



Living evidence-informed guideline on the early detection of oral squamous cell carcinoma and potentially malignant disorders

Cytology adjuncts to determine the need for biopsy,
Version 2026 1.0

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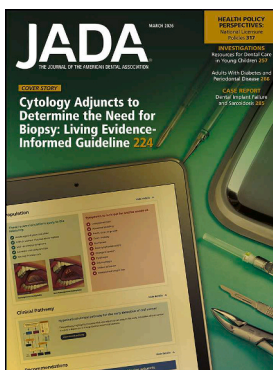
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ABSTRACT

Background. Early detection of oral potentially malignant disorders and oral cavity cancer can improve patient prognosis. The guideline panel addressed the use of cytology adjuncts to screen adults without mucosal abnormalities and determine the need for biopsy among adults with mucosal abnormalities.

Types of Studies Reviewed. The guideline panel used the Grading of Recommendations Assessment, Development and Evaluation Evidence to Decision framework to formulate recommendations. The authors conducted reviews to assess the benefits and harms of cytology adjuncts and people and clinician values and preferences as they relate to adjunct tests and biopsy of mucosal abnormalities. As part of the framework, the panel also considered resources required, equity, acceptability, and feasibility when formulating recommendations.

Results. The panel formulated 3 recommendations and 3 good practice statements. For adults with and without mucosal abnormalities, they formulated conditional recommendations against cytology adjuncts. Their use should be reserved for specific circumstances among adults with mucosal abnormalities when a biopsy is not possible or indicated. In the good



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practice statements, clinicians are urged to perform a clinical oral examination in all adult patients.

Conclusions and Practical Implications. Biopsy remains the first choice for reaching a definitive diagnosis of an oral potentially malignant disorder and oral squamous cell carcinoma, and cytology adjuncts should be reserved for specific situations when the clinician and patient agree it is the best course of action. When implementing or adapting these recommendations, local contexts should be considered to ensure equitable access to early detection.

Key Words. Oral cancer; potentially malignant disorder; early detection; living guideline; cytology.

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WHY IS THIS GUIDELINE NEEDED?

It is estimated that approximately 38,000 new cases of mouth and tongue cancer would have been diagnosed in the United States in 2025, and someone would have died as a result every 64 minutes (ie, 8,180 expected deaths).¹ “Oral potentially malignant disorders (OPMDs) constitute a heterogeneous group of clinically defined conditions associated with a variable risk of progression to oral squamous carcinoma.”² OPMDs can manifest clinically as oral leukoplakia, erythroplakia, proliferative verrucous leukoplakia, oral lichen planus, actinic keratosis (actinic cheilitis), oral lupus erythematosus, or oral submucous fibrosis. Smoking (smoked and some forms of smokeless tobacco) and alcohol consumption are the primary risk factors for oral cavity cancer and most OPMDs, and sun exposure is the primary risk factor for lip cancer. However, in the past several years, a shift in the incidence of oral cavity cancers among people without these risk factors has also been observed. The malignant transformation rate of OPMDs varies widely,³ and they may or may not have histologic evidence of dysplasia at the time of biopsy. Early detection and diagnosis of OPMDs and oral cavity cancer (specifically oral cavity and lip squamous cell carcinoma) is critical and is linked to improved prognosis.

The reference (or gold) standard for establishing a definitive diagnosis of an OPMD and oral squamous cell carcinoma (OSCC) is a punch or scalpel biopsy followed by histopathologic assessment. Adjunct tests such as cytology are commercially available to primary care clinicians in the United States for potential use in their diagnostic workups (Box 1). Such a cytology test requires the clinician to collect a cell sample from an oral mucosal abnormality with a brush. Ideally, if the test accuracy was deemed acceptable, clinicians would determine the need to perform another cytology test or biopsy among patients with abnormal-appearing cells (ie, a positive cytology result), while reassuring patients with normal-appearing cells (ie, a negative cytology result) they do not have an OPMD or OSCC.

