserved for oral lesions with ominous clinical features considered highly suggestive of malignancy.
PMDs‡	A target condition for this review, PMDs are identified through a clinical diagnosis and encompass oral mucosal entities (lesions or disorders) that have an increased risk of the development of cancer. PMDs can be diagnosed clinically as leukoplakia, erythroplakia, erythroleukoplakia, or submucous fibrosis, and these lesions may occur among those with hereditary disorders with an increased risk of malignant transformation and among heavy tobacco and alcohol users. These diagnoses usually are assigned in a primary care setting through CVTE, through the presence of dysplasia (that is, the only definitive indicator for potential malignancy or malignancy), and can be determined only through biopsy and histopathologic assessment.
OSCC§	A target condition for this review, OSCC is the most common cancer of the oral cavity and is diagnosed after histopathologic assessment of tissue obtained at biopsy. OSCC is a malignancy derived from the squamous epithelium or oral mucosa.
Triage Test	A triage test is used in an early stage of the diagnostic process to identify patients with a particular finding that will be informative for subsequent steps in the testing pathway.
Adjuncts or Index Tests	An adjunct is a test, device, technique, or technology marketed to assist primary care clinicians, possibly as a triage test, in the detection of PMDs or seemingly malignant lesions for the assessment of their biological relevance.
Biopsy or Criterion Standard	Biopsy followed by histopathologic assessment, a procedure used to detect dysplasia, is the criterion standard diagnostic test for PMDs and OSCC. Biopsy can be either incisional or excisional. An incisional biopsy is a surgical technique involving a scalpel or punch to sample a portion of a PMD for subsequent histopathologic examination and a definitive diagnosis. An excisional biopsy is a surgical technique involving a scalpel or punch that removes all clinically abnormal mucosa of a clinically evident lesion for subsequent histopathologic examination and a definitive diagnosis.
Index Tests (Adjuncts) Versus Criterion Standard (Biopsy)	An index test for a given lesion or condition is evaluated for diagnostic accuracy by comparison with a reference standard or criterion standard diagnostic test.
True-Positive Test Result	A true-positive test result indicates that an adjunct correctly helped identify a patient as having a PMD or malignant disorder. A timely referral to a specialist or biopsy will be performed.
False-Positive Test Result	A false-positive test result indicates that an adjunct incorrectly helped identify a patient as having a PMD or malignant disorder. The patient would undergo additional unnecessary testing and biopsy.
True-Negative Test Result	A true-negative test result indicates that an adjunct correctly helped identify a patient as not having a PMD or malignant disorder. The patient will receive reassurance that he or she is healthy.
* CVTE: Conventional visual and tactile examination. † PMD: Potentially malignant disorder. ‡ The literature indicates that there is no universal agreement on the definition and application of the term <i>potentially malignant disorder</i> (PMD), and we attempted to reconcile inconsistencies as well as possible. § OSCC: Oral squamous cell carcinoma.	

eTABLE 1 (CONTINUED)

TERM	DEFINITION
False-Negative Test Result	A false-negative test result indicates that an adjunct incorrectly helped identify a patient as not having a PMD or malignant disorder. The appropriate diagnosis would be missed, worsening the prognosis of the disease.
Sensitivity	Sensitivity is the ability of a test to help identify those with the disease correctly, also known as the <i>true-positive rate</i> .
Specificity	Specificity is the ability of a test to help identify those without the disease correctly, also known as the <i>true-negative rate</i> .
Positive Likelihood Ratio	A positive likelihood ratio indicates how much more likely a positive test result is in patients with the condition versus in patients without the condition.
Negative Likelihood Ratio	A negative likelihood ratio indicates the probability of a patient without the target condition having a negative test result.
Pretest Probability	Pretest probability is the proportion of people in the population at risk who have the disease at a specific time or time interval (that is, the point prevalence or the period prevalence of the disease). In other words, it is the probability, before the diagnostic test is performed, that a patient has the disease. Clinicians can estimate pretest probabilities from routine data, practice data, or clinical judgment.
Posttest Probability	Posttest probability is the proportion of patients testing positive who truly have the disease. It is similar to the positive predictive value but apart from the test performance also includes a patient-based probability of having disease.
Verification Bias	Verification bias is a type of bias in which the results of an adjunct affect whether the criterion standard is used to verify the test result.

eTABLE 2

Levels of quality of evidence (certainty in the evidence).*	
QUALITY LEVEL	DEFINITION
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very Low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

* Reproduced with permission of the publisher from Balshem and colleagues.²¹

eTABLE 3

List of excluded studies.	
REFERENCE	REASON FOR EXCLUSION
1. Abt, E., DNA-image cytometry has promise for oral cancer detection. <i>Evidence-Based Dentistry</i> , 2015. 16(4): p. 106-7.	Commentary
2. Afrogheh, A., et al., An evaluation of the Shandon Papsin liquid-based oral test using a novel cytologic scoring system. <i>Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology</i> , 2012. 113(6): p. 799-807.	Liquid-based cytologic testing, not commercially available
3. Agarwal, A., et al., Exploratory study to evaluate changes in serum lipid levels as early diagnostic and/or prognostic indicators for oral submucous fibrosis and cancer among gutkha consumers in India. <i>Asian Pacific Journal of Cancer Prevention: APJCP</i> , 2015. 16(15): p. 6439-6444.	Case-control study and unclear application of a criterion standard
4. Aggarwal, S., S.C. Sharma, and S.N. Das, Galectin-1 and galectin-3: plausible tumour markers for oral squamous cell carcinoma and suitable targets for screening high-risk population. <i>Clinica Chimica Acta</i> , 2015. 442: p. 13-21.	Oral squamous cell carcinoma cases were confirmed already
5. Agha-Hosseini, F. and I. Mirzaii-Dizgah, p53 as a neoplastic biomarker in patients with erosive and plaque like forms of oral lichen planus. <i>Journal of Contemporary Dental Practice [Electronic Resource]</i> , 2013. 14(1): p. 1-3.	No criterion standard
6. Agha-Hosseini, F., I. Mirzaii-Dizgah, and N.S. Miri-Zarandi, Unstimulated salivary p53 in patients with oral lichen planus and squamous cell carcinoma. <i>Acta Medica Iranica</i> , 2015. 53(7): p. 439-443.	Case-control study
7. Akhtar, K., et al., Transition of immunohistochemical expression of E-cadherin and vimentin from premalignant to malignant lesions of oral cavity and oropharynx. <i>Oman Medical Journal</i> , 2016. 31(3): p. 165-169.	Prognosis, not diagnostic test study
8. Al-Omar, E., Future of optical biopsy in diagnosis of oral squamous cell carcinoma (OSCC): A review and meta-analysis of relevant published studies. <i>Lasers in Surgery and Medicine</i> , 2016. 48: p. 39-40.	Systematic review of optical biopsy
9. Alpaslan, C., et al., The role of direct fluorescence visualization for screening of oral cancer in dental patients and its impact on raising awareness. <i>Oral Oncology</i> , 2013. 49: p. 552.	Abstract only
10. Anderson, W.D., et al., Oral lesions you can't afford to miss. <i>Journal of Family Practice</i> , 2015. 64(7): p. 392-399.	Review of different lesion types
11. Andratschke, M., et al., Cytological and immunocytological monitoring of oropharyngeal dysplasia and squamous cell carcinomas. <i>Anticancer Research</i> , 2015. 35(12): p. 6517-6520.	Oral squamous cell carcinoma cases were confirmed already
12. Anonymous, DenMat, LED dental's VELscope Vx: saving lives by detecting oral cancer early. <i>Compendium of Continuing Education in Dentistry</i> , 2013. 34(1): p. 74.	News article about VELscope
13. Anonymous, U.S. Task Force unable to recommend for or against oral cancer screenings by physicians. <i>Journal of the California Dental Association</i> , 2014. 42(2): p. 86.	Review article
14. Aravindh Babu, N., et al., Salivary markers in cancer diagnosis—A review. <i>Research Journal of Pharmaceutical, Biological and Chemical Sciences</i> , 2014. 5(2): p. 1655-1658.	Review of salivary biomarkers
15. Bacci, C., et al., A comparison between histologic and clinical diagnoses of oral lesions. <i>Quintessence International</i> , 2014. 45(9): p. 789-94.	Comparison of histologic and clinical diagnosis; no mention of any adjuncts of interest
16. Balasubramaniam, A.M., et al., Autofluorescence based diagnostic techniques for oral cancer. <i>Journal of pharmacy and bioallied sciences</i> . 2015. 7(Suppl 2): p. S374-7.	Review of autofluorescence adjuncts
17. Bhatia, N., M.A. Matias, and C.S. Farah, Assessment of a decision making protocol to improve the efficacy of VELscope™ in general dental practice: a prospective evaluation. <i>Oral Oncology</i> , 2014. 50(10): p. 1012-9.	Not all patients receiving VELscope examination received criterion standard
18. Bhoopathi, V. and A.K. Mascarenhas, Utility of oral cancer diagnostic adjuncts in the adult US populations. <i>Journal of Oral Pathology & Medicine</i> , 2013. 42(5): p. 363-7.	Imputed oral cancer prevalence and oral cancer prevalence in high- and low-risk groups. This article describes sensitivity analyses of experimenting with different values for sensitivity and specificity.
* The authors of the 2015 Cochrane review ⁸ included Sharwani 2006a, Sharwani 2006b, Remmerbach 2009, Leunig 2000, and Kulapaditharom 1998, but we excluded them in this review.	

eTABLE 3 (CONTINUED)

REFERENCE	REASON FOR EXCLUSION
19. Bumb, D., et al., Oral visual examination for early detection of potentially malignant mucosal disorders in an opportunistic population. <i>Oral Oncology</i> , 2014. 50(1): p. e3-4.	Letter to the editor
20. Casparis, S., et al., Transepithelial brush biopsy—Oral CDx—A noninvasive method for the early detection of precancerous and cancerous lesions. <i>Journal of Clinical and Diagnostic Research</i> , 2014. 8(2): p. 222-226.	Cannot construct a 2 × 2 table; 207 patients did not receive confirmation biopsy
21. Chaudhari, V.V., et al., Sediment cytology in diagnostic evaluation of oral neoplasms. <i>Indian Journal of Dental Research: Official Publication of Indian Society for Dental Research</i> , 2014. 25(2): p. 147-149.	Details a technique for obtaining cytologic smears from a biopsy specimen
22. Cheng, Y.S., T. Rees, and J. Wright, A review of research on salivary biomarkers for oral cancer detection. <i>Clinical and Translational Medicine</i> , 2014. 3(1): p. 3.	Review article about salivary biomarkers
23. Cheng, Y.S., T. Rees, and J. Wright, Updates regarding diagnostic adjuncts for oral squamous cell carcinoma. <i>Texas Dental Journal</i> , 2015. 132(8): p. 538-49.	Review article
24. Chhabra, N., S. Chhabra, and N. Sapra, Diagnostic modalities for squamous cell carcinoma: an extensive review of literature—considering toluidine blue as a useful adjunct. <i>Journal of Maxillofacial & Oral Surgery</i> , 2015. 14(2): p. 188-200.	Review of different adjuncts
25. Desai, V.D. and P. Narang, Utility of toluidine blue staining in the detection of oral epithelial dysplasia: A diagnostic adjunct. <i>Indian Journal of Public Health Research and Development</i> , 2015. 6(1): p. 80-85.	Criterion standard applied before index test
26. Dolens Eda, S., et al., Cytopathology: a useful technique for diagnosing oral lesions? a systematic literature review. <i>Diagnostic Cytopathology</i> , 2013. 41(6): p. 505-14.	Systematic review
27. Douthwaite, S., et al., Contact endoscopy as a novel technique in the detection and diagnosis of oral cavity and oropharyngeal mucosal lesions in the head and neck. <i>Journal of Laryngology and Otology</i> , 2014. 128(2): p. 147-152.	No examination of any of the adjuncts of interest
28. Edwards, P.C., Oral cancer screening for asymptomatic adults: Do the United States Preventive Services Task Force draft guidelines miss the proverbial forest for the trees? <i>Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology</i> , 2013. 116(2): p. 131-134.	Review article of the United States Preventive Services guidelines
29. Elvers, D., et al., Margins of oral leukoplakia: autofluorescence and histopathology. <i>British Journal of Oral & Maxillofacial Surgery</i> , 2015. 53(2): p. 164-9.	Target condition was not appropriate
30. Epstein, J.B., Screening for oral potentially malignant epithelial lesions and squamous cell carcinoma: a discussion of benefit and risk. <i>Journal (Canadian Dental Association)</i> , 2014. 80: p. e47.	Review article of the United States Preventive Services guidelines
31. Francisco, A.L., et al., Fluorescence spectroscopy for the detection of potentially malignant disorders and squamous cell carcinoma of the oral cavity. <i>Photodiagnosis & Photodynamic Therapy</i> , 2014. 11(2): p. 82-90.	Cannot calculate sensitivity and specificity
32. Frustino, J., et al., Sensitivity and specificity of autofluorescent screening in addition to white light exam across anatomical subsites of the oral cavity and oropharynx. <i>Oral Oncology</i> , 2013. 49: p. S49.	Abstract only
33. Fuller, C., et al., Adjunctive diagnostic techniques for oral lesions of unknown malignant potential: Systematic review with meta-analysis. <i>Head & Neck</i> , 2015. 37(5): p. 755-62.	Systematic review
34. Gillani, M., et al., Diagnostic accuracy, sensitivity, specificity and positive predictive value of fine needle aspiration cytology (FNAC) in intra oral tumors. <i>Asian Pacific Journal of Cancer Prevention: Apjcp</i> , 2012. 13(8): p. 3611-5.	Comparison of fine-needle aspiration versus biopsy in tumors
35. Gillenwater, A.M., et al., Observation of patients with oral potentially malignant disorders using autofluorescence imaging and spectroscopy. <i>Otolaryngology—Head and Neck Surgery (United States)</i> , 2013. 1): p. P71-P72.	Abstract only

eTABLE 3 (CONTINUED)

