ADA CE Program ARTICLE 1

COVER STORY

Evidence-based clinical practice guideline for the evaluation of potentially malignant disorders in the oral cavity

A report of the American Dental Association

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ABSTRACT

Background. An expert panel convened by the American Dental Association (ADA) Council on Scientific Affairs and the Center for Evidence-Based Dentistry conducted a systematic review and formulated clinical recommendations to inform primary care clinicians about the potential use of adjuncts as triage tools for the evaluation of lesions, including potentially malignant disorders (PMDs), in the oral cavity.

Types of Studies Reviewed. This is an update of the ADA's 2010 recommendations on the early diagnosis of PMDs and oral squamous cell carcinoma. The authors conducted a systematic search of the literature in MEDLINE and Embase via Ovid and the Cochrane Central Register of Controlled Trials to identify randomized controlled trials and diagnostic test accuracy studies. The authors used the Grading of Recommendations Assessment, Development and Evaluation approach to assess the certainty in the evidence and to move from the evidence to the decisions.

Results. The panel formulated 1 good practice statement and 6 clinical recommendations that concluded that no available adjuncts demonstrated sufficient diagnostic test accuracy to support their routine use as triage tools during the evaluation of lesions in the oral cavity. For patients seeking care for suspicious lesions, immediate performance of a biopsy or referral to a specialist remains the single most important recommendation for clinical practice. In exceptional cases, when patients decline a biopsy or live in rural areas with limited access to care, the panel suggested that cytologic testing may be used to initiate the diagnostic process until a biopsy can be performed (conditional recommendation, low-quality evidence).

Conclusions and Practical Implications. The authors urge clinicians to remain alert and take diligent action when they identify a PMD. The authors emphasize the need for counseling because patients may delay diagnosis because of anxiety and denial.

Key Words. American Dental Association; oral squamous cell carcinoma; potentially malignant disorders; clinical recommendations; diagnostic test accuracy.

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The American Cancer Society estimates that there will be 49,670 new cancer cases in the oral cavity and oropharynx in 2017, with 9,700 deaths from this disease.[1] More than 80% of these malignancies will be squamous cell carcinomas in the oral cavity (oral squamous cell carcinomas [OSCCs]) and oropharynx (oropharynx squamous cell carcinomas [OPSCCs]).[1] For OSCC specifically, 32,670 new cases and 6,650 deaths are estimated.[1] Various factors increase a person's risk of developing OSCC, including increasing age, tobacco use, excessive alcohol use,

This article has an accompanying online continuing education activity available at: http://jada.ada.org/ce/home.

immunosuppression, poor diet, a history of potentially malignant disorders (PMDs) or malignant disorders, and certain inherited diseases such as Fanconi anemia.[1,2] The median age at diagnosis is 63 years, with more than 97% of US OSCC and OPSCC cases occurring among adults 35 years or older.[2] The age-adjusted incidence rate (IR) of OSCC and OPSCC in the United States is 11.37 per 100,000 per year.[2] In the sex comparison, both the IR (16.7 versus 6.2 per 100,000) and mortality rate (3.8 versus 1.3 per 100,000) were more than twice as high among men as among women.[2] The US 5-year relative survival rate is 64.3%.[2] However, survival rates for OSCC are highly stage dependent,[1] with 83.7% of people alive 5 years after diagnosis when a localized cancer is diagnosed and 64.2% and 38.5% of people alive 5 years after diagnosis when regional and distant metastases are diagnosed, respectively. Approximately 70% of all new cases are diagnosed at a late stage, underscoring the importance of early detection and prevention.[1]

Extra Supplemental material is available online.

Historical data reveal substantial changes in the epidemiology of OSCC.[3] Overall, OSCC IRs for most sites, including the lip, gingiva, and floor of the mouth, have decreased in the United States over the past few decades, consistent with decreases in the prevalence of the major risk factors—tobacco and alcohol use.[3] However, the IR for oral tongue squamous cell carcinoma (anterior two-thirds of the tongue) appears to have increased in white men and women, although the causes of this increase remain unknown.[4,5] In addition, the IR for OPSCC, including the base of tongue (posterior one-third of the tongue), tonsil, soft palate, and pharyngeal wall, has increased significantly over the past several decades, particularly in white men.[3] Investigators attribute the dramatic increase in OPSCC to an increased exposure to human papillomavirus (HPV), a common viral infection. Although tobacco and alcohol use are associated with OPSCC, over the past 20 years HPV infection has surpassed tobacco and alcohol as a major risk factor; HPV causes 75% of all OPSCC cases, which is driven by an increase in oral sex.[6-8] One type in particular, HPV 16, causes most OPSCCs.

Clinicians perform the conventional visual and tactile examination (CVTE) intraorally and extraorally in dental patients after a review of the patient's full medical, social, and dental history. This history includes assessing patient-reported symptoms such as globus sensation (persistent lump in throat), unexplained ear or oropharyngeal pain, hoarseness, and so on and performing a lymph node evaluation and examination of the neck. A major purpose of CVTE is to identify any type of mucosal or submucosal abnormality, which has been observed in as many as 10% of patients.[9] Although clinicians will consider a small proportion of these lesions suspicious, early clinical identification and subsequent definitive diagnosis of PMDs or OSCC likely may reduce disease-related morbidity and mortality.

Important considerations regarding CVTE include the following:

- mucosal and submucosal abnormalities most commonly manifest as leukoplakia, and other manifestations can include speckled leukoplakia (that is, erythroleukoplakia) or erythroplakia, with or without ulceration;
- generally, biopsies performed in erythroplakia or persistently ulcerated lesions are more likely to produce results indicating OSCC or moderate to severe epithelial dysplasias[10];
- not all leukoplakias will show microscopic features of epithelial dysplasia in a biopsy specimen[10];
- the clinical and histopathologic progression of a leukoplakia over time is inconsistent in terms of predicting which lesions will progress and how quickly they might progress[11,12];
- dysplasia can be present in clinically normal mucosa[13];
- oral cancer does not necessarily originate from a single cell but may arise from a number of cells in an area (field cancerization) that can lead to satellite lesions.[14]

Despite the importance of performing CVTE in all adult dental patients, this technique alone may not always help discriminate between innocuous and suspicious lesions, mucosal abnormalities that may require differing management after evaluation.

In other, nonoral anatomic sites with similar challenges, adjunctive tests, devices, or technologies (that is, adjuncts) assist in disease detection and discrimination. Examples of these other adjuncts include mammography, Papanicolaou smears, and colonoscopy. Given the success of adjuncts at other anatomic sites, a number of candidate adjuncts, purported to aid in the evaluation and discrimination of mucosal lesions, have become commercially available and marketed in the primary care setting.[15]

This clinical practice guideline is an update and major revision of the American Dental Association's (ADA) 2010 guideline titled, "Evidence-based Clinical Recommendations Regarding Screening for Oral Squamous Cell Carcinomas," and is the product of an expert panel convened by the ADA Council on Scientific Affairs.[16]

ABBREVIATION KEY. **ADA:** American Dental Association. **CVTE:** Conventional visual and tactile examination. **GRADE:** Grading of Recommendations Assessment, Development and Evaluation. **HPV:** Human papillomavirus. **OPSCC:** Oropharynx squamous cell carcinoma. **OSCC:** Oral squamous cell carcinoma. **PMD:** Potentially malignant disorder.

The ADA Center for Evidence-Based Dentistry, in collaboration with the Cochrane Oral Health Group, led the evidence synthesis and methodology used to formulate the recommendation statements presented in this article.[15,17,18]

This report is based on a systematic review and meta-analysis of the diagnostic test accuracy and patient-important outcomes of various adjuncts.[15] The intention is to provide clinicians with updated evidence-based recommendations and suggest a clinical pathway regarding whether and when to use these adjuncts as triage tools for the evaluation of adult patients with no clinically evident lesions and clinically evident lesions, including PMDs, in the oral cavity.

DEFINITION OF POTENTIALLY MALIGNANT DISORDERS AND ORAL SQUAMOUS CELL CARCINOMA IN THE ORAL CAVITY

PMDs and OSCC are the target conditions for this clinical practice guideline. PMDs are mucosal lesions that have an increased risk of developing into OSCC. These could include leukoplakia, erythroplakia, erythroleukoplakia, and submucous fibrosis, and these lesions may be found in those with hereditary disorders with an increased risk of developing malignant transformation and in heavy tobacco and alcohol users. OSCC is derived from the surface stratified squamous epithelium and is the most common form of cancer in the oral cavity. OSCC can be diagnosed definitely only via biopsy and histopathologic assessment, though preliminary clinical or visual diagnosis of PMDs during CVTE is often the impetus for following the major diagnostic pathway.

POTENTIAL ROLE OF ADJUNCTS IN PRIMARY CARE

Although adjuncts (that is, index tests) can triage, replace a criterion standard test, or enhance or act as an add-on to an existing test,[19] we were interested in the following adjuncts for their principal role as triage tools after CVTE in primary care settings (Figure 1):

- cytologic testing (for example, OralCDx [OralScan Laboratories, Inc.], OralCyte [ClearCyte Diagnostics Inc.], ClearPrep OC [Resolution Biomedical]);
- autofluorescence (for example, VELscope [LED Dental], OralID [Forward Science]);
- tissue reflectance (for example, ViziLite Plus [DenMat Holdings, LLC], Microlux DL [AdDent Inc.]);
- vital staining (for example, toluidine blue);
- salivary adjuncts (for example, OraRisk [Oral DNA Labs], SaliMark [PeriRx LLC], OraMark [OncAlert Labs], MOP genetic oral cancer screening [PCG Molecular], OraGenomics);
- additional adjuncts of interest (for example, Identafi [StarDental]).

Histopathologic assessment of tissue obtained during a biopsy is the criterion standard for detecting dysplasia and definitively diagnosing the target conditions. In this guideline, we did not assess adjuncts regarding their ability to replace this criterion standard diagnostic test for PMDs and OSCC (Table 1) (Figures 2-5).