Clinicians in primary care settings in the United States need guidance on whether to use cytology adjuncts in their diagnostic workups. A 2017 guideline⁵ served this purpose, but as novel technologies and living guideline methodologies have emerged in the past several years, an update was needed. This is the first in a series of articles with recommendations as part of the living evidence-informed guideline on the early detection of OPMDs and OSCC (which includes potentially malignant disorders and squamous cell carcinoma of the lip). Oropharyngeal cancer is not included in the scope of the recommendations in this guideline as cytology adjuncts cannot access this anatomic region. The purpose of this article is to provide a summary of the methods and resulting living evidence-informed recommendations for the use of available cytology adjuncts in the United States for the early detection of OPMDs and OSCCs.

HOW WERE THESE RECOMMENDATIONS DEVELOPED?

The multilayered digital guideline platform MAGICapp (MAGIC Evidence Ecosystem Foundation) (Box 2)⁶ and accompanying publications⁹⁻¹⁴ contain an expanded description of how the recommendations in this guideline were developed.

In brief, a multidisciplinary guideline panel (including representation from patients, primary care clinicians [ie, general dentists and dental hygienists], and specialists [ie, head and neck surgeons, oral and maxillofacial pathologists, and oral medicine specialists]) met in June 2025 to define the scope, purpose, target users (ie, those for whom the recommendations are intended to be

ABBREVIATION KEY

COE:	Clinical oral examination.
NA:	Not applicable.
OPMD:	Oral potentially malignant disorder.
OSCC:	Oral squamous cell carcinoma.

Box 1. Key concepts: Understanding the role of tests in health care decision making.

- In what situations can I apply a test to my patient?
Tests can be applied in several situations and contexts, including screening or surveillance, risk assessment and classification, ruling in diagnosis, ruling out diagnosis, treatment triage, treatment monitoring, staging, and determining prognosis.⁴
- What role can a new test play in my diagnostic workup?
“A test that has not previously been used in the intended role or for the intended purpose”⁴ is a new test. New tests can serve several roles along the diagnostic journey to a definitive diagnosis and subsequent management. They can be replacements for existing tests, added on after an existing test (ie, add-ons or sequential or serial testing), administered before an existing test (ie, triage or adjunct tests), or conducted at the same time as existing tests (ie, parallel tests).
- What does the result of a test tell us about the likelihood that a person has a condition?
Tests distinguish people with a higher likelihood of having a condition (positive test result) and those with a lower likelihood of having a condition (negative test result). Contrary to popular belief, tests are not perfect. Among the positive results, some people do not have a condition (ie, false-positive result), and analogously, among the negative results, some people do have the condition (ie, false-negative result). Triage or adjunct tests used in primary care aim to minimize false-negative results at the expense of false-positive results.
- What is an adjunct in the context of this guideline?
An adjunct is a test, device, technique, or technology marketed to assist primary care clinicians in the detection of a condition.
- How were cytology adjuncts evaluated when developing these recommendations?
In this guideline, cytology adjuncts are evaluated for their role in primary care settings to determine the need for biopsy or referral to a specialist and not to establish a definitive diagnosis. Cytology was evaluated for its role after the extraoral and intraoral clinical oral examination when screening healthy patients (ie, no mucosal abnormalities or symptoms) and ruling out a diagnosis in patients with mucosal abnormalities.

Box 2. Linked evidence supporting these recommendations.

- Living systematic review⁷ (<https://doi.org/10.1016/j.adaj.2025.12.008>)
- People and clinician values and preferences scoping review⁸ (doi:10.1016/j.adaj.2026.01.005)
- Living evidence-informed guideline on MAGICapp (<https://app.magicapp.org/#/guideline/EK0ldj>)⁶
 - Scope, purpose, target users, and guideline questions
 - Recommendations, supporting research evidence, and judgments
 - Conflict of interest declarations
 - Full methodology
 - Interest holders

used), guideline questions, and to rank person-important outcomes in order of priority for decision making. No members of the panel had financial conflicts related to cytology adjuncts, and intellectual conflicts were managed according to established standards.^{12,15} Interest holders reviewed and provided feedback for the panel’s consideration.⁶