REFERENCE	REASON FOR EXCLUSION
36. Giovannacci, I., et al., Non-invasive visual tools for diagnosis of oral cancer and dysplasia: A systematic review. <i>Medicina Oral, Patología Oral y Cirugía Bucal</i> , 2016. 21(3): p. e305-e315.	Systematic review of adjuncts
37. Goodson, M.L., et al., Brush versus scalpel: Consensus agreement on orcellex brush cytology versus incisional biopsy. <i>Oral Oncology</i> , 2013. 49: p. S96-S97.	Abstract only
38. Gottehrer, N. and J. Martin, Evaluation of salivary transcriptome markers for early detection of squamous cell cancer in a prospective blinded trial. <i>Cancer Research. Conference: 106th Annual Meeting of the American Association for Cancer Research, AACR</i> , 2015. 75(15 SUPPL. 1).	Abstract only
39. Graveland, A.P., et al., Molecular screening of oral precancer. <i>Oral Oncology</i> , 2013. 49(12): p. 1129-1135.	Cannot calculate sensitivity and specificity
40. Gupta, S., et al., Clinical correlative study on early detection of oral cancer and precancerous lesions by modified oral brush biopsy and cytology followed by histopathology. <i>Journal of Cancer Research and Therapeutics</i> , 2014. 10(2): p. 232-238.	Cannot construct a 2 × 2 table; criterion standard not applied to all lesions
41. Gupta, V. and K.M. Hiwale, Oral lesions: A comparative study of cytology and histopathology in rural population of India. <i>Acta Cytologica</i> , 2013. 57: p. 105.	Abstract only
42. Gupta, V., K.M. Hiwale, and A. Bhake, Cytopathological criteria of oral carcinoma: A study in rural population of India. <i>Acta Cytologica</i> , 2013. 57: p. 107.	Abstract only
43. Hartmann, S., et al., Oral brush biopsy and melanoma-associated antigens A (MAGE-A) staining in clinically suspicious lesions. <i>Journal of Cranio-Maxillofacial Surgery</i> , 2015. 43(10): p. 2214-2218.	Biomarkers were measured from the biopsy specimen; not a salivary diagnostic
44. Jayanth Kumar, V. and T.N. Uma Maheswari, In-vivo autofluorescence spectroscopy in oral cancer diagnosis: A systematic review. <i>International Journal of Pharma and Bio Sciences</i> , 2014. 5(1): p. B252-B260.	Systematic review
45. Jayaprakash, V., et al., Autofluorescence visualization for detecting potentially malignant white oral mucosal lesions. <i>Oral Oncology</i> , 2013. 49: p. S50.	Abstract only
46. Jo, J.A., et al., In vivo early detection of oral epithelial cancer by endogenous fluorescence lifetime imaging (FLIM) Endoscopy. <i>Molecular Imaging and Biology</i> , 2016. 1): p. S1359-S1360.	Poster presentation
47. Kabiraj, A., et al., Screening of oral potentially malignant disorders using exfoliative cytology: A diagnostic modality. <i>Journal of Cancer Epidemiology</i> , 2016. 2016 (no pagination)(8134832).	No criterion standard
48. Kasthuri, M., et al., Toluidine blue staining in the diagnosis of oral precancer and cancer: Stains, technique and its uses—A review. <i>Biomedical and Pharmacology Journal</i> , 2015. 8SE: p. 519-522.	Review article
49. Kaur, J. and R. Jacobs, Combination of autofluorescence imaging and salivary protoporphyrin in oral precancerous and cancerous lesions: Non-invasive tools. <i>Journal of Clinical & Experimental Dentistry</i> , 2015. 7(2): p. e187-191.	Case-control study
50. Kaur, M., et al., Evaluation of brush cytology and DNA image cytometry for the detection of cancer of the oral cavity. <i>Diagnostic Cytopathology</i> , 2016. 44(3): p. 201-205.	Cytologic testing with DNA image cytometry
51. Kordbacheh, F., N. Bhatia, and C.S. Farah, Patterns of differentially expressed genes in oral mucosal lesions visualised under autofluorescence (VELscopeTM). <i>Oral Diseases</i> , 2016. 22(4): p. 285-296.	Adjunct was not applied clinically.
52. Krishnan, R., et al., Association of serum and salivary tumor necrosis factor-alpha with histological grading in oral cancer and its role in differentiating premalignant and malignant oral disease. <i>Asian Pacific Journal of Cancer Prevention: Apjcp</i> , 2014. 15(17): p. 7141-7148.	Case-control study; cannot tell which patients were included in sensitivity and specificity calculations

eTABLE 3 (CONTINUED)

REFERENCE	REASON FOR EXCLUSION
53. Kulapaditharom, B. and V. Boonkitticharoen, Laser-induced fluorescence imaging in localization of head and neck cancers. <i>Ann Otol Rhinol Laryngol</i> , 1998. 107(3): p. 241-246.*	Cannot construct 2 × 2 table
54. Lalla, Y., M. Matias, and C.S. Farah, Oral mucosal disease in an Australian urban Indigenous community using autofluorescence imaging and reflectance spectroscopy. <i>Australian Dental Journal</i> , 2015. 60(2): p. 216-224.	Cannot construct a 2 × 2 table; only 2 participants received the criterion standard
55. Laronde, D.M., et al., Decision making on detection and triage of oral mucosa lesions in community dental practices: screening decisions and referral. <i>Community Dentistry & Oral Epidemiology</i> , 2014. 42(4): p. 375-384.	Use of VELscope was exploratory; no criterion standard applied
56. Leon, M., B. Centeno, and E. Kostas-Polston, Comparison of liquid based cytology of direct brush and saliva specimens in oral and oropharyngeal squamous cell carcinomas. <i>Laboratory Investigation</i> , 2015. 95: p. 96A.	Data for histologic diagnosis not available
57. Liao, L.J., et al., Initial outcomes of an integrated outpatient-based screening program for oral cancers. <i>Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology</i> , 2015. 119(1): p. 101-106.	No mention of the adjuncts of interest
58. Liu, D., et al., Non-invasive techniques for detection and diagnosis of oral potentially malignant disorders. <i>Tohoku Journal of Experimental Medicine</i> , 2016. 238(2): p. 165-177.	Review of adjuncts
59. Ma, J.M., et al., Brush biopsy with DNA-image cytometry: a useful and noninvasive method for monitoring malignant transformation of potentially malignant oral disorders. <i>European Archives of Oto-Rhino-Laryngology</i> , 2014. 271(12): p. 3291-3295.	Cytologic testing with DNA image cytometry
60. Mandlik, D., et al., Use of 90 Hopkin's telescopic examination as an OPD tool to clinically evaluate and record oral cavity lesions: Our experience in early detection, especially in patients with limited mouth opening. <i>Journal of Clinical and Diagnostic Research</i> , 2015. 9(6): p. XC01-XC04.	90 Hopkin telescopic examination not an adjunct of interest; patients with confirmed oral squamous cell carcinoma in the study sample
61. Marques, A.E., et al., Assessing oral brushing technique as a source to collect DNA and its use in detecting human papilloma-virus. <i>Pathology, Research & Practice</i> , 2013. 209(5): p. 291-295.	Human papilloma virus diagnosis in healthy people with brush cytologic testing; no criterion standard was applied
62. McNamara, K.K., et al., The role of direct visual fluorescent examination (VELscope) in routine screening for potentially malignant oral mucosal lesions. <i>Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology</i> , 2012. 114(5): p. 636-643.	Criterion standard not applied to the whole population
63. Messadi, D.V., Diagnostic aids for detection of oral precancerous conditions. <i>International Journal of Oral Science</i> , 2013. 5(2): p. 59-65.	Review article
64. Messadi, D.V., et al., The clinical effectiveness of reflectance optical spectroscopy for the in vivo diagnosis of oral lesions. <i>International Journal of Oral Science</i> , 2014. 6(3): p. 162-167.	Cannot construct a 2 × 2 table because the authors report only cluster of differentiation 4 counts not a final diagnosis
65. Mori, K., et al., Oral cancer diagnosis via a ferrocenylnaphthalene diimide-based electrochemical telomerase assay. <i>Clinical Chemistry</i> , 2013. 59(1): p. 289-295.	Oral squamous cell carcinomas were confirmed already; adjunct not of interest
66. Nagi, R., et al., Efficacy of light based detection systems for early detection of oral cancer and oral potentially malignant disorders: Systematic review. <i>Medicina Oral, Patologia Oral y Cirugia Bucal</i> , 2016. 21(4): p. e447-e455.	Systematic review
67. Navone, R., et al., Diagnostic cytopathology and DNA HPV testing for oral cancer screening. <i>Oral Diseases</i> , 2016. 22: p. 35.	Abstract only
68. Navone, R., et al., Oral microhistology: An innovative technique for oral lesion diagnosis. <i>Oral Diseases</i> , 2016. 22: p. 36.	Conference abstract
69. Ohnishi, Y., et al., Usefulness of a fluorescence visualization system for the detection of oral precancerous and early cancerous lesions. <i>Oncology Reports</i> , 2016. 36(1): p. 514-520.	Rat model; patients already had oral cancer
70. Omar, E.A., Current concepts of optical biopsy in diagnosis of oral squamous cell carcinoma (OSCC): Literatures review. <i>Head and Neck</i> , 2015. 37: p. E133-E134.	Conference abstract

eTABLE 3 (CONTINUED)

REFERENCE	REASON FOR EXCLUSION
71. Paderni, C., et al., Direct visualization of oral-cavity tissue fluorescence as novel aid for early oral cancer diagnosis and potentially malignant disorders monitoring. <i>International Journal of Immunopathology & Pharmacology</i> , 2011. 24(2 Suppl): p. 121-128.	Cannot construct a 2 × 2 table; thresholds are not clear for positivity
72. Porter, S., et al., Non-invasive diagnostic AIDS for oral cancer and epithelial dysplasia. <i>Oral Diseases</i> , 2016. 22: p. 23.	Abstract only
73. Rashid, A. and S. Warnakulasuriya, The use of light-based (optical) detection systems as adjuncts in the detection of oral cancer and oral potentially malignant disorders: A systematic review. <i>Journal of Oral Pathology and Medicine</i> , 2015. 44(5): p. 307-328.	Systematic review
74. Remmerbach, T.W., et al., Toward a multimodal cell analysis of brush biopsies for the early detection of oral cancer. <i>Cancer</i> , 2009. 117(3): p. 228-235.*	Cannot construct a 2 × 2 table
75. Richards, D., Adjunctive tests cannot replace scalpel biopsy for oral cancer diagnosis. <i>Evidence-Based Dentistry</i> , 2015. 16(2): p. 46-47.	Commentary
76. Sahebamee, M., et al., Conventional versus Papanicolaou-stained cytobrush biopsies in the diagnosis of oral squamous cell carcinoma. <i>Oral Health & Dental Management</i> , 2014. 13(3): p. 619-622.	Cannot construct a 2 × 2 table
77. Salih, M.M., O.H. Maha, and A.H.E. Nabi, Comparison between exfoliative cytology and histopathology in detecting oral squamous cell carcinoma. <i>Acta Cytologica</i> , 2016. 60: p. 215.	Abstract only
78. Santos, A., et al., Oral cancer's early diagnosis: The contribution of contact endoscopy. <i>Otolaryngology-Head and Neck Surgery (United States)</i> , 2014. 1): p. P61.	Abstract only
79. Santos, T., et al., Toluidine blue can be useful to identify severe oral dysplasia with high Ki-67 Labeling index. <i>Oral Oncology</i> , 2013. 49: p. S131.	Abstract only
80. Sawan, D. and A. Mashlah, Evaluation of premalignant and malignant lesions by fluorescent light (VELscope). <i>Journal of International Society of Preventive & Community Dentistry</i> , 2015. 5(3): p. 248-254.	Cannot construct a 2 × 2 table
81. Sekine, J. and H. Sasaki, Diagnostic performance of oral cancer cytology in a pilot study. <i>Acta Cytologica</i> , 2016. 60: p. 137.	Conference abstract
82. Siebers, T.J.H., et al., The value of the oral brush in identifying precancerous and cancerous lesions. <i>Oral Oncology</i> , 2013. 49: p. S70.	Abstract only
83. Sharwani, A., et al., Fluorescence spectroscopy combined with 5-aminolevulinic acid-induced protoporphyrin IX fluorescence in detecting oral premalignancy. <i>J Photochem Photobiol B</i> , 2006. 83(1): p. 27-33.*	5-Aminolevulinic acid not commercially available in the United States
84. Sharwani, A., et al., Assessment of oral premalignancy using elastic scattering spectroscopy. <i>Oral Oncol</i> , 2006. 42(4): p. 343-349.*	Elastic scattering spectroscopy not commercially available in the United States
85. Spivakovsky, S. and M.G. Gerber, Little evidence for the effectiveness of chemiluminescence and autofluorescent imaging devices as oral cancer screening adjuncts. <i>Evidence-Based Dentistry</i> , 2015. 16(2): p. 48.	Commentary
86. Sudheendra, U.S., H.S. Sreeshyla, and R. Shashidara, Vital tissue staining in the diagnosis of oral precancer and cancer: Stains, technique, utility, and reliability. <i>Clinical Cancer Investigation Journal</i> , 2014. 3(2): p. 141-145.	Review article
87. Vashisht, N., et al., Chemiluminescence and Toluidine blue as diagnostic tools for detecting early stages of oral cancer: An invivo study. <i>Journal of Clinical and Diagnostic Research</i> , 2014. 8(4).	Cannot construct a 2 × 2 table
88. Wang, J.H., et al., Bimodal optical diagnostics of oral cancer based on Rose Bengal conjugated gold nanorod platform. <i>Bio-materials</i> , 2013. 34(17): p. 4274-4283.	Phase 1 study
89. Yang, S.W., et al., Light sources used in evaluating oral leukoplakia: Broadband white light versus narrowband imaging. <i>International Journal of Oral and Maxillofacial Surgery</i> , 2013. 42(6): p. 693-701.	Adjunct is endoscopy.
90. Leunig, A., et al., Detection of squamous cell carcinoma of the oral cavity by imaging 5-aminolevulinic acid-induced protoporphyrin IX fluorescence. <i>Laryngoscope</i> , 2000. 110(1): p. 78-83.*	5-Aminolevulinic acid not commercially available in the United States

eTABLE 4

Characteristics of the included studies.								
STUDY	COUNTRY	SETTING	PARTICIPANTS	AGE, Y, RANGE, MEAN (STANDARD DEVIATION) OR MEDIAN	SEX, NO. (%)	INDEX TEST*	NO. OF LESIONS INCLUDED IN ANALYSES	SEVERITY†
Mashberg,⁵⁵ 1980	United States	Veterans Administration medical center, secondary	The investigators conducted a thorough examination of the oral soft tissue in most patients; if asymptomatic mucosal alterations were visible, then the investigators referred patients for an evaluation, and then rescheduled the patients 10 to 14 days later for reevaluation and tuberculosis testing. Implied that the 14-day period was part of the recruitment process and that patients were not deemed part of the study if the lesions did not persist. Conditions recorded: squamous cell carcinoma (invasive), carcinoma in situ, atypia, and benign (hyperplasia, keratosis, inflammation, and so on)	Not reported	Not reported	Vital staining, toluidine blue	235	Asymptomatic mucosal alterations
Silverman and Colleagues,⁵⁸ 1984	United States	Oral medicine clinic, secondary	"The study group comprised 132 consecutive patients seen in the oral medicine clinic who were suspected of having oral carcinomas or precancerous (dysplastic) lesions."	Not reported	Not reported	Vital staining, toluidine blue	132	"Suspected of having oral carcinomas or precancerous (dysplastic) lesions"
Warnakulasuriya and Johnson,⁶⁰ 1996	Sri Lanka and Pakistan	Dental surgeon clinic, secondary	All patients had been referred to, or had attended, the specialist centers with unconfirmed oral mucosal lesions.	60 (15)	Female: 29 (28.4), male: 73 (71.6)	Vital staining, OraScan (Zila Inc), toluidine blue	86	Invasive and dysplastic lesions (such as benign keratoses)
Onizawa and Colleagues,²⁹ 1999	Japan	Oral and maxillofacial division at hospital, tertiary	Participants had been referred to the Division of Oral and Maxillofacial Surgery, University Hospital of Tsukuba Hospital, Japan, for examination and treatment of oral lesions.	23-92, 60	Female: 53 (40.8), male: 77 (59.2)	Autofluorescence, fluorescence photography with ultraviolet flash	124	Unclear
* We compared all index tests against biopsy results as the criterion standard.								
† The target condition was oral squamous cell carcinoma, potentially malignant disorders, or dysplasia in all studies.								