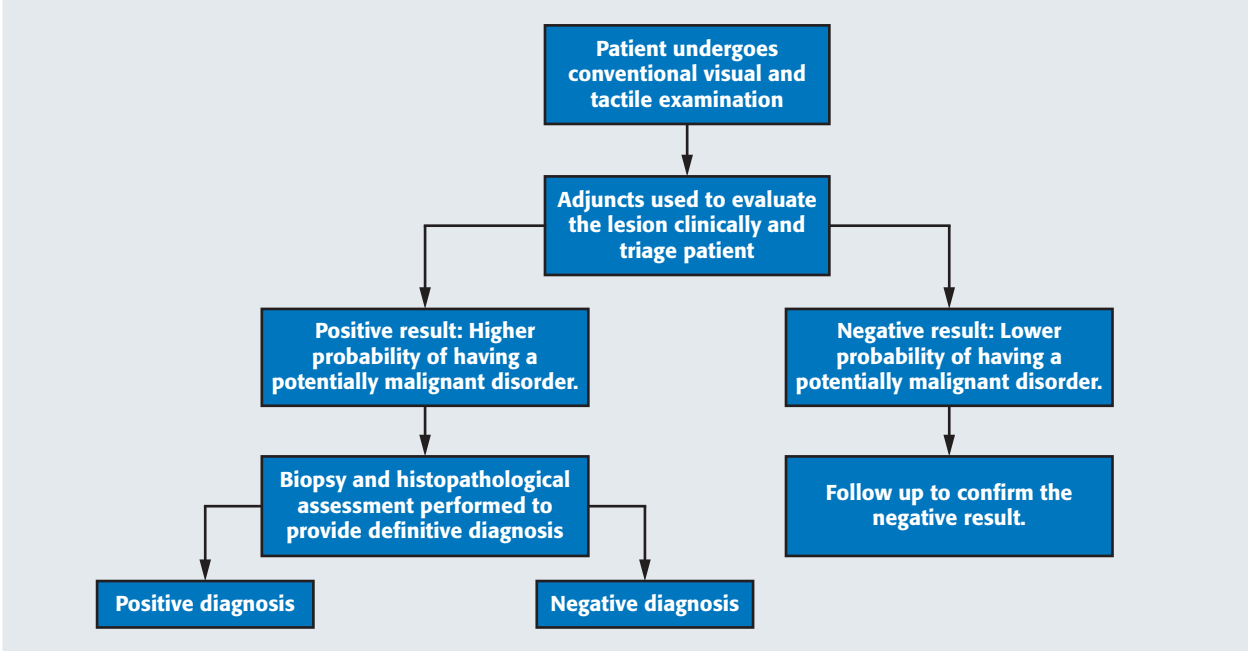

Figure 1. Adjuncts as potential triage tools to determine the need for a biopsy.

METHODS

We followed the Appraisal of Guidelines Research & Evaluation reporting checklist II and the GIN-McMaster Guideline Development Checklist[20] when we conducted and reported this clinical practice guideline.[21]

Guideline panel configuration and conflict of interest management. The ADA Council on Scientific Affairs nominated and convened the 2017 expert panel for its clinical and subject matter expertise. The panel was configured carefully to include multidisciplinary viewpoints—general dentists, hygienists, oral medicine specialists, otolaryngologists, oncologists, oral and maxillofacial pathologists, oral and maxillofacial surgeons, and epidemiologists. Whenever possible, we attempted to avoid involving expert panelists with extensive conflicts of interest. We asked all panel members who initially were invited to complete a form providing information about any potential financial and intellectual conflicts of interest within the past 2 years. For the sake of transparency, we summarized and presented all potential conflicts to the entire panel at the beginning of both in-person meetings. As part of the methodology, we planned that any member of the panel considered to be highly conflicted would need to refrain from participating in the formulation of recommendations for which we identified conflicts.[22]

Scope and target audience. The scope of this guideline includes patients with no lesions, innocuous or nonsuspicious lesions, lesions suspected to be potentially malignant (that is, PMDs), and malignant lesions (that is, OSCC) in the oral cavity. We did not include sarcomas or carcinomas of the lips, oropharynx, and salivary glands within the scope of this guideline. The target audience for this guideline includes general and specialty dentists, physicians and physician's assistants, dental therapists, dental hygienists, nurses, and nurse practitioners. Community dental health coordinators and policy makers also can use the recommendation statements to inform clinical decision making, programmatic decisions, and public health policy.

Retrieving the evidence. This guideline is informed partially by 4 systematic reviews.[17,18,23,24] The Cochrane Oral Health Group originally developed 2, and 2 are non-Cochrane reviews.[17,18,23,24] The ADA Center for Evidence-Based Dentistry updated both Cochrane reviews to guarantee that the panel was using the most up-to-date information when formulating recommendations. We used the 2 non-Cochrane reviews to inform the clinical question about salivary adjuncts, and, because they were published in 2016 and 2017, we decided not to update them. We selected diagnostic test accuracy estimates and outcomes important to patients a priori and ranked the latter according to their relative importance in regard to clinical decision making (critical, important, and not important to clinical decision making).[25]

We searched several databases during the update of the systematic reviews: MEDLINE, Cochrane Central Register of Controlled Trials, and Embase. Two of us (M.P.T., O.U.) screened the results of the search process independently and in duplicate by using titles and abstracts and, in a second stage, by using full-text articles. We then extracted the retrieved data, conducted meta-analyses of diagnostic test accuracy estimates, and presented the evidence by using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) summary of findings tables for diagnostic test accuracy. In addition to conducting a comprehensive search to update preexisting systematic reviews, we also conducted a search to summarize the evidence on patients' values and preferences for the evaluation of PMDs and OSCC. Detailed information related to the systematic reviews, methodology for updating, and methods supporting this guideline is published elsewhere.[15]

Outcomes important to patients and diagnostic test accuracy estimates. The panel selected and ranked outcomes important to patients, including oral cancer mortality (critical), survival (critical), unnecessary biopsy (critical), quality of life (important), all-cause mortality (important), incidence of oral cancer (important), anxiety and stress (important), and costs (important). In the absence of evidence informing these outcomes, the panel suggested the inclusion of diagnostic test accuracy estimates, including sensitivity, specificity, and positive and negative likelihood ratios (LRs), and their 95% confidence intervals (CIs). The application of any adjunct in the context of a study can result in 4 categories: true positive, false positive, true negative, and false negative.[19] For further explanation of outcomes included in this guideline, see the Appendix[15,17,19] (available online at the end of this article). In the absence of outcomes important to patients, the panel defined the downstream consequences of a patient obtaining a true-positive, false-positive, true-negative, or false-negative result and weighed the balance between benefits and harms on the basis of the magnitude of these results.

We calculated LRs and their 95% CIs by using measures of sensitivity and specificity and used them during the decision-making process. They are either positive or negative and provide information about how much a test result will change the probability of a patient having or not having the target condition. For example, a positive LR will indicate how much more likely someone with a positive test result will have the target condition than will someone without the target condition, whereas a negative LR will indicate how much more likely someone with a negative test result will not have the target condition than will someone with the target condition. Regarding the interpretation of LRs, we considered that the further an LR was from a value of 1, the more support we had for either the presence (LR $>$ 1) or absence (LR $<$ 0.1) of a target condition—that is, a

TABLE 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 *community-based screening* or *population-based screening*, 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 (persistent lump in throat), unexplained ear pain or oropharyngeal pain, hoarseness, and so on.
No Clinically Evident Lesions (Figure 2)	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 a morphologically altered tissue noted at CVTE.
Clinically Evident, Seemingly Innocuous, or Nonsuspicious Lesions (Figure 3)	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 (Figure 4)	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 possibly. 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 (Figure 5)	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 developing 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 undergoing malignant transformation and among heavy tobacco and alcohol users. These diagnoses usually are assigned in a primary care setting through CVTE and through the presence of dysplasia (that is, the only definitive indicator for potential malignancy or malignancy) and can be determined only through a 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 during a 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	A biopsy followed by histopathologic assessment, a procedure used to detect dysplasia, is the criterion standard diagnostic test for PMDs and OSCC. A 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 (a 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 a biopsy will be performed.

* 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 *potentially malignant disorder*, and the authors attempted to reconcile inconsistencies as well as possible.
§ OSCC: Oral squamous cell carcinoma.

TABLE 1 (CONTINUED)

TERM	DEFINITION
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.
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 *true-positive rate*.
Specificity	Specificity is the ability of a test to help identify those without the disease correctly, also known as the *true-negative rate*.
Positive Likelihood Ratio	A positive likelihood ratio indicates how much the odds of the disease increase when a test is positive.
Negative Likelihood Ratio	A negative likelihood ratio indicates how much the odds of the disease decrease when a test is negative.
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.

positive LR can help rule in disease, and a negative LR can help rule out disease, especially as the LRs move further from the null value of 1.[26] When a positive LR is greater than or equal to 10, it usually means the adjunct is very effective at ruling in disease. When the prevalence of the target condition is low, this rule does not necessarily apply. By comparing pretest and posttest probabilities, we were able to ascertain whether the probability of an accurate diagnosis increased (indicated by an increase in posttest probability) or decreased (indicated by a decrease in posttest probability).[26]

To illustrate how adjuncts would perform when used in primary care settings, we attempted to find the most recent prevalence data for PMDs and OSCC in adults living in the United States. Neither the available literature nor any of the organizations we contacted (Centers for Disease Control and Prevention, National Institute of Dental and Craniofacial Research, and National Cancer Institute) had recent data available, so we used a combination of the 2013 Surveillance, Epidemiology, and End Results Program data from the National Institutes of Health and 2010 census data to estimate an OSCC prevalence of 0.25% among adults 45 years or older in the United States.[27,28] This prevalence does not include PMDs, so for illustrative purposes, we imputed a prevalence of 2.0% to illustrate the performance of these adjuncts when including these disorders. We calculated the proportion of true-positive, false-positive, true-negative, and false-negative results expressed in a population of 100,000 people.