In July 2025, the guideline panel developed recommendations and good practice statements following the Grading of Recommendations Assessment, Development and Evaluation Evidence to Decision framework for diagnostic tests.^{16,17} Recommendations are “actionable statement[s] about the choice between two or more management or policy options (interventions) in a specific population and, if relevant, in a specific setting.”¹⁸ They are accompanied by certainty of the evidence and strength of the recommendation. Good practice statements are “necessary actionable and clear guideline statements”¹⁸ that provide guidance supported by a vast amount of indirect evidence. Summarizing and assessing the certainty of this evidence is considered poor use of

resources and time.^{18,19} We developed evidence retrieval methods and synthesis protocols for the factors in the Grading of Recommendations Assessment, Development and Evaluation Evidence to Decision framework. Systematic reviews and the supporting digital platform for this guideline (Box 2) present the synthesized evidence. Recommendations and good practice statements went through external review by interest holders and the public from August through September 2025.⁶ We will continually monitor the evidence, and the guideline panel will update the recommendation if the new evidence warrants a change in the certainty of the evidence, strength, direction, or wording or there are new considerations for contextual factors (eg, feasibility, resource usage, values, and preferences). Otherwise, the new evidence will be incorporated into the systematic review only and the recommendation will remain unchanged.

WHO ARE THE TARGET USERS OF THESE RECOMMENDATIONS AND GOOD PRACTICE STATEMENTS?

The target users of these recommendations and good practice statements are clinicians, including general dentists and specialty dentists, primary care physicians and physician assistants, dental therapists, dental hygienists, nurses, and nurse practitioners. Community dental health coordinators and policy makers can also use recommendations and good practice statements to inform clinical decision making, programmatic decisions, and public health policy.

WHAT ARE THE RECOMMENDATIONS AND GOOD PRACTICE STATEMENTS?

Good practice statement 1

Clinicians should obtain from all adult patients an updated medical, social, and dental history and perform a clinical oral examination (COE), including both an extraoral and intraoral examination (Table).

Good practice statement 2

Clinicians should explain to all adult patients the importance and purpose of the COE, which includes early detection of mucosal abnormalities such as OPMDs and oral cavity cancer (Table).

Recommendation 1

The guideline panel suggests against the use of cytology adjuncts to determine the need for biopsy or a referral among adult patients with any mucosal abnormality in the oral cavity or on the lip (conditional, low certainty) (Table).

Rationale

This conditional recommendation against cytology adjuncts applies to adults with mucosal abnormalities in the oral cavity or on the lip with or without symptoms. Considering the totality of the evidence, including the uncertainty in the benefits and harms of cytology adjuncts, we issued a conditional recommendation against cytology adjuncts for determining the need for biopsy. However, we acknowledge that these tests could serve a purpose when a biopsy is not feasible, possible, or indicated. The specific evidence we used to arrive at this overall judgment is as follows

■ Balance between benefits and harms and certainty of the evidence: Low certainty of evidence from 5 test accuracy studies (795 lesions) suggests that cytology adjuncts may have acceptable accuracy. A systematic review summarizing this evidence contains data for these 5 studies (cytology adjuncts commercially available in the United States) and an additional 31 studies (cytology adjuncts not commercially available in the United States).⁷ We determined accuracy by means of assessing the absolute number of false-positive results (ie, unnecessary biopsies, anxiety, stress, and costs) and false-negative results (ie, delayed diagnosis and treatment) across 3 illustrative prevalence estimates. The panel determined that these absolute estimates had to be below 25% for false-positive results and 5% for false-negative results for the test to be deemed accurate (Figure 1). We downgraded the certainty in these accuracy estimates due to risk of bias in the primary studies (ie, patient selection, application of index and reference test, and inadequate reporting), indirectness (ie, applicability or generalizability of the estimates to primary care settings) of the data, and imprecision (for false-positive results only). Although sensitivity and specificity estimates are generally considered invariant to disease prevalence (eg,

Table. Summary of guideline questions, good practice statements, and recommendations.