eTABLE 4 (CONTINUED)

STUDY	COUNTRY	SETTING	PARTICIPANTS	AGE, Y, RANGE, MEAN (STANDARD DEVIATION) OR MEDIAN	SEX, NO. (%)	INDEX TEST*	NO. OF LESIONS INCLUDED IN ANALYSES	SEVERITY†
Sciubba, ⁴⁴ 1999	United States	Dentists specializing in oral and maxillofacial pathology, oral medicine, and oral surgery obtained the specimens in the course of their routine clinical practice, secondary	"Suspicious lesions (categorized as Class I) were analysed by use of both OralCDx (OralScan Laboratories, Inc.) and scalpel biopsy. Apparently innocuous lesions (categorized as Class II) that, in the investigators' opinion, required no further attention other than clinical follow-up were tested only by use of OralCDx. Patients with apparently innocuous lesions that produced abnormal OralCDx results, as defined below, subsequently were subjected to scalpel biopsy at the investigators' discretion."	18-83, 55	Female: 502 (53), male: 443 (47)	Cytologic testing, OralCDx	298	"Intraoral lesions displaying an epithelial component" then classified into suspicious and innocuous
Onofre and Colleagues, ⁵⁷ 2001	Brazil	Hospital-based sample, tertiary	"Fifty patients with potentially malignant epithelial lesions and superficial oral ulcerations suggestive of malignancy were selected from those treated at the Oral Medicine Service, Faculty of Dentistry, Araraquara, Brazil from August 1993 to May 1995 (n = 1957)." "Not included in this study were patients who refused to be submitted to biopsy (n = 21), those who abandoned treatment, or those who had clinically obvious invasive carcinomas or lesions without risk or suspicion of malignancy."	55.2 (13.4)	Female: 22 (44), male: 28 (56)	Vital staining, toluidine blue	50	Potentially malignant epithelial lesions and superficial oral ulcerations suggestive of malignancy
Svirsky and Colleagues, ⁴⁶ 2002	United States	Pathology laboratories, secondary	Method of patient selection: 298 patients underwent scalpel biopsy who also had undergone brush biopsy that had abnormal results	18-89, 52	Female: 146 (51), male: 152 (49)	Cytologic testing, OralCDx	298	Patients undergoing brush biopsy
Cheng and Yang, ⁵³ 2003a	China	University clinic, secondary	Patients with mucosal lesion	7-76, 58.3	Female: 53 (89), male: 7 (11)	Vital staining, Oratest (Zila Inc.) rinse	30	Not stated
Cheng and Yang, ⁵³ 2003b	China	University clinic, secondary	Patients with mucosal lesion	7-76, 58.3	Female: 53 (89), male: 7 (11)	Vital staining, Oratest stain	30	Not stated
Navone and Colleagues, ³⁹ 2004	Italy	Oral pathology service of university hospital, tertiary	Method of patient selection: patients with lesions clinically identified as suggestive of carcinoma or dysplasia	68.9 (14.33)	Female: 44 (49), male: 45 (51)	Cytologic testing, Cytobrush (Cooper Surgical)	78	Unclear

eTABLE 4 (CONTINUED)

STUDY	COUNTRY	SETTING	PARTICIPANTS	AGE, Y, RANGE, MEAN (STANDARD DEVIATION) OR MEDIAN	SEX, NO. (%)	INDEX TEST*	NO. OF LESIONS INCLUDED IN ANALYSES	SEVERITY†
Scheifele and Colleagues,⁴³ 2004	Germany	Hospital-based sample, tertiary	80 consecutive patients between July 2002 and September 2003. Inclusion criteria: "(1) an OralCDx brush biopsy of a lesion with the clinical diagnosis oral leukoplakia (OL), oral lichen planus (OLP), or obvious oral squamous cell carcinoma (OSCC); and (2) a scalpel biopsy that had been performed within one month before or after the brush biopsy of the same lesion." Only those who underwent scalpel biopsy were included in the study, not full spectrum of disease, leading to potential sampling bias	58.6 (13.1)	Female: 33 (41.3), male: 47 (58.8)	Cytologic testing, OralCDx	96	OralCDx brush biopsy of a lesion with the clinical diagnosis of oral leukoplakia, oral lichen planus, or oral squamous cell carcinoma
Chen and Colleagues,⁵² 2007	Taiwan	Unclear	Suspicious oral lesions	Not reported	Not reported	Vital staining, methylene blue	58	Homogeneous leukoplakia, heterogeneous leukoplakia, erythroplakia, and ulceration
Du and Colleagues,⁵⁴ 2007	China	Hospital, tertiary	Superficial ulceration suggestive of malignancy: oral leukoplakia, oral lichen planus, oral leukokeratosis Excluded: benign oral lesions and lesions without a histologic result after clinical diagnosis	50.1 (12.6)	Female: 67 (52.3), male: 61 (47.7)	Vital staining, rose bengal	128	All patients suspected of having malignancy, leukoplakia, lichen planus, or leukokeratosis
Farah and McCullough,⁶³ 2007	Australia	Oral medicine specialist, tertiary	55 patients referred to an oral medicine specialist service over a 3-month period for assessment of an oral mucosal white lesion were screened prospectively with ViziLite (DenMat Holdings, LLC)	Female: 58.7 (2.47), male: 56.81 (2.2)	Female: 29 (53), male: 26 (47%)	Tissue reflectance, ViziLite	55	Oral mucosal white lesion
Gupta and Colleagues,⁷⁰ 2007	India	Otorhinolaryngology outpatient clinic, secondary	Screening of 96 patients with suspicious oral lesions who sought care at the outpatients clinics of the Otorhinolaryngology Department, Swaroop Rani Nehru Hospital, Allahabad, India	Benign and malignant: 19-75, 38; squamous cell carcinoma: 35-74, 52	Benign and malignant: female: 22 (34.4), male: 42 (65.6); squamous cell carcinoma: female: 8 (25), male: 24 (75)	Cytologic testing and vital staining, toluidine blue and brush cytologic testing	96	"Suspicious pre-malignant or malignant lesions of the oral cavity irrespective of site, stage and sex were selected."
Epstein and Colleagues,⁶⁷ 2008	United States	University and cancer clinics, secondary	Investigators identified patients who had a history of oral lesions or were at high risk of developing an oral lesion and asked them to participate.	59.64 (12.53)	Female: 43 (51.19); male: 41 (48.8)	Tissue reflectance and vital staining, ViziLite and toluidine blue	97	Patients identified with a lesion at conventional visual examination

eTABLE 4 (CONTINUED)

STUDY	COUNTRY	SETTING	PARTICIPANTS	AGE, Y, RANGE, MEAN (STANDARD DEVIATION) OR MEDIAN	SEX, NO. (%)	INDEX TEST*	NO. OF LESIONS INCLUDED IN ANALYSES	SEVERITY†
Mehrotra and Colleagues,³⁷ 2008	India	Otorhinolaryngology and pathology department at medical college, secondary	"Ninety-four patients with suspicious oral lesions from Departments of Otorhinolaryngology and Pathology, Moti Lal Nehru Medical College, Allahabad, India, were studied in a random manner."	10-80	Female: 19 (24), male: 60 (76)	Cytologic testing, baby toothbrush	79	"Only lesions with an abnormal epithelial surface including erythroplakia, leukoplakia without dysplasia and oral submucous fibrosis were included."
Navone and Colleagues,⁴⁰ 2008	Italy	Oral medicine section of a university hospital, tertiary	Patients with oral potentially malignant epithelial lesions, referred to the Oral Medicine Section of the University of Turin, Turin, Italy, entered this study. Patients with clinical features suggestive of carcinoma were not excluded. "In the present study, all included patients already had a clinically suspicious lesion."	Not reported	Not reported	Cytologic testing, curette	158	Potentially malignant epithelial lesions
Allegra and Colleagues,⁴⁸ 2009	Italy	Department of otolaryngology–head and neck surgery, tertiary	Patients with oral mucosal lesions	42-82, 59	Female: 13 (40.6), male: 19 (59.4)	Vital staining, toluidine blue	45	Nonneoplastic, mild dysplasia, moderate dysplasia, severe dysplasia, in situ carcinoma, invasive carcinoma
McIntosh and Colleagues,⁶⁴ 2009	Australia	Oral medicine specialist unit, tertiary	"Patients presenting to an oral medicine specialist unit for assessment of an oral mucosal lesion were recruited into the study." "The only criterion for inclusion was referral for examination of an oral mucosal white lesion that was deemed to be clinically suspicious and warranted further evaluation by routine measures including definitive histopathology."	26-87.2, 56.6	Female: 27 (54), male: 23 (46)	Tissue reflectance, MicroLux (AdDent Inc.)	50	"Clinically suspicious lesions, sufficient to be referred to an oral medicine specialist unit for assessment"
Delavarian and Colleagues,³² 2010	Iran	University clinic, secondary	Lesions clinically diagnosed as oral potentially malignant lesions (leukoplakia) or malignant lesions (oral squamous cell cancer and verrucous carcinoma)	22-79, 54 (17.38)	Female: 12 (48), male: 13 (52)	Cytologic testing, OralCDx	26	Lesions clinically diagnosed as oral potentially malignant lesions (leukoplakia) or malignant lesions (oral squamous cell cancer and verrucous carcinoma)

eTABLE 4 (CONTINUED)

STUDY	COUNTRY	SETTING	PARTICIPANTS	AGE, Y, RANGE, MEAN (STANDARD DEVIATION) OR MEDIAN	SEX, NO. (%)	INDEX TEST*	NO. OF LESIONS INCLUDED IN ANALYSES	SEVERITY†
Mehrotra and Colleagues,²⁸ 2010	India	Outpatient department of hospital, secondary	Patients selected for study after detection of a clinically innocuous lesion (Class II) during routine dental care "Patients with Class II lesions for subsequent evaluation with the light-based adjunct screening tools We excluded patients with Class I lesions detected with a conventional overhead examination light (and referred them for treatment) and those without any oral lesions."	Median: 41	Male to female ratio of 7.5:1	Autofluorescence, VELscope (LED Dental)	156	Identified as Class II before biopsy, so patients with lesions classified as Class I ("suspicious enough to warrant a biopsy") were excluded
Mehrotra and Colleagues,²⁸ 2010	India	Outpatient department of hospital, secondary	Method of patient selection: patients selected for study after detection of a clinically innocuous lesion (Class II) during routine dental care "Patients with Class II lesions for subsequent evaluation with the light-based adjunct screening tools We excluded patients with Class I lesions detected with a conventional overhead examination light (and referred them for treatment) and those without any oral lesions."	Median: 39	Male to female ratio of 8.7:1	Tissue reflectance and vital staining, ViziLite Plus (DenMat Holdings, LLC)	102	Identified as Class II before biopsy, so patients with lesions classified as Class I ("suspicious enough to warrant a biopsy") were excluded
Nagaraju and Colleagues,⁵⁶ 2010	India	Department of oral medicine and radiology, dental college and hospital, secondary	The study group consisted of 60 participants of both sexes, 30 participants with clinically suspicious premalignant lesions and 30 participants with clinically suspicious malignant lesions. "Subjects who fulfilled the following criteria were selected for the study: leukoplakia, speckled leukoplakia, erosive lichen planus, oral malignancy."	Not reported	Not reported	Vital staining, toluidine blue and Lugol iodine	60	Premalignant lesions (degree of dysplasia), malignant lesions (degree of differentiation)
Awan and Colleagues,²⁴ 2011a	United Kingdom	Oral medicine clinics, secondary	Patients seeking care at an oral medicine clinic with white, red, or mixed lesions	58.5 (11.9)	Female: 56 (44.4), male: 70 (55.6)	Autofluorescence, VELscope	116	White, red, and mixed white and red patches
Awan and Colleagues,⁶⁶ 2011b	United Kingdom	Oral medicine clinics, secondary	Patients seeking care at an oral medicine clinic with white, red, or mixed lesions	58.5 (11.9)	Female: 56 (44.4), male: 70 (55.6)	Tissue reflectance, ViziLite	116	White, red, and mixed white and red patches

eTABLE 4 (CONTINUED)

STUDY	COUNTRY	SETTING	PARTICIPANTS	AGE, Y, RANGE, MEAN (STANDARD DEVIATION) OR MEDIAN	SEX, NO. (%)	INDEX TEST*	NO. OF LESIONS INCLUDED IN ANALYSES	SEVERITY†
Cancela-Rodríguez and Colleagues,⁵⁰ 2011	Spain	University clinic, secondary	Patients with mucosal lesions	13-100, 55.3 (16.1)	Female: 83 (51.9), male: 77 (48.1)	Vital staining, toluidine blue	160	Participants with benign lesions or clinically suspicious premalignant or malignant lesions that were white or red, exophytic, or manifesting as nonhealing ulcers
Güneri and Colleagues,⁶⁹ 2011	Turkey	University clinic, secondary	"Thirty-five patients with oral mucosal lesions identified by the Orofacial Lesions Council of Ege University, Izmir, Turkey, were seen for further evaluation."	56.2	Female: 22 (62.9), male: 13 (37.1)	Cytologic testing and vital staining, toluidine blue and Cytobrush	43	"Lesions selected for further examination with Tblue staining and brush cytology were homogenous and non-homogenous leukoplakia, reticular erosive/ulcerated lichenoid lesions, and superficial ulcerations suspicious of malignancy."
Koch and Colleagues,³⁵ 2011a	Germany	Maxillofacial surgery clinic in a hospital, tertiary	"All patients attended the Maxillofacial Surgery Clinic at the University Hospital in Mainz, Germany and were examined between September 2005 and December 2007...to be included lesion was required to be clinically diagnosed as SCC or suspicious epithelial lesion and most suspicious area of lesion was tested and biopsied"	62.8 (18.3)	Approximately 2:1 (unclear)	Cytologic testing, Cytobrush Plus GT (Cooper Surgical)	182	Clinically diagnosed as squamous cell carcinoma or suspicious epithelial lesions
Koch and Colleagues,²⁷ 2011b	Germany	Maxillofacial surgery clinic, secondary	"78 patients participating in the study attended the outpatient clinic of the Oral and Maxillofacial Surgery clinic of the Mainz University Medical Centre and suffered from suspicious oral mucosal lesions"	61.7	Female: 32 (41), male: 46 (59%)	Autofluorescence, "Two different investigation methods were applied: the standard examination by white light and the examination by a 400-nanometer wavelength light source that is supposed to trigger a green light emission (>500 nm) in normal mucosa." Documented with digital reflex photography	78	41% red, like erythroplakia (17%) or erythroleukoplakia (24%); 21% white, like leukoplakia

eTABLE 4 (CONTINUED)