Patient values and preferences. We conducted a systematic search to identify primary studies and systematic reviews in which the investigators reported on patients' values and preferences in the assessment of clinically evident lesions in the oral cavity. "Patients' values and preferences" refers to

> the relative importance individuals place on the health outcomes; since we consider an intervention in the context of the consequences it incurs, the preferences for or against an intervention is a consequence of the relative importance individuals place on the expected or definite health outcomes it incurs.[29]

Investigators conducted most of the studies in countries other than the United States, focused on the detection of lesions in the context of screening programs (screening programs are not the focus of this guideline), and provided no evidence about how patients valued the different outcomes linked to the use of adjuncts. For additional information about patients' values and preferences, results, and panel considerations, see the Appendix[15,17,19] (available online at the end of this article).

Assessing the certainty in the evidence. The GRADE working group's guidance indicates an assessment of the certainty in the evidence or the quality of the evidence

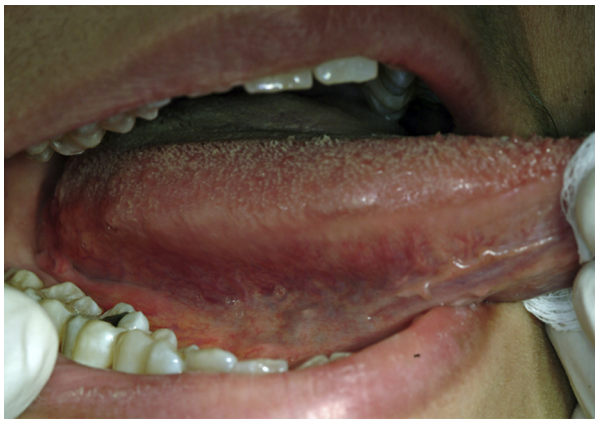

Figure 2. No clinically evident lesion.

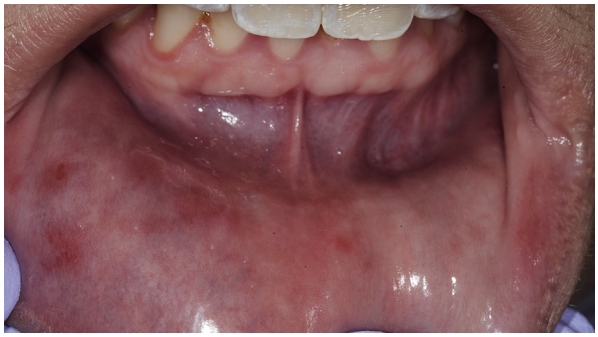

Figure 3. Clinically evident, seemingly-innocuous or non-suspicious lesion.

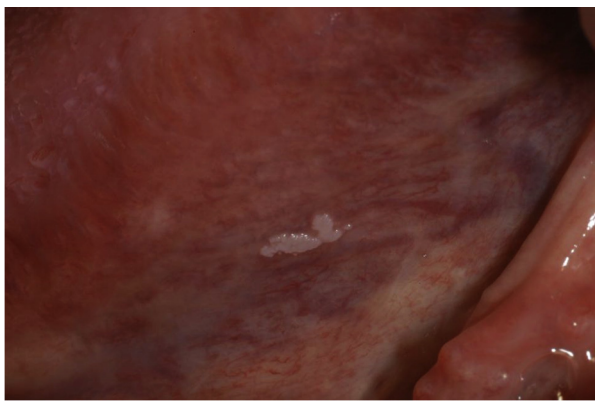

Figure 4. Clinically evident suspicious lesion.

(high, moderate, low, or very low) (Table 2).[30-33] This is an essential step in the guideline development process because it reflects the confidence of the panel regarding the estimates of effect used to draft the recommendation statements. We determined and reported the certainty in the evidence at an outcome level, across the body of evidence, and this certainty is driven by whether there

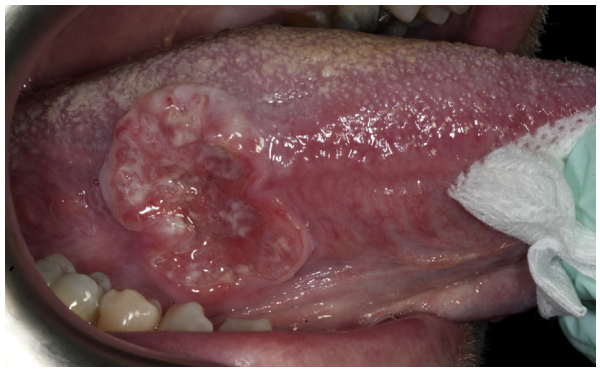

Figure 5. Seemingly malignant lesion.

were serious or very serious issues among the following domains: risk of bias, imprecision, inconsistency, indirectness, and publication bias.[19,34]

Moving from the evidence to decisions. We used the GRADE evidence-to-decision framework[35] to inform the process of formulating recommendations and to determine the strength of these statements. We assessed several domains during this process, including patient values and preferences, certainty in the evidence (quality of the evidence), balance between desirable and undesirable consequences (net effect), and resource use. In GRADE, the strength of recommendations can be either strong or conditional. Implications for stakeholders such as patients, clinicians, and policy makers vary between strong and conditional recommendations (Table 2).[31,32]

Process of formulating recommendations. We formulated the clinical questions, outcomes of interest, and final recommendations contained in this article during 2 in-person expert panel meetings held in September 2016 and January 2017. Methodologists from the ADA Center for Evidence-Based Dentistry (M.P.T., O.U., A.C.L.) facilitated both meetings. We used guidance from the GRADE approach, deliberation, and consensus during implementation of the evidence-to-decision framework. If consensus was elusive, we presented all possible options with assessments for a panel vote.

Stakeholder and public feedback. We contacted internal ADA and external stakeholders on 2 occasions: at the beginning of the guideline development process to obtain feedback on the definition of the scope and purpose, target audience and population, clinical questions, adjuncts, and outcomes for decision making and after formulating recommendations to obtain input about the clarity and appropriateness of the recommendation statements and the assessment of the quality of the evidence and strength of the recommendations.[36] In addition, we posted a draft of the guideline's scope and purpose, target audience and users, and recommendation statements on the ADA's website with the purpose of obtaining

comments from the general public. The panel and methodological team logged and considered these comments and incorporated them when writing this article.

Guideline updating process. The ADA Center for Evidence-Based Dentistry routinely monitors relevant literature and databases. Updates for this guideline will be conducted every 5 years or when new emerging evidence indicates a potential change in the recommendation statements from the expert panel. Any updated versions of this guideline will be available at the ADA Center for Evidence-Based Dentistry's website: ebd.ada.org/guideline.

RECOMMENDATIONS

How do you use these recommendations? This clinical practice guideline contains the expert panel's clinical questions and final recommendations addressing these questions. Recommendations are intended to assist patients, clinicians, and other stakeholders in the decision-making process. We developed this guideline with the perspective that clinicians' expertise is essential in ascertaining situations in which a deviation from the recommendations is warranted. We graded recommendation statements as either strong or conditional on the basis of how the expert panel suggested clinicians act when presented with the evidence (Table 2).[31,32]

What is the difference between recommendations and good practice statements? Recommendations should be developed via a comprehensive search of the evidence and further include a formal rating of the quality of the evidence. Good practice statements, however, provide guidance that is supposed to be supported by an overwhelming amount of indirect evidence. Attempts to summarize and assess the quality of this evidence would have been a poor use of the panel's time (Table 3).[37]

Good practice statement. The panel suggests that clinicians should obtain an updated medical, social, and dental history and perform an intraoral and extraoral CVTE in all adult patients.[38]

Recommendation statements 1 through 4 are informed by the following results. ***Cytologic testing (innocuous lesions).*** Data from 1 included study (N = 79 lesions) showed that when cytologic testing is used in patients with clinically evident innocuous lesions, 96% of patients with the target condition (PMDs or OSCC) will be classified correctly, and 90% of patients who are healthy will be classified correctly (sensitivity, 0.96; 95% CI, 0.81 to 1.00; specificity, 0.90; 95% CI, 0.79 to 0.97).[39] Patients who test positive for the target condition via cytologic testing are 10 times more likely to have the disease than are those without the disease (positive LR, 10.01; 95% CI, 4.34 to 23.12). Patients who test negative for the target condition via cytologic testing are 0.04 times as likely not to have the disease as are those with the disease (negative LR, 0.04; 95% CI, 0.01 to 0.28). In absolute terms, for a population of 100,000 people, with a PMD and OSCC prevalence of 0.25% (250 people), 240 people with the target condition will be identified correctly, and 10 will not. Of the remaining 99,750 people who are healthy, 89,775 of them will be identified correctly as healthy, and 9,975 will not. The guideline panel determined the overall quality of the evidence for this comparison to be low because of serious issues of risk of bias and indirectness (eTable 1,[39] available online at the end of this article).

Cytologic testing (suspicious lesions). Data from 15 included studies (N = 2,148 lesions) showed that when

TABLE 2

Definition of quality of the evidence and strength of recommendations.*,†

Definition of Quality of or Certainty in the Evidence	
CATEGORY	**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 the effect.

Definition of Strong and Conditional Recommendations and Implications for Stakeholders		
IMPLICATIONS	**STRONG RECOMMENDATIONS**	**CONDITIONAL RECOMMENDATIONS**
For Patients	Most patients in this situation would want the recommended course of action, and only a small proportion would not. Formal decision aids are not likely to be needed to help patients make decisions consistent with their values and preferences.	Most patients in this situation would want the suggested course of action, but many would not.
For Clinicians	Most patients should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful helping patients make decisions consistent with their values and preferences.
For Policy Makers	The recommendation can be adopted as policy in most situations.	Policy making will require substantial debate and involvement of various stakeholders.

* Reproduced with permission of the publisher from Balshem and colleagues.
† Sources: Andrews and colleagues.[31,32]

TABLE 3

Summary of good practice statements and clinical recommendations for the evaluation of potentially malignant disorders and oral squamous cell carcinomas in the oral cavity.