GUIDELINE QUESTION	RECOMMENDATION OR GOOD PRACTICE STATEMENT	CERTAINTY OF EVIDENCE AND STRENGTH
No Question	Good practice statement 1: Clinicians should obtain from all adult* patients an updated medical, social, and dental history and perform a COE, [†] including both an extraoral and intraoral examination.	NA [‡]
No Question	Good practice statement 2: Clinicians should explain to all adult patients the importance and purpose of the COE, which includes early detection of mucosal abnormalities such as OPMDs [§] and oral cavity cancer.	NA
Should the Panel Recommend Cytology as an Adjunct to Determine the Need for Biopsy or a Referral Among Adults With Any Mucosal Abnormality in the Oral Cavity or on the Lip With or Without Symptoms to Detect OPMDs or OSCC?	Recommendation 1: The guideline panel suggests against the use of cytology adjuncts [¶] to determine the need for biopsy or a referral among adult patients with any mucosal abnormality in the oral cavity or on the lip.	Low, conditional
Should the Panel Recommend Cytology as an Adjunct to Determine the Need for Biopsy or a Referral Among Adults With Any Mucosal Abnormality in the Oral Cavity or on the Lip With or Without Symptoms to Detect OPMDs or OSCC?	Recommendation 2: If biopsy of a mucosal abnormality in the oral cavity or on the lip is not possible, advisable, or indicated, [#] the guideline panel suggests clinicians** offer a cytology adjunct to adult patients to further inform the need for biopsy. ^{††} This is particularly relevant for mucosal abnormalities ^{‡‡} that manifest as clinically worrisome.	Low, conditional
No Question	Good practice statement 3: If the clinician** detects persistence or progression ^{§§} of the mucosal abnormality in the oral cavity or on the lip despite a negative cytology test result, they should perform a biopsy or refer the patient to a specialist. ^{¶¶}	NA
Should the Panel Recommend Cytology as an Adjunct to Screen for the Potential Need for Biopsy or a Referral Among Asymptomatic Adults With No Clinically Evident Mucosal Abnormality in the Oral Cavity or on the Lip to Detect OPMDs or OSCC?	Recommendation 3: The guideline panel suggests against the use of cytology adjuncts to screen for the potential need for biopsy, or a referral among asymptomatic adult patients with no clinically evident ^{##} oral mucosal abnormality in the oral cavity or on the lip.	Low, conditional

* Adult refers to people 18 years and older, as most cases of oral potentially malignant disorder (OPMDs) and cancer (ie, oral squamous cell carcinoma [OSCC]) occur in this population. However, sometimes people younger than 18 years can develop OPMDs or OSCC, and so clinicians should remain vigilant for signs and symptoms in all patients. † An extraoral and intraoral clinical oral examination (COE) is a systematic examination (during new patient visits, routine recall appointments, or emergency encounters) that combines visual inspection of the head and neck region with palpation. It involves visual inspection of the face, lips, tongue, and oral structures under white-light illumination to detect clinically observable tissue abnormalities or morphologic changes in size, color, and texture. This is combined with regional palpation using gloved fingers to assess changes in temperature and consistency of the mucosa, skin, bone, joints, and lymph nodes. The examination follows a consistent approach to detect abnormalities that may require further evaluation, particularly in those with concerning symptoms (eg, unexplained pain or sensitivity, particularly to mechanical stimuli during oral function; abnormal bleeding; the perception of a new patch, ulcer, or growth; new tooth mobility; numbness; neck lymphadenopathy; change in speech; dysphagia; odynophagia; globus sensation; hoarseness; or unexplained weight loss). Signs and symptoms can be variable, persistent (lasting more than 2-3 weeks), progressive, and may overlap with benign conditions.²⁰ ‡ NA: Not applicable. § OPMDs are identified through clinical evaluation and “constitute a heterogeneous group of clinically defined conditions associated with a variable risk of progression to oral squamous carcinoma.”² OPMDs can manifest clinically as oral leukoplakia, erythroplakia, proliferative verrucous leukoplakia, oral lichen planus, actinic keratosis (actinic cheilitis), oral lupus erythematosus, or oral submucous fibrosis. These clinical diagnoses are usually assigned in a primary care setting through COE and can be confirmed only through a biopsy and histopathologic assessment as being dysplastic or cancerous.²¹ ¶ In the context of this guideline, OPMDs include potentially malignant disorders of the lip. ¶¶ Cytology adjuncts refer to tests commercially available for users to purchase legally in the free market in the United States. # A biopsy may not be possible or advisable for the following reasons: the patient may decline the clinician’s recommendation to perform a biopsy of the lesion or refer to a specialist, the biopsy may be deemed too risky due to underlying health conditions or patient-specific factors, or the biopsy site may not be easily accessible or could pose additional risks to the patient. ** Clinicians are the target users for this guideline, although only those trained to perform a biopsy should do so. †† A positive or atypical cytology test result reinforces the need for a biopsy or referral. A negative cytology test result indicates the need for interval follow-up of the patient if the target mucosal abnormality persists. ‡‡ Examples of clinical diagnoses that, depending on the clinical setting and manifestation, may not require a biopsy include classic recurrent aphthous ulcer, leukoedema, linea alba, herpes labialis, denture stomatitis, and pseudomembranous candidiasis. §§ Persistence or progression of a mucosal abnormality will vary depending on baseline clinical features and patient and environmental factors (eg, genetics, age, and behavioral habits). In general, a biopsy or referral should be considered when abnormalities persist for 10-14 days without a definitive diagnosis and treatment plan. ¶¶ Specialist refers to clinicians with advanced training, for example, in oral and maxillofacial surgery, oral and maxillofacial pathology, oral medicine, or otolaryngology–head and neck surgery. ## No clinically evident abnormalities refers to the absence of any clinically detectable tissue abnormality or symptoms during the clinical oral examination of the patient.