STUDY	COUNTRY	SETTING	PARTICIPANTS	AGE, Y, RANGE, MEAN (STANDARD DEVIATION) OR MEDIAN	SEX, NO. (%)	INDEX TEST*	NO. OF LESIONS INCLUDED IN ANALYSES	SEVERITY†
Mehrotra and Colleagues,³⁶ 2011	India	Outpatient otorhinolaryngology department at a medical college, secondary	"Patients who were at least 18 years of age presenting with unrelated complaints to the outpatient Department of Otorhinolaryngology, Moti Lal Nehru Medical College in Allahabad, were screened by a team of specialist and residents-in-training between July and November 2010. Patients with an oral epithelial abnormality that appeared clinically benign—minimally suspicious—and did not have an obvious etiology such as trauma or infection were prospectively enrolled." "Patients with oral lesions suggestive of dysplasia or cancer were excluded."	25-75, 45.5	Female: 30 (35.3), male: 55 (64.7)	Cytologic testing, OralCDx	79	"Patients with an oral epithelial abnormality that appeared clinically benign—minimally suspicious—and did not have an obvious etiology such as trauma or infection were prospectively enrolled."
Scheer and Colleagues,³¹ 2011	Germany	Department of oral and craniomaxillofacial surgery, secondary	"Oral and VELscope examinations were performed on 64 patients referred to the Department of Oral and Craniomaxillofacial Surgery to rule out invasive squamous cell carcinoma." "Patients with advanced squamous cell carcinomas were excluded." Twenty patients with previous history raised concern that examiners were already aware of patients' diagnoses	59.8	Female: 25 (39.1), male: 39 (60.9)	Autofluorescence, VELscope	64	Patients with advanced squamous cell carcinoma excluded
Upadhyay and Colleagues,⁵⁹ 2011	India	College of dental science clinic, secondary	"47 patients visiting the Dental clinics of Manipal College of Dental Sciences, Manipal"	31-75, 53.83	Female: 10 (21.3), male: 37 (78.7)	Vital staining, toluidine blue	47	"Clinically a provisional diagnosis of homogeneous Leukoplakia, speckled Leukoplakia, Erythroplakia & Erosive lichen planus"
Awan and Colleagues,⁴⁹ 2012	United Kingdom	Oral medicine clinics at 2 London, UK, hospitals, secondary	Patients seeking care at an oral medicine clinic with white, red, or mixed lesions	Older than 16	Female: 36 (39), male: 56 (61)	Vital staining, toluidine blue	92	White, red, and mixed white and red patches

eTABLE 4 (CONTINUED)

STUDY	COUNTRY	SETTING	PARTICIPANTS	AGE, Y, RANGE, MEAN (STANDARD DEVIATION) OR MEDIAN	SEX, NO. (%)	INDEX TEST*	NO. OF LESIONS INCLUDED IN ANALYSES	SEVERITY†
Farah and Colleagues,²⁵ 2012	Australia	Oral medicine specialist unit, tertiary	"Patients presenting to an oral medicine specialist unit for assessment of an oral mucosal lesion were recruited into the study." "Patients known to have oral epithelial dysplasia or squamous cell carcinoma were not included in this study."	Female: 59.1 (12.8), Male: 57.8 (11.88)	Female: 66 (58.9), male: 46 (41.1)	Autofluorescence, VELscope	118	Severity: "oral mucosal white or mixed red/white lesion that was deemed ... to be clinically suspicious"
Mojsa and Colleagues,⁶⁸ 2012	Poland	University medical college, secondary	Method of patient selection: "Thirty consecutive patients with lesions suggestive of being premalignant identified by a conventional clinical oral examination under incandescent light were included into the study."	23-80, 50.3 (15.7)	Female: 9 (30), male: 21 (70)	Tissue reflectance and vital staining, ViziLite Plus	41	Not stated
Ng and Colleagues,⁴¹ 2012	Canada	Community referral-based oral medicine clinic, secondary	"Retrospective chart review of a consecutive selection of patients who had both a biopsy and a concurrent QC assessment from 2008 to 2010" "Patients ... with suspicious oral lesions were evaluated with concurrent but independent HP and quantitative cytology assessments."	Median: 58	Female: 89 (52.0), male: 82 (48)	Cytologic testing, Oral Advance	171	Potentially malignant disorders and oral squamous cell carcinoma
Rahman and Colleagues,⁴² 2012	India	3-day screening camp, primary	Investigators issued pamphlets inviting people to a self-examination 3-day event; 849 attended, 158 had red and white lesions, only 86 consented. "The study included 86 participants suspected of having oral premalignant lesions or OSCC."	26-60, 43 (12.53)	Female: 18 (21.0), male: 68 (79.1)	Vital staining, Cytobrush	86	"Suspected of having oral premalignant lesions or oral squamous cell carcinoma"
Rahman and Colleagues,⁴² 2012	India	3-day screening camp, primary	Investigators issued pamphlets inviting people to a self-examination 3-day event; 849 attended, 158 had red and white lesions, only 86 consented. "The study included 86 participants suspected of having oral premalignant lesions or OSCC."	26-60, 43 (12.53)	Female: 18 (21.0), male: 68 (79.1)	Cytologic testing, Cytobrush	86	"Suspected of having oral premalignant lesions or oral squamous cell carcinoma"

eTABLE 4 (CONTINUED)

STUDY	COUNTRY	SETTING	PARTICIPANTS	AGE, Y, RANGE, MEAN (STANDARD DEVIATION) OR MEDIAN	SEX, NO. (%)	INDEX TEST*	NO. OF LESIONS INCLUDED IN ANALYSES	SEVERITY†
Seijas-Naya and Colleagues,⁴⁵ 2012	Spain	University oral medicine, oral surgery and implantology department, secondary	"Samples obtained through OralCDx ® on 24 patients who visited the Master of Oral Medicine, Oral Surgery and Implantology of the University of Santiago de Compostela, referred by the SERGAS (Servizo Galego de Saúde—Galician Public Healthcare System), between February 2009 and May 2010 who showed clinical and histological lesions that were consistent with oral leukoplakia in different clinical forms"	62.38 (12.14)	Female: 12 (50), male: 12 (50)	Cytologic testing, OralCDx	24	"Showed clinical and histological lesions that were consistent with oral leukoplakia in different clinical forms"
Ujaoney and Colleagues,⁶⁵ 2012	India	Oral diagnosis, medicine, and radiology department at a dental college, secondary	"Consecutive outpatients who visited the study centre and who clinically presented with at least one precancerous lesion were recruited in this study."	44.4 (17.1)	Female: 4 (7.3), male: 51 (92.7)	Tissue reflectance and vital staining, ViziLite Plus	99	Lesions other than Class I (clinically diagnosed)
Ujaoney and Colleagues,⁶⁵ 2012	India	Oral diagnosis, medicine, and radiology department at a dental college, secondary	"Consecutive outpatients who visited the study centre and who clinically presented with at least one precancerous lesion were recruited in this study."	44.4 (17.1)	Female: 4 (7.3), male: 51 (92.7)	Tissue reflectance, ViziLite	99	Lesions other than Class I (clinically diagnosed)
Chaudhari and Colleagues,⁵¹ 2013	India	Yerwada Central Jail, primary and secondary	Investigators suspected 175 inmates of having lesions at risk of developing into a malignancy (precancerous lesions and conditions) and malignant lesions.	19-69, 34.98 (12.65)	Female: 0 (0), male: 82 (100)	Vital staining, toluidine blue	82	Inmates suspected of having lesions at risk of developing into a malignancy (precancerous lesions and conditions) and malignant lesions
Chaudhari and Colleagues,⁵¹ 2013	India	Yerwada Central Jail, primary and secondary	Investigators suspected 175 inmates of having lesions at risk of developing into a malignancy (precancerous lesions and conditions) and malignant lesions.	19-69, 34.98 (12.65)	Female: 0 (0), male: 82 (100)	Vital staining, Lugol iodine	82	Inmates suspected of having lesions at risk of developing into a malignancy (precancerous lesions and conditions) and malignant lesions
Fontes and Colleagues,³³ 2013	Brazil	Outpatient clinic at a hospital, secondary	The study sample consisted of 172 patients with oral lesions clinically suggestive of malignancy.	20-93	Female: 58 (33.7), male: 114 (66.3)	Cytologic testing, Cytobrush	164	Oral lesions suggestive of malignancy

eTABLE 4 (CONTINUED)

STUDY	COUNTRY	SETTING	PARTICIPANTS	AGE, Y, RANGE, MEAN (STANDARD DEVIATION) OR MEDIAN	SEX, NO. (%)	INDEX TEST*	NO. OF LESIONS INCLUDED IN ANALYSES	SEVERITY†
Hanken and Colleagues,²⁶ 2013	Germany	Department of oral and maxillofacial surgery, secondary	120 patients with suspicious oral premalignant lesions (leukoplakia, erythroplakia, lichen planus, or pemphigus vulgaris)	41-76	Female: 35 (58.3), male: 25 (41.7)	Autofluorescence, VELscope	60	Suspicious oral premalignant lesions
Kammerer and Colleagues,³⁴ 2013	Germany	Department of oral and maxillofacial surgery, secondary	Investigators included 88 oral lesions of uncertain class in this study. Investigators included only clinically suspicious but not evidently malignant oral lesions.	27-88, 62	Female: 25 (35.7), male: 45 (64.3)	Cytologic testing, Cytobrush Plus GT	76	Uncertain class
Petruzzi and Colleagues,³⁰ 2014	Italy	Oral pathology and medicine outpatient clinic, secondary	Patients with a history of oral lesions or at high risk of developing oral lesions	56.7	Female: 22 (45.0), male: 27 (55.0)	Autofluorescence, VELscope	56	Clinically suspicious lesions (prealignant or malignant oral mucosal lesions)
Chainani-Wu and Colleagues,⁶² 2015	United States	Oral medicine clinic, secondary	Patients seeking care at the tertiary oral medicine referral clinic at the University of California, San Francisco for initial or follow-up evaluations, who had oral leukoplakia, erythroleukoplakia, or erythroplakia diagnosed	42-90, 61 (10.6)	Female: 20 (46.5), male: 23 (53.5)	Tissue reflectance, ViziLite	70	Higher-risk oral premalignant lesions or higher-risk areas within lesions were important.
Chainani-Wu and Colleagues,⁶² 2015	United States	Oral medicine clinic, secondary	Patients seeking care at the tertiary oral medicine referral clinic at the University of California, San Francisco for initial or follow-up evaluations, who had oral leukoplakia, erythroleukoplakia, or erythroplakia diagnosed	42-90, 61 (10.6)	Female: 20 (46.5), male: 23 (53.5)	Tissue reflectance and vital staining, ViziLite and toluidine blue	70	Higher-risk oral premalignant lesions or higher-risk areas within lesions were important.
Singh and Shukla,⁶¹ 2015	India	Department of otorhinolaryngology and head and neck surgery, secondary	50 patients with lesions in the oral cavity that were suggestive of malignancy. The most common symptoms for seeking care was a nonhealing ulcer in the oral cavity (88%) followed by pain (44%), face swelling (22%), neck swelling (12%), growth (10%), difficulty in swallowing (6%), reduced mouth opening (6%), pain in the ear (4%), and swelling in the oral cavity (4%)	49.2	Female: 19 (38), male: 31 (62)	Vital staining, toluidine blue	50	Suspicious lesions

eTABLE 4 (CONTINUED)