CLINICAL QUESTION	RECOMMENDATION	QUALITY OF THE EVIDENCE	STRENGTH OF RECOMMENDATION
No Corresponding Clinical Question	Good practice statement: The panel suggests that clinicians* should obtain an updated medical, social, and dental history and perform an intraoral and extraoral conventional visual and tactile examination† in all adult patients.	No quality of evidence rating	No strength of recommendation assigned
2. Among Adults With Clinically Evident, Nonsuspicious Lesions, or Other Symptoms,‡ Should We Recommend the Use of Adjuncts to Identify Potentially Malignant or Malignant Disorders in the Oral Cavity?	Recommendation 1: The panel suggests that for adult patients with a clinically evident oral mucosal lesion with an unknown clinical diagnosis considered to be seemingly innocuous or nonsuspicious of malignancy, or other symptoms, clinicians should follow up periodically with the patient to determine the need for further evaluation. If the lesion has not resolved and the clinical diagnosis of a potentially malignant disorder cannot be ruled out, then clinicians should perform a biopsy of the lesion or refer the patient to a specialist.§	Low	Conditional
3. Among Adults With Clinically Evident, Suspicious Lesions, or Other Symptoms, Should We Recommend Adjuncts to Identify Potentially Malignant or Malignant Disorders in the Oral Cavity?	Recommendation 2: The panel suggests that for adult patients with a clinically evident oral mucosal lesion considered to be suspicious of a potentially malignant or malignant disorder, or other symptoms, clinicians should perform a biopsy of the lesion or provide immediate referral to a specialist.	Low	Conditional
2. Among Adults With Clinically Evident, Nonsuspicious Lesions, or Other Symptoms, Should We Recommend the Use of Adjuncts to Identify Potentially Malignant or Malignant Disorders in the Oral Cavity? **3. Among Adults With Clinically Evident, Suspicious Lesions, or Other Symptoms, Should We Recommend Adjuncts to Identify Potentially Malignant or Malignant Disorders in the Oral Cavity?**	Recommendation 3: The panel does not recommend cytologic adjuncts for the evaluation of potentially malignant disorders among adult patients with clinically evident, seemingly innocuous, or suspicious lesions. Should a patient decline the clinician's recommendation for performing a biopsy of the lesion or referral to a specialist, the clinician can use a cytologic adjunct to provide additional lesion assessment. A positive or atypical cytologic test result reinforces the need for a biopsy or referral. A negative cytologic test result indicates the need for periodic follow-up of the patient. If the clinician detects persistence or progression of the lesion, immediately performing a biopsy of the lesion or referral to a specialist is indicated.	Low	Conditional
2. Among Adults With Clinically Evident, Nonsuspicious Lesions, or Other Symptoms, Should We Recommend the Use of Adjuncts to Identify Potentially Malignant or Malignant Disorders in the Oral Cavity? **3. Among Adults With Clinically Evident, Suspicious Lesions, or Other Symptoms, Should We Recommend Adjuncts to Identify Potentially Malignant or Malignant Disorders in the Oral Cavity?**	Recommendation 4: The panel does not recommend autofluorescence, tissue reflectance, or vital staining adjuncts for the evaluation of potentially malignant disorders among adult patients with clinically evident, seemingly innocuous, or suspicious lesions.	Low to very low	Conditional
1. Among Apparently Healthy Adults With No Clinically Evident Lesions, Should We Recommend the Use of Adjuncts to Identify Potentially Malignant or Malignant Disorders in the Oral Cavity?	Recommendation 5: The panel suggests that for adult patients with no clinically evident lesions or symptoms, no further action is necessary at that time.	Low	Conditional

* *Clinician* refers to the target audience for this guideline, but only those trained to perform a biopsies (that is, dentists) should do so.
† *Examination* refers to initial, routine, or emergency visits.
‡ *Symptoms* could include globus sensation, unexplained ear or oropharyngeal pain, and hoarseness.
§ *Specialist* refers to clinicians with advanced training in oral and maxillofacial surgery, oral and maxillofacial pathology, oral medicine, periodontology, and otolaryngology–head and neck surgery.

cytologic testing is used in patients with clinically evident, suspicious lesions, 92% of patients with the target condition (PMDs or OSCC) will be classified correctly, and 94% of patients who are healthy will be classified correctly (sensitivity, 0.92; 95% CI, 0.86 to 0.98; specificity, 0.94; 95% CI, 0.88 to 0.99).[40-54] Patients who test positive for the target condition via cytologic testing are 14 times more likely to have the disease than are those without the disease (positive LR, 14.18; 95% CI, 5.82 to 34.59). Patients who test negative for the target condition via cytologic testing are 0.08 times as likely not to have the disease as are those with the disease (negative LR, 0.08; 95% CI, 0.04 to 0.18). In absolute terms, for a population of 100,000 people, with a PMD

TABLE 3 (CONTINUED)

CLINICAL QUESTION	RECOMMENDATION	QUALITY OF THE EVIDENCE	STRENGTH OF RECOMMENDATION
1. Among Apparently Healthy Adults With No Clinically Evident Lesions, Should We Recommend the Use of Adjuncts to Identify Potentially Malignant or Malignant Disorders in the Oral Cavity? **2. Among Adults With Clinically Evident, Nonsuspicious Lesions, or Other Symptoms, Should We Recommend the Use of Adjuncts to Identify Potentially Malignant or Malignant Disorders in the Oral Cavity?** **3. Among Adults With Clinically Evident, Suspicious Lesions, or Other Symptoms, Should We Recommend Adjuncts to Identify Potentially Malignant or Malignant Disorders in the Oral Cavity?**	Recommendation 6: The panel does not recommend commercially available salivary adjuncts for the evaluation of potentially malignant disorders among adult patients with or without clinically evident, seemingly innocuous, or suspicious lesions, and their use should be considered only in the context of research.	Low	Conditional

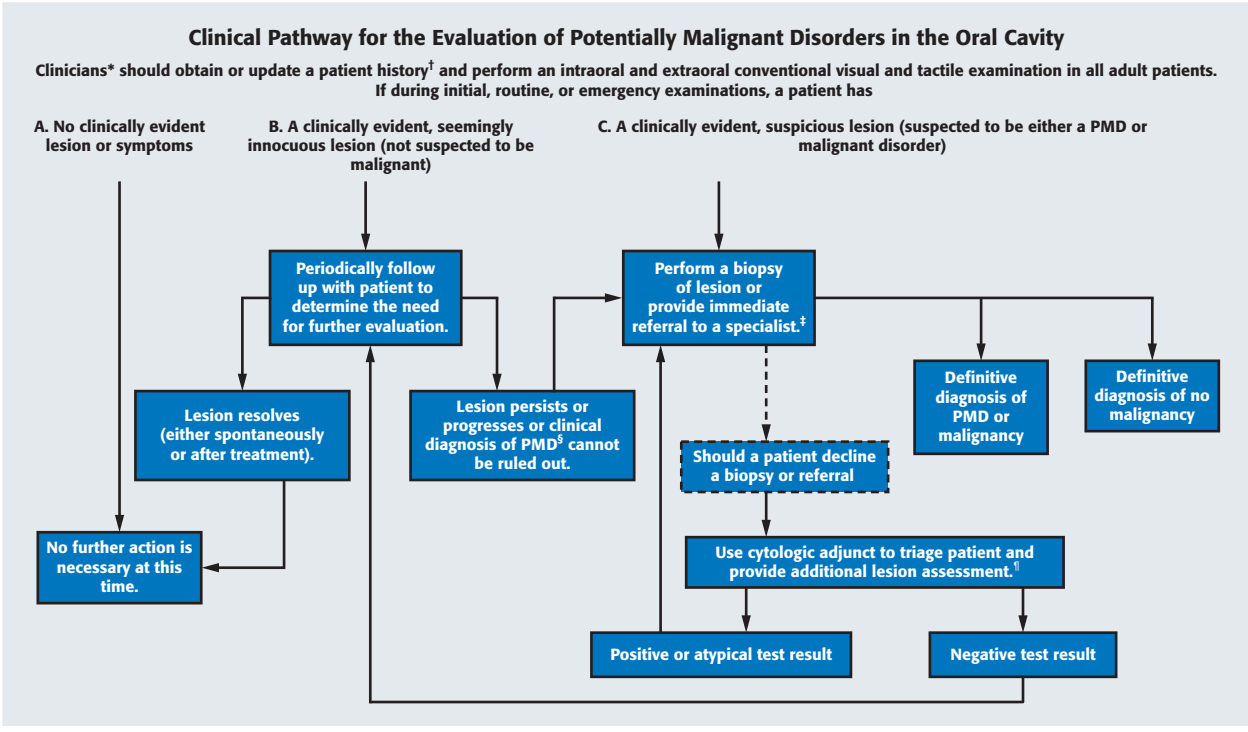

Figure 6. Clinical pathway for the evaluation of potentially malignant disorders (PMDs) in the oral cavity. * Clinician refers to general dentists, specialists, and hygienists. † Along with evaluation of lesions, clinicians should take a comprehensive history that considers signs and symptoms of disease. Symptoms could include globus sensation, unexplained ear pain and/or oropharyngeal pain, and hoarseness. ‡ Specialists have advanced training in Oral and Maxillofacial Surgery, Oral and Maxillofacial Pathology, Oral Medicine, Periodontology, and Otolaryngology-Head and Neck Surgery (ENT). § PMD: Potentially malignant disorders. ¶ If cytology adjunct is used, downstream consequences of true positive, false positive, true negative, and false negative test results should be considered. Most importantly, clinicians need to periodically monitor cytology test-negative patients to minimize the downstream consequences of a potential false negative result (i.e. to avoid a delayed definitive diagnosis or treatment).

and OSCC prevalence of 0.25% (250 people), 230 people with the target condition will be identified correctly, and 20 will not. Of the remaining 99,750 people who are healthy, 93,765 of them will be identified correctly as healthy, and 5,985 will not. The guideline panel determined the overall quality of the evidence for this comparison to be low because of serious issues of risk of bias and indirectness (eTable 2,[40-54] available online at the end of this article).