histopathologically confirmed presence of dysplasia or cancer in the current context), the panel deemed that this general principle may not be applicable to this scenario. According to the literature, the degree of false positivity (ie, specificity) is affected by means of the background prevalence of benign lesions (eg, hyperkeratosis, traumatic ulcers, oral mucositis, papillomas, verruca vulgaris, hairy leukoplakia, and hyperplastic candidiasis). This is particularly problematic for atypical cytologic results, which constitute a considerable proportion of positive findings and mandate biopsy. Likewise, the sensitivity of cytology is expected to differ according to histopathologic severity of disease (ie, expected to be higher for severe dysplasia or cancer). In contrast, for architectural dysplasia, the epithelium often has a substantially thickened layer of

Cytology adjuncts to evaluate mucosal abnormalities					
Patients	Adults with any mucosal abnormality in the oral cavity or on the lip, with or without symptoms*				
Index test	Cytology adjuncts commercially available in the United States				
Reference standard	Biopsy followed by histopathologic assessment				
Target condition	OPMDs and oral squamous cell carcinoma (including potentially malignant disorders and cancers of the lip)				
Setting	Primary care				
Diagnostic impact or outcomes	Effect				
Morbidity or mortality	No studies in which researchers evaluated the impact were identified, so the outcome was estimated on the basis of the diagnostic accuracy of the test and the expected consequences of each result.				
Diagnostic accuracy and outcomes	Effect				
Pooled data	795 patients/795 lesions (5 studies in a systematic review ²¹⁻²⁵)				
Pooled sensitivity	0.96 (95% CI, 0.86 to 0.99)				
Pooled specificity	0.86 (95% CI, 0.60 to 0.96)				
Pooled positive likelihood ratio	6.87 (95% CI, 2.02 to 23.39)				
Pooled negative likelihood ratio	0.05 (95% CI, 0.01 to 0.17)				
Outcome	Downstream consequences	Effect per 100,000 patients tested† (95% CI)			Certainty (Grading of Recommendations Assessment, Development and Evaluation)
		Prevalence, 1.03%‡	Prevalence, 1.5%§	Prevalence, 10.3%¶	
True-positive results (patients with need for biopsy)	Patients will be correctly identified as having a potentially malignant disorder or cancer and a timely referral to a specialist or biopsy will be carried out.	989 (886 to 1,020)	1,440 (1,290 to 1,485)	9,888 (8,858 to 10,197)	⊕⊕○○ Low ^{#,**,††}
False-negative results (patients incorrectly classified as not needing a biopsy)	Appropriate diagnosis would be missed, worsening the prognosis of the disease.	41 (10 to 144)	60 (15 to 210)	412 (103 to 1,442)	⊕⊕○○ Low ^{#,**,††}
True-negative results (patients not needing a biopsy)	Patients will receive reassurance that they do not have a potentially malignant disorder or cancer.	85,114 (59,382 to 95,011)	84,710 (59,100 to 94,560)	77,142 (53,820 to 86,112)	⊕⊕○○ Low ^{#,**,††}
False-positive results (patients incorrectly classified as needing a biopsy)	Patients would be incorrectly identified as having a potentially malignant disorder or cancer and would undergo additional unnecessary testing and biopsy.	13,856 (3,959 to 39,588)	13,790 (3,940 to 39,400)	12,558 (3,588 to 35,880)	⊕○○○ Very low ^{#,**,††,§§}