STUDY	COUNTRY	SETTING	PARTICIPANTS	AGE, Y, RANGE, MEAN (STANDARD DEVIATION) OR MEDIAN	SEX, NO. (%)	INDEX TEST*	NO. OF LESIONS INCLUDED IN ANALYSES	SEVERITY†
Trakroo and Colleagues,⁴⁷ 2015	India	Department of oral medicine radiology, secondary	Investigators selected patients with suspicious premalignant and malignant lesions, irrespective of age and sex. Investigators selected patients with oral premalignant disorders such as homogeneous leukoplakia, speckled leukoplakia, verrucous leukoplakia, erythroplakia, tobacco pouch keratosis, erosive lichen planus, and oral carcinoma and patients with a history of using tobacco and related products and alcohol consumption.	20-70	Female: 7 (14), male: 43 (86)	Cytologic testing, brush biopsy	50	Malignant and premalignant lesions
Nanayakkara and Colleagues,³⁸ 2016	Sri Lanka	Unclear	Investigators conducted the study in 116 patients with oral leukoplakia lesions diagnosed and 76 patients with suspicious oral malignancy.	21-95	Female: 43 (22.4), male: 149 (77.6)	Cytologic testing, spatula	181	Suspicious oral malignancy and oral leukoplakia
Nanayakkara and Colleagues,³⁸ 2016	Sri Lanka	Unclear	Investigators conducted the study in 116 patients with oral leukoplakia lesions diagnosed and 76 patients with suspicious oral malignancy.	21-95	Female: 43 (22.4), male: 149 (77.6)	Cytologic testing, Cytobrush	181	Suspicious oral malignancy and oral leukoplakia

eTABLE 5

Summary of main findings for patients' values and preferences for the evaluation of potentially malignant disorders.				
STUDY	TITLE	STUDY DESIGN	SETTING AND POPULATION	FINDINGS
Scott and Colleagues,⁸⁰ 2009	Barriers and triggers to seeking help for potentially malignant oral symptoms: implications for interventions	Cross-sectional study including 82 participants (semistructured interviews)	Newly referred patients older than 18 years, English speaking, with potentially malignant oral mucosal symptoms (that is, localized nonrecurrent ulcer, localized persistent oral pain, a white or red patch, a lump or swelling in the oral cavity) (United Kingdom)	<p>"In this study, 53 percent of participants waited 31 days before seeking help from an HCP, and 37 percent waited more than 3 months."</p> <p>"Participants' initial interpretation was related to the decision to seek help, with attribution of symptoms to a minor, self-correcting condition resulting in postponement of help seeking. Relatedly, a change in symptoms or persistence of symptoms was regarded as an indication that something was wrong and in turn triggered a visit to an HCP."</p> <p>"If 'at-risk' individuals are introduced to this '3-week rule,' it would standardize the duration given for symptoms to resolve. Furthermore, if it were emphasized that HCP's want to see any oral change that lasts more than 3 weeks, this may reduce the patients' concern of wasting HCP's time and raise confidence in help seeking."</p> <p>"The data suggested that emotions play a role in the help-seeking process. Previous work has indicated that fear of consultation (in terms of embarrassment and to the idea of cancer) may prevent a patient from seeking help for cancer symptoms (8). This study has indicated that emotions can also act as a trigger to help seeking."</p>
Fingeret and Colleagues,⁷⁴ 2010	Multidimensional analysis of body image concerns among newly diagnosed patients with oral cavity cancer	Cross-sectional study including 75 participants (self-completed questionnaire)	Patients with newly diagnosed oral cavity cancer scheduled to undergo surgical treatment (United States)	"Results from the clinical interview indicated that 77% of participants (N=58) identified current and/or future appearance-related concerns. These concerns were primarily related to impending surgery and involved future scarring/disfigurement at the surgical site, loss of teeth, loss of hair, and speech concerns."
Goodson and Colleagues,⁷⁵ 2011 (Abstract)	Accuracy and patient acceptance of brush cytology for diagnosis of potentially malignant lesions and oral cancer	Cross-sectional study including 22 participants (method for collecting data unclear)	Patients with a malignant or potentially malignant disorder in the oral mucosa (United Kingdom)	"Twenty-two patients recorded their brush biopsy experience on a VAS scale (0 not satisfied to 10 very satisfied), with a mean score of 8.8 (range 4–10)."
Rogers and Colleagues,⁷⁹ 2011	Reasons for delayed presentation in oral and oropharyngeal cancer: the patients' perspective	Cross-sectional study including 106 participants (phone interviews)	Patients treated for oral and oropharyngeal squamous cell carcinoma known to be alive and disease free (United Kingdom)	<p>"In the survey patients were asked who they first sought advice from and who was the first healthcare professional they contacted, both questions being open-ended. Patients responded that the first advice they received came either from family doctors (39%, n = 28), dentists (34%, n = 24) or family/friends (23%, n = 16) with three unknown."</p> <p>"Patients were asked who they first spoke to about their symptoms they had noticed. For 41% (16/39) their spouse or partner (eight wife, five husband, two partner, one girlfriend) was the first person they spoke with, for 5% (2/39) it was immediate family (one son, one daughter) and for 15% (6/39) it was a friend (four friend, one ex-wife, one son's girlfriend). However 38% (15/39) said they spoke to nobody about it."</p> <p>"Patients suggested that strategies to raise awareness and early presentation should involve increased public awareness through media coverage (television advertisements and programmes, radio, newspaper and magazine columns) with the use of more drastic visual aids on posters and leaflets in dental, GP surgeries and pharmacies so people know what to look out for. There should be improved Internet resources and an education strategy that more clearly involves schools. Also they felt that there needs to be an emphasis on regular dental or medical check ups, so that asymptomatic lesions and minor symptoms can be acted upon earlier. The lay public should be encouraged to self-examine their mouth whilst tooth brushing and to speak out about their symptoms as soon as they have even the slightest concern."</p>

eTABLE 5 (CONTINUED)

STUDY	TITLE	STUDY DESIGN	SETTING AND POPULATION	FINDINGS
Awojobi and Colleagues,⁷³ 2012	Patients' perceptions of oral cancer screening in dental practice: a cross-sectional study	Cross-sectional study including 180 participants (self-completed questionnaire)	Patients with no previous history of oral cancer General dental practices (United Kingdom)	"Only a minority (1%) reported extreme levels of anxiety, worry and concern about oral cancer screening." "There was a generally positive attitude to screening with a mean score of 13.04 (95%CI 12.68, 13.41). Approximately 21% of respondents had very positive attitudes to being screened obtaining the highest possible score of 16." "Ninety-two percent of respondents indicated that they would like their Dentists to tell them if their mouths were being checked for signs of oral cancer." "Moreover, 97% said they would like help from their Dentists to help them reduce their risk of getting oral cancer."
Henry and Colleagues,⁷⁷ 2013 (Abstract)	Myth or reality: are head and neck cancer patients at increased risk for suicidal thoughts and gestures? Preliminary results	Cross-sectional study including 46 participants (self-reported questionnaire)	Forty-six patients with newly diagnosed head and neck cancer completed both baseline and 3-month follow-up measures (Canada)	"Lifetime pre-cancer and 3 months suicidal ideations were 10.8% and 8.5%, respectively; suicidal attempts were 2.4% and 0%; and 2.2% committed suicide <3 months (during the course of treatment). Suicidal thoughts at 3 months were related to: lifetime pre-HNC suicidal ideations ($p = 0.034$) or past psychiatric diagnosis ($p = 0.001$), higher levels of anxiety/depression ($p = 0.001$) and body image concerns ($p = 0.001$), lower quality of life functionally ($p = 0.0009$) and for H&N-specific issues ($p = 0.01$; especially difficulties breathing $p = 0.001$, alcohol $p = 0.002$, pain in mouth/throat/neck $p = 0.01$)." "Suicidal ideations found in our study were significantly higher than those found in the general population (1 year: men 1.8%; women 2%)."
Karbach and Colleagues,⁷⁸ 2014	Oral health-related quality of life of patients with oral lichen planus, oral leukoplakia, or oral squamous cell carcinoma	Cross-sectional study including 154 participants (self-reported questionnaire)	Consecutive new patients with a clinical diagnosis of oral lichen planus, oral leukoplakia, or oral squamous cell carcinoma (Germany)	"A trend toward a difference among the 3 groups was observed after comparing the total OHIP-G 14 score ($P = .086$). Patients with OL (7.0 +/- 10.2) showed the lowest total OHIP-G 14 scores, patients with OLP (9.4 +/- 11.4) showed the highest total OHIP-G 14 scores, and patients with OSCC (8.8 +/- 8.6) registered scores between those of patients with OL and patients with OLP."
Paudyal and Colleagues,⁷¹ 2014	A systematic review of patient acceptance of screening for oral cancer outside of dental care settings	Systematic review including 12 studies	Studies reporting acceptability of oral cancer screening to people without a diagnosis (United Kingdom, United States, Canada, India)	Preference for care provision "Three studies evaluated patients' preferences for care provision for oral cancer screening [34–36]. In all three studies, participants stated their preference for having primary care physicians perform the oral cancer examination. General practice was seen as an appropriate setting for screening due to its local nature, ease of access, familiarity and relevance for a health-related intervention [34,36]. Participants stated their preference for receiving information about oral cancer through personal interaction with their primary care practitioners [34]. Lack of trust towards dentists was stated as a barrier in one study where participants perceived a dentist as a 'tooth specialist', rather than a 'mouth specialist', who lacked the power of a doctor to make referrals and write prescriptions [34]."
Paudyal and Colleagues,⁷¹ 2014	A systematic review of patient acceptance of screening for oral cancer outside of dental care settings	Systematic review including 12 studies	Studies reporting acceptability of oral cancer screening to people without a diagnosis (United Kingdom, United States, Canada, India)	Cost and related factors "Financial cost was perceived as an influencing factor for the acceptance of screening. In Dodd et al. [35], willingness to accept a free oral cancer examination was high among males (100%; $n = 32$) whereas younger females did not uniformly agree with the idea. The females in the study stated that they would decline the opportunity to be screened even if screening was conducted at their worksite and offered free. Participants in another focus group study also perceived that the screening should be cost free and speedy [34]. However, there were stark differences in participants' characteristics, cultural beliefs regarding oral cancer, and health care provision across these two studies conducted in different countries, which may have affected participants' opinion about the financial cost related to screening."

eTABLE 5 (CONTINUED)

STUDY	TITLE	STUDY DESIGN	SETTING AND POPULATION	FINDINGS
Paudyal and Colleagues,⁷¹ 2014	A systematic review of patient acceptance of screening for oral cancer outside of dental care settings	Systematic review including 12 studies	Studies reporting acceptability of oral cancer screening to people without a diagnosis (United Kingdom, United States, Canada, India)	Anxiety related to symptom and screening procedure "Patients perceived that knowing more about oral cancer may make them more anxious should they notice any disease symptom [36]. However, studies aimed at increasing knowledge and awareness of oral cancer reported that access to information does not increase pre-procedural fear and anxiety of participants [31–33]. One study reported that information leaflets did not change concerns regarding MSE, although one-to-one interaction sessions were helpful in reducing MSE related anxiety [31]. Similar results were reported in other studies where anxiety associated with the screening was not influenced by leaflet access [33], or were reduced [32]. One study reported pre-procedural anxiety in one third of participants (31%), however, on completion of the screening, there was almost unanimous agreement that the procedure was painless [30]."
Paudyal and Colleagues,⁷¹ 2014	A systematic review of patient acceptance of screening for oral cancer outside of dental care settings	Systematic review including 12 studies	Studies reporting acceptability of oral cancer screening to people without a diagnosis (United Kingdom, United States, Canada, India)	Impact of intervention on compliance of screening "In one study conducted among a high-risk population in India [26], compliance with instructions to perform MSE following access to an information leaflet was high, with 87% of the participants practising MSE and 95% believing that early detection could improve the chances of cure. Whilst the sensitivity of MSE was very low at 18%, the specificity was high at 99.9% (PPV = 72%, NPV = 99%). In another study, participants underwent an oral examination by their dentist and then performed MSE after reading an instructive leaflet [28]. The study found that half of the participants (51%) correctly diagnosed the symptoms and the majority (74%) of participants found MSE easy to perform. However, the sensitivity and specificity of MSE was 33% (95% CI 11–65%) and 17% (95% CI, 6–40%) respectively."
Paudyal and Colleagues,⁷¹ 2014	A systematic review of patient acceptance of screening for oral cancer outside of dental care settings	Systematic review including 12 studies	Studies reporting acceptability of oral cancer screening to people without a diagnosis (United Kingdom, United States, Canada, India)	Patient experiences and acceptance of specific screening activities "The acceptance of oral visual examinations (OVE) conducted in community screening programmes varied across studies. In a study conducted among tobacco users in India, overall acceptance and satisfaction levels of OVE in a mobile setting were encouraging, with 98% of the participants feeling comfortable with oral screening tests [27]. Similarly another study in Canada also reported high acceptance of OVE (98%) among high-risk individuals (based on risk factors, lack of access to care, and the high frequency of oral mucosal anomalies), but, acceptance of biopsy for abnormal findings and follow-up was low with only 12 out of 31 (39%) patients with clinical leukoplakia accepting the biopsy [29]. In contrast, a study from South Africa, reported poor acceptance of OVE conducted in mobile clinics with only 4.9% (out of the 1320 eligible adults in the community) accepting a screen during the 6-week period [34]. Of those who accepted the examination, only 12% were high-risk participants (specified as men older than 40 years of age)." "Feaver et al. [30] found that the use of Orascreen (a screen using toluidine blue dye) in aiding the screening for oral cancer was highly acceptable to patients; 100% individuals accepted the screening, 83% described screening as 'a comfortable experience' and 95% of the respondents expressed a willingness take part in future oral health screening."

eTABLE 5 (CONTINUED)

STUDY	TITLE	STUDY DESIGN	SETTING AND POPULATION	FINDINGS
Allen and Farah,⁷² 2015	Patient perspectives of diagnostic delay for suspicious oral mucosal lesions	Cross-sectional study including 85 participants (self-completed questionnaire)	Patients referred for suspicious oral mucosal lesion (leukoplakia, erythroplakia or erythroleukoplakia) Private oral medicine clinic (Australia)	"Patients had a median of 20 days and a mean of 28.7 days between referral to first visit at a specialist." "Patients who reported feeling anxious were asked to give reasons for feeling anxious and the most common reason was fear of detection."
Hassona and Colleagues,⁷⁶ 2015	Mouth cancer awareness and beliefs among dental patients	Cross-sectional study including 1,200 participants (close-ended questionnaire)	Patients attending dental clinics for examination and dental treatment (hospital based) Patients with a diagnosis of oral cancer or referred for assessment of a suspicious oral mucosal lesion (Jordan)	"86.1% [of the participants] believed that regular dental visits can help in the early detection of oral cancer and 67.5% thought that dentists are qualified to diagnose oral cancer." "When asked about actions that they would take if they noticed an oral lesion, 39.9% stated that they would consult a dentist, 26.8% that they would consult a physician, 17.9% that they would apply home remedies (olive oil, sesame paste, water and salt, mouth wash, or iodine), and 7.3% would take no action ('wait and see')."

eTABLE 6

Assessing the Methodological Quality of Systematic Reviews assessment for: Walsh and colleagues.⁵ Clinical assessment to screen for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults. *Cochrane Database Syst Rev.* 2013;11:CD010173.*

<p>1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of the review. Note: Need to refer to a protocol, ethics approval, or pre-determined/a priori published research objectives to score a "yes." x Yes <input type="checkbox"/> No <input type="checkbox"/> Can't answer <input type="checkbox"/> Not applicable</p>
<p>2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place. Note: 2 people do study selection, 2 people do data extraction, consensus process or one person checks the other's work. x Yes <input type="checkbox"/> No <input type="checkbox"/> Can't answer <input type="checkbox"/> Not applicable</p>
<p>3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g., Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found. Note: If at least 2 sources + one supplementary strategy used, select "yes" (Cochrane register/Central counts as 2 sources; a grey literature search counts as supplementary). x Yes <input type="checkbox"/> No <input type="checkbox"/> Can't answer <input type="checkbox"/> Not applicable</p>
<p>4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc. Note: If review indicates that there was a search for "grey literature" or "unpublished literature," indicate "yes." SIGLE database, dissertations, conference proceedings, and trial registries are all considered grey for this purpose. If searching a source that contains both grey and non-grey, must specify that they were searching for grey/unpublished lit. x Yes <input type="checkbox"/> No <input type="checkbox"/> Can't answer <input type="checkbox"/> Not applicable</p>
<p>5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided. Note: Acceptable if the excluded studies are referenced. If there is an electronic link to the list but the link is dead, select "no." x Yes <input type="checkbox"/> No <input type="checkbox"/> Can't answer <input type="checkbox"/> Not applicable</p>
<p>6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed, e.g., age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported. Note: Acceptable if not in table format as long as they are described as above. x Yes <input type="checkbox"/> No <input type="checkbox"/> Can't answer <input type="checkbox"/> Not applicable</p>
<p>7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant. Note: Can include use of a quality scoring tool or checklist, e.g., Jadad scale, risk of bias, sensitivity analysis, etc., or a description of quality items, with some kind of result for EACH study ("low" or "high" is fine, as long as it is clear which studies scored "low" and which scored "high"; a summary score/range for all studies is not acceptable). x Yes <input type="checkbox"/> No <input type="checkbox"/> Can't answer <input type="checkbox"/> Not applicable</p>
<p>* Source: Shea and colleagues.¹⁶</p>

eTABLE 6 (CONTINUED)