Autofluorescence (innocuous lesions). Data from 1 included study (N = 156 lesions) showed that when autofluorescence adjuncts are used in patients with clinically evident innocuous lesions, 50% of patients with the target condition (PMDs or OSCC) will be classified correctly, and 39% of patients who are healthy will be classified correctly (sensitivity, 0.50; 95% CI, 0.21 to 0.79; (specificity, 0.39; 95% CI, 0.31 to 0.47).[55] Patients who test positive for the target condition via autofluorescence are 0.82 times more likely to have the disease than are those without the disease (positive LR, 0.82; 95% CI, 0.46 to 1.46). Patients who test negative for the target condition via autofluorescence are 1.29 times as likely not to have the disease as are those with the disease (negative LR, 1.29; 95% CI, 0.70 to 2.35). In absolute terms, for a population of 100,000 people, with a PMD and OSCC prevalence of 0.25% (250 people), 125 people with the target condition will be identified correctly, and 125 will not. Of the remaining 99,750 people who are healthy, 38,903 of them will be identified correctly as healthy, and 60,847 will not. The guideline panel determined the overall quality of the evidence for this comparison to be low because of serious issues of risk of bias and indirectness (eTable 3,[55] available online at the end of this article).

Tissue reflectance and vital staining (innocuous lesions). Data from 1 included study (N = 102 lesions) showed that when tissue reflectance and vital staining adjuncts are used in patients with clinically evident innocuous lesions, 0% of patients with the target condition (PMDs or OSCC) will be classified correctly, and 76% of patients who are healthy will be classified correctly (sensitivity, 0.00; 95% CI, 0.00 to 0.60; specificity, 0.76; 95% CI, 0.66 to 0.84).[55] A positive LR was not possible to calculate for this comparison because the sensitivity was 0.00. Patients who test negative for the target condition via tissue reflectance and vital staining are 1.32 times as likely not to have the disease as are those with the disease (negative LR, 1.32; 95% CI, 1.18 to 1.48). In absolute terms, for a population of 100,000 people, with a PMD and OSCC prevalence of 0.25% (250 people), 0 people with the target condition will be identified correctly, and 250 will not. Of the remaining 99,750 people who are healthy, 75,810 of them will be identified correctly as healthy, and 23,940 will not. The guideline panel determined the overall quality of the evidence for this comparison to be low because of serious issues of risk of bias and indirectness (eTable 4,[55] available online at the end of this article).

Autofluorescence (suspicious lesions). Data from 7 included studies (N = 616 lesions) showed that when autofluorescence adjuncts are used in patients with clinically evident, suspicious lesions, 90% of patients with the target condition (PMDs or OSCC) will be classified correctly, and 72% of patients who are healthy will be classified correctly (sensitivity, 0.90; 95% CI, 0.76 to 1.00; specificity, 0.72; 95% CI, 0.35 to 1.00).[56-62] Patients who test positive for the target condition via autofluorescence are 3.17 times more likely to have the disease than are those without the disease (positive LR, 3.17; 95% CI, 0.85 to 11.80). Patients who test negative for the target condition via autofluorescence are 0.14 times as likely not to have the disease as are those with the disease (negative LR, 0.14; 95% CI, 0.03 to 0.64). In absolute terms, for a population of 100,000 people, with a PMD and OSCC prevalence of 0.25% (250 people), 225 people with the target condition will be identified correctly, and 25 will not. Of the remaining 99,750 people who are healthy, 71,820 of them will be identified correctly as healthy, and 27,930 will not. The guideline panel determined the overall quality of the evidence for this comparison to be low because of serious issues of risk of bias and indirectness (eTable 5,[56-62] available online at the end of this article).

Vital staining (suspicious lesions). Data from 15 included studies (N = 1,453 lesions) showed that when vital staining adjuncts are used in patients with clinically evident, suspicious lesions, 87% of patients with the target condition (PMDs or OSCC) will be classified correctly, and 71% of patients who are healthy will be classified correctly (sensitivity, 0.87; 95% CI, 0.80 to 0.94; specificity, 0.71; 95% CI, 0.61 to 0.82).[45,63-76] Patients who test positive for the target condition via vital staining are 3 times more likely to have the disease than are those without the disease (positive LR, 3.04; 95% CI, 2.06 to 4.48). Patients who test negative for the target condition via vital staining are 0.18 times as likely not to have the disease as are those with the disease (negative LR, 0.18; 95% CI, 0.10 to 0.32). In absolute terms, for a population of 100,000 people, with a PMD and OSCC prevalence of 0.25% (250 people), 217 people with the target condition will be identified correctly, and 33 will not. Of the remaining 99,750 people who are healthy, 70,823 of them will be identified correctly as healthy, and 28,927 will not. The guideline panel determined the overall quality of the evidence for this comparison to be low because of serious issues of risk of bias and indirectness (eTable 6,[45,63-76] available online at the end of this article).

Tissue reflectance (suspicious lesions). Data from 5 included studies (N = 390 lesions) showed that when tissue reflectance adjuncts are used in patients with clinically evident, suspicious lesions, 72% of patients with the target condition (PMDs or OSCC) will be classified correctly, and 31% of patients who are healthy will be classified correctly (sensitivity, 0.72; 95% CI, 0.62 to 0.81; specificity, 0.31; 95% CI, 0.25 to 0.36).[77-81] Patients who

test positive for the target condition via tissue reflectance are equally likely to have the disease as are those without the disease (positive LR, 1.04; 95% CI, 0.90 to 1.20). Patients who test negative for the target condition via tissue reflectance are 0.91 times as likely not to have the disease as are those with the disease (negative LR, 0.91; 95% CI, 0.63 to 1.30). In absolute terms, for a population of 100,000 people, with a PMD and OSCC prevalence of 0.25% (250 people), 180 people with the target condition will be identified correctly, and 70 will not. Of the remaining 99,750 people who are healthy, 30,923 of them will be identified correctly as healthy, and 68,827 will not. The guideline panel determined the overall quality of the evidence for this comparison to be low because of serious issues of risk of bias and indirectness (eTable 7,[77-81] available online at the end of this article).

Cytologic testing and vital staining (suspicious lesions). Data from 2 included studies (N = 139 lesions) showed that when cytologic testing and vital staining adjuncts are used in patients with clinically evident, suspicious lesions, 95% of patients with the target condition (PMDs or OSCC) will be classified correctly, and 68% of patients who are healthy will be classified correctly (sensitivity, 0.95; 95% CI, 0.86 to 0.99; specificity, 0.68; 95% CI, 0.56 to 0.78).[82,83] Patients who test positive for the target condition via cytologic testing and vital staining are 3 times more likely to have the disease than are those without the disease (positive LR, 2.97; 95% CI, 2.14 to 4.12). Patients who test negative for the target condition via cytologic testing and vital staining are 0.07 times as likely not to have the disease as are those with the disease (negative LR, 0.07; 95% CI, 0.02 to 0.22). In absolute terms, for a population of 100,000 people, with a PMD and OSCC prevalence of 0.25% (250 people), 238 people with the target condition will be identified correctly, and 12 will not. Of the remaining 99,750 people who are healthy, 67,830 of them will be identified correctly as healthy, and 31,920 will not. The guideline panel determined the overall quality of the evidence for this comparison to be very low because of serious issues of risk of bias, imprecision, and indirectness (eTable 8,[82,83] available online at the end of this article).

Tissue reflectance and vital staining (suspicious lesions). Data from 4 included studies (N = 307 lesions) showed that when tissue reflectance and vital staining adjuncts are used in patients with clinically evident, suspicious lesions, 81% of patients with the target condition (PMDs or OSCC) will be classified correctly, and 69% of patients who are healthy will be classified correctly (sensitivity, 0.81; 95% CI, 0.71 to 0.89; specificity, 0.69; 95% CI, 0.63 to 0.75).[78,81,84,85] Patients who test positive for the target condition via tissue reflectance and vital staining are 2.6 times more likely to have the disease than are those without the disease (positive LR, 2.62; 95% CI, 2.10 to 3.27). Patients who test negative for the target condition via tissue reflectance and vital staining are 0.27 times as likely not to have the disease as are those with the disease (negative LR, 0.27; 95% CI, 0.17 to 0.44). In absolute terms, for a population of 100,000 people, with a PMD and OSCC prevalence of 0.25% (250 people), 203 people with the target condition will be identified correctly, and 47 will not. Of the remaining 99,750 people who are healthy, 68,828 of them will be identified correctly as healthy, and 30,922 will not. The guideline panel determined the overall quality of the evidence for this comparison to be low because of serious issues of risk of bias and indirectness (eTable 9,[78,81,84,85] available online at the end of this article).

- ***Recommendation 1.*** The panel suggests that for adult patients with a clinically evident oral mucosal lesion with an unknown clinical diagnosis considered to be seemingly innocuous or nonsuspicious of malignancy, or other symptoms, clinicians should follow up periodically with the patient to determine the need for further evaluation. If the lesion has not resolved and the clinical diagnosis of a PMD cannot be ruled out, then clinicians should perform a biopsy of the lesion or refer the patient to a specialist. **(Conditional recommendation, low-quality evidence.)**
- ***Recommendation 2.*** The panel suggests that for adult patients with a clinically evident oral mucosal lesion considered to be suspicious of a PMD or malignant disorder, or other symptoms, clinicians should perform a biopsy of the lesion or provide immediate referral to a specialist. **(Conditional recommendation, low-quality evidence.)**
- ***Recommendation 3.*** The panel does not recommend cytologic adjuncts for the evaluation of PMDs among adult patients with clinically evident, seemingly innocuous, or suspicious lesions. Should a patient decline the clinician's recommendation for performing a biopsy of the lesion or referral to a specialist, the clinician can use a cytologic adjunct to provide additional lesion assessment. **(Conditional recommendation, low-quality evidence.)**

A positive or atypical cytologic test result reinforces the need for a biopsy or referral. A negative cytologic test result indicates the need for periodic follow-up of the patient. If the clinician detects persistence or progression of the lesion, immediately performing a biopsy of the lesion or referral to a specialist is indicated.