Figure 1. Summary of findings table for the early detection of oral squamous cell carcinoma and oral potentially malignant disorders (OPMDs) with cytology adjuncts commercially available in the United States.⁷ ⊕⊕○○: Very low certainty. ⊕⊕○○: Low certainty. * Symptoms could include unexplained pain or sensitivity (particularly to mechanical stimuli during oral function); abnormal bleeding; the perception of a new patch, ulcer, or growth; or symptoms such as new tooth mobility, numbness, neck lymphadenopathy, change in speech, dysphagia, odynophagia, globus sensation, hoarseness, and unexplained weight loss. † Absolute effects estimates illustrate the expected number of true-positive results, false-positive results, true-negative results, and false-negative results in a population of 100,000 patients with different hypothetical pretest probabilities (prevalences). ‡ This estimate represents the prevalence of OPMDs (1%) and oral cancer incidence (0.03%) among adults in the United States.^{27,28} § This estimate represents the prevalence of dysplastic or malignant lesions among adults with mucosal abnormalities in the United States (n = 386,250/25,000,000 [1.5%]).²⁷⁻²⁹ ¶ This estimate represents the prevalence of OPMDs and oral cavity cancer (histo-benign and with dysplasia) among adults with mucosal abnormalities in the United States (n = 2,575,000/25,000,000 [10.3%]).²⁷⁻²⁹ # The positivity threshold for the reference test included atypia, dysplasia to cancer in all studies. The positivity threshold for the index test included atypia for Scheifele and colleagues²² (n = 10/28), Sciubba²³ (n = 52/116), Mehrotra and colleagues²⁶ (n = 30/31), and Seijas-Naya and colleagues²⁵ (n = 9/9). Values in parentheses are the number of atypical results of the total positive results (atypical or positive results). It is unclear whether there were atypical results in Svirsky and colleagues.²⁴ ** Downgraded 1 level for indirectness. The investigators conducted the studies in a secondary care setting. Most patients had a higher probability of having a cancerous or potentially malignant

corrugated orthokeratin and therefore sensitivity is expected to be lower. However, few studies have reported sensitivity and specificity stratified on disease status (eg, mild, moderate, severe dysplasia, architectural dysplasia, or cancer). Because the relative mix of benign lesions, OPMDs with dysplasia, and oral cavity cancer are known to differ according to clinical setting, sensitivity and specificity estimates may not be generalizable across settings.

- **People and clinician values and preferences⁸:** This recommendation reflects values and preferences from patients and clinicians reported in the biomedical literature. Clinicians recognize biopsy as the gold standard and acknowledge responsibility for referring suggestive cases; however, some patients would prefer less invasive adjunctive tests, creating potential tension between recommended practices and patients' preferences. Standardized communication protocols are needed for disclosing OPMDs, as clinicians typically attempt to balance diagnosis disclosure with minimizing patient distress and anguish.
- **Resource considerations and cost-effectiveness:** From a societal perspective, there may not be any cost savings to using cytology to determine the need for a biopsy, due to the high cost of cytology tests.⁶ We did not identify any cost-effectiveness studies applicable to the US context.
- **Equity:** Population-level screening programs often widen health disparities, benefiting advantaged populations while leaving vulnerable groups behind.³⁰⁻³⁴ Most commonly affected are rural communities, racial and ethnic minority groups, and low-income, uninsured, and less educated populations. Contributing factors include financial barriers, workforce shortages, geographic isolation, systemic bias, limited access to care, and cultural and language barriers.
- **Acceptability and feasibility:** Cytology adjuncts have low usage among people with private dental insurance. *CDT 2026: Current Dental Terminology* code³⁵ for cytology (D7288) comprised a total of 17 dental insurance claims from 7 million people (American Dental Association Health Policy Institute, written communication, July 28, 2025). We did not have access to data for usage according to medical codes. In addition, the processing and analysis of cytology test results can take up to 1 week, adding more time to reach a definitive diagnosis. This wait period to arrive at a definitive diagnosis may not be acceptable to some interest holders. The panel did not identify any concerns in relation to the feasibility of implementing the test.