<p>8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations. Note: Might say something such as “the results should be interpreted with caution due to poor quality of included studies.” Cannot score “yes” for this question if scored “no” for question 7.</p> <p>x Yes <input type="checkbox"/> No <input type="checkbox"/> Can’t answer <input type="checkbox"/> Not applicable</p>
<p>9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e., Chi-squared test for homogeneity, I²). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e., is it sensible to combine?). Note: Indicate “yes” if they mention or describe heterogeneity, i.e., if they explain that they cannot pool because of heterogeneity/variability between interventions.</p> <p>x Yes <input type="checkbox"/> No <input type="checkbox"/> Can’t answer <input type="checkbox"/> Not applicable</p>
<p>10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test, Hedges-Olken). Note: If no test values or funnel plot included, score “no.” Score “yes” if mentions that publication bias could not be assessed because there were fewer than 10 included studies.</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Can’t answer x Not applicable</p>
<p>11. Was the conflict of interest included? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies. Note: To get a “yes,” must indicate source of funding or support for the systematic review AND for each of the included studies.</p> <p>x Yes <input type="checkbox"/> No <input type="checkbox"/> Can’t answer <input type="checkbox"/> Not applicable</p>

eTABLE 7

Assessing the Methodological Quality of Systematic Reviews assessment for: Macey and colleagues.⁴ Diagnostic tests for oral cancer and potentially malignant disorders in patients presenting with clinically evident lesions. *Cochrane Database Syst Rev.* 2015;5:CD010276.*

<p>1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of the review. Note: Need to refer to a protocol, ethics approval, or pre-determined/a priori published research objectives to score a "yes." x Yes <input type="checkbox"/> No <input type="checkbox"/> Can't answer <input type="checkbox"/> Not applicable</p>
<p>2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place. Note: 2 people do study selection, 2 people do data extraction, consensus process or one person checks the other's work. x Yes <input type="checkbox"/> No <input type="checkbox"/> Can't answer <input type="checkbox"/> Not applicable</p>
<p>3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g., Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found. Note: If at least 2 sources + one supplementary strategy used, select "yes" (Cochrane register/Central counts as 2 sources; a grey literature search counts as supplementary). x Yes <input type="checkbox"/> No <input type="checkbox"/> Can't answer <input type="checkbox"/> Not applicable</p>
<p>4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc. Note: If review indicates that there was a search for "grey literature" or "unpublished literature," indicate "yes." SIGLE database, dissertations, conference proceedings, and trial registries are all considered grey for this purpose. If searching a source that contains both grey and non-grey, must specify that they were searching for grey/unpublished lit. x Yes <input type="checkbox"/> No <input type="checkbox"/> Can't answer <input type="checkbox"/> Not applicable</p>
<p>5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided. Note: Acceptable if the excluded studies are referenced. If there is an electronic link to the list but the link is dead, select "no." x Yes <input type="checkbox"/> No <input type="checkbox"/> Can't answer <input type="checkbox"/> Not applicable</p>
<p>6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed, e.g., age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported. Note: Acceptable if not in table format as long as they are described as above. x Yes <input type="checkbox"/> No <input type="checkbox"/> Can't answer <input type="checkbox"/> Not applicable</p>
<p>7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant. Note: Can include use of a quality scoring tool or checklist, e.g., Jadad scale, risk of bias, sensitivity analysis, etc., or a description of quality items, with some kind of result for EACH study ("low" or "high" is fine, as long as it is clear which studies scored "low" and which scored "high"; a summary score/range for all studies is not acceptable). x Yes <input type="checkbox"/> No <input type="checkbox"/> Can't answer <input type="checkbox"/> Not applicable</p>
<p>* Source: Shea and colleagues.¹⁶</p>

eTABLE 7 (CONTINUED)

<p>8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations. Note: Might say something such as “the results should be interpreted with caution due to poor quality of included studies.” Cannot score “yes” for this question if scored “no” for question 7.</p> <p>x Yes <input type="checkbox"/> No <input type="checkbox"/> Can’t answer <input type="checkbox"/> Not applicable</p>
<p>9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e., Chi-squared test for homogeneity, I²). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e., is it sensible to combine?). Note: Indicate “yes” if they mention or describe heterogeneity, i.e., if they explain that they cannot pool because of heterogeneity/variability between interventions.</p> <p>x Yes <input type="checkbox"/> No <input type="checkbox"/> Can’t answer <input type="checkbox"/> Not applicable</p>
<p>10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test, Hedges-Olken). Note: If no test values or funnel plot included, score “no.” Score “yes” if mentions that publication bias could not be assessed because there were fewer than 10 included studies.</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Can’t answer x Not applicable</p>
<p>11. Was the conflict of interest included? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies. Note: To get a “yes,” must indicate source of funding or support for the systematic review AND for each of the included studies.</p> <p>x Yes <input type="checkbox"/> No <input type="checkbox"/> Can’t answer <input type="checkbox"/> Not applicable</p>

eTABLE 8

Assessing the Methodological Quality of Systematic Reviews assessment for: Gualtero and Suarez Castillo.²³ Biomarkers in saliva for the detection of oral squamous cell carcinoma and their potential use for early diagnosis: a systematic review. *Acta Odontol Scand.* 2016;74(3):170-177.*

<p>1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of the review. Note: Need to refer to a protocol, ethics approval, or pre-determined/a priori published research objectives to score a "yes." x Yes <input type="checkbox"/> No <input type="checkbox"/> Can't answer <input type="checkbox"/> Not applicable</p>
<p>2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place. Note: 2 people do study selection, 2 people do data extraction, consensus process or one person checks the other's work. <input type="checkbox"/> Yes <input type="checkbox"/> No x Can't answer <input type="checkbox"/> Not applicable</p>
<p>3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g., Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found. Note: If at least 2 sources + one supplementary strategy used, select "yes" (Cochrane register/Central counts as 2 sources; a grey literature search counts as supplementary). <input type="checkbox"/> Yes x No <input type="checkbox"/> Can't answer <input type="checkbox"/> Not applicable</p>
<p>4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc. Note: If review indicates that there was a search for "grey literature" or "unpublished literature," indicate "yes." SIGLE database, dissertations, conference proceedings, and trial registries are all considered grey for this purpose. If searching a source that contains both grey and non-grey, must specify that they were searching for grey/unpublished lit. <input type="checkbox"/> Yes x No <input type="checkbox"/> Can't answer <input type="checkbox"/> Not applicable</p>
<p>5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided. Note: Acceptable if the excluded studies are referenced. If there is an electronic link to the list but the link is dead, select "no." <input type="checkbox"/> Yes x No <input type="checkbox"/> Can't answer <input type="checkbox"/> Not applicable</p>
<p>6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed, e.g., age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported. Note: Acceptable if not in table format as long as they are described as above. x Yes <input type="checkbox"/> No <input type="checkbox"/> Can't answer <input type="checkbox"/> Not applicable</p>
<p>7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant. Note: Can include use of a quality scoring tool or checklist, e.g., Jadad scale, risk of bias, sensitivity analysis, etc., or a description of quality items, with some kind of result for EACH study ("low" or "high" is fine, as long as it is clear which studies scored "low" and which scored "high"; a summary score/range for all studies is not acceptable). x Yes <input type="checkbox"/> No <input type="checkbox"/> Can't answer <input type="checkbox"/> Not applicable</p>
<p>* Source: Shea and colleagues.¹⁶</p>

eTABLE 8 (CONTINUED)

<p>8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations. Note: Might say something such as “the results should be interpreted with caution due to poor quality of included studies.” Cannot score “yes” for this question if scored “no” for question 7.</p> <p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Can’t answer <input type="checkbox"/> Not applicable</p>
<p>9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e., Chi-squared test for homogeneity, I²). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e., is it sensible to combine?). Note: Indicate “yes” if they mention or describe heterogeneity, i.e., if they explain that they cannot pool because of heterogeneity/variability between interventions.</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Can’t answer <input checked="" type="checkbox"/> Not applicable</p>
<p>10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test, Hedges-Olken). Note: If no test values or funnel plot included, score “no.” Score “yes” if mentions that publication bias could not be assessed because there were fewer than 10 included studies.</p> <p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Can’t answer <input type="checkbox"/> Not applicable</p>
<p>11. Was the conflict of interest included? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies. Note: To get a “yes,” must indicate source of funding or support for the systematic review AND for each of the included studies.</p> <p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Can’t answer <input type="checkbox"/> Not applicable</p>

eTABLE 9

Assessing the Methodological Quality of Systematic Reviews assessment for: Stuani and colleagues.²³ Salivary biomarkers as tools for oral squamous cell carcinoma diagnosis: a systematic review. *Head Neck*. 2017;39(4):797-811.*

1. Was an 'a priori' design provided?

The research question and inclusion criteria should be established before the conduct of the review.

Note: Need to refer to a protocol, ethics approval, or pre-determined/a priori published research objectives to score a "yes."

x Yes

- No
 Can't answer
 Not applicable

2. Was there duplicate study selection and data extraction?

There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.

Note: 2 people do study selection, 2 people do data extraction, consensus process or one person checks the other's work.

x Yes

- No
 Can't answer
 Not applicable

3. Was a comprehensive literature search performed?

At least two electronic sources should be searched. The report must include years and databases used (e.g., Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.

Note: If at least 2 sources + one supplementary strategy used, select "yes" (Cochrane register/Central counts as 2 sources; a grey literature search counts as supplementary).

x Yes

- No
 Can't answer
 Not applicable

4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?

The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.

Note: If review indicates that there was a search for "grey literature" or "unpublished literature," indicate "yes." SIGLE database, dissertations, conference proceedings, and trial registries are all considered grey for this purpose. If searching a source that contains both grey and non-grey, must specify that they were searching for grey/unpublished lit.

x Yes

- No
 Can't answer
 Not applicable

5. Was a list of studies (included and excluded) provided?

A list of included and excluded studies should be provided.

Note: Acceptable if the excluded studies are referenced. If there is an electronic link to the list but the link is dead, select "no."

x Yes

- No
 Can't answer
 Not applicable

6. Were the characteristics of the included studies provided?

In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed, e.g., age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.

Note: Acceptable if not in table format as long as they are described as above.

x Yes

- No
 Can't answer
 Not applicable

7. Was the scientific quality of the included studies assessed and documented?

'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.

Note: Can include use of a quality scoring tool or checklist, e.g., Jadad scale, risk of bias, sensitivity analysis, etc., or a description of quality items, with some kind of result for EACH study ("low" or "high" is fine, as long as it is clear which studies scored "low" and which scored "high"; a summary score/range for all studies is not acceptable).

x Yes

- No
 Can't answer
 Not applicable

* Source: Shea and colleagues.¹⁶

eTABLE 9 (CONTINUED)

<p>8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations. Note: Might say something such as “the results should be interpreted with caution due to poor quality of included studies.” Cannot score “yes” for this question if scored “no” for question 7.</p> <p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Can’t answer <input type="checkbox"/> Not applicable</p>
<p>9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e., Chi-squared test for homogeneity, I²). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e., is it sensible to combine?). Note: Indicate “yes” if they mention or describe heterogeneity, i.e., if they explain that they cannot pool because of heterogeneity/variability between interventions.</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Can’t answer <input checked="" type="checkbox"/> Not applicable</p>
<p>10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test, Hedges-Olken). Note: If no test values or funnel plot included, score “no.” Score “yes” if mentions that publication bias could not be assessed because there were fewer than 10 included studies.</p> <p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Can’t answer <input type="checkbox"/> Not applicable</p>
<p>11. Was the conflict of interest included? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies. Note: To get a “yes,” must indicate source of funding or support for the systematic review AND for each of the included studies.</p> <p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Can’t answer <input type="checkbox"/> Not applicable</p>

eTABLE 10

Additional study characteristics of included studies.				
STUDY	INDEX TEST*	POSITIVITY THRESHOLD (INDEX TEST)	POSITIVITY THRESHOLD (CRITERION TEST)	CONFLICTS OF INTEREST AND SOURCE OF FUNDING
Mashberg,⁵⁵ 1980	Vital staining, toluidine blue	"Positive for malignancy if the lesion stains dark blue (royal or navy); either the entire lesion or a portion of it may stain solidly or stippled. Occasional equivocal stains are considered positive unless proven otherwise."	All dysplasia is positive.	Not reported
Silverman and Colleagues,⁵⁸ 1984	Vital staining, toluidine blue	Dye uptake was considered positive	All dysplasia is positive.	Not reported
Warnakulasuriya and Johnson,⁶⁰ 1996	Vital staining, OraScan toluidine blue	Any dye retention classified as positive	All dysplasia is positive.	KASSW supported by Dunhill Medical Trust Consumables in project funded by Zila Pharmaceuticals
Onizawa and Colleagues,²⁹ 1999	Autofluorescence, fluorescence photography with ultraviolet flash	"The autofluorescence of the lesions was judged according to the intensity of fluorescence depicted on the films. Lesions with red or pink fluorescence under the SC-39 filter, and those with red or orange fluorescence under the SC-52 or -48 filter were defined as positive, whereas lesions without these colors of fluorescence were defined as negative."	All dysplasia is positive.	Not reported
Sciubba,⁴⁴ 1999	Cytologic testing, OralCDx	Negative: no epithelial abnormality; atypical: abnormal epithelial changes of uncertain diagnostic significance; positive: definitive cellular evidence of epithelial dysplasia or carcinoma; inadequate: incomplete transepithelial biopsy specimens (these specimens were excluded from the study); atypical cases included as positive	All dysplasia is positive.	Funded by OralScan Laboratories, which produces OralCDx products
Onofre and Colleagues,⁵⁷ 2001	Vital staining, toluidine blue	Followed recommendations of Mashberg (Mashberg 1980, [†] : <ul style="list-style-type: none"> ■ "inadequate cell count" ■ "negative" ■ "atypical epithelial cells" ■ "positive for dysplasia or OSCC" Atypical and positive results recorded as positive; inadequate results excluded	All dysplasia is positive.	"We are indebted to the Mario A.S. Paino Laboratory of Clinical Pathology."
Svirsky and Colleagues,⁴⁶ 2002	Cytologic testing, OralCDx	Stated no conflict of interests, declaration of some funding from OralCDx, but involvement of OralCDx laboratories is stated for retrospective analysis; unclear whether there were any atypical results	All dysplasia is positive.	Declaration of some funding from OralCDx, but involvement of OralCDx laboratories is stated for retrospective analysis
Cheng and Yang,⁵³ 2003a	Vital staining, Oratest rinse	Blue staining of the lesion predicts a positive outcome; blurred blue staining, which could not be washed out by the mouthwash fluid, was also considered positive	Unclear	Not reported

* We compared all index tests against biopsy results as the criterion standard.