- ***Recommendation 4.*** The panel does not recommend autofluorescence, tissue reflectance, or vital staining adjuncts for the evaluation of PMDs among adult patients with clinically evident, seemingly innocuous, or suspicious lesions. **(Conditional recommendation, low-quality evidence to very low-quality evidence.)**
- ***Recommendations 5 and 6 are informed by the following results.*** No primary studies of salivary adjuncts met our selection criteria, nor were any included in the 2015 Cochrane review, so we conducted a search for relevant systematic reviews. Two systematic reviews, published in 2016 and 2017, met our selection criteria.[23,24]

Most of the studies contained in these reviews had small sample sizes and were moderate- to low-quality diagnostic-test, case-control studies. These salivary adjuncts showed a wide range of diagnostic test accuracy summary values, with sensitivity ranging from 0.5 to 0.9 and specificity ranging from 0.63 to 0.90. The specificity of these biomarkers was much lower than what the panel considered acceptable for recommending in clinical practice, although there was a significant elevation of certain biomarkers in patients with the target condition versus levels in those without the target condition. For future consideration, a major indication for salivary adjuncts could be for people with no lesions, early-stage lesions, or lesions with nonclassical features if the diagnostic test accuracy is improved.

- ***Recommendation 5.*** The panel suggests that for adult patients with no clinically evident lesions or symptoms, no further action is necessary at that time. **(Conditional recommendation, low-quality evidence.)**
- ***Recommendation 6.*** The panel does not recommend commercially available salivary adjuncts for the evaluation of PMDs among adult patients with or without clinically evident, seemingly innocuous, or suspicious lesions, and their use should be considered only in the context of research. **(Conditional recommendation, low-quality evidence.)**

DISCUSSION

Implications for practice and a suggested clinical pathway. The expert panel did not recommend vital staining, autofluorescence, tissue reflectance, or salivary adjuncts as triage tools for adult patients. Cytologic adjuncts showed relatively greater sensitivity and specificity than did other adjuncts. This finding suggests that cytologic testing could be used as a triage tool to rule out disease (that is, a negative cytologic test result) in patients who seek care for clinically evident, seemingly innocuous lesions (for which possible malignancy cannot be ruled out) or patients with suspicious lesions who decline initial recommendation for a biopsy or referral. A positive or atypical cytologic test result would inform further the urgent need for a biopsy and histopathologic diagnosis, and it may help the patient consent to undergoing a biopsy of the lesion. In the case of a negative cytologic test result, the low rate of false-negative results indicates that the probability of the adjunct to help identify the absence of the target condition correctly is high. Even so, the panel emphasizes the need to monitor cytologic test results periodically in patients with negative test results to minimize the downstream consequences of a false-negative result (that is, to avoid a delayed definitive diagnosis or treatment).

Investigators in a few studies on cytologic testing also mentioned this adjunct's usefulness as a frontline evaluation in rural or low-resource areas where access to care is limited. The panel notes that it could be used in these situations in which a biopsy or histopathologic assessment is clearly not possible.[50] Furthermore, the Cochrane review authors note that vital staining, autofluorescence, and tissue reflectance adjuncts are "dependent on the visual assessment of the lesion," whereas cytologic testing requires "adequate training and experience of correctly harvesting basal cells from the oral mucosa."[17] The panel also suggests adhering to manufacturers' instructions if and when a cytologic adjunct is used.

When applying these recommendations in primary care settings such as dental offices or clinics, one must consider that investigators in much of the existing literature describe the use of adjuncts in secondary and tertiary care settings such as specialty clinics or hospitals. This is an important consideration because investigators have not studied the diagnostic test accuracy of the adjuncts thoroughly in primary care settings, where the prevalence of disease could modify the diagnostic test accuracy of these adjuncts. Another point to consider is that clinicians in secondary and tertiary care settings are advanced in relevant experience and skill and can evaluate and triage lesions more appropriately by using CVTE alone than can primary care clinicians. Furthermore, referral to a specialist for a biopsy (clinicians with advanced training in oral and maxillofacial surgery, oral and maxillofacial pathology, oral medicine, periodontology, and otolaryngology–head and neck surgery) is indicated when clinicians are not trained or skilled adequately to perform a biopsy.

As a way to facilitate the implementation of the recommendations contained in this guideline, the panel has created a clinical pathway that clinicians in primary care settings can follow when evaluating adults with and those without clinically evident lesions in the oral cavity (Figure 6). Furthermore, a *For the Patient* page for clinicians to use when communicating the guideline's recommendations with their patients is in this issue.[86]

Implications for research. We emphasize the need to conduct epidemiologic studies to develop a better estimation of the prevalence of PMDs and OSCC in populations with different baseline risks. Having more reliable estimates in different clinical settings would have increased the confidence of the expert panel and better facilitated the decision-making process. In addition, patients' values and preferences require more attention from the research community. In an ideal scenario, the relative importance of health outcomes should be informed by results from those studies and considered by the panel as a key factor when using the evidence-to-decision framework. For additional information about implications for research, see the Appendix[15,17,19] (available online at the end of this article).

CONCLUSIONS

In adult patients with clinically evident, potentially malignant, or seemingly malignant lesions, clinicians should perform a biopsy of the lesion immediately or refer the

patient to a specialist. If a patient declines a biopsy or cannot be referred, cytologic adjuncts could act as a triage tool to offer additional information for clinical decision making. ■

SUPPLEMENTAL DATA

Supplemental data related to this article can be found at: http://dx.doi.org/10.1016/j.adaj.2017.07.032.

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APPENDIX

▬ Continuation of METHODS, Patient Important Outcomes and Diagnostic Test Accuracy Estimates: When drafting guidance on the clinical use of adjuncts, we found that outcomes that are important to patients such as morbidity and mortality are ideal for decision making because they provide direct information about the effectiveness of the adjunct. In many cases, outcomes that are important to patients are not reported in the literature, and other types of more indirect outcomes or surrogate outcomes, such as estimates of diagnostic test accuracy, can be used during the decision-making process instead.[19] We could assume that the correct classification (true-positive results and true-negative results) could be linked to a potential health benefit or desirable consequence, whereas an incorrect classification (false-positive results and false-negative results) could be considered as harm or an undesirable consequence.

▬ Continuation of METHODS, Patients Values and Preferences: The panel acknowledges the high level of anxiety and denial that some patients may experience as a result of being informed of the presence of a lesion suspected of potential malignancy. The investigators in the summarized studies reported that anxiety and denial are among the factors that can obstruct the evaluation and management of these lesions, resulting in a high probability of creating undesirable delays in the diagnostic and treatment process. During the decision-making process, the panel placed a higher value on minimizing the proportion of false-negative results (results that incorrectly help rule out potentially malignant disorders [PMDs]) while maintaining a moderate to low proportion of false-positive results (results that incorrectly help rule in PMDs). The panel also emphasized the need and responsibility of clinicians to provide effective and timely counseling to any patient clinically identified as having a suspicious lesion. The authors of the systematic review informing this guideline describe more information about the methods for searching, identifying, selecting, and summarizing evidence for patients' values and preferences in the systematic review article.[15]

■ Continuation of DISCUSSION, Implications for Research: The lack of relevant studies in which investigators reported on the prevalence of PMDs and oral squamous cell carcinoma in the US adult population and outcomes that are important to patients was a major shortcoming during the development of this guideline and the accompanying systematic review.[15] We were able to estimate a prevalence and use diagnostic test accuracy estimates and their downstream consequences as indirect evidence to inform our recommendations. In addition, investigators in most included studies conducted them in secondary and tertiary settings, settings usually reserved for determining definitive diagnoses, whereas the application of this guideline was intended for the evaluation of lesions in primary care settings. We suggest that investigators in future research initiatives study and report outcomes that are important to patients and conduct studies in primary care settings.

■ The overall quality of the evidence was low to very low because of issues of risk of bias. We suggest that the methodological quality of future research be improved through routinely using The Quality Assessment Tool for Diagnostic Test Accuracy Studies-2 (University of Bristol, Bristol, United Kingdom), minimizing verification bias, and clearly reporting positivity thresholds for index tests and criterion standards, data used to create contingency tables, and levels of dysplasia (benign, mild dysplasia, moderate dysplasia, severe dysplasia, and oral squamous cell carcinoma).[17] In the absence of outcomes that are important to patients, it is essential to have accessible, well-reported data that can be used to replicate contingency tables for the purpose of moving from evidence to decisions.

Overall, the expert panel would be highly interested in high-quality, randomized controlled trials in which the investigators report outcomes that are important to patients and cross-sectional studies on the diagnostic test accuracy of adjuncts. This is especially true for cytologic and salivary adjuncts in regard to their potential use as triage tools during the evaluation of adults with no lesions and clinically evident lesions in primary care settings.

eTABLE 1

Cytologic adjuncts to evaluate clinically evident, seemingly innocuous, or nonsuspicious lesions.*

TEST RESULT	EFFECT PER 100,000 PATIENTS TESTED, NO. (95% CONFIDENCE INTERVAL)		NO. OF LESIONS (STUDIES)	QUALITY OF THE EVIDENCE (GRADE§)	DOWNSTREAM CONSEQUENCES
	Prevalence 0.25%†	Prevalence 2.0%‡			
True-Positive Results (Patients Needing a Biopsy)	240 (203-250)	1,920 (1,620-2,000)	79 (1)	Low¶,#,**	Patients will be identified correctly as having a potentially malignant or malignant disorder, and timely referral to a specialist or a biopsy will be performed.
False-Negative Results (Patients Incorrectly Classified as Not Needing a Biopsy)	10 (0-47)	80 (0-380)			An appropriate diagnosis would be missed, worsening the prognosis of the disease.
True-Negative Results (Patients Without Need for a Biopsy)	89,775 (78,803-96,758)	88,200 (77,420-95,060)	79 (1)	Low¶,#,**	Patients will receive reassurance that they do not have a potentially malignant or malignant disorder.
False-Positive Results (Patients Incorrectly Classified as Needing a Biopsy)	9,975 (2,992-20,947)	9,800 (2,940-20,580)			Patients would be identified incorrectly as having a potentially malignant or malignant disorder and would undergo additional unnecessary testing and a biopsy.