Recommendation 2

If biopsy of a mucosal abnormality in the oral cavity or on the lip is not possible, advisable, or indicated, the guideline panel suggests that clinicians offer a cytology adjunct to adult patients to further inform the need for biopsy. This is particularly relevant for mucosal abnormalities that manifest as clinically worrisome (conditional, low certainty) ([Table](#)).

Good practice statement 3

If the clinician detects persistence or progression of the mucosal abnormality in the oral cavity or on the lip despite a negative cytology test result, they should perform a biopsy or refer the patient to a specialist ([Table](#)).

Rationale

Although the certainty of the evidence for cytology adjuncts is low, the data suggest its accuracy may be acceptable. The panel acknowledged that although a biopsy is preferred, it may not be possible for any of the following reasons: the patient may decline the clinician's recommendation to perform a biopsy of the lesion or referral to a specialist, the biopsy may be deemed too risky due to underlying health conditions or patient-specific factors; or the biopsy site may not be easily accessible or could pose additional risks to the patient. In these situations, the alternative would be

disorder. †† Downgraded 1 level due to risk of bias. In general, 4 studies had high risk of bias²²⁻²⁵ and 1 had an unclear risk of bias.²⁶ These 4 studies²²⁻²⁵ had high risk of bias in patients' selection and 1 study²⁶ was at unclear risk in patients' selection. Studies were judged with unclear risk of bias for index test (n = 3), reference standard (n = 4), and flow and timing (n = 1). One study also had high risk of bias for reference test and flow and timing.²⁵ Regarding applicability: 3 studies had low risk of bias for patients' selection^{22,23,25} and 2 had unclear applicability of patients' selection.^{24,26} Two studies had low risk applicability for reference standard,^{25,26} 2 had unclear applicability for reference standard,^{22,24} and 1 had high-risk applicability for the reference standard.²³ All studies were judged to have unclear applicability regarding the index test. §§ Downgraded 1 level due to imprecision. Using a threshold for acceptable false-negative results of 5% and false-positive results of 25%, across all 3 prevalence estimates the lower bound of the 95% CI suggests an important difference favoring the test and the upper bound suggests an important difference not favoring the test.

Box 3. What you need to know.

- Although the test accuracy estimates and the essence of the recommendations did not change drastically since the 2017 version of this guideline,⁵ important methodological advancements and additions to the recommendations and remarks warranted an update.
- Clinicians should perform a clinical oral examination, including an extraoral and intraoral examination, in all adult patients.
- The guideline panel formulated a conditional recommendation against cytology adjuncts. Future high-quality research could alter this recommendation.
- Cytology adjuncts could be used in certain situations among patients with mucosal abnormalities to determine the need for establishing a definitive diagnosis through a biopsy and histopathologic assessment. People with negative cytology test results should be closely monitored for progression or persistence of the abnormality.

sending the patient home without a definitive diagnosis or a plan for accessing a biopsy. To avoid this, the panel suggests cytology adjuncts be used with patients when a biopsy is not possible or feasible. The results of the cytology adjunct provide the clinician and patient with information to make a shared decision about their treatment plan. Resources and efforts can be funneled toward ensuring patients with a higher chance of having an OPMD or OSCC (ie, positive cytology test) have access to a biopsy.

Recommendation 3

The guideline panel suggests against the use of cytology adjuncts to screen for the potential need for biopsy or a referral among asymptomatic adult patients with no clinically evident oral mucosal abnormality in the oral cavity or on the lip (conditional, low certainty) (Table).

Rationale

This recommendation applies to asymptomatic adults with no mucosal abnormalities. We did not identify diagnostic test impact or accuracy evidence to inform this recommendation. Considering patients value accurate and reliable tests and this test is associated with a high out-of-pocket cost, the panel suggested against using cytology adjuncts to screen apparently healthy adults in the absence of direct data supporting its effectiveness and accuracy in this population.

HOW DO I IMPLEMENT OR ADAPT THESE RECOMMENDATIONS TO SPECIFIC CONTEXTS AND SETTINGS?