† Source: Mashberg 1980.⁵⁵

‡ Source: Sciubba 1999.⁴⁴

eTABLE 10 (CONTINUED)

STUDY	INDEX TEST*	POSITIVITY THRESHOLD (INDEX TEST)	POSITIVITY THRESHOLD (CRITERION TEST)	CONFLICTS OF INTEREST AND SOURCE OF FUNDING
Cheng and Yang,⁵³ 2003b	Vital staining, Oratest stain	Blue staining of the lesion predicts a positive outcome; blurred blue staining, which could not be washed out by the mouthwash fluid, was also considered positive	Unclear	Not reported
Navone and Colleagues,³⁹ 2004	Cytologic testing, Cytobrush	Not reported 1 atypical result but unclear how it was classified	Unclear	Not reported
Scheifele and Colleagues,⁴³ 2004	Cytologic testing, OralCDx	Based on previous study (Sciubba 1999 [†]): <ul style="list-style-type: none"> ■ "inadequate cell count" ■ "negative" ■ "atypical epithelial cells" ■ "positive for dysplasia or OSCC" 	All dysplasia is positive.	"OralCDx test kits and OralCDx analyses for this study were provided by the German OralCDx centre...Germany."
Chen and Colleagues,⁵² 2007	Vital staining, methylene blue	Unclear	All dysplasia is positive.	"Grant supported by NSC-94-2314B075 and VGH94242C"
Du and Colleagues,⁵⁴ 2007	Vital staining, rose bengal	"Staining result of a lesion was classified as 1, 2, 3 or 4 according to the shade tabs. In the present study, staining results of 3 and 4 were regarded as RB positive staining, while staining results of 1 and 2 were regarded as RB negative staining."	All dysplasia is positive.	"Grant sponsor: Science and Technology Bureau of Wuhan City, People's Republic of China; Grant number: 20026002084."
Farah and McCullough,⁶³ 2007	Tissue reflectance, ViziLite	Unclear; although the authors state that all lesions appeared "aceto-white" under chemiluminescent light and that they considered them "ViziLite positive," it is not clear that this detail was used in the diagnostic decision	Unclear	None
Gupta and Colleagues,⁷⁰ 2007	Cytologic testing and vital staining, toluidine blue and brush cytologic testing	Participants' results classed as positive or negative but no thresholds or inadequate or equivocal results reported. The authors analyzed the following parameters in the smear: enlarged nuclei, variation in nuclear size and shape (pleomorphism), nuclear borders, nuclear-to-cytoplasmic ratio, number of nuclei, hyperchromatism, chromatin pattern and distribution, and discrepancy in maturation.	All dysplasia is positive.	Not reported

eTABLE 10 (CONTINUED)

STUDY	INDEX TEST*	POSITIVITY THRESHOLD (INDEX TEST)	POSITIVITY THRESHOLD (CRITERION TEST)	CONFLICTS OF INTEREST AND SOURCE OF FUNDING
Epstein and Colleagues,⁶⁷ 2008	Tissue reflectance and vital staining, Vizilite and toluidine blue	"The investigator reported their subjective assessment of the impact of chemiluminescence upon lesions characteristics of brightness, sharpness, surface texture, and/or size using a four point Likert scale (decreased, no change, slight improvement, marked improvement). After the toluidine blue staining the investigator recorded the staining pattern either as negative, incomplete, or complete total lesion staining." Potential confusion over "incomplete." Sequence of tests: visual, light based, vital stain, then criterion standard	Mild and moderate dysplasia classified as negative and severe dysplasia classified as positive This was reclassified to include all dysplasia as biopsy positive.	Funded by Trylon Corp Inc, authors linked to Zila Inc.
Mehrotra and Colleagues,³⁷ 2008	Cytologic testing, baby toothbrush	Investigators categorized cells showing changes as malignant: "enlarged nuclei, variation in nuclear size and shape (pleomorphism), nuclear borders, nucleo:cytoplasmic ratio, number of nuclei, binucleation, keratinization, tadpole forms, and hyperchromatism chromatin" No atypical results reported	All dysplasia is positive.	Not discussed
Navone and Colleagues,⁴⁰ 2008	Cytologic testing, curette	"The diagnosis of dysplasia or carcinoma was based on recognized WHO criteria. The diagnosis was recorded as either negative or positive for the presence of neoplasia or dysplasia, whatever the grade." Atypical results not reported	All dysplasia is positive.	"This study has been supported in part by MURST ex-60% Universita' di Torino', Ricerca Finalizzata Regione Piemonte' and by a grant of Compagnia di San Paolo Programma Oncologia', Torino, Italy."
Allegra and Colleagues,⁴⁸ 2009	Vital staining, toluidine blue	"Lesions that showed dark blue staining were considered to be positive for premalignant or malignant tissue, while those with light staining, or totally not coloured, were considered negative."	All dysplasia is positive.	Not reported
McIntosh and Colleagues,⁶⁴ 2009	Tissue reflectance, Microlux	"After rinsing with the acetic acid solution, the manufacturer states that irregular cells will take on a whitish hue which will contrast with the surrounding tissues making it more obvious to the examiner." "Borders were designated either as diffuse or sharp."	All dysplasia is positive.	None

eTABLE 10 (CONTINUED)

STUDY	INDEX TEST*	POSITIVITY THRESHOLD (INDEX TEST)	POSITIVITY THRESHOLD (CRITERION TEST)	CONFLICTS OF INTEREST AND SOURCE OF FUNDING
Delavarian and Colleagues,³² 2010	Cytologic testing, OralCDx	Investigators categorized the pathologic findings into 3 groups: positive, dysplastic epithelial changes; negative, absence of any evidence suggesting dysplasia; inadequate sampling, no atypical results reported.	All dysplasia is positive.	University support acknowledged
Mehrotra and Colleagues,²⁸ 2010	Autofluorescence, VELscope	Normal mucosa (a negative VELscope finding) appears as a bright green glow, whereas abnormal mucosa (a positive VELscope finding) is identified by a loss of fluorescence and appears dark.	Unclear	None
Mehrotra and Colleagues,²⁸ 2010	Tissue reflectance and vital staining, ViziLite Plus	A positive ViziLite finding appeared aceto-white. The ViziLite Plus with TBlue system also contains a toluidine blue dye, which is intended to be used only to mark lesions that are positive according to the ViziLite screening for follow-up examination.	Unclear	None
Nagaraju and Colleagues,⁵⁶ 2010	Vital staining, toluidine blue and Lugol iodine	For either or both of the tests, staining results were positive.	All dysplasia is positive.	Not reported
Awan 2011a²⁴	Autofluorescence, VELscope	"The possible outcome of the autofluorescence examination was determined by the manufacturer's literature i.e. FVL—fluorescence visualization loss, FVR—fluorescence visualization retained and FVI—fluorescence visualization increased. Both examiners were calibrated by an experienced professional from the LED Diagnostics (the manufacturer)."	All dysplasia is positive.	"We thank Dr. Connie Yang for assistance in setting up the data entry system and Dr. Derek Cooper for the data analysis. VELscope system for the study was supplied by LED Diagnostics."
Awan 2011b⁶⁶	Tissue reflectance, ViziLite	Aceto-white = positive; Normal illumination = negative	All dysplasia is positive.	"We thank Dr. Connie Yang for assistance in setting up the data entry system and Dr. Derek Cooper for the data analysis. VELscope system for the study was supplied by LED Diagnostics."
Cancela-Rodriguez and Colleagues,⁵⁰ 2011	Vital staining, toluidine blue	"The stain was considered positive when the surface mucosa took on a blue colour, either if the entire lesion was stained or just a portion of it. Those that do not take colouration or with equivocal findings were considered negatives."	All dysplasia is positive.	Not reported

eTABLE 10 (CONTINUED)

STUDY	INDEX TEST*	POSITIVITY THRESHOLD (INDEX TEST)	POSITIVITY THRESHOLD (CRITERION TEST)	CONFLICTS OF INTEREST AND SOURCE OF FUNDING
Guneri and Colleagues,⁶⁹ 2011	Cytologic testing and vital staining, toluidine blue and Cytobrush	"The pattern of dye retention and the intensity of stain retention were recorded (2, dark blue staining; 1, minimal blue staining; 0, no blue staining). Occasionally, normal mucosa also appeared light blue, but this staining was not interpreted as positive." Sequence of tests: staining, brush biopsy, followed by criterion standard	Mild and moderate dysplasia classified as negative and severe dysplasia and carcinoma in situ classified as positive	"The study was funded by Ege University Scientific Research Projects Fund (2005-DIS-014)."
Koch 2011a³⁵	Cytologic testing, Cytobrush Plus GT	All dysplasia is positive. No atypical results reported.	All dysplasia is positive.	Not reported
Koch 2011b²⁷	Autofluorescence: "Two different investigation methods were applied: the standard examination by white light and the examination by a 400-nm wavelength light source that is supposed to trigger a green light emission (>500 nm) in normal mucosa." Documented with digital reflex photography	Positivity threshold: "SCC, and dysplasia [identified] depending on two different autofluorescence features: (1) A black or dark green aspect, as well as red indicating dysplasia or SCC (positive). Also, a speckled, heterotopic aspect of both green and autofluorescence negative or reddish regions indicated a positive finding (2) The presence of red mucosal autofluorescence was evaluated as a separate indicator for dysplasia or SCC (positive)."	All dysplasia is positive.	None
Mehrotra and Colleagues,³⁶ 2011	Cytologic testing, OralCDx	Three categories: negative, no epithelial abnormality; atypical, abnormal epithelial changes; positive definitive evidence of epithelial dysplasia or carcinoma Atypical results considered positive	Unclear	None
Scheer and Colleagues,³¹ 2011	Autofluorescence, VELscope	"The complete loss of the normal tissue fluorescence (fluorescence visualization loss [FVL]) was rated as malignant or dysplastic alteration. Red or orange fluorescence was not considered as malignant."	All dysplasia is positive.	Not reported
Upadhyay and Colleagues,⁵⁹ 2011	Vital staining, toluidine blue	Used Mashberg levels ⁵⁵ : "doubtful light blue stain was considered as positive until biopsy proves the contrary"	All dysplasia is positive.	No conflicts
Awan and Colleagues,⁴⁹ 2012	Vital staining, toluidine blue	"Among the test group (n = 82), 46 (56.1%) were positive for TBlue as they retained the dye. An almost equal number did not retain TBlue and therefore were recorded as negative for the test."	All dysplasia is positive.	"This study did not receive any grant funding by the industry but the test kits were supplied free of charge by Zila Inc."

eTABLE 10 (CONTINUED)

STUDY	INDEX TEST*	POSITIVITY THRESHOLD (INDEX TEST)	POSITIVITY THRESHOLD (CRITERION TEST)	CONFLICTS OF INTEREST AND SOURCE OF FUNDING
Farah and Colleagues,²⁵ 2012	Autofluorescence, VELscope	"Lesions that showed loss of autofluorescence were deemed positive, and lesions that did not show any loss of autofluorescence were deemed negative. In addition, all lesions that lost autofluorescence were blanched to evaluate diascopic fluorescence, and those that were deemed negative for loss of autofluorescence only if complete blanching was achieved."	Unclear	Not reported
Mojsa and Colleagues,⁶⁸ 2012	Tissue reflectance and vital staining, ViziLite Plus	"Chemiluminescence examination including the brightness, sharpness, surface texture, and size of the lesion using a 4-point scale (decreased, no change, slight improvement, marked improvement)" "Tolonium chloride examination including the staining pattern using a 3-point scale (negative, incomplete, complete)" Not clear which level of coloration equates to negative, incomplete, or positive	All dysplasia is positive.	Not reported
Ng and Colleagues,⁴¹ 2012	Cytologic testing, Oral Advance	"The histopathologic diagnosis was classified into 4 groups according to the presence and the degree of epithelial dysplasia, as summarized in Table II: benign, low-risk PMD, high-risk PMD, and SCC." Atypical results not reported	All dysplasia is positive.	Not reported
Rahman and Colleagues,⁴² 2012	Vital staining, Cytobrush	Unclear	Mild dysplasia classified as negative and moderate and severe dysplasia classified as positive	Not reported
Rahman and Colleagues,⁴² 2012	Cytologic testing, Cytobrush	Unclear; atypical results considered positive	Mild dysplasia classified as negative and moderate and severe dysplasia classified as positive	Not reported
Seijas-Naya and Colleagues,⁴⁵ 2012	Cytologic testing, OralCDx	"Positive for presence of dysplasia or carcinoma. All categories are atypical (cellular changes of uncertain diagnosis), positive for dysplasia or carcinoma, negative (normal cells) and inappropriate (incomplete transepithelial sample)." Unclear whether atypical results were considered positive or negative	All dysplasia is positive.	Not reported

eTABLE 10 (CONTINUED)