* Setting: primary care. Sensitivity, 0.96 (95% confidence interval [CI], 0.81 to 1.00). Specificity, 0.90 (95% CI, 0.79 to 0.97). Positive likelihood ratio, 10.01 (95% CI, 4.34 to 23.12). Negative likelihood ratio, 0.04 (95% CI, 0.01 to 0.28). Source: Mehrotra and colleagues.[39]

† 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.

¶ The sampling method, the positivity threshold for dysplasia in regard to the reference standard, and to what extent examiners were calibrated during interpretation of the index test are unclear.

The investigators conducted the study in a secondary care setting. Most patients had a higher probability of having a malignant or potentially malignant disorder.

** The positivity threshold for the index test included atypical results.

eTABLE 2

Cytologic adjuncts to evaluate clinically evident, suspicious lesions.*

TEST RESULT	EFFECT PER 100,000 PATIENTS TESTED, NO. (95% CONFIDENCE INTERVAL)		NO. OF LESIONS (STUDIES)	QUALITY OF THE EVIDENCE (GRADE§)	DOWNSTREAM CONSEQUENCES
	Prevalence 0.25%†	Prevalence 2.0%‡			
True-Positive Results (Patients Needing a Biopsy)	230 (215-245)	1,840 (1,720-1,960)	2,148 (15)	Low¶,#,**	Patients will be identified correctly as having a potentially malignant lesion, and timely referral to a specialist or a biopsy will be performed.
False-Negative Results (Patients Incorrectly Classified as Not Needing a Biopsy)	20 (5-35)	160 (40-280)			An appropriate diagnosis would be missed, worsening the prognosis of the disease.
True-Negative Results (Patients Without Need for a Biopsy)	93,765 (87,780-98,753)	92,120 (86,240-97,020)	2,148 (15)	Low¶,#,**	Patients will receive reassurance that they do not have a potentially malignant or malignant disorder.
False-Positive Results (Patients Incorrectly Classified as Needing a Biopsy)	5,985 (997-11,970)	5,880 (980-11,760)			Patients would be identified incorrectly as having a potentially malignant or malignant disorder and would undergo additional unnecessary testing and a biopsy.

* Setting: primary care. Pooled sensitivity, 0.92 (95% confidence interval [CI], 0.86 to 0.98). Pooled specificity, 0.94 (95% CI, 0.88 to 0.99). Positive likelihood ratio, 14.18 (95% CI, 5.82 to 34.59). Negative likelihood ratio, 0.08 (95% CI, 0.04 to 0.18). Sources: Delavarian and colleagues,[54] Fontes and colleagues,[53] Kammerer and colleagues,[52] Koch and colleagues,[51] Mehrotra and colleagues,[50] Nanayakkara and colleagues,[49] Navone and colleagues,[48] Navone and colleagues,[47] Ng and colleagues,[46] Rahman and colleagues,[45] Scheifele and colleagues,[44] Sciubba,[43] Seijas-Naya and colleagues,[42] Svirsky and colleagues,[41] and Trakroo and colleagues.[40]

† 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, index and reference tests were conducted in an unblinded fashion, and in some cases the time between index and reference test was greater than 2 weeks. It was unclear whether all participants received the reference test. Poor-quality reporting did not provide sufficient information to judge key risk of bias domains.

\# 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 reference test included from mild dysplasia to cancer in all studies except for those of Kammerer and colleagues,[52] Navone and colleagues,[48] and Rahman and colleagues.[45] The positivity threshold included atypia for Rahman and colleagues,[45] Scheifele and colleagues[44] (10/96), Sciubba[43] (52/298), and Svirsky and colleagues.[41] Parentheses indicate the number of atypical results out of the total (atypical + positive results).

eTABLE 3

Autofluorescence adjuncts to evaluate clinically evident, seemingly innocuous, or nonsuspicious lesions.*

TEST RESULT	EFFECT PER 100,000 PATIENTS TESTED, NO. (95% CONFIDENCE INTERVAL)		NO. OF LESIONS (STUDIES)	QUALITY OF THE EVIDENCE (GRADE§)	DOWNSTREAM CONSEQUENCES
	Prevalence 0.25%†	Prevalence 2.0%‡			
True-Positive Results (Patients Needing a Biopsy)	125 (53-198)	1,000 (420-1,580)	156 (1)	Low¶,#,**	Patients will be identified correctly as having a potentially malignant or malignant disorder, and timely referral to a specialist or a biopsy will be performed.
False-Negative Results (Patients Incorrectly Classified as Not Needing a Biopsy)	125 (52-197)	1,000 (420-1,580)			An appropriate diagnosis would be missed, worsening the prognosis of the disease.
True-Negative Results (Patients Without Need for a Biopsy)	38,903 (30,923-46,883)	38,220 (30,380-46,060)	156 (1)	Low¶,#,**	Patients will receive reassurance that they do not have a potentially malignant or malignant disorder.
False-Positive Results (Patients Incorrectly Classified as Needing a Biopsy)	60,847 (52,867-68,827)	59,780 (51,940-67,620)			Patients would be identified incorrectly as having a potentially malignant or malignant disorder and would undergo additional unnecessary testing and a biopsy.

* Setting: primary care. Sensitivity, 0.50 (95% confidence interval [CI], 0.21 to 0.79). Specificity, 0.39 (95% CI, 0.31 to 0.47). Positive likelihood ratio, 0.82 (95% CI, 0.46 to 1.46). Negative likelihood ratio, 1.29; (95% CI, 0.70 to 2.35). Source: Mehrotra and colleagues.[55]

† 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.

¶ We judged the patient selection and index test domains as being at high risk of bias.

The investigators conducted the study in a secondary care setting. Most patients had a higher probability of having a malignant or potentially malignant disorder.

** The positivity threshold for the reference test was unclear.

eTABLE 4

Tissue reflectance and vital staining adjuncts to evaluate clinically evident, seemingly innocuous, or nonsuspicious lesions.*

TEST RESULT	EFFECT PER 100,000 PATIENTS TESTED, NO. (95% CONFIDENCE INTERVAL)		NO. OF LESIONS (STUDIES)	QUALITY OF THE EVIDENCE (GRADE§)	DOWNSTREAM CONSEQUENCES
	Prevalence 0.25%†	Prevalence 2.0%‡			
True-Positive Results (Patients Needing a Biopsy)	0 (0-150)	0 (0-1,200)	102 (1)	Low¶,#,**	Patients will be identified correctly as having a potentially malignant or malignant disorder, and timely referral to a specialist or a biopsy will be performed.
False-Negative Results (Patients Incorrectly Classified as Not Needing a Biopsy)	250 (100-250)	2,000 (800-2,000)			An appropriate diagnosis would be missed, worsening the prognosis of the disease.
True-Negative Results (Patients Without Need for a Biopsy)	75,810 (65,835-83,790)	74,480 (64,680-82,320)	102 (1)	Low¶,#,**	Patients will receive reassurance that they do not have a potentially malignant or malignant disorder.
False-Positive Results (Patients Incorrectly Classified as Needing a Biopsy)	23,940 (15,960-33,915)	23,520 (15,680-33,320)			Patients would be identified incorrectly as having a potentially malignant or malignant disorder and would undergo additional unnecessary testing and a biopsy.

* Setting: primary care. Sensitivity, 0.00 (95% confidence interval [CI], 0.00 to 0.60). Specificity, 0.76 (95% CI, 0.66 to 0.84). Positive likelihood ratio, not available. Negative likelihood ratio, 1.32 (95% CI, 1.18 to 1.48). Source: Mehrotra and colleagues.[55]
† 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.
¶ We judged the patient selection and index test domains as being at high risk of bias.
# The investigators conducted the study in a secondary care setting. Most patients had a higher probability of having a malignant or potentially malignant disorder.
** The positivity threshold for the reference test in regard to dysplasia was unclear.

eTABLE 5

Autofluorescence adjuncts to evaluate clinically evident, suspicious lesions.*

TEST RESULT	EFFECT PER 100,000 PATIENTS TESTED, NO. (95% CONFIDENCE INTERVAL)		NO. OF LESIONS (STUDIES)	QUALITY OF THE EVIDENCE (GRADE§)	DOWNSTREAM CONSEQUENCES
	Prevalence 0.25%†	Prevalence 2.0%‡			
True-Positive Results (Patients Needing a Biopsy)	225 (190-250)	1,800 (1,520-2,000)	616 (7)	Low¶,#,**	Patients will be identified correctly as having a potentially malignant or malignant disorder, and timely referral to a specialist or a biopsy will be performed.
False-Negative Results (Patients Incorrectly Classified as Not Needing a Biopsy)	25 (0-610)	200 (0-480)			An appropriate diagnosis would be missed, worsening the prognosis of the disease.
True-Negative Results (Patients Without Need for a Biopsy)	71,820 (34,913-99,750)	70,560 (34,300-98,000)	616 (7)	Low¶,#,**	Patients will receive reassurance that they do not have a potentially malignant or malignant disorder.
False-Positive Results (Patients Incorrectly Classified as Needing a Biopsy)	27,930 (0-64,837)	27,440 (0-63,700)			Patients would be identified incorrectly as having a potentially malignant or malignant disorder and would undergo additional unnecessary testing and a biopsy.