A summary of the key takeaways from this article can be found in Box 3. These living recommendations are intended to assist clinicians in the decision-making process. Clinician experience and expertise is essential when identifying situations when a deviation from the recommendation is warranted. The strength of all recommendations in this guideline is weak or conditional, meaning different courses of action could be appropriate depending on the people and clinician values and preferences (Figure 2). If the clinician and patient decide a cytology adjunct is the best choice, clinicians must proactively and diligently follow up with patients with negative cytology results to rule out the possibility of a false-negative test result. If the mucosal abnormality persists for more than 10 through 14 days, we urge clinicians to biopsy the abnormality or refer the patient to a specialist for a biopsy as soon as possible.

Although these recommendations and good practice statements apply to primary care settings, some people are unable to make it to these settings for a COE. Populations with low socioeconomic status tend to experience lower screening rates and greater barriers to access.^{30,37} Standard screening and diagnostic approaches may inadvertently widen disparities if not adapted to local needs. Strategies and efforts may need to extend beyond traditional oral health care settings and incorporate community-based programs, primary care integration, targeted interventions for vulnerable populations, and integration of oral cancer development prediction models with risk stratifications.³⁸

		Strong recommendation	Weak (conditional) recommendation
Certainty of evidence		High certainty ++++ Very confident that the true effect lies on one side of a threshold (or within a range where the decision would not change).	Low certainty ++○○ Confidence is limited; the true effect may lie on either side of the threshold, and it is possible that the decision could change with further evidence.
		Moderate certainty +++○ Moderately confident that the true effect lies on one side of the threshold (or within the decision-consistent range), but there is some chance it lies on the other side.	Very low certainty ++○○○ Very little confidence in where the true effect lies in relation to the threshold. The true effect is likely to be substantially different from the best estimate, and decisions based on this evidence are very uncertain.
Interest holder	Patients	Most patients in this situation would want the recommended course of action, and only a small proportion would not.	Most patients would want the recommended course of action, but many would not. Values and preferences are expected to differ.
	Clinicians	Most patients should undergo the intervention. Adherence to this recommendation could be used as a quality criterion or performance indicator.	Recognize that different choices will be appropriate for different patients. Clinicians must help patients arrive at a decision consistent with their values and preferences. Decision aids may be useful.
	Policy makers	The recommendation can be adopted as a policy in most situations.	Policy making will require substantial debate and involvement of interest holders. Implementation will likely vary depending on circumstances, resources, and social values.
	Third-party payers	Coverage and reimbursement are generally warranted because most patients would be expected to choose the intervention.	Coverage decisions are likely to vary. Payers may consider conditional coverage, restrictions (eg, subgroups), or requiring shared decision making. Resource use and patient preferences are especially relevant.

Figure 2. Implications of strength of recommendations and definition of certainty of evidence.³⁶

The data informing the benefits and harms in this guideline were obtained from studies evaluating tests commercially available in the United States. A global evidence synthesis containing all cytology-related diagnostic test accuracy studies, regardless of commercial availability status in the United States, is available for adaptation to other contexts.⁷ The research in this global evidence synthesis (which includes the research used to inform this guideline) had several limitations, including a lack of data on person-important outcomes (eg, OSCC mortality and adverse events) and risk-of-bias issues. In addition, when adapting this research to local contexts, it may not be directly applicable to primary care settings, and this should be reflected in the certainty of the evidence assessments. Because future large-scale epidemiologic studies or randomized controlled trials are unlikely to be conducted, rigorously conducted diagnostic test accuracy studies can serve a similar purpose. Future studies should also consider recruiting patients who are more representative of the spectrum of patients seen in primary care settings. Finally, factors such as resource requirements, equity, values and preferences, and cost-effectiveness may vary in other contexts.

CONCLUSIONS

Clinicians should perform a clinical oral examination in all adult patients. The guideline panel suggests against the use of cytology adjuncts. Their use should be reserved for very specific situations among adults with mucosal abnormalities to determine the need for a biopsy. People with negative cytology tests results must be closely monitored for progression or persistence of the abnormality. ■

DISCLOSURE

Dr. Melville volunteers as a clinical advisory board member for Proteocyte AI, a privately owned medical technology company. Dr. Agrawal has equity ownership in OrisDX, a salivary diagnostics start-up, and has a submitted patent related to head and neck cancer genetics and salivary biomarkers. Dr. Pearson is a scientific advisory board member for Thermo Fisher and Daiichi Sankyo and received travel funding from Caris and research funding from Abbvie and Merck. None of the other authors reported any disclosures.

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