STUDY	INDEX TEST*	POSITIVITY THRESHOLD (INDEX TEST)	POSITIVITY THRESHOLD (CRITERION TEST)	CONFLICTS OF INTEREST AND SOURCE OF FUNDING
Ujaoney and Colleagues,⁶⁵ 2012	Tissue reflectance and vital staining, ViziLite Plus	"Dark staining lesions were considered positive; faint lesions were considered equivocal; and those which did not take up the stain were considered negative. Using these categories, lesions were classified as TBLU-positive if it was observed to be positive and TBLU-negative if the result was either equivocal or negative...The lesions that reflected the blue-white light were considered CHEM-positive. Any new lesion, not visible during conventional visual examination under incandescent light, but visible after chemiluminescent illumination test was noted and documented." "We considered a lesion to be CHTB-positive if it was both CHEM-positive and TBLU-positive; otherwise the lesion was considered to be CHTB-negative."	Moderate and severe or carcinoma classified as positive and mild dysplasia classified as negative	None
Ujaoney and Colleagues,⁶⁵ 2012	Tissue reflectance, ViziLite	"The lesions that reflected the blue-white light were considered CHEM-positive. Any new lesion, not visible during conventional visual examination under incandescent light, but visible after chemiluminescent illumination test was noted and documented."	Moderate and severe or carcinoma classified as positive and mild dysplasia classified as negative	None
Chaudhari and Colleagues,⁵¹ 2013	Vital staining, toluidine blue	Unclear	All dysplasia is positive.	Not reported
Chaudhari and Colleagues,⁵¹ 2013	Vital staining, Lugol iodine	Unclear	All dysplasia is positive.	Not reported
Fontes and Colleagues,³³ 2013	Cytologic testing, Cytobrush	Squamous cell carcinoma, carcinoma, malignancy suggestive of squamous cell carcinoma, and epithelial dysplasia considered positive. Atypical results considered negative but unclear the proportion of lesions that were atypical	All dysplasia is positive.	"This study was supported by grants from Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), a Brazilian governmental institution. The authors certify that they have no commercial or associative interest that represents a conflict of interest in connection with the manuscript."
Hanken and Colleagues,²⁶ 2013	Autofluorescence, VELscope	"According to the existing literature, the complete loss of the normal tissue fluorescence (fluorescence visualization loss) was rated as malignant or dysplastic. A fluorescence in red or orange was not rated as malignant according to the literature [11,14]."	All dysplasia is positive.	None

eTABLE 10 (CONTINUED)

STUDY	INDEX TEST*	POSITIVITY THRESHOLD (INDEX TEST)	POSITIVITY THRESHOLD (CRITERION TEST)	CONFLICTS OF INTEREST AND SOURCE OF FUNDING
Kammerer and Colleagues,³⁴ 2013	Cytologic testing, Cytobrush Plus GT	“Negative’ in cases with benign changes or with the finding of mild dysplastic epithelial cells (SIN 1) only, 17, 20, 35 and as ‘positive’ if cells with moderate or severe dysplasia (SIN 2, SIN 3) or malignant tumor cells.” No atypical results reported	Moderate and severe dysplasia classified as positive and mild dysplasia classified as negative	None
Petruzzi and Colleagues,³⁰ 2014	Autofluorescence, VELscope	“According to the literature, the loss of the normal tissue fluorescence was judged as a malignant or dysplastic alteration. Red or orange fluorescence was not considered as malignant according to the literature.”	All dysplasia is positive.	None
Chainani-Wu and Colleagues,⁶² 2015	Tissue reflectance, ViziLite	Investigators described ViziLite examination results that demonstrated increased brightness in comparison with the visual examination results as ViziLite positive.	Severe and squamous cell carcinoma are positive and mild and moderate dysplasia classified as negative	Not reported
Chainani-Wu and Colleagues,⁶² 2015	Tissue reflectance and vital staining, ViziLite and toluidine blue	Unclear	Severe and squamous cell carcinoma are positive and mild and moderate dysplasia classified as negative	Not reported
Singh and Shukla,⁶ 2015	Vital staining, toluidine blue	“A dark blue (royal or navy) stain is considered positive if either the entire lesion being stained or a portion of it is stained or stippled (Figs. 1, 2). A light blue staining is considered doubtful. If there is no colour absorbed by the lesion, it is taken as a negative stain.”	All dysplasia is negative.	Not reported
Trakroo and Colleagues,⁴⁷ 2015	Cytologic testing, brush biopsy	All dysplasia positive. Atypical results included but unclear whether they are classified as negative or positive	All dysplasia is positive.	None
Nanayakkara and Colleagues,³⁸ 2016	Cytologic testing, spatula	Mild dyskaryosis, moderate dyskaryosis, severe dyskaryosis, and malignancy classified as positive No atypical results reported	All dysplasia is positive.	Not reported
Nanayakkara and Colleagues,³⁸ 2016	Cytologic testing, Cytobrush	Mild dyskaryosis, moderate dyskaryosis, severe dyskaryosis, and malignancy classified as positive No atypical results reported	All dysplasia is positive.	None

eTABLE 11

Vital staining adjuncts to evaluate clinically evident, suspicious lesions.								
VITAL STAINING	SENSITIVITY	95% CI*	SPECIFICITY	95% CI	POSITIVE LIKELIHOOD RATIO	95% CI	NEGATIVE LIKELIHOOD RATIO	95% CI
With Verification Bias†	0.87	0.80 to 0.94	0.71	0.61 to 0.92	3.04	2.06 to 4.48	0.18	0.10 to 0.32
Verification Bias Minimized‡	0.87	0.79 to 0.95	0.7	0.59 to 0.82	2.92	1.95 to 4.8	0.19	0.10 to 0.36

* CI: Confidence interval.
† We calculated the estimates with data from the following studies: Allegra and colleagues⁴⁸ 2009, Awan and colleagues⁴⁹ 2012, Cancela-Rodriguez and colleagues⁵⁰ 2011, Chen and colleagues⁵² 2007, Cheng and Yang⁵³ 2003, Du and colleagues⁵⁴ 2007, Mashberg⁵⁵ 1980, Nagaraju and colleagues⁵⁶ 2010, Onofre and colleagues⁵⁷ 2001, Rahman and colleagues⁴² 2012, Silverman and colleagues⁵⁸ 1984, Upadhyay and colleagues⁵⁹ 2011, Warnakulasuriya and Johnson⁶⁰ 1996, Chaudhari and colleagues⁵¹ 2013, and Singh and Shukla⁶¹ 2015.
‡ We calculated the estimates with data from the following studies: Allegra and colleagues⁴⁸ 2009, Awan and colleagues⁴⁹ 2012, Cancela-Rodriguez and colleagues⁵⁰ 2011, Chen and colleagues⁵² 2007, Cheng and Yang⁵³ 2003, Du and colleagues⁵⁴ 2007, Mashberg⁵⁵ 1980, Nagaraju and colleagues⁵⁶ 2010, Onofre and colleagues⁵⁷ 2001, Rahman and colleagues⁴² 2012, Silverman and colleagues⁵⁸ 1984, Upadhyay and colleagues⁵⁹ 2011, Warnakulasuriya and Johnson⁶⁰ 1996, and Singh and Shukla⁶¹ 2015.

eTABLE 12

Cytologic adjuncts to evaluate clinically evident, suspicious lesions.								
CYTOLOGIC TESTING	SENSITIVITY	95% CI*	SPECIFICITY	95% CI	POSITIVE LIKELIHOOD RATIO	95% CI	NEGATIVE LIKELIHOOD RATIO	95% CI
With Verification Bias†	0.92	0.86 to 0.98	0.94	0.88 to 0.99	14.18	5.82 to 34.59	0.08	0.04 to 0.18
Verification Bias Minimized‡	0.93	0.86 to 0.99	0.94	0.90 to 0.98	16.14	8.15 to 31.94	0.08	0.03 to 0.20

* CI: Confidence interval.
† We calculated the estimates with data from the following studies: Delavarian and colleagues³² 2010, Koch and colleagues³⁵ 2011a, Mehrotra and colleagues³⁷ 2008, Navone and colleagues³⁹ 2004, Navone and colleagues⁴⁰ 2008, Ng and colleagues⁴¹ 2012, Rahman and colleagues⁴² 2012, Sciubba⁴⁴ 1999, Seijas-Naya and colleagues⁴⁵ 2012, Svirsky and colleagues⁴⁶ 2002, Fontes and colleagues³³ 2013, Kammerer and colleagues³⁴ 2013, Nanayakkara and colleagues³⁸ 2016, Trakroo and colleagues⁴⁷ 2015, and Scheifele and colleagues⁴³ 2004.
‡ We calculated the estimates with data from the following studies: Delavarian and colleagues³² 2010, Koch and colleagues³⁵ 2011a, Mehrotra and colleagues³⁷ 2008, Navone and colleagues⁴⁰ 2008, Ng and colleagues⁴¹ 2012, Rahman and colleagues⁴² 2012, Sciubba⁴⁴ 1999, Fontes and colleagues³³ 2013, Kammerer and colleagues³⁴ 2013, Nanayakkara and colleagues³⁸ 2016, Trakroo and colleagues⁴⁷ 2015, and Scheifele and colleagues⁴³ 2004.

eTABLE 13

Vital staining adjuncts to evaluate clinically evident, suspicious lesions (verification bias minimized?)*

TEST RESULT	EFFECT PER 100,000 PATIENTS TESTED, NO. (RANGE) (95% CONFIDENCE INTERVAL [CI])		NO. OF PARTICIPANTS (STUDIES)	QUALITY OF THE EVIDENCE (GRADE) [§]	COMMENTS
	Prevalence 0.25% [†]	Prevalence 2.0% [‡]			
True-Positive Results (Patients Needing Biopsy)	217 (198 to 238)	1,740 (1,580 to 1,900)	1,289 (14)	Low ^{¶, #, **}	Patients will be identified correctly as having a potentially malignant or malignant disorder, and timely referral to a specialist or biopsy will be performed.
False-Negative Results (Patients Incorrectly Classified as Not Needing Biopsy)	33 (12 to 52)	260 (100 to 420)			An appropriate diagnosis would be missed, worsening the prognosis of the disease.
True-Negative Results (Patients Without Need for Biopsy)	69,825 (58,853 to 81,795)	68,600 (57,820 to 80,360)	1,289 (14)	Low ^{¶, #, **}	Patients will receive reassurance that they do not have a potentially malignant or malignant disorder.
False-Positive Results (Patients Incorrectly Classified as Needing Biopsy)	29,925 (17,955 to 40,897)	29,400 (17,640 to 40,180)			Patients would be identified incorrectly as having a potentially malignant or malignant disorder and would undergo additional unnecessary testing and biopsy.

* Setting: Primary care. Pooled sensitivity: 0.87 (95% confidence interval, 0.79 to 0.95). Pooled specificity: 0.70 (95% confidence interval, 0.59 to 0.82). Positive likelihood ratio, 2.92 (95% confidence interval, 1.95 to 4.38); negative likelihood ratio, 0.19; (95% confidence interval, 0.10 to 0.36). Sources: Allegra and colleagues⁴⁸ 2009, Awan and colleagues⁴⁹ 2012, Cancela-Rodriguez and colleagues⁵⁰ 2011, Chen and colleagues⁵² 2007, Cheng and Yang⁵³ 2003, Du and colleagues⁵⁴ 2007, Mashberg⁵⁵ 1980, Nagaraju and colleagues⁵⁶ 2010, Onofre and colleagues⁵⁷ 2001, Rahman and colleagues⁴² 2012, Silverman and colleagues⁵⁸ 1984, Upadhyay and colleagues⁵⁹ 2011, Warnakulasuriya and Johnson⁶⁰ 1996, and Singh and Shukla⁶¹ 2015.

† We estimated the prevalence by using data from the National Cancer Institute Surveillance, Epidemiology, and End Results Program (300,682 people living with oral cavity and pharynx cancer in the United States in 2013) and the 2010 census data for adults 45 years or older collected by the US Census Bureau.

‡ The panel provided illustrative prevalence as an estimation of the number of histopathologic diagnoses from dysplasia to cancer.

§ GRADE: Grading of Recommendations Assessment, Development and Evaluation.

¶ Patient selection and exclusion from analysis were inappropriate. Poor-quality reporting did not provide sufficient information to judge key domains for risk of bias.

Investigators conducted most studies in secondary and tertiary care settings. Most patients had a higher probability of having a malignant or potentially malignant disorder.

** The positivity threshold for the criterion standard included from mild dysplasia to cancer in all studies except for those of Rahman and colleagues 2012, Singh and Shukla 2015, and Cheng and Yang 2003.

eTABLE 14

Cytologic adjuncts to evaluate clinically evident, suspicious lesions (verification bias minimized?)*

TEST RESULT	EFFECT PER 100,000 PATIENTS TESTED. NO. (RANGE)		NO. OF PARTICIPANTS (STUDIES)	QUALITY OF THE EVIDENCE (GRADE) [§]	COMMENTS
	Prevalence 0.25% [†]	Prevalence 2.0% [‡]			
True-Positive Results (Patients Needing Biopsy)	233 (215 to 248)	1,860 (1,720 to 1,980)	1,748 (12)	Moderate ^{¶, #}	Patients will be identified correctly as having a potentially malignant or malignant disorder, and timely referral to a specialist or biopsy will be performed. An appropriate diagnosis would be missed, worsening the prognosis of the disease.
False-Negative Results (Patients Incorrectly Classified as Not Needing Biopsy)	17 (2 to 35)	140 (20 to 280)			
True-Negative Results (Patients Without Need for Biopsy)	93,765 (89,775 to 97,755)	92,120 (88,200 to 96,040)	1,748 (12)	Moderate ^{¶, #}	Patients will receive reassurance that they do not have a potentially malignant or malignant disorder. Patients would be identified incorrectly as having a potentially malignant or malignant disorder and would undergo additional unnecessary testing and biopsy.
False-Positive Results (Patients Incorrectly Classified as Needing Biopsy)	5,985 (1,995 to 9,975)	5,880 (1,960 to 9,800)			

* Setting: Primary care. Pooled sensitivity: 0.93 (95% confidence interval, 0.86 to 0.99). Pooled specificity: 0.94 (95% confidence interval, 0.90 to 0.98). Positive likelihood ratio, 16.14 (95% confidence interval, 8.15 to 31.94); negative likelihood ratio, 0.08 (95% confidence interval, 0.03 to 0.20). Sources: Delavarian and colleagues³² 2010, Koch and colleagues³⁵ 2011a, Mehrotra and colleagues³⁷ 2008, Navone and colleagues⁴⁰ 2008, Ng and colleagues⁴¹ 2012, Rahman and colleagues⁴² 2012, Sciubba⁴⁴ 1999, Fontes and colleagues³³ 2013, Kammerer and colleagues³⁴ 2013, Nanayakkara and colleagues³⁸ 2016, Trakroo and colleagues⁴⁷ 2015, and Scheifele and colleagues⁴³ 2004.

[†] We estimated the prevalence by using data from the National Cancer Institute Surveillance, Epidemiology, and End Results Program (300,682 people living with oral cavity and pharynx cancer in the United States in 2013) and the 2010 census data for adults 45 years or older collected by the US Census Bureau.

[‡] The panel provided illustrative prevalence as an estimation of the number of histopathologic diagnoses from dysplasia to cancer.

[§] GRADE: Grading of Recommendations Assessment, Development and Evaluation.

[¶] Investigators conducted most studies in secondary and tertiary care settings. Most patients had a higher probability of having a malignant or potentially malignant disorder.

[#] The positivity threshold for the criterion standard included from mild dysplasia to cancer in all studies except for that of Rahman and colleagues⁴² 2012. The positivity threshold for the index test also included atypical results in the studies of Sciubba⁴⁴ 1999, Scheifele and colleagues⁴³ 2004, and Rahman and colleagues⁴² 2012.