* Setting: Primary care. Pooled sensitivity, 0.90 (95% confidence interval [CI], 0.76 to 1.00). Pooled specificity, 0.72 (95% CI, 0.35 to 1.00). Positive likelihood ratio, 3.17 (95% CI, 0.85 to 11.80). Negative likelihood ratio, 0.14; (95% CI, 0.03 to 0.64). Sources: Awan and colleagues,[56] Farah and colleagues,[57] Hanken and colleagues,[58] Koch and colleagues,[59] Onizawa and colleagues,[60] Petruzzi and colleagues,[61] and Scheer and colleagues.[62]

† 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 risk of bias domains.

The 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 reference test included from mild dysplasia to cancer in all studies except for that of Awan and colleagues[56] and Farah and colleagues.[57]

eTABLE 6

Vital staining adjuncts to evaluate clinically evident, suspicious lesions.*

TEST RESULT	EFFECT PER 100,000 PATIENTS TESTED, NO. (95% CONFIDENCE INTERVAL)		NO. OF LESIONS (STUDIES)	QUALITY OF THE EVIDENCE (GRADE§)	DOWNSTREAM CONSEQUENCES
	Prevalence 0.25%†	Prevalence 2.0%‡			
True-Positive Results (Patients Needing a Biopsy)	217 (200-235)	1,740 (1,600-1,880)	1,453 (15)	Low¶,#,**	Patients will be identified correctly as having a potentially malignant or malignant disorder, and timely referral to a specialist or a biopsy will be performed.
False-Negative Results (Patients Incorrectly Classified as Not Needing a Biopsy)	33 (15-50)	260 (120-400)			An appropriate diagnosis would be missed, worsening the prognosis of the disease.
True-Negative Results (Patients Without Need for a Biopsy)	70,823 (60,848-81,795)	69,580 (59,780-80,360)	1,453 (15)	Low¶,#,**	Patients will receive reassurance that they do not have a potentially malignant or malignant disorder.
False-Positive Results (Patients Incorrectly Classified as Needing a Biopsy)	28,927 (17,955-38,902)	28,420 (17,640-38,220)			Patients would be identified incorrectly as having a potentially malignant or malignant disorder and would undergo additional unnecessary testing and a biopsy.

* Setting: primary care. Pooled sensitivity, 0.87 (95% confidence interval [CI], 0.80 to 0.94). Pooled specificity, 0.71 (95% CI, 0.61 to 0.82). Positive likelihood ratio, 3.04 (95% CI, 2.06 to 4.48). Negative likelihood ratio, 0.18 (95% CI, 0.10 to 0.32). Sources: Allegra and colleagues,[76] Awan and colleagues,[75] Cancela-Rodriguez and colleagues,[74] Chaudhari and colleagues,[73] Chen and colleagues,[72] Cheng and Yang,[71] Du and colleagues,[70] Mashberg,[69] Nagaraju and colleagues,[68] Onofre and colleagues,[67] Rahman and colleagues,[45] Silverman and colleagues,[66] Singh and Shukla,[65] Upadhyay and colleagues,[64] and Warnakulasuriya and Johnson.[63]

† 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. It was unclear whether all participants received the reference test. Poor-quality reporting did not provide sufficient information to judge key risk of bias domains.

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 reference test included from mild dysplasia to cancer in all studies except for those of Cheng and Yang,[71] Rahman and colleagues,[45] and Singh and Shukla.[65]

eTABLE 7

Tissue reflectance adjuncts to evaluate clinically evident, suspicious lesions.*

TEST RESULT	EFFECT PER 100,000 PATIENTS TESTED, NO. (95% CONFIDENCE INTERVAL)		NO. OF LESIONS (STUDIES)	QUALITY OF THE EVIDENCE (GRADE§)	DOWNSTREAM CONSEQUENCES
	Prevalence 0.25%†	Prevalence 2.0%‡			
True-Positive Results (Patients Needing a Biopsy)	180 (155-203)	1,440 (1,240-1,620)	390 (5)	Low¶,#,**	Patients will be identified correctly as having a potentially malignant or malignant disorder, and timely referral to a specialist or a biopsy will be performed.
False-Negative Results (Patients Incorrectly Classified as Not Needing a Biopsy)	70 (47-95)	560 (380-760)			An appropriate diagnosis would be missed, worsening the prognosis of the disease.
True-Negative Results (Patients Without Need for a Biopsy)	30,923 (24,938-35,910)	30,380 (24,500-35,280)	390 (5)	Low¶,#,**	Patients will receive reassurance that they do not have a potentially malignant or malignant disorder.
False-Positive Results (Patients Incorrectly Classified as Needing a Biopsy)	68,827 (63,840-74,812)	67,620 (62,720-73,500)			Patients would be identified incorrectly as having a potentially malignant or malignant disorder and would undergo additional unnecessary testing and a biopsy.

* Setting: primary care. Pooled sensitivity, 0.72 (95% confidence interval [CI], 0.62 to 0.81). Pooled specificity, 0.31 (95% CI, 0.25 to 0.36). Positive likelihood ratio, 1.04 (95% CI, 0.90 to 1.20). Negative likelihood ratio, 0.91 (95% CI, 0.63 to 1.30). Sources: Awan and colleagues,[77] Chainani-Wu and colleagues,[78] Farah and McCullough,[79] McIntosh and colleagues,[80] and Ujaoney and colleagues.[81]

† 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.

¶ Only 1 of 4 studies had a low risk of bias. Poor-quality reporting did not provide sufficient information to judge key risk of bias domains.

Investigators conducted all 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 reference test included from mild dysplasia to cancer in all studies except for those of Chainani-Wu and colleagues,[78] Farah and McCullough,[79] and Ujaoney and colleagues.[81]

eTABLE 8

Cytologic testing and vital staining adjuncts to evaluate clinically evident, suspicious lesions.*

TEST RESULT	EFFECT PER 100,000 PATIENTS TESTED, NO. (95% CONFIDENCE INTERVAL)		NO. OF LESIONS (STUDIES)	QUALITY OF THE EVIDENCE (GRADE§)	DOWNSTREAM CONSEQUENCES
	Prevalence 0.25%†	Prevalence 2.0%‡			
True-Positive Results (Patients Needing a Biopsy)	238 (215-248)	1,900 (1,720-1,980)	139 (2)	Very low¶,#,**,††	Patients will be identified correctly as having a potentially malignant or malignant disorder, and timely referral to a specialist or a biopsy will be performed.
False-Negative Results (Patients Incorrectly Classified as Not Needing a Biopsy)	12 (2-35)	100 (20-280)			An appropriate diagnosis would be missed, worsening the prognosis of the disease.
True-Negative Results (Patients Without Need for a Biopsy)	67,830 (55,860-77,805)	66,640 (54,880-76,440)	139 (2)	Very low¶,#,**,††	Patients will receive reassurance that they do not have a potentially malignant or malignant disorder.
False-Positive Results (Patients Incorrectly Classified as Needing a Biopsy)	31,920 (21,945-43,890)	31,360 (21,560-43,120)			Patients would be identified incorrectly as having a potentially malignant or malignant disorder and would undergo additional unnecessary testing and a biopsy.

* Setting: primary care. Pooled sensitivity, 0.95 (95% confidence interval [CI], 0.86 to 0.99). Pooled specificity, 0.68 (95% CI, 0.56 to 0.78). Positive likelihood ratio, 2.97 (95% CI, 2.14 to 4.12). Negative likelihood ratio, 0.07 (95% CI, 0.02 to 0.22). Sources: Guneri and colleagues[82] and Gupta and colleagues.[83]

† 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.

¶ Poor-quality reporting prevented us from assessing risk of bias for key domains.

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

** There was a small sample size of only 139 lesions.

†† The positivity threshold for the reference test included from mild dysplasia to cancer in addition to atypical results in the study of Guneri and colleagues[82] but not in that of Gupta and colleagues.[83]

eTABLE 9

Tissue reflectance and vital staining adjuncts to evaluate clinically evident, suspicious lesions.*

TEST RESULT	EFFECT PER 100,000 PATIENTS TESTED, NO. (95% CONFIDENCE INTERVAL)		NO. OF LESIONS (STUDIES)	QUALITY OF THE EVIDENCE (GRADE§)	DOWNSTREAM CONSEQUENCES
	Prevalence 0.25%†	Prevalence 2.0%‡			
True-Positive Results (Patients Needing a Biopsy)	203 (178-223)	1,620 (1,420-1,780)	307 (4)	Low¶,#,**	Patients will be identified correctly as having a potentially malignant lesion, and timely referral to a specialist or a biopsy will be performed.
False-Negative Results (Patients Incorrectly Classified as Not Needing a Biopsy)	47 (27-72)	380 (220-580)			An appropriate diagnosis would be missed, worsening the prognosis of the disease.
True-Negative Results (Patients Without Need for a Biopsy)	68,828 (62,843-74,813)	67,620 (61,740-73,500)	307 (4)	Low¶,#,**	Patients will receive reassurance that they do not have a potentially malignant or malignant disorder.
False-Positive Results (Patients Incorrectly Classified as Needing a Biopsy)	30,922 (24,937-36,907)	30,380 (24,500-36,260)			Patients would be identified incorrectly as having a potentially malignant or malignant disorder and would undergo additional unnecessary testing and a biopsy.

* Setting: primary care. Pooled sensitivity, 0.81 (95% confidence interval [CI], 0.71 to 0.89). Pooled specificity, 0.69 (95% CI, 0.63 to 0.75). Positive likelihood ratio, 2.62 (95% CI, 2.10 to 3.27). Negative likelihood ratio, 0.27 (95% CI, 0.17 to 0.44). Sources: Chainani-Wu and colleagues,[78] Epstein and colleagues,[84] Mojsa and colleagues,[85] and Ujaoney and colleagues.[81]

† 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.

¶ Three of 4 studies showed high risk of bias in patient selection and the application of the index test.

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

** The positivity threshold for the reference test included from mild dysplasia to cancer in all studies except for those of Chainani-Wu and colleagues[78] and Ujaoney and colleagues.[